

Department of Clinical Investigation

Annual Research Progress Report

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Fiscal Year 1988

Madigan Army Medical Center
 Tacoma, Washington 98431-5454

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ANNUAL PROGRESS REPORT

30 September 1988

DEPARTMENT OF CLINICAL INVESTIGATION

MADIGAN ARMY MEDICAL CENTER

TACOMA, WASHINGTON 98431-5454

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19. ABSTRACT (Continue on reverse if necessary and identify by block number) This report covers all research protocols that were administratively or technically supported by the Department of Clinical Investigation, Madigan Army Medical Center, during FY 88. Included in the individual reports are title, investigators, funding, objective, technical approach, and progress for FY 88. Also included in the report are personnel rosters for the Department; committee members, funding information, and presentations and publications emanating from Madigan Army Medical Center during this period.					
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ANNUAL RESEARCH PROGRESS REPORT

FISCAL YEAR 1988

DEPARTMENT OF CLINICAL INVESTIGATION
MADIGAN ARMY MEDICAL CENTER
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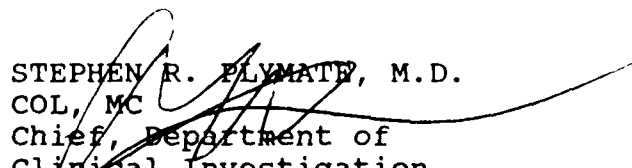
In conducting the research described in this report, the investigators adhered to the "Guide for the Care and Use of Laboratory Animals" as prepared by the Committee on the Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Institutes of Health, and Title 9, 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.

ACKNOWLEDGEMENTS

I would like to take this opportunity to thank Nancy Whitten for the effort which is obvious in the compilation, preparation, and editing of this publication.

FORWARD

During the past fiscal year, research at Madigan Army Medical Center has proceeded well as is evidenced by the publications and presentations from the various departments. During this fiscal year we have seen the addition of a Computer Analyst/Statistician (temporary position) which has vastly improved our support of and rapport with investigators. The research endeavors have been supported vigorously by the Commander and other Headquarters personnel. Without the support of these individuals, productivity would have been much less. In addition, the Clinical Investigation Activity at Health Services Command has increasingly been responsive to our problems and needs, and we would like to thank them for their support in the last year. Finally, the staff at the Department of Clinical Investigation, to include LTC Jones, MAJ MacMillan, MAJ Hannan, CPT van Hamont, 1LT Hoop, Ms Nancy Whitten, Ms Eugenia Hough, and Mr Troy Patience, as well as the laboratory technologists and the animal care technicians, have performed in an exemplary manner during the past fiscal year. Their work reflects not only upon this department but upon the entire hospital. This report is a summary of the activities which have taken place in the research arena at Madigan Army Medical Center during fiscal year 1988.


STEPHEN R. PLYMATE, M.D.
COL, MC
Chief, Department of
Clinical Investigation

UNIT SUMMARY FY 88

1. Objective

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

2. Technical Approach

<u>DESCRIPTION</u>	<u>RANK</u>	<u>MANPOWER</u> <u>MOS</u>
Chief PLYMATE, Stephen R., M.D., COL, MC	O6	61C9A
C, Clinical Studies Service JONES, Robert E., M.D., LTC, MC	O5	61C9B
C, Surg & Animal Care Svc (Sep 87-Mar 88) HAYRE, Michael D., D.V.M., MAJ, VC	O4	64C9B
C, Surg & Animal Care Svc (Aug-Sep 88) MacMILLAN, JAMES G., D.V.M., MAJ, VC	O4	64C9B
C, Microbiology Svc (Jun-Sep 88) van HAMONT, JOHN E. CPT, MS	O3	68A9B
C, Biochemistry Svc HANNAN, Charles J., Ph.D., MAJ, MS	O4	68C9C
C, Physiology Svc (Sep 87 - Jun 88) FRIEDL, Karl E., Ph.D, CPT, MS	O3	68J9B
C, Biological Research Svc HOOP, RITA C., M.S., 1LT, MS	O2	68C00
NCOIC SGT CAMPBELL, Naomi	E5	91T2R
Med Lab Spec SP4 GONZALEZ/RESTO, Alexander	E4	92B10
OR Tech SGT ROBBINS, John L.	E5	91D2R
Vet Animal Spec (Sep 87- Jun 88) SGT SCHILLER, Bradley J.	E5	91T10
Vet Animal Spec SP4 WESTMORELAND, Jacalyn	E4	91T10
Vet Animal Spec PV2 WILLON, Thomas	E2	91T10

<u>DESCRIPTION</u>	<u>RANK</u>	<u>MOS</u>
Med Tech KETTLER, Thomas M.	GS9	0644
Med Tech MATEJ, Louis A.	GS9	0644
Med Tech WRIGHT, JAMES	GS9	0644
Computer Programmer Analyst (temp) PATIENCE, TROY	GS9	0334
Edit Asst/Steno WHITTEN, Nancy J.	GS6	1087
Sec/Steno HOUGH, Eugenia R.	GS5	0318
Maintenance Worker KAEO, Curtis	WG7	4749

FUNDING FY 88

MEDCASE Equipment	\$159,130.00
Capital Equipment	14,015.00
Civilian Salaries	179,699.00
Consumable Supplies	92,683.00
Contractual Services	19,054.00
TDY	1,631.00
Transportation	20.00
Printing	743.00
<u>TOTAL</u>	\$466,975.00

3. Progress

During FY 88 there were 311 active protocols that received administrative and/or technical support during the year. Of these, 200 are presently ongoing; 81 were completed; 27 were terminated, and 3 are in a suspended status awaiting revisions.

There were 84 publications, three theses were completed and accepted from approved research studies, and there were 56 presentations at regional, national, or international meetings.

C O M M I T T E E M E M B E R S

Commander

Madigan Army Medical Center
BG Darryl H. Powell, M.D., MC

INSTITUTIONAL REVIEW BOARD

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the Human Use Committee, and the Laboratory Animal Use Committee

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COL Elmer M. Casey, Jr., M.D., MC

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- *Department of Ministry & Pastoral Care
- *Social Work Service
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Alternate Non-Institutional Member: Lyndel Cubberley, M.S.
American Lake VA Medical Center

*Member, Human Use Committee
+Member, Animal Use Committee

THE BYRON L. STEGER RESEARCH AWARD

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 1988:

Brady, W. Kim MAJ, MC	Reliability of a Rapid Latex Fixation Test for Detecting Group B Streptococci in the Genital Tract of Parturients at Term
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Other Nominees were:

Dunning, David M. CPT, MC	Radiation Sensitivity of Human Prostate Adenocarcinoma as Determined by ³ H-Thymidine Incorporation
Gorman, Patrick D. CPT, MC	A Comparison of Ampicillin and Trimethoprim- Sulfamethoxazole in the Treatment of Acute Pyelonephritis
James, Linda K. CPT, MC	Effects of Peripherally Administered Parenteral Nutrition on Plasma Fibronectin
Kugler, John P. CPT, MC	An Evaluation of the Impact of a Military Health Care System on Differences in Neonatal Outcome Between Whites and Blacks in a Washington County
Nickels, David A. CPT, MC	Cortisol Response in Febrile Children
Rezanski, Thomas A. CPT, MC	Effects of Androgen Depletion on the Growth of Human Prostate Tumor in Athymic Mice
Smith, Dale B. CPT, MC	A Device for the Intraoperative Identification of the Recurrent Laryngeal Nerve in Piglets

PUBLICATIONS

FISCAL YEAR 88

MADIGAN ARMY MEDICAL CENTER

DEPARTMENT OF CLINICAL INVESTIGATION

Backous DD, Friedl KE,
Smith NJ, Parr TJ,
Carpine WD

Soccer Injuries and Their Relation
To Physical Maturity. Amer J Dis
Child 142(8): 839-42, 1988

Chute CG, Baron JA,
Plymate SR, Kiel DP,
Pavia AT, Lozner EC,
Keefe T, MacDonald GJ

Sex Hormones and Coronary Artery
Disease. Amer J Med 83(5): 853-59,
1987

Davis JA, Hayre MD
Linn JM

Delayed Cutaneous Hypersensitivity
Response in Tetanus Toxoid Sensitized
Rhesus Monkeys - Predictor of Anergy
and Value in Tuberculin Skin Testing.
Lab Animal Science 38(4): 413-16, 1988.

Friedl KE, Hannan CJ,
Jones RE, Kettler TM,
Plymate SR

Serum Lipid and Sex Hormone Binding
Globulin Changes in Men After Admin-
istration of 17A-Methyltestosterone,
Testosterone Enanthate, and Testos-
terone Enanthate with Testolactone.
Clin Res 36(1): 122A, 1988

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Mader TH, Patience TH,
Schadler PW

Effect of Eye Color on Heart Rate
Response to Intramuscular Administra-
tion of Atropine. J Auton Nerv Syst
24(1): 51-56, 1988

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istration With 2-Pralidoxime Chloride
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#87-1, (USAMRDC): 1987

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Bernhard WN, Mohr LC

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Healthy Men During a Mountaineering
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239-42, 1988

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During Hypocapnia in Halothane
Anesthetized Monkeys.. Ann NY Acad
Sci 529(0): 172-74, 1988

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Risse SC, Raskind MA,
Plymate SR | Laboratory Evaluation for Cushing's
Syndrome in Psychiatric Patients
with Cortisol Nonsuppression Following
the Overnight Dexamethasone Suppression
Test. Biological Psychiatry 22(10):
1264-70, 1987 |
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Risse SC, Kopeikin H,
Cubberley L, Raskind MA | TSH Responses to Two TRH Doses in
Men With Alzheimer's Disease. Psycho-
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Globulin in the Human Hepatoma Hep
G2 Cell Line by Peptide Hormones
and Sex Steroids.. Clin Res 36(0):
126A, 1988 |
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Insulin and Prolactin. J Clin
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Normal Germ-Cell Relationships in
Testosterone-Treated Rhesus Monkeys.
Ann NY Acad Sci 513(0): 322-324, 1987 |
| Tenover JS, Matsumoto AM,
Plymate SR, Bremner WJ | The Effects of Aging in Normal Men
on Bioavailable Testosterone and
Luteinizing Hormone Secretion -
Response to Clomiphene Citrate.
J Clin Endo Metab 65(6): 1118-26, 1987 |

DEPARTMENT OF EMERGENCY MEDICINE

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| Broder JN | The Ferric Chloride Screening Test.
Ann Emer Med 16(10): 1188, 1987 |
| Cloonan CC | Management of Gunshot Wounds in the
Emergency Department. Trauma Quarterly
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White D, Dunning D

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Colorectal Cancer. Pro Ann Meet
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DIRECTORATE OF NUTRITION CARE

Cooke AJ, Plymate SR,
Martinet B, Dukes MW

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DEPARTMENT OF OB/GYN

Brady WK, Read JA

Vaginal Delivery of Twins After
Previous Cesarean-Section. New
Eng J Med 319(2): 118-19, 1988

Duff P

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Delivery: A Simple Cost-Effective
Strategy for Prevention of Post-
operative Morbidity. Amer J Obstet
Gynecol 157(4): 794-98, 1987

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Single-Dose Cefazolin Versus
Cefonicid for Antibiotic Prophylaxis
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Outcome of Trial of Labor in Patients
with a Single Previous Low Trans-
verse Cesarean Section for Dystocia.
Obstet Gynecol 71(3): 380-84, 1988

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Mil Med 153(9): 485-87, 1988

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tomatic Bacteriuria in Obstetric
Patients. Obstet Gynecol 71(6):
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Magelssen DJ, Dashow EE

External Cephalic Version at Term:
Is A Tocolytic Necessary?
Obstet Gynecol 70(6): 896-99, 1987

Soisson AP, Molina CY,
Benson WL

Endocervical Curettage in the
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Patients with Adequate Colposcopy.
Obstet Gynecol 71(1): 109-11, 1988

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Suture Materials. Clin Obstet
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PREVENTIVE MEDICINE SERVICE

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Lednar WM, Smith DW,
Miller RN

Building-Associated Risk of Febrile
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Trainees. JAMA 259(14): 2108-12, 1988

DEPARTMENT OF PEDIATRICS

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Bass JW, Nevin-Woods C,
Weir MR

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Infection in the Military Population
in Hawaii. Pediatr Infec Dis J 7(2):
138-40, 1988

DEPARTMENT OF PSYCHIATRY

Garland FN, Robichaud MR

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Mil Med 152(12): 608-12, 1987

DEPARTMENT OF SURGERY

Bickerstaff LK, Harris SC
Leggett RS, Cheah KC

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Arch Surg 123(1): 49-51, 1988

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Mil Med 153(4): 171-75, 1988

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Brown WB

Acinetobacter Calcoaceticus Foot Infection Secondary to High-Pressure Injection Injury: A Case Report.
Foot Ankle 8(4): 216-22, 1988

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Catlin FI

Choanal Atresia and Associated Anomalies The Charge Association.
Int J Pediatr Otorhinolaryngol 15(2): 129-36, 1988

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Suprarenal Occurrence of an Adenomatoid Tumor. J Urol 139(2): 348-49, 1988

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Chismire KJ, Stephan MJ

Enlarged Pupillary Membranes.
J Pediatr Ophthalmol Strabis 25(2): 73-74, 1988

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Harris S, Andersen C

Necrotizing Fasciitis As A Complication of Percutaneous Endoscopic Gastrostomy. J Parenter Enteral Nutr 11(6): 583-85, 1987

Morris MR

Unusual Lymphadenopathies or Cystic Lesions and the Parotid Gland.
Otolaryngol H&N Surg 98(3): 268, 1988

Piatt JH, Hudson AR,
Hoffman HJ

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Neurosurgery 22(4): 715-23, 1988

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THESES

Kugler JP	An Evaluation of Neonatal Outcomes for Blacks and Whites in Military and Civilian Health Care Systems in A Washington County Thesis. 1988, Univ Washington, Master of Public Health
Iversen JS	The Needs of Family Members of Cancer Patients. 1988, Univ Washington Master of Nursing
Dettori JR	Early Mobilization: Its Effects on Grade 2 and Grade 3 Lateral Ankle Injuries. 1988, Univ Washington Master of Public Health

PRESENTATIONS

FISCAL YEAR 88

MADIGAN ARMY MEDICAL CENTER

Author(s)	Title	Meeting
DEPARTMENT OF CLINICAL INVESTIGATION		
Friedl KE	Non-parametric Statistics in Clinical Studies	Mary Lipscomb Hamrick Army Medical Specialist Corps Research Course, Leesburg, VA August 88
Friedl KE	Reporting Research Results: Graphic and Ethical Considerations.	Mary Lipscomb Hamrick Army Medical Specialist Corps Research Course, Leesburg, VA August 88
Friedl KE Hannan CJ Jones RE Kettler TM Plymate SR	Serum Lipid and Sex Hormone Binding Globulin Changes in Men After Administration of 17 α Methyltestosterone Testosterone Enanthate and Testosterone Enanthate With Testolactone	American Federation for Clinical Research, Western Region. Carmel, CA February 88
Friedl KE Hannan CJ Jones RE Kettler TM Plymate SR	Serum Lipid and Sex Hormone Binding Globulin Changes in Men After Administration of 17 α -Methyltestosterone Testosterone Enanthate and Testosterone Enanthate with Testolactone	American Federation for Clinical Research, National Meeting, Washington, DC May 88
Friedl KE Plymate SR Jones RE Matej LA Wright J	Consequences of Inhibition of Estradiol Production in Association with High Dose Androgen Administration	8th International Congress of Endo- crinology Kyoto, Japan July 88
Nestler JE Barlascini CO Matt DW Steingold KA Plymate SR Clore JN Blackard WG	Suppression of Insulin by Diazoxide Raises Serum Sec Hormone Binding Globulin Levels in Obese Women with Polycystic Ovary Disease.	The Endocrine Society New Orleans, LA June 88

PRESENTATIONS - MAMC - FY 88

Plymate SR Friedl KE Hannan CJ Jones RE	Evidence That Sex Hormone Binding Globulin Affects Cellular Availability of Testosterone in Men	The Endocrine Society, 70th Annual Meeting New Orleans, LA June 88
Plymate SR Matej LA Jones RE Friedl KE	Regulation of Sex Hormone Binding Globulin in the Human Hepatoma Hep G2 Cell Line by Peptide Hormones and Sex Steroids.	American Federation for Clinical Research, Western Region Carmel, CA February 88
Plymate SR Petra PH Namkung PC Hayre MD	Modulation of Serum Estradiol (E2) Levels and the Metabolic Clearance Rate of E2 by Acute Changes in Serum Sex Hormone Binding Globulin Concentrations	Society for Gyne- cologic Investigation Baltimore, MD March 88
Rose M Greathouse D Sanders G Fridel KE Harlan B Sweeney JK	Individual Consultation on Research Ideas, Projects, and Manuscripts.	Mary Lipscomb Hamrick Army Medical Specialist Corps Research Course. Leesburg, VA August 88
Wilkinson CW Galt SA Roberts TS Plymate SR	Characterization of Peptides Derived from Pro-Opiomelan- cortin (POMC) in A Nelson's Syndrome Pituitary Tumor.	Society for Neuroscience New Orleans, LA November 1987

DEPARTMENT OF EMERGENCY MEDICINE

Rice MM	Medicolegal Aspects of Prehospital Care	Tri Service Symposium on Emergency Medicine San Antonio, TX April 88
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DEPARTMENT OF FAMILY PRACTICE

Kugler JP	An Evaluation of the Impact of a Military Health Care System on Differences in Neonatal Outcome Between Whites and Blacks in a Washington County.	Uniformed Services Chapter of the American Academy of Family Physicians, March 88
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DEPARTMENT OF MEDICINE

Carlin KJ Jones RE Treece GL Matej LA Plymate SR	Effect of Calcium Channel Blockers on HCG Stimulated Testosterone Production.	American Society of Andrology, May 88
Carlin KJ Plymate SR Jones RE Treece GL Matej LA	Effects of Calcium Channel Blockers on Testosterone Production.	4th Annual Army Regional American College of Physicians Meeting San Francisco, CA October 87
Colman L Porter B Redmond J Olson D Stimac G Dunning D	Short T1 Inversion Recovery (STIR) Sequence Magnetic Resonance Imaging in Evaluation of Spinal Metastases	American Society for Clinical Oncology New Orleans, LA May 88
Davidson H Bowersox J Lee RB	Experience with Groshong versus Hickman Central Venous Catheters	American Society for Clinical Oncology New Orleans, LA May 88
Dunning DM Loop SM	In Vitro Radiation Survival Curves from Human Prostate Cancer Cell Lines Using a 3-H Thymidine Uptake Assay.	4th Annual Hematology-Oncology Scientific Meeting - Outstanding Research Award. San Fran 10/24/87
Horan MP Covelli HD Redmond J Barnes M Wallingford JL Friedl KE	Local Effects of Radiotherapy on Stage III Non-Oat Cell Lung Cancer.	53rd Annual Scientific Assembly, American College of Chest Physicians Atlanta, GA October 87
Jones RE Plymate SR	Ejaculated Human Sperm Can Incorporate Docosahexaenoic Acid (22:6) and Palmitic Acid (16:0) Into Phosphatidylcholine (PC) Through A Coenzyme A (CoASH) Dependent Mechanism.	American Society of Andrology Houston, TX March 88
Jones RE Plymate SR	Docosahexaenoyl Coenzyme A Synthesis in Human Sperm: A Comparison to Palmitoyl Coenzyme A Synthesis.	4th Annual Army Regional American College of Physicians Meeting San Francisco, CA October 87

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Knodel DH Greenman PH Treece GL Jones RE Bowersox JN	Atrial Natriuretic Peptide in the Postoperative Patient.	4th Annual Army Regional American College of Physicians Meeting San Francisco, CA October 87
Kollef MH Peller T Knodel A	Delayed Pleuropulmonary Complications of the Internal Mammary Artery Conduit for Coronary Artery Revascularization	Joint meeting American Lung/Thoracic Soc Las Vegas, NV 05/08/88
Mullarkey MF Andrade WP Blumenstein BA Bailey GA	Methotrexate in the Treatment of Corticosteroid-Dependent Asthma. A Double-Blind Crossover Study With Follow-Up	44th Ann Meet Amer Acad Allergy Immunol Anaheim, CA March 88
Perkins JA	Nasal Polyps, A Manifestation of Allergy?	Amer Acad Otolaryngol Head & Neck Surgery Washington, DC September 88
Roth BJ	The Serum Effusion Albumin Gradient in the Evaluation of Pleural Effusions	Washington State ACP Meeting Yakima, WA August 88
Schoenfeld SL McCulloch DK Klauff LJ Nuovo JA Mordes JP Nepom G Palmer JP	Insulin Autoantibodies as Detected by Radioimmunoassay are Rare in Autoimmune Thy- roid and Rheumatoid Disease First Degree Relatives of IDDM and BB Rats is Dependent Upon Assay Methodology	International Research Symposium - The Immu- nology of Diabetes Woods Hole, MA October 87
Sierra R Colman L White D Dunning D	Sequential Therapy with Methotrexate and Infusional 5-FU in Advanced Colorectal Cancer	American Society of Clinical Oncology, New Orleans, LA May 88

DIRECTORATE OF NUTRITION CARE

Cooke AJ Plymate SR Rawlings VR Friedl KE	Soldier Nutrition and Performance Appraisal.	Mary Lipscomb Hamrick Army Medical Specialist Corps Research Course Leesburg, VA August 88
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Brady WK	Latex Fixation Test for Detecting Group B Streptococci in the Genital Tract of Parturients at Term	Infectious Disease Society for Obstetrics-Gynecology Snomass, CO 08/01/88
Brady WK	Refractory Postabortal Fever: In Pursuit of "Zebras"	Armed Forces District, American College of OB/GYN Denver, CO 10/01/87
Brady WK	Pulmonary Hypoplasia in Liveborn Infant After In-Utero Death of Monozygotic Twin	Armed Forces District, American College of OB/GYN Denver, CO 10/01/87
Elg SA Lee RB	Complications of Subclavian Catheters in Gynecologic Patients.	16th Annual Meeting, Western Association of Gynecologic Oncologists, Jackson Hole, WY 06/25/88
Lee RB Burke T Park RC	Estrogen Replacement Therapy Following Treatment for Stage I Endometrial Carcinoma - A Preliminary Report.	Western Association of Gynecologic Oncologists Jackson Hole, WY 06/24/88
Milligan DA	Chronic Spinal Headache After Caesarian Section, A Case Report and Review of the Literature	Armed Forces District, American College of OB/GYN Denver, CO 10/01/87
Milligan DA Watson WJ	Nephrolithiasis in Pregnancy	Armed Forces District, American College of OB/GYN Denver, CO 10/01/87

PHYSICAL MEDICINE & REHABILITATION SERVICE

Dettori JR	Early Ankle Mobilization: Effects on Grade Two and Grade Three Lateral Ankle Sprains	Mary Lipscomb Hamrick Army Medical Specialist Corps Research Course, Leesburg, VA 08/10/88
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DEPARTMENT OF PEDIATRICS

Sweeney JK	Physiological and Behavioral Effects of Neurological Assessment in Preterm and Full-Term Neonates	Mary Lipscomb Hamrick Army Medical Specialist Corps Research Course, Leesburg, VA August 88
Sweeney JK	Neonatal Physical Therapy Intervention and Interdisciplinary High Risk Infant Followup: A Corollary To Regional Newborn Care.	Mary Lipscomb Hamrick Army Medical Specialist Corps Research Course, Leesburg, VA August 88
Sweeney JK	Neonatal Hydrotherapy: An Adjunct to Developmental Intervention in an Intensive Care Nursery Setting.	Mary Lipscomb Hamrick Army Medical Specialist Corps Research Course, Leesburg, VA August 88
Sweeney JK	Physiological Adaptation of Neonates to Neurological Assessment.	Mary Lipscomb Hamrick Army Medical Specialist Corps Research Course, Leesburg, VA August 88

DEPARTMENT OF SURGERY

Beck RA	The Changing Picture of Facial Fractures: Five Year Review	Annual Clinical Meeting, Washington State Chapter, American College of Surg Sunriver, OR 06/24/88
Belville WD	The Penile Corpora	Annual Meeting, Tacoma Surgical Club Tacoma, WA 04/01/88
Belville WD	Secondary Penile Malignancies: The Spectrum of Presentation	Northwest Urological Society Meeting Portland, OR 12/01/87
Belville WD	Secondary Penile Malignancies: The Spectrum of Presentation	The Kimbrough Urological Seminar Washington, DC 11/01/87

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Bowersox JC Andersen CA	Response of Human Venous Endothelial Cells to Seeding on Extracellular Matrices.	Washington State Chapter of the American College of Surgeons Sunriver, OR 06/01/88
James LK Smith SB Bowersox JC	Effects of Peripherally Administered Parenteral Nutrition on Plasma Fibronectin	Northwest Chapter Chapter, American Surgeo College of Surgeons
James LK Smith SB Bowersox JC	Effects of Peripherally Administered Parenteral Nutrition on Plasma Fibronectin	Gary P. Wratten Symposiu Tacoma, WA 04/13/88
Kiesling VJ	Sclerotherapy for Adult Hydroceles	Northwest Urological Society Portland, OR 12/01/87
Kiesling VJ	The Use of the Gracilis Myocutaneous Flaps for Complicated Urinary Fistulas	The Tacoma Surgical Club Tacoma, WA 04/01/88
Kiesling VJ	Sclerotherapy for Adult Hydroceles	The Kimbrough Urological Seminar Washington, DC 11/01/87
Liening DA	Hypothyroidism Following Radiotherapy for Head and Neck Cancer	Annual Meeting of the American Academy of Otolaryngology - Head and Neck Surgery. Washington, DC 09/27/88
Rozanski TA	Photodynamic Therapy of Human Prostate Cancer <i>in Vitro</i>	Northwest Urologic Society Portland, OR 12/01/87
Rozanski TA	Photodynamic Therapy of Human Prostate Cancer <i>in Vitro</i>	Kimbrough Urological Seminar Washington, DC 11/01/87
Rozanski TA Loop S	Effects of Androgen Depletion on Human Prostate Tumor Cell Growth in the Athymic Balb/C Mouse	Kimbrough Urological Seminar Washington, DC 10/01/87
Rozanski TA Loop S	Effects of Androgen Depletion on Human Prostate Tumor Cell Growth in the Athymic Balb/C Mouse	Western Section, American Urologic Association, San Francisco, CA 03/01/88

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DETAIL SHEETS
FOR
PROTOCOLS

DEPARTMENT OF CLINICAL INVESTIGATION

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 83/64 Status: Completed

Title: The Effect of 20 α -Hydroxy-4-Pregnen-3-One Treatment on Spermatogenesis and Gonadotrophins in Rats

Start Date: 20 May 83 Estimated Completion Date: Dec 87

Department: Clinical Investigation Facility: MAMC

Principal Investigator: CPT Karl E. Friedl, MSC

Associate Investigators:

COL Bruce L. Fariss, MC LTC James L. Kelley, MC

COL Stephen R. Plymate, MC Mina Garrison, DAC, B.S., M.T.

Key Words: Physiological role, direct and indirect actions

Accumulative Est Accumulative Periodic Review:

MEDCASE Cost: -0- OMA Cost: \$2750.00 Jul 87

Study Objective: To examine the possibility of a physiological role for the steroid metabolite 20 α -hydroxy-4-pregnen-3-one in the hypothalamic-pituitary testes axis.

Technical Approach: 32 young adult male rats will be anesthetized and castrated on the day prior to treatment and randomized into 4 groups. 32 intact rats from the same shipment will also be randomized into 4 groups. The groups from both experiments will be injected daily for 30 days with 1 mg progesterone, 1 mg 20 α -OHP, 5 mg 20 α -OHP, or sesame oil. After 30 days of treatment they will be guillotined. Trunk blood will be collected into heparinized containers, centrifuged, and plasma aliquots for the hormone assay will be made and frozen. The testes will be removed from the intact animals, decapsulated and weighed. The left testis will be divided and preserved for histology. The right testis will be frozen until assay of intratesticular T, E₂, and androgen binding protein. For all animals, the ventral prostate and seminal vesicles will be ligated, removed, and weighed. Epididymides will be weighed from intact animals and the right epididymis will be frozen for later assay of T, E₂, and ABP. Testes will be sectioned at 4 microns, and 22 tubules representing 7th stage cellular associations will be used per animal. Spermatogonia, spermatocytes, and S7 spermatids will be counted and expressed in terms of Sertoli cell nuclei counts. Unusual features such as necrotic germ cells and high lipid content of Sertoli cells will be noted. Means of counts and tubule diameters will be compared between the 4 groups by t test. Steroids and gonadotrophins will be measured for all 8 groups by RIA and compared between intact groups and castrated groups by t test. The relationship between the quantitative assessment of spermatogenesis and hormonal changes will be compared between intact groups.

Progress: This protocol was terminated without further work in FY 88 due to time constraints and the transfer of the principal investigator. Preliminary data indicated that 20 α -OHP acts on both the hypothalamic/pituitary and the testis mechanisms by substantial activation of the seminiferous tubule component of the testes as demonstrated by significant increases in androgen binding protein concentrations. This data was presented at the 7th International Congress of Endocrinology in 1984.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 86/101 Status: Completed

Title: Atropine Absorption After Administration with 2-Pralidoxime Chloride by Automatic Injector. A Comparison Between Injection of the Drugs Into the Same Intramuscular Site and Separate Intramuscular Sites

Start Date: Jan 87 Est Completion Date: Jun 87

Department: Clinical Investigation Facility: MAMC

Principal Investigator: CPT Karl E. Friedl, MS

Associate Investigators: LTC Thomas Mader, MC

COL Stephen R. Plymate, MC LTC Robert Smallridge, MC

LTC Robert Jones, MC MAJ Charles Hannan, MS

Key Words: atropine, single vs separate injections, autoinjector

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: \$30,000.00* Jan 88

Study Objective: To determine if the absorption of atropine by autoinjector is equally effective when administered at a single intramuscular injection site compared to two separate intramuscular injection sites.

Technical Approach: In alternate experiments, one week apart, 20 healthy males (ages 19-30) will be injected with the MARK-I delivery system and with the multichambered autoinjector delivery system. After an overnight fast, the subjects will be connected to an ECG machine and an indwelling catheter with heparin lock will be inserted into the antecubital vein. Subjects will sit quietly on a bed at an approximate 45° angle. After a minimum 30 minute quiescent period a baseline ECG will be recorded and a 4 ml blood sample will be taken for pre-test CPK. Then the drug will be administered and the subjects will be asked to rate the degree of pain. Blood samples will be drawn at 3, 6, 10, 15, 20, 30, 40, and 50 minutes and at 1, 1.5, 2, 2.5, 3, 4, 5, 6, 9, and 12 hours. An ECG will be recorded and pupillary diameters will also be estimated at these time intervals. Subjects will be asked to remain supine during the testing. An additional 4 ml blood sample will be drawn for post-injection CPK. Atropine and pralidoxime assays will be performed. Two way ANOVA analysis and t-test will be used for statistical analysis when comparing the different groups.

Progress: Detailed results of this study have been reported in MAMC Reports #86-1 and #87-1 through the USA Medical and Research Development Command. A paper was also published on the effect of eye color on heart rate response to IM administration of atropine and a paper entitled "Drug Delivery Systems for Chemical Defense" will also be published in the Army RD&A Bulletin. Atropine absorption was more rapid following injection by the Mark I but there was no significant difference between serum atropine concentrations achieved. Differences between injectors were not apparent at time points beyond the first 30-40 minutes and there was no difference in peak effect or time to peak effect.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 88/11 Status: Completed

Title: Bioequivalence of Nandrolone Decanoate to Testosterone Enanthate in Men

Start Date: 16 Oct 87 Est Completion Date: Dec 87

Department: Clinical Investigation Facility: MAMC

Principal Investigator: CPT Karl E. Friedl, MS

Associate Investigators: LTC Anthony C. Zold, MS COL

Stephen R. Plymate, MC MAJ Joseph R. Dettori, AMSC

LTC Robert E. Jones, MC MAJ Charles J. Hannan, MS

Key Words: testosterone enanthate, nandrolone decanoate, bio-equivalence, men, androgen, SHBG, GTT

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: \$5,000.00 N/A

Study Objective: To determine which androgen actions are dissociated from the anabolic actions with structural modification of the androstane nucleus such as nandrolone decanoate, a standard clinical anabolic steroid, and to determine which nonandrogenic actions are added by such modification.

Technical Approach: Forty healthy active duty Army males, ages 18-30, within standards of the Army Weight Control Program will be randomized to four groups of 10 men each and treated with steroids weekly for six weeks with the following tests performed before and after the test period: glucose tolerance test; serum lipid analysis (10 hr fasted); anthropometric measures; hydrostatic weights; semen analysis, including quantitative fructose measurement; testicular volume; SHBG and salivary testosterone; liver enzymes; psychological testing for aggression; and Cybex strength testing. Each subject will provide his own baseline control. Subjects will be randomized to one of the following treatments: (1) Testosterone enanthate, 100 mg/wk i.m.; (2) Testosterone enanthate, 300 mg/wk i.m.; (3) Nandrolone decanoate, 100 mg/wk, i.m.; or (4) Nandrolone decanoate, 300 mg/wk i.m. Group I is a partial placebo control group which controls for conscious weight training and dietary habit changes. Analysis of results will include 2-way analysis of variance for differences between treatment groups and between baseline and steroid measurements. Duncan's test will further pinpoint specific group differences for significant analysis of variances.

Progress: A manuscript has been submitted for consideration for publication. A paper has been accepted for presentation at the 1988 Society for Neuroscience meeting in November. Increases in plasma homovanillic acid were noted in the nandrolone groups but not in the testosterone enanthate groups. Estrogen levels were within normal ranges in the nandrolone groups, but above normal concentrations were found in the high testosterone group. Nandrolone influence on the dopaminergic system which is reflected in increased HVA may be related to some incidents of psychopathology found in androgenic steroid abusers.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 85/36 Status: Completed

Title: Physiological Changes with Weight Loss. Part 3: Serum Lipids (Part 2 completed FY 86)

Start Date: 18 Jan 85 Est completion Date: Jan 87

Department: Clinical Investigation Facility MAMC

Principal Investigator: MAJ Charles J. Hannan, MS

Associate Investigators:

COL Stephen R. Plymate, MAJ Arthur Knodel, MC

LTC Robert E. Jones, MC CPT Karl E. Friedl, MS

MAJ T. Kaduce, MS, USAR Thomas Kettler, GS/09

Key Words: Diet, no exercise, serum lipids, body fat

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: \$8155.00 Oct 87

Study Objective: To determine if there is a measurable change in 12-hr fasted serum lipids during an extended period of caloric restriction (with & without exercise) and if any change is maintained after a reduced weight is established. A second objective is to examine the relationship of alterations in lipid levels which are observed in this study with endocrine changes observed in the associated study with the same subjects.

Technical Approach: Healthy male non-smokers who have been referred because they are over the Army weight standard will be randomized into three groups: (1) 0-5% below maximum allowable fat standard; blood samples and hydrostatic weight initially and at six months; (2) over the fat standard and on a diet; and (3) over the fat standard and on a diet and exercise. Groups 2 and 3 will have blood samples, caliper measurements, and hydrostatic weights performed once a week after an overnight fast. Subjects will fill out a questionnaire at the first session, submit a weekly food intake sheet, and take part in weekly counselling sessions. Serum will be analyzed for changes in both free and total cholesterol and triglycerides.

**This protocol was reviewed by the IRB in April 1986. At that time additional funding was approved because the costs of the ultracentrifugation and HPLC had not been adequately reflected in the original protocol. Further identification of apolipoproteins separated by HPLC was also approved. Isoelectric focusing will be done to specifically identify proteins in HPLC eluents.

Progress: Sample analysis has been completed. The data are being integrated with data from parts 1 and 2 of the study. A manuscript is being prepared for submission for publication.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 85/83 Status: Completed

Title: Mechanisms in Blood-Brain Barrier Function: Animal Models

Start Date: 23 Aug 85 Est Completion Date: Dec 87

Department: Clinical Investigation Facility: MAMC

Principal Investigator: MAJ Charles J. Hannan, MS

Associate Investigators:

COL Stephen R. Plymate, MC CPT Mark Flanery, MC

LTC Robert E. Jones, MC Alan A. Artru, M.D.

LTC James Temo, ANC Judy Y. Sey, Ph.D.

MAJ Leslie Yarbrough, VC Thomas Kettler, B.S.

Key Words: patency, anesthesia, biochemical markers

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: \$12,848.00 Jan 88

Study Objective: To evaluate patency of the blood-brain barrier (BBB) during anesthesia and to evaluate various cerebral spinal fluid (CSF) biochemical markers of BBB status.

Technical Approach: Three animal models with three inhalation anesthetics (halothane, isoflurane, and enflurane) will be used: (1) two strains of mice, the relatively short-lived NZB and the longer-lived C57BL mouse, will be used at different ages in biochemical studies in vitro with isolated cerebral capillaries; (2) Fisher 344 rats will be used in acute experiments to measure regional brain uptake of BBB permeability tracers such as ³H-water while anesthetized; and (3) macaques, anesthetized with the 3 agents will be prepared for CSF collection by lumbar puncture.

Progress: Previous reports of halothane-induced increase of BBB permeability employed halothane concentrations of >1.5%, but the duration of exposure was brief. In the present study 5 hours of 0.5% halothane with normocapnia or modest hypocapnia caused no alteration of BBB permeability. In previous studies, hypocapnia increased BBB permeability only when P_aCO₂ was reduced to <18 torr. In the present studies, 0.5% halothane combined with P_aCO₂ = 21-24 torr resulted in increased BBB permeability. A synergistic increase in BBB permeability may be produced by halothane and hypocapnia, but further studies in the same animal model will be necessary.

A paper was presented at the 4th Colloquium in Biological Sciences, New York Academy of Sciences and a paper was published in the Annals of the New York Academy of Sciences 529:172-74, 1988.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 87/41 Status: Completed

Title: Age Related Effects in Blood-Brain Transport of Hormones:
I. Testosterone

Start Date: Jan 87 Est Completion Date: May 87

Department: Clinical Investigation Facility: MAMC

Principal Investigator: MAJ Charles Hannan, MS

Associate Investigators: COL Stephen R. Plymate, MC

SGT Naomi Campbell

William Bremner, M.D.

Lisa Meyers, M.D.

Key Words: blood-brain transport, hormones, testosterone

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: \$945.00 N/A

Study Objective: This study will measure the transport across the blood-brain barrier (BBB) of testosterone in plasma from young and old males.

Technical Approach: Serum will be obtained from five to eight healthy men in each of two groups: young (age 20-35) and old (age 50 and over). The right carotid artery of a 200-400 gram rat will be isolated and a total volume of 200 μ l consisting of 0.5 μ Ci 14 C-butanol and 0.1 μ Ci 3 H-testosterone along with the serum from either young or old subjects will be injected as a bolus. Fifteen seconds after injection, the animal will be decapitated and the brain removed. The right hemisphere will be isolated and dissolved and liquid scintillation cocktail will be added before radioactivity is measured. The percent of steroid available to the brain will be calculated as follows:

$$\text{Brain uptake index (BUI)} = \frac{{}^3\text{H dpm} / {}^{14}\text{C dpm (brain)}}{{}^3\text{H dpm} / {}^{14}\text{C dpm (injected)}}$$

Testosterone and SHBG will be measured by established methods which are routinely used in our laboratory.

The brain uptake index will be calculated for each group and compared by Student's t test.

Progress: Approximately 20 rats were used to evaluate the transport of testosterone from blood to brain when in serum from young or old men. There is some indication of age-related effects. This work is being written up for inclusion with other related project results.

Detail Summary Sheet

Date: 30 Sep 88	Protocol No.: 87/86	Status: On-going
Title: Role of γ -Endorphin Processing in the Age-specific Development of Phenylethylamine-Induced Stereotypy		
Start Date: 19 Jun 87	Est Completion Date: Sep 90	
Department: Clinical Investigation	Facility: MAMC	
Principal Investigator: MAJ Charles Hannan, MS		
Associate Investigators: Charles W. Wilkinson, M.D. American Lake VA Medical Center		
Key Words: stereotypy, phenylethylamine-induced, age specific, γ -endorphin, rats		
Accumulative MEDCASE	Est Accumulative	Periodic Review:
Cost: -0-	OMA Cost: -0-	Sep 88

Study Objective: To determine if γ -E and related peptides play a role in the expression of PEA induced stereotypy.

Technical Approach: Male Fischer 344 rats will be used in this study. (1) Acute endorphin-PEA relationship: Regional cerebral γ E-type peptides will be measured after a one hour analysis of PEA-induced behavior in young and aged rats. A single IP injection of PEA (50 mg/kg) or saline control will be used. Comparisons will be made between young and aged animals in the measures of γ E-type peptide concentrations and in behavioral measures. Also, correlations between behavior and γ E-type peptide concentrations will be examined. (2) Dose response of microinfused PEA: A dose response relationship will be determined for PEA bilaterally microinfused into the caudate nuclei of young and aged rats. PEA or saline control will be microinfused for two weeks while behavioral measures of stereotypy are continuously monitored. (3) Effect of PEA infusions into the caudate nucleus on regional γ E-type peptides: The time course for the development of sensitivity to PEA during microinfusions into the caudate nucleus will be determined based upon the dose response to PEA. Based on these results, four appropriate time periods during development of the maximum stereotypy response will be selected to terminate animals in order to measure regional γ E-type peptides in both young and aged rats. (4) Effect of mesolimbic infusions of γ E peptides on response to PEA infused into caudate: γ E-type peptides will be infused bilaterally into nucleus accumbens (mesolimbic area will actually be receiving the infusion product). Simultaneously, a dose of PEA as determined from the dose response studies will be infused into the caudate nuclei. Two weeks of behavioral evaluation will be used to determine the effect of the γ E-type peptides upon the PEA-induced stereotypy.

Progress: This project was proposed for a a joint VA-DoD grant, but was not funded. Some very limited experiments will be done with DCI funding. These experiments have not yet begun due to delayed establishment of baseline animal behavioral monitor device results.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 87/97 Status: Completed

Title: Efficacy of Liposome-Encapsulated Bovine Hemoglobin as a Red Cell Substitute

Start Date: 21 Aug 87 Est Completion Date: Dec 87

Department: Clinical Investigation Facility: MAMC

Principal Investigator: MAJ Michael D. Hayre, VC

Associate Investigators: MAJ Kip Hartman, MC

Key Words: red cell substitute, liposome-encapsulated bovine hemoglobin, rats

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: -0-** N/A

Study Objective: To determine the efficacy of liposome-encapsulated bovine hemoglobin (LEBH) as a red cell replacement by demonstrating that respiration and cardiac function are maintained in the absence of sufficient red cells. The effects of transfusion with LEBH on major organ histology and function will be studied, as well as the antigenic potential of the solution. Questions regarding in vivo cardiovascular responses and stability, RES, renal and hematologic toxicity, and antigenicity will also be addressed.

Technical Approach: An isovolemic exchange transfusion will be performed in rats replacing 95% of each animal's normal blood with LEBH, saline/albumin, or saline/albumin filled liposome. Arterial and venous catheters will be placed via a cutdown exposing the right carotid artery and jugular vein. During the exchange procedure, hematocrit, ECG, mean arterial pressure, and venous pressure will be continuously monitored. Arterial and mixed venous blood gases will be measured and hemoglobin concentration and O₂ contents assayed. At the end of the exchange transfusions, 15 of the rats receiving LEBH will be given euthanasia and necropsied. The remaining animals will be returned to the holding area for a period of 14 days. At the end of the 14 days these animals will also be given euthanasia and necropsied with section of major organ systems prepared for histopathology. At the beginning of the study and prior to euthanasia, 0.3 ml blood samples will be obtained from each animal for evaluation of antibovine hemoglobin antibodies in the serum.

Progress: This project has been completed and the data are being analyzed.

** Funding provided by Department of the Navy, Naval Research Lab, Washington, DC

Detail Summary Sheet

Date: 30 Sep 88	Protocol No.: 87/94	Status: On-going
Title: Surgical Resuscitation: The Role of Blood Substitutes		
Start Date: 17 Jul 87	Est Completion Date: May 89	
Department: Pediatrics	Facility: MAMC	
Principal Investigator: 1LT Rita C.Hoop, MS		
Associate Investigators: MAJ Kip Hartman, MC		
MAJ Michael D. Hayre, VC		
Lorrie Langdale, M.D.		
Key Words: blood, substitutes, LEBH, swine model		
Accumulative MEDCASE	Est Accumulative	Periodic Review:
Cost: -0-	OMA Cost: -0-**	Aug 88

Study Objectives: To assess the immediate and delayed biophysiologic response to interval small volume infusions of liposome encapsulated bovine hemoglobin (LEBH) in Microswine; to assess the efficacy and physiologic response to LEBH transfusion in a total exchange transfusion model and in a resuscitation from normovolemic anemia model; and to document the effects of single unit infusion in non-human primates, paralleling the Microswine studies.

Technical Approach: To assess safety and immune response in a single unit infusion, each animal will receive an infusion of 200 ml of the test solution. Test solutions will be 5% albumin in phosphate buffered saline, liposomes without hemoglobin encapsulation, and LEBH (6 animals/group). Animals will be infused at 14 days in the same manner and then euthanized at 4 weeks and a necropsy performed. All measurements during both time frames will be repeated at the same intervals. Alterations in the hepatic, renal, pulmonary and hematology systems will be documented. The immune response to low dose infusion of LEBH will be evaluated by ELISA. To document the effects of single dose infusion in non-human primates, 10 adult *Macaca nemestrina* will undergo the same procedures when the Microswine study is completed. To assess the efficacy, physiology, and immune response in a large dose transfusion, 4 animals will undergo a total exchange transfusion with LEBH to Hct=0%. Two animals will serve as controls, undergoing exchange transfusion with 5% albumin phosphate buffered saline toward Hct=0%. After induction of normovolemic anemia, 6 animals will undergo plasma exchange with LEBH and 6 controls will be autotransfused with packed red cells. Alterations in the hepatic, renal, pulmonary and hematology systems will be documented. The immune response to large dose infusion and delayed challenge with LEBH will be evaluated by ELISA.

Progress: The particular blood substitute which was tested in rats in a previous protocol was found to be toxic, causing a precipitous drop in heart rate. Therefore, continuation of this protocol is pending the availability of a safer alternative product. The principal investigator was changed in July 1988 due to the reassignment of MAJ Hartman.

**Funded by a joint VA/DoD grant.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 83/83 Status: On-going

Title: Relationship of Body Fat to Control of Synthesis by the Liver of Testosterone Estradiol Binding Globulin (TeBG) and Sex Hormones

Start Date: 16 Sep 83 Est Completion Date: Sep 86

Department: Clinical Investigation Facility: MAMC

Principal Investigator: COL Stephen R. Plymate, MC

Associate Investigators:

COL Bruce L. Fariss, MC

CPT Karl E. Friedl, MSC

COL Gary L. Treece, MC

Mina J. Garrison, B.S., M.T.

MAJ Stanley P. Liebenberg, VC Louis A. Matej, B.S., M.T.

Key Words: Hep G2 cells, testosterone, estradiol, PRL, insulin

Accumulative MEDCASE

Est Accumulative

Periodic Review:

Cost: -0-

OMA Cost: \$500.00

Aug 88

Study Objective: To determine the metabolic parameters responsible for modifying production of TeBG in weight gain.

Technical Approach: The investigators originally planned to use female beagles for this protocol. When restrictions were placed on the use of dogs in research, the investigators conducted this study *in vitro* using a human hepatoma cell line, Hep G2, grown to confluence in Dulbecco's Minimum Essential Median (DMEM) with 10% FCS. Additions of T_4 , insulin, estradiol, and testosterone were then begun daily for three days with DMEM without FCS, and media were collected at the end of each three day period and assayed for SHBG using a radioimmunoassay specific for human SHBG. At the end of each experiment, the cells were harvested and counted in each flask. SHBG production was normalized for cell number. Each hormone addition was performed in triplicate per experiment.

Progress: The investigators continued to study cultures during FY 88.

An article was published in The Journal of Clinical Endocrinology and Metabolism (67:460, 1988) and a second article is in press (Steroids). A paper was presented at the meeting of The American Federation for Clinical Research, Western Region, February 1988 (abstract #130, Clinical Research, Feb 88).

The investigators conclude that insulin and prolactin inhibit SHBG production and that testosterone, T_4 , and estradiol stimulate SHBG production *in vitro*. These findings suggest that insulin and prolactin may be important factors in the regulation of SHBG production *in vivo*.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 83/84 Status: On-going

Title: Evaluation of Efficacy of Varicocele Repair

Start Date: Sep 83 Est Completion Date: Oct 86

Department: Clinical Investigation Facility: MAMC

Principal Investigator: COL Stephen R. Plymate, MC

Associate Investigators MAJ Brian Miles, MC

C. A. Paulsen, M.D.

Richard E. Berger, M.D.

Key Words: Infertile and fertile men, LH/RH stimulation tests, semen analysis, sperm penetration assay

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: -0- Aug 88

Study Objective: To determine the efficacy of varicocele repair in improving fertility in the infertile male.

Technical Approach: Four groups (75 men each) will be studied: (1) infertile men scheduled for varicocele repair, (2) infertile men without varicoceles; (3) fertile men scheduled for varicocele repair, and (4) fertile men without varicoceles. Prior to entering into this study all subjects will have a complete history and physical examination done, including assessment of the presence or absence of a varicocele as well as calibrated measurement of testicular size. Each group will have 8-10 semen analyses, 2 sperm penetration assays at least 4 weeks apart, and 2 LH/RH stimulation tests performed. Blood samples will be drawn every 15 min for 2 hrs after the injection of the LH/RH. Following repair of the varicocele, seminal fluid analyses every 2-4 wks, sperm penetration assay at 6 and 12 months after the varicocele ligation, and LH/RH at 6 and 12 months after the varicocele ligation will be performed.

Progress: Approximately 145 subjects have been entered in this study. Initial data showed that after ligation LH response to LHRH was not significantly different in either group, but there was a trend toward normal FSH response. Sperm penetration assays were not predictive of fertility before or after ligation. Even though sperm production tended to increase in the fertile group, the data suggested that present methods of assessing testicular function do not permit clear evidence of changes in fertility status in men with ligated varicoceles. In further studies, serum inhibin levels were measured on a single baseline blood sample to further delineate the hypothalamic-pituitary-testicular relationships in normal fertile men as well as normal and infertile men with a varicocele. In the normal men, serum inhibin interacted negatively with FSH and with the FSH response to a GnRH test, but it had a positive correlation to the geometric mean sperm count. These correlations were not seen in either group of infertile men. These data plus the known decrease in sperm production in the presence of a varicocele suggest that gonadal damage is associated with a varicocele regardless of fertility status.

A manuscript is being prepared for publication.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 86/19 Status: Terminated

Title: Transhepatic Lipoprotein Gradients and Their Relationship to Sex Steroid Concentrations

Start Date: 15 Nov 85 Est Completion Date: Sep 86

Dept/Svc: Medicine/Endocrine Facility: MAMC

Principal Investigator: COL Stephen R. Plymate, MC

Associate Investigators:

LTC John W. Kirk, MC

MAJ Daniel H. Knodel, MC

MAJ Charles J. Hannan, MS

Thomas M. Kettler, B.S., DAC

Key Words: sex steroids, HDL2, HDL3, apolipoprotein AI and AII

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: 200.00 Jan 88

Study Objective: To examine the changes in high density lipoprotein cholesterol fractions HDL2 and HDL3, apolipoprotein AI and apolipoprotein AII (Apo AI and Apo AII) concentrations that occur as blood passes through the liver in male patients presenting for heart catheterization. Further, to investigate the relationship between sex steroid levels and different transhepatic lipoprotein gradients.

Technical Approach: Ten male subjects scheduled for routine right and left heart catheterization will be recruited for this pilot study. Patients with unstable angina and acute or subacute myocardial infarctions will be excluded from the study. During right heart catheterization, as the catheter is passed up the femoral vein and through the inferior vena cava, the hepatic vein will be catheterized and a 5 cc sample of blood will be drawn. During the left catheterization procedure, a 5 cc sample of arterial blood will be drawn. Testosterone, estradiol, SHBG and calculated non-SHBG bound T will be determined by methods previously described (Plymate et al., J Clin Endocrinol and Metab 52:1246, 1981). Total cholesterol and triglycerides will be measured by the methods of Friedl, Plymate and Paulsen (Contraception 31:409-420, 1985). HDL fractions II and III and apolipoprotein AI and AII will be measured by the methods of Hannan, et al (Analysis of apolipoprotein AI by high-performance liquid chromatography and radioimmunoassay, to be submitted to Clinical Chemistry). Statistics will be performed as appropriate, using the SPSS and STAT graphics programs.

Progress: Dr. Plymate became the principal investigator on this study in January 1988 due to the reassignment of Dr. Knodel. In previous years, four patients were entered in the study. No additional patients were entered in this study in FY 88. The protocol was terminated in April 1988 due to time constraints on the principal investigator.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 87/24 Status: On-going

Title: Chemical Characterization of Sex Hormone Binding Globulin (SHBG)

Start Date: Nov 86 Est Completion Date: Jun 87

Department: Clinical Investigation Facility: MAMC

Principal Investigator: COL Stephen R. Plymate, MC

Associate Investigators: COL Carl Stones, MC

MAJ Charles J. Hannan, MSC

MAJ Robert E. Jones, MC

Philip H. Petra, Ph.D., Univ Washington

Louis A. Matej, B.S., DAC

Key Words: sex hormone binding globulin, production, structure

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: \$814.00 Feb 88

Study Objective: To determine the factors that regulate SHBG production and its structure and the effects of changes in structure on its steroid binding properties.

Technical Approach: Blood from second trimester pregnancy plasma will be purified and amino acid sequencing will be performed. Once sequencing has been completed, the appropriate cDNA probe will be obtained from a cDNA library obtained from HepG2 cells. The cDNA probe will be tritiated and the studies using insulin, growth hormone, prolactin, estradiol, and testosterone will be performed on the HepG2 cell cultures with subsequent cDNA hybridization. When these experiments are complete, media will be assayed by RIA or DCC binding assay for SHBG, and RNA will be extracted from the cells. Basically, the cells will be placed in freshly constituted homogenization buffer and disrupted using a polytron homogenizer. The extracts will be left overnight at 4°C and then centrifuged at 2000g for 30 mins. The precipitate pellet will be washed and dissolved in 50 mM tris buffer pH 5 containing 10% SDS and extracted twice with phenylmethylchloride. RNAs will then be precipitated with ethanol dissolved in 10% SDS. Following this, northern blot analysis using 10 mg of RNA will be performed by electrophoresis on 1% agarose formaldehyde gels. Following northern blot analysis, the RNA will be hybridized using either ³H or ³²P labelled cDNA probe. After hybridization has occurred, audioradiography will be performed using Kodax XR5 film and quantitation of mRNA synthesis will be determined using scanning densitometer.

Progress: Studies using growth hormone have been completed and a paper is being written. The investigators are continuing to perform studies using other hormones.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 87/30 Status: On-going

Title: Direct Effects of Sex Hormone Binding Globulin of Plasma on the Metabolic Clearance Rate and Hypothalamic/Pituitary Feedback of Testosterone and Estradiol in the Pigtail Macaque (*Macaca Nemestrina*)

Start Date: Mar 87 Est Completion Date: Jul 88

Department: Clinical Investigation Facility: MAMC

Principal Investigator: COL Stephen R. Plymate, MC

Associate Investigators: MAJ Charles Hannan, MS

Philip H. Petra, Ph.D.

Key Words: testosterone, estradiol, SHBG, metabolic clearance rate, hypothalamic/pituitary feedback, pigtail macaque

Accumulative MEDCASE Est accumulative Periodic Review:

Cost: -0- OMA Cost: \$2100.00 Aug 88

Study Objective: To aid in the understanding of which determinants allow sex steroids to be effective.

Technical Approach: Six male pigtail macaque monkeys will be pre-conditioned to a primate restraining chair. At least 48 hrs before the study, in-dwelling catheters will be implanted under ketamine HCl anesthesia. Polyethylene tubing will be inserted into the left femoral vein and polyvinyl tubing into the right femoral artery and vein. The animals will be fitted with a special vest to protect the catheters, placed in a primate restraining chair, and allowed to recover for 24-48 hrs. Blood pressure will be continuously monitored during the study. After recovery from the placement of the catheters, tritiated labelled testosterone and estradiol will be infused following a bolus to give a constant rate of tritiated labelled testosterone or estradiol per 2 ml of infusate per hour. Infusions will be continued for six hrs. Blood samples will be collected every 10 min and every hour the plasma will be separated and the red cells resuspended in physiologic buffer and infused back into the animal. Following the initial determination of the metabolic clearance rate (MCR) and LH pulse frequency, the animals will be removed from the chair and allowed at least four weeks of rest. Then they will be infused with SHBG for a three hour period of time. After the initial three hour infusion of SHBG, an antibody to SHBG will be infused and LH pulse frequency and the MCR of testosterone and estradiol will be determined. In addition, plasma SHBG, testosterone, dihydrotestosterone, and LH pulse frequency will be measured at the beginning and end of each experiment and albumin concentration will be estimated.

Progress: The animals were studied as planned and a paper was presented at the 1988 meeting of the Society for Gynecologic Investigation. The data suggest that an increase in SHBG binds E_2 , decreases the E_2 MCR and testosterone available for feedback on LH. A sudden decrease in SHBG also causes a decrease in E_2 MCR, most likely because the released ng quantities of testosterone and the pg quantities of E_2 compete for the steroid clearance pathways.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 87/82 Status: Completed

Title: Differences in the Hypothalamic-Pituitary-Gonadal Axis
Between Young and Elderly Men Before and After
Testosterone Replacement

Start Date: Apr 88 Est Completion Date: Apr 91

Department: Clinical Investigation Facility: MAMC

Principal Investigator: COL Stephen R. Plymate, MC

Associate Investigators: William Bremner, M.C, Ph.D.

Joyce S. Tenover, M.D.

MAJ Charles J. Hannan, MS

CPT Karl E. Friedl, MS

Key Words: hypothalamic-pituitary-gonadalaxis, testosterone

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: -0- N/A

Study Objective: To further elucidate the mechanism of the differences in the hypothalamic pituitary testicular axis, bioavailable testosterone (T), and total T in young and elderly men, and to determine the significance of these changes in the aging process as well as explore whether treatment can safely alleviate some of the changes which occur with age and physical stress.

Technical Approach: Four groups of men will be studied: 21-30 yrs; 30-50 yrs; and ≥ 60 yrs, $T \leq 3.5$ ng/ml; and ≥ 60 yrs, $T \geq 3.5$ mg/ml. In a double blind cross-over trial subjects will receive either a placebo or 50 mg T enanthate, I.M., twice weekly for 3 months and then crossed over. CBC, platelet count, LFT, general blood chemistry, grip strength, and testicular size will be performed monthly. Dihydrotestosterone, SHBG, nSHBG-T, E_2 , FSH, LH bioassay and LH pulses, lean body mass measurement, total cholesterol, triglycerides, HDL cholesterol, fractions 2 and 3, apo A-1 protein, fasting insulin glucose, glycosylated hemoglobin, and changes in cardiac risk factors will be measured at 0, 3, and 6 months. Prostate size will be estimated by ultrasound in men >55 years of age. Factors which affect SHBG production and are found to be different between young and elderly men will be examined in vitro for their effects on SHBG production by Hep G2 cells. Testosterone and estradiol clearance studies will be done in rats before and after the infusion of purified SHBG, both native and deglycosylated. SHBG from young and elderly individuals both before and after T treatment will be examined by isoelectric focusing to determine if changes in isoelectric forms explain the effects of SHBG levels with aging or androgen treatment. Serum from treated subjects will be put through the Pardridge/Oldendorf brain uptake assay to determine the effect of SHBG in each group on rate of uptake of T and estradiol into the brain and prostate.

Progress: Since funding for this protocol was to be provided by a joint VA/DoD grant which was denied, a limited study of 20 normal males (10 mean age 27.3 and 10 mean age 70.7) was conducted to evaluate whether there is a 24-hr variation in nSHBG-T in young men and if aging is associated with a blunting of that rhythm. No animal studies were performed. The results of this abbreviated study have been accepted for publication in the Journal of Andrology.

Detail Summary Sheet

Date: 30 Sep 88	Protocol No.: 87/83	Status: Terminated
Title: Clinical Trial of Pergolide Mesylate in the Treatment of Amenorrhea-Galactorrhea or Sexual Dysfunction Due to Prolactin Secreting Pituitary Tumors		
Start Date: 15 May 87	Est Completion Date: May 1988	
Dept/Service: Medicine/Endocrine	Facility: MAMC	
Principal Investigator: COL Stephen R. Plymate, MC		
Associate Investigators: COL Gary L. Treece, MC MAJ Jennifer A. Nuovo, MC		
Key Words: tumor, pituitary, prolactin, pergolide		
Accumulative MEDCASE	Est Accumulative	Periodic Review:
Cost: -0-	OMA Cost: -0-	N/A

Study Objective: To determine the usefulness of pergolide mesylate in the treatment of prolactin-secreting pituitary tumors and in the restoration of normal sexual function.

Technical Approach: This study is open to patients of either sex who have responded poorly to bromocriptine or whose tumor, because of surgery or irradiation, is not measurable. Patients must have been diagnosed as having a pituitary tumor ≥ 5 mm that may or may not have been treated with radiotherapy or surgery. Patients must have elevation of prolactin levels on baseline measurements taken 2-7 days prior to taking pergolide. Growth hormone levels may also be elevated. Women of child bearing potential must use a mechanical means of contraception. Patients will be started on 25 μ g of pergolide taken orally with the evening meal the first three days. If the patient has no adverse experiences, the dose will be raised to 50 μ g given with the evening meal on the fourth day. The doses will not be increased to 50 μ g until the patient is able to tolerate the 25 μ g dose without adverse experiences. The daily dose may be increased by 25 to 50 μ g increments until a satisfactory suppression of prolactin levels is achieved, up to a maximum of 1000 μ g. If adverse experiences are encountered at doses of 50 μ g or more, the dose may be reduced to as little as 25 μ g or the therapy discontinued. Patients will be treated with pergolide until either there is a loss of efficacy of pergolide, the patient can not tolerate the drug at an effective dose, the patient becomes pregnant, or no further therapy is needed. If there is no evidence of response after three months, the patient will be taken off the study. To be evaluable, a patient must receive a minimum of two months of daily pergolide therapy. However, if there is no suppression of prolactin levels after one month at the maximum dose per day, the case will be considered evaluable and included in the analysis of results as a therapeutic failure.

Progress: Dr. Plymate was named the principal investigator on this study upon the resignation of Dr. Nuovo in July 1988. Dr. Plymate entered no patients on the study and terminated the protocol in September 1988 due to time constraints of other commitments. The two patients who had previously agreed to enter the study were never started on the medication due to a delay in receiving the medication from the manufacturer.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 88/20 Status: On-going

Title: Studies on the Production and Glycosylation of SHBG
by HepG2 Cells Using ³⁵S-Labelled Methionine

Start Date: 11 Dec 87 Est Completion Date: Jun 89

Department: Clinical Investigation Facility: MAMC

Principal Investigator: COL Stephen R. Plymate, MC

Associate Investigators: Benito Que, M.D.
MAJ Charles J. Hannan, MS Thomas M. Kettler, B.S., M.T.
CPT Karl E. Friedl, MS Louis A. Matej, B.S., M.T.
Philip H. Petra, M.D. James R. Wright, B.A. M.T.

Key Words: HepG2, ³⁵S methionine, SHBG, steroids, peptides

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: \$602.00 N/A

Study Objective: To determine the effects of previously identified steroid and peptide hormones which have been shown to affect sex hormone binding globulin (SHBG) levels, in vivo and in vitro in the HepG2 cell culture, on production, secretion, and glycosylation of SHBG and to determine the effects of these agents on production of the messenger ribonucleic acid (mRNA) for SHBG in this cell culture system.

Technical Approach: HepG2 cells will be grown to confluence in 25 cm² flasks. Confluent cells will then be either continuously labelled with ³⁵S-methionine for 4 hours or pulse labelled for 10 minutes in methionine free media. In the case of the pulse labeling, the label will be chased with a 20,000 fold excess of methionine for three hours following the initial pulse. Flasks will be pretreated with either basal media, T₄, estradiol, testosterone, or insulin in the concentrations which we have shown in a previous study to have the greatest stimulatory or inhibitory effects on SHBG production by these cells. Following the initial labeling of the cells with ³⁵S methionine, both the supernate and cell lysate will be subjected to specific immunoprecipitation. Following the immunoprecipitation, cells from these same flasks that have not been lysed will be lysed and subjected to dot-blot analysis using a specific cDNA probe from a HepG2 library for the SHBG mRNA. When all data have been collected, differences in synthesis versus processing will be assessed between the various treatments using the ANOVA method.

Progress: cDNA hybridization of SHBG message in HepG2 cells has begun and is working successfully. ³⁵S methionine label has also been continued.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 88/42 Status: On-going

Title: Protocol for the Study of Sex Steroid Effects
on Lipid Metabolism

Start Date: 18 Mar 88 Est Completion Date: Apr 89

Department: Clinical Investigation Facility: MAMC

Principal Investigator: COL Stephen R. Plymate, MC

Associate MAJ Charles Hannan, MS Stephen Babirak, M.D.

Investigators: CPT Karl Friedl, MS John D. Brunzell, M.D.

CPT Curtis J. Hobbs, MC Tom Kettler, B.S.

1LT Rita Hoop, MS Louis Matej, B.S.

Key Words: testosterone enanthate, testolactone, vascular disease

Accumulative MEDCASE Est accumulative Periodic Review:

Cost: -0- OMA Cost: \$2800.00 N/A

Study Objective: The regulation of enzymes that metabolize lipids is in part under the control of gonadal steroids. The objective of this protocol is to study the regulation of these enzymes and their products in order to aid in the understanding of the pathogenesis of vascular disease and to help further evaluate the risk factors associated with steroid replacement.

Technical Approach: Twelve healthy young males, 20-40 years, with normal liver profile, CBC, UA, EKG, LDL, HDL, and TG will be studied. A complete physical examination, including measurement of testicular size, a liver function test, and a CBC will be done prior to treatment as well as three fasting blood samples drawn at least three days apart for TG, HDL₂, HDL₃, LDL, total cholesterol, Apo proteins AI and II, Apo B, Apo CIII, LH, FSH, T, SHBG, and E₂. Subjects will also submit three semen samples and two four-hour urine samples for urinary measurements of LH and FSH. Anthropomorphic measurements will be made by caliper measurements and tape measurements of the neck and waist. A needle fat biopsy will be taken from the buttock of each man and analyzed for aromatase, lipase, and lipase mRNA by cDNA hybridization. These studies, except for semen analysis, CBC, liver function tests, and fat biopsy, will be repeated at 2, 4, 6, and 10 weeks. Semen analyses will be repeated at 6 and 10 weeks. CBC's, liver function tests, and fat biopsy will be repeated at 6 weeks. After the two-week baseline period, six subjects will be randomized to receive testosterone enanthate, 200 mg im, each week for 6 weeks and six subjects will be randomized to receive testosterone enanthate, 200 mg im, each week plus testolactone, 250 mg po qid, for six weeks. Subjects will be interviewed and have a physical examination at 2, 4, and 6 weeks of the study and at 4 weeks post-study.

Progress: The mRNA for lipoprotein lipase is currently being measured in fat biopsies.

Detail Summary Sheet

Date: 30 Sep 88	Protocol No.: 88/70	Status: On-going
Title: Characterization of Serovar-Specific Ureaplasma Antigens by Analysis with Monoclonal Antibodies		
Start Date: 19 Aug 88	Est Completion Date: Oct 90	
Department: Clinical Investigation	Facility: MAMC	
Principal Investigator: CPT John E. van Hamont, MS		
Associate Investigators: None		
Key Words: <i>Ureaplasma urealyticum</i> , antigens, serovar-specific		
Accumulative MEDCASE	Est Accumulative	Periodic Review:
Cost: -0-	OMA Cost: \$3700.00	N/A

Study Objective: To identify and define antigenic determinants specifically associated with the 14 serovars of *Ureaplasma urealyticum*.

Technical Approach: Mice will be immunized with ureaplasma serovar antigens by either intrasplenic injection of aqueous antigen or subcutaneous injection of antigen with adjuvant followed by an IV booster of aqueous antigen. The spleen cells from the immunized mice will then be fused with P.653 myeloma cells. The cell culture supernatants from the resulting hybridoma clones will then be screened for antibody reactive with homologous ureaplasma antigens as well as with growth medium components. The investigator will then characterize reactive monoclonals for serovar and subgroup specificity via the growth inhibition assay, metabolic inhibition assay, mycoplasmacidal assay, and direct fluorescent assay. The monoclonals identified as having type specificity will be used in the analysis of colloidal gold labeling procedures for localization of type-specific antigen by electron microscopy and for affinity column chromatography purification of type specific antigen from ureaplasma cell lysates. The monoclonals and antigens thus characterized will be used in the development of assays for future identification of clinical isolates of *Ureaplasma* and analysis of host serological responses.

Progress: The investigator is awaiting shipment of materials and reagents needed for the performance of this protocol.

D E T A I L S H E E T S
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DENTAL ACTIVITY

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 88/39 Status: On-going

Title: Pulpotomy in the Primary Dentition: A Clinical
Evaluation of Two Techniques

Start Date: 18 Mar 88 Est Completion Date: Mar 91

Unit: Dental Clinic #3 Facility: MAMC

Principal Investigator: MAJ James R. Allinder, DC

Associate Investigators: COL Gerald Aaron, DC

Peter K. Domoto, D.D.S., M.P.H.

John M. Davis, D.D.S., M.S.D.

Key Words: electrosurgical, formocresol, children

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: \$100.00 N/A

Study Objective: To compare the clinical success rates of the electrosurgical pulpotomy and formocresol pulpotomy techniques and to describe the various radiographic and clinical findings and advantages and disadvantages associated with each technique.

Technical Approach: Subjects will have a routine dental examination to include routine radiographs. Subjects will be defined as patients ages 2-12 years who have two or more carious primary teeth which are indicated for a vital pulpotomy. Selection of teeth will be based on dental history, clinical appearance, and bite-wing and periapical radiographs. Individual teeth will be randomly assigned to either the electrosurgical or the formocresol technique. Randomization will be determined depending on the number and location of the quadrants involved. Teeth within the same quadrant will be given the same treatment since it would be difficult to rule out crossover effects in the same quadrant. Treatments within the same patient will be compared only when they occur in different quadrants. Dental and post-operative histories will be recorded. A clinical examination including routine periapical radiographs will be performed at 6, 12, and 18 months following initial treatment. Clinical success will be determined by absence of abnormal radiographic or clinical findings and the maintenance of the treated teeth in a normal functional relationship in the dental arch. The data from this study will be incorporated with data from two parallel studies being done in the Tacoma area. Approximately 450 patients will be studied between the three studies. Since responses to treatment within the same patient can be expected to be more similar than for teeth from different patients, the basic unit of analysis will be the patient, rather than individual teeth. If two teeth are treated in the same patient McNemar's test for correlated proportion will be used for statistical analysis. If more than two teeth are treated, the Mantel-Haenszel test for stratified analysis will be used.

Progress: Five patients have been entered at MAMC.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 88/46 Status: On-going

Title: A Comparison of Dental Needs of Abused and Neglected Children and Nonabused, Neglected Children in the Military Population

Start Date: 15 Apr 88 Est Completion Date: Nov 88

Unit: Dental Activity Facility: MAMC

Principal Investigator: CPT Patrice E. Greene, DC

Associate Investigators: COL Gerald R. Aaron, DC
LTC Timothy Davis, MS

Key Words: dental exam, questionnaire, dental history

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: \$200.00 N/A

Study Objective: To compare the dental needs of children ages 2-12 who are confirmed by MAMC Social Work Services as abuse and neglect cases to a control group who have not been confirmed as abuse and neglect cases but who are from a similar socioeconomic background.

Technical Approach: Approximately 100 children confirmed to be abuse/neglect cases by the Social Work Service, MAMC, will be consecutively studied. A parent or legal guardian will complete a questionnaire designed to obtain information on length of time in service, location of previous assignments, length of time at previous and present assignments, sponsor's rank, educational level of the parents, the child's dental history, use of military and civilian dental care facilities, parent's opinion of the child's present dental needs, and response to and critique of the military family members dental plan. The dentist will complete a dental screening exam that determines the dental needs of the child. Dental status of the children will be reported to the parents. One hundred non-abused/non-neglected control subjects, matched for age, sex, race, and similar socioeconomic background, will be studied in the same fashion as the study subjects. Data will be analyzed using the chi square test.

Progress: Dental screenings have been completed on 38 children, 2-12 years old, in the study group and 1500 in the control group. Parents filled out a questionnaire for each child. The investigator plans to enter at least 12 more children in the study group.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 87/35 Status: On-going

Title: A Comparison of Blood Glucose Levels Obtained From Blood
Incidental to Dental Procedures versus Antecubital Vein
Blood

Start Date: Jan 87 Est Completion Date: Apr 87

Department: Dentistry Facility: MAMC

Principal Investigator: LTC Stanley S. Levsky, DC

Associate Investigator: COL Gary L. Treece, MC

Key Words: blood glucose, antecubital vein, samples obtained
from dental procedures, hyperglycemia, Chemstrip BG

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: \$150.00 Sep 88

Study Objective: To determine the relevance of Chemstrip BG determinations of blood glucose levels in blood obtained incidental to dental cleaning or treatment and to test the feasibility of screening for hyperglycemia in the dental clinic.

Technical Approach: One hundred consecutive patients >18 years of age who undergo teeth cleaning or other dental procedures will be studied. Patients who exhibit intraoral bleeding during the dental procedure will have that blood tested with the Chemstrip BG. Blood will be taken from the dental instrument for use on the Chemstrip BG. These samples will be obtained before any irrigation solutions are used in order to avoid contamination by the solution. Immediately after the Chemstrip BG is obtained, peripheral blood will be obtained by venipuncture. A portion of this blood will be used for a Chemstrip BG test in order to compare the two sources on the Chemstrip BG. The remainder of the venous sample will be submitted to the Pathology Lab for determination of whole blood glucose and plasma glucose. The Chemstrips will be visually read as well as read with the assistance of an Accu-Chek II Reflectance Meter. The difference between the blood glucose levels by the different methodologies will be recorded for each patient and submitted to statistical analysis using the Student's t test. The effect of salivary contamination of intraoral samples will be studied by intentional contamination of multiple samples.

Progress: 33 patients have been entered. The method does appear to be a clinically useful and economical method to screen for diabetes as part of the etiology in patients with periodontal disease.

Accuracy of the method will be determined after 100 subjects have been entered.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 88/38 Status: On-going

Title: A Comparison of the Cariogenicity of Plaque from Mother-Infant Pairs Using a Caries Activity Test

Start Date: 18 Mar 88 Est Completion Date: Nov 88

Unit: Dental Clinic #3 Facility: MAMC

Principal Investigator: MAJ Mark Rogow, DC

Associate Investigators: COL Lawrence H. Shire, DC

Peter K. Domoto, D.D.S., M.P.H.

Key Words: history, questionnaire, caries bacterial activity test

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: \$150.00 N/A

Study Objective: To compare the caries risk of mothers in the permanent dentition and their infants in the early primary dentition stage and to compare the caries risk predicted by this test and the mother's past caries experience.

Technical Approach: Mothers and their infants 8-15 months of age will be asked to participate. Mothers will complete a dental record for her infant and for herself and a questionnaire to elicit information regarding the child's health, perinatal history, antibiotic use, present prescription medicine, fluoride supplements, dental care, and breast feeding history. The mother and the infant will then have a dental examination and a caries bacterial activity test will be performed. Decayed, missing, and filled teeth of both mother and infant will be recorded. Test vials will be incubated for 48 hrs and read by a blinded observer at 24 and 48 hrs, with the 48-hr reading used as the final test score. The test results will be determined by comparing the color of the test vial and four reference color vials, using fluorescent illumination. The tests will be scored on a scale of 0 for blue, 1 for green, 2 for yellow-green, and 3 for yellow, with 0.5, 1.5, and 2.5 used for vials which are intermediate in color between the reference vials. Subjects whose test results indicate a high risk of caries will be notified by mail. The chi square test will be used for data analysis.

Progress: Seventy-four (74) of the 100 proposed mother-infant pairs were studied this fiscal year. No findings or conclusions have been reached at this point.

D E T A I L S H E E T S
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DEPARTMENT OF EMERGENCY MEDICINE

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 82/25 Status: On-going

Title: Emergency Room Procedure Training

Start Date: Feb 82 Est Completion Date: Feb 87

Department: Emergency Medicine Facility: MAMC

Principal Investigator: LTC Cloyd B. Gatrell, MC

Associate Investigators: COL Frederick Burkle, MC
LTC Samuel T. Coleridge, MC
MAJ Steven C. Dronen, MC
MAJ Stanley P. Liebenberg, VC
MAJ Matthew M. Rice, MC
MAJ Mel D. Robinson, MC

Key Words: Training techniques, invasive & life-saving procedures

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: \$1360.00 Jan 88

Study Objective: To provide training to acquire the necessary manipulative skills in performing invasive, life-saving procedures for the Emergency Medicine Residency Program.

Technical Approach: The procedures listed below will be performed in two separate sessions 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.

PART I:

1. Femoral vein cutdown
2. Peritoneal lavage
3. Tube thoracostomy
4. Thoracotomy
5. Aortic cross-clamping
6. Control of pulmonary hemorrhage
7. Cardiac wound repair
8. Endotracheal intubation
9. Percutaneous transtracheal ventilation
10. Cricothyroidotomy

PART II:

1. Tissue pressure monitoring
2. Arterial pressure monitoring
3. Swan-Ganz catheter placement
4. Transvenous ventricular pacemaker placement
5. Transthoracic ventricular pacemaker placement
6. Pericardiocentesis
7. Segstaken-Blakemore tube placement
8. Auto transfusion from hemothorax
9. Twist drill decompression
10. Skull trephination

Progress: This protocol was revised in March 1988. Due to the departure of MAJ Robinson, the principal investigator was changed to LTC Gatrell, and MAJ Rice was added as an associate investigator. The protocol was rewritten to conform with the present format for animal studies and the animal model was changed to the goat.

No procedures have been performed on this protocol during FY 88.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 87/56 Status: Completed

Title: Assessment of a Rapid Theophylline Assay in the Outpatient Setting

Start Date: Mar 87 Est Completion Date: Aug 87

Department: Emergency Medicine Facility: MAMC

Principal Investigator: CPT William Hurley, MC

Associate Investigators: MAJ Cloyd Gatrell, MC

MAJ Charles Henley, MC

CPT Stephen Saglio, MC

Key Words: theophylline, assay (Accu-Level), rapid, assessment

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: \$1440.00 N/A

Study Objective: To study the accuracy, time saving, cost effectiveness, and reliability of a rapid, blood theophylline assay (Accu-Level, Syntex Medical Diagnostics, Palo Alto, CA) in the Emergency Room and Family Practice Clinic.

Technical Approach: Thirty subjects from whom STAT theophylline levels are obtained as part of their normal care will be studied and the data will be examined to determine if a range (low, intermediate, and high) of theophylline levels has been included in order to determine the efficacy of the assay at all levels. If this range is seen, the data will be analyzed for statistical significance and more patients will be studied if necessary. The treating physician will determine if the patient had coffee or cola in the past 8 hours. Blood will be drawn in the usual fashion and an aliquot will be taken by pre-measured pipette for analysis by the rapid theophylline assay. The identify of the patient, other medications, diagnosis, time blood drawn, the values and reporting times of the rapid assay and laboratory results will be recorded. The report form for the assay will be initialed in order to control for any difference in the method of performing the assay. The levels obtained by laboratory analysis and rapid assay will be compared by chi-square analysis using the laboratory findings as the standard. Linear regression and the determination of correlation coefficients will also be used. Cost comparisons will be done between the rapid assay, the MAMC laboratory, other hospital laboratories, and private laboratories. Additional, limited studies are planned consisting of concentration curves to correlate the assay system with known concentrations of theophylline in whole blood, serum, and plasma in order to see if a predictable relationship exists between the sample type and the resulting value.

Progress: Sixty-one patients were studied. The 61 test strip levels correlated highly with the laboratory results and produced results more rapidly. Caffeine intake did not influence the test and clinical estimation of theophylline toxicity was poor. Cost was significantly lower than charges at local hospitals, but higher than incurred by the MAMC laboratory.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 88/62 Status: On-going

Title: A Pilot Study on the Safety and Efficacy of Nifedipine in the Treatment of Biliary Colic

Start Date: 15 Jul 88 Est Completion Date: Jun 89

Dept/Svc: Emergency Medicine Facility: MAMC

Principal Investigator: LT John H. Mastalski, MC, USNR

Associate Investigators: CPT Lee E. Payne, MC, USAF

Key Words: biliary colic, nifedipine, placebo, efficacy, safety

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: \$200.00 N/A

Study Objective: To determine the safety and efficacy of nifedipine, 10 mg orally, for the treatment of acute biliary colic in the emergency room.

Technical Approach: Fifty patients, ages 18-70 years, seen in the Emergency Room with a clinical diagnosis of biliary colic or ultrasound proven cholelithiasis will be studied. Only those patients with ultrasound proven cholelithiasis will be included in the data analysis. Patients with hypotension, heart block greater than first degree, hepatitis, jaundice, any evidence of choledocholithiasis, temperature >101, any evidence of choleangitis/cholecystitis or pregnancy will be excluded. A history will be taken and physical exam done on patients presenting with right upper quadrant pain. Initial vital signs will be recorded. The patient will complete a visual analogue scale to grade the pain. The patient will then be placed on a cardiac monitor and dynamap continuous blood pressure monitor. An IV will be established and lab work completed. Chest x-rays and abdominal films will be performed as needed. Nifedipine or a placebo will be given by a double blind protocol. The patient will be monitored over a one-hour period with pain evaluation and blood pressure recordings every 15 minutes. If the patient has equivocal improvement in pain over an hours time, an anticholinergic will be used as deemed necessary by the treating physician. A surgical consultation will be made as needed. A biliary ultrasound and surgical consultation will be made on patients with the diagnosis of biliary colic. Results of the surgical consultation will be recorded for each patient. Patients will be evaluated for pain relief, blood pressure response, vital sign changes, ECG changes, and side effects. Chi square analysis will be used to determine if nifedipine given orally is significantly better than placebo in alleviating the pain of biliary colic.

Progress: The investigator is awaiting final approval from HSC before commencing this study.

D E T A I L S H E E T S
F O R
P R O T O C O L S

DEPARTMENT OF FAMILY PRACTICE

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 88/27 Status: Completed

Title: Evaluating the Relationship Between Family Function and Illness Using FACES III

Start Date: 19 Feb 88 Est Completion Date: Apr 88

Department: Family Practice Facility: MAMC

Principal Investigator: MAJ Terry J. Golden, MC

Associate Investigators: MAJ Charles E. Henley, MC

Key Words: medical illness, family communication, hospital visits

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: \$620.00 N/A

Study Objective: To determine if a relationship exists between scores on FACES and medical illness in the family.

Technical Approach: Three hundred (300) adult patients will complete the FACES questionnaire which elicits information such as communication between family members, discipline, decision making, rules, responsibilities, family activities, and emotional interactions between family members. Medical records of all family members will be reviewed. Medical illness within the family will be graded and number of contacts with the medical system over the past 24 months will be counted. Data will be analyzed descriptively, seeking association, not causal relationship. Data will be dichotomized into functional/dysfunctional families. Chi square analysis will be performed to look for strength of association between scores on FACES and medical illness.

Progress: The study has been completed and the investigator is preparing a thesis.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 88/23 Status: Suspended

Title: A Study of an Intervention Involving Screening, Patient, and Provider Education in an Attempt to Reduce the Incidence of Preterm Delivery

Start Date: 15 Jan 88 Est Completion Date: Dec 88

Department: Family Practice Facility: MAMC

Principal Investigator: CPT Bruce Greenburg, MC

Associate Investigators:

COL John A. Read, MC MAJ John P. Kugler, MC

MAJ William K. Brady, MC CPT Arthur H. Herpolsheimer, MC

MAJ Charles E. Henley, MC CPT Rebecca A. Rush, MC

Key Words: preterm delivery, intervention, education, screening

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: \$300.00 N/A

Study Objective: To implement a screening questionnaire to attempt to identify patients at high risk for premature delivery; to implement an intervention program for those identified at high risk in an attempt to prevent premature delivery; and to attempt to identify the presence of specific risk factors for premature delivery for active duty pregnant patients.

Technical Approach: Approximately 2000 patients will be studied in each of two groups (intervention and nonintervention comparison). A high risk screen will be completed, which will elicit information regarding weight; height; birth control; scale of how much the patient desires the pregnancy; alcohol and tobacco consumption; history of premature delivery, uterine anomalies, induced abortion, and present pregnancy. Patients determined by the screening standards to be high risk will be entered in an intervention program that consists of watching a videotape which will provide patients with instructions on nutrition, premature risks, and the signs and symptoms of premature labor; weekly cervical exams at 20 weeks; and standard premature labor therapy for any patient diagnosed to be in premature labor. Patients considered low risk by the screening standards will receive routine OB care with rescreening at 26 weeks. Those who are redefined as low risk by this screening will receive routine OB care until delivery and those redefined as high risk will be entered in the intervention program. Physician and nursing staff will be given inservices on the early identification of the high risk patient and the diagnosis of premature labor. The intervention group and the comparison group will be assessed by income status, race, maternal age, and parity. The outcome variable will be the percent of premature deliveries for each group. The intervention will also be assessed in its totality along with other possible occurrences that could affect outcome such as new and more effective tocolytics. Therapies available during the intervention period will be compared with therapies during the comparison period.

Progress: This protocol has been suspended until the principal investigator revises the protocol as required by the IRB.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 84/69 Status: On-going

Title: Preventive Cardiology Demonstration and Education
Research Grant

Start Date: 17 Aug 84 Est Completion Date: Jun 88

Department: Family Practice Facility: MAMC

Principal Investigator: MAJ Charles E. Henley, MC

Associate Investigators:

LTC David W. Roberts, MC

Craig S. Scott, Ph.D.

Daniel J. Erickson, M.D.

Steven C. Macdonald, M.P.H.

William Neighbor, M.D.

Douglas C. Schaad, M.Ed.

Robert L. Van Citters, M.D.

Marcia Hunt, B.A.

Key Words: attitudes, knowledge, clinical practice, intervention group, residents.

Accumulative MEDCASE

Est Accumulative

Periodic Review:

Cost: -0-

OMA Cost: -0-

Jan 88

Study Objective: The primary aim of the NHLBI Education/Demonstration Preventive Cardiology Project is introducing concepts and practice relating to primary prevention of coronary disease into the basic training of Family Practice residents in the University of Washington Family Practice Residency Network. The hypothesis to be tested is that a core curriculum of preventive cardiology integrated into the existing curriculum of a Family Practice residency training program will result in measurable modification of the attitudes, knowledge, and clinical practice of an intervention group of residents as compared to internal and external controls.

Technical Approach: All residents in the Madigan Family Practice Residency will be asked to test for their attitudes and knowledge of preventive cardiology. Following testing, a curriculum in preventive cardiology will be developed. This curriculum will be developed and administered in conjunction with the staff of the Department of Family Practice at Madigan. In an attempt to personalize the process of cardiovascular risk assessment, an individual cardiovascular risk profile will be made available to the residents. Clinical practice of preventive cardiology by residents will be measured by an audit of patient charts at twice yearly intervals. The audit will be conducted by Preventive Cardiology staff auditors from the University of Washington.

Progress: At the request of Mr. Henley, the suspension of this protocol was lifted when he took over the protocol in January 1988. The initial patient chart reviews is being done and then the data analysis phase will begin.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 87/77 Status: On-going
Title: Evaluation of Trainee Clinical Performance in Geriatrics
Start Date: 15 May 87 Est Completion Date: Nov 89
Department: Family Practice Facility: MAMC
Principal Investigator: MAJ Charles Henley, MC
Associate Investigators:
Philip Rakestraw, Ph.D. Barbara Simpson, M.S.W.
Carol Milner, Ph.D. CPT Ellen Pinholt, MC
Key Words: geriatrics, trainees, evaluation
Accumulative MEDCASE Est Accumulative Periodic Review:
Cost: -0- OMA Cost: -0- Sep 88

Study Objectives: To evaluate the clinical accuracy of elderly simulated patients, to establish the reliability and validity of elderly simulated patients in clinical performance evaluation, and to compare clinical simulations with existing methods of clinical evaluation for residents.

Technical Approach: Phases 1 and 2 of this study will consist of the development and testing of case simulations from 4 actual cases: 1 depression, 1 dementia, and 2 multiple diagnostic problems including 1 with depression and 1 with dementia. The simulations will be performed for Team 1 (six professionals) who will do a workup and calculate weighted aggregate scores for the Comprehensive Older Persons' Evaluation (COPE). Team 2 will do a medical workup of the simulations using their usual workup format. These workups will be videotaped and reviewed for elements present or absent from the COPE instrument. Team 2 will then use the simulation for the purpose of developing weighted aggregate scores to compare to the weighted scores of Team 1. If differences between the teams are detected, reevaluation and revisions will be conducted. Phase 3 will begin with the residents doing a workup of either a depression or a dementia case by their usual format, and the patient interactions will be evaluated by a preceptor. The simulated patient will be asked to rate a resident's performance on measures of interpersonal skills, communication, and professional manners. The resident will be asked to complete a self-evaluation using the same parameters. The resident will then do a workup using the COPE instrument which will include the same primary diagnosis but will include other medical problems and complications. Data will be analyzed using aggregate scores on the COPE and the evaluations completed by the preceptors, patients, and residents. Comparisons will be made between the original aggregate scores on the COPE established by the preceptor teams to the student scores on the COPE and the performance using the "usual" workup between the professionals and residents. The first simulation performance scores will be compared to the second simulation performance scores to look for evidence of improvement of any identified shortcomings.

Progress: This protocol was submitted for a joint VA/DoD grant which was not approved. The investigators are conducting a pilot study and Phase I of the study while other avenues of funding are explored.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 87/114 Status: Completed

Title: An Analysis of Perinatal Outcome and Its Various
 Determinants Among Blacks and Whites in
 Pierce County, Washington

Start Date: 18 Sep 87 Est Completion Date: 30 May 88

Department: Family Practice Facility: MAMC

Principal Investigator: MAJ John P. Kugler, MC

Associate Investigators: MAJ Charles E. Henley, MC, MAMC

Frederick A. Connell, M.D., USPHS

Durlen Hickok, M.D., Swedish Hospital

Key Words: perinatal outcome, determinants, blacks, whites

Accumulative MEDCASE

Est Accumulative

Periodic Review:

Cost: -0-

OMA Cost: -0-

N/A

Study Objective: To analyze perinatal outcome data in Tacoma-Pierce County among the black and white populations and to evaluate systems of health care delivery, level of pre-natal care, income, age, parity, and smoking status differences and to determine potential associations with more adverse perinatal outcomes.

Technical Approach: Analysis from birth certificates and linked death certificates for a 3-year period will include all black and white infants born in Pierce County to mothers residing in Pierce County and delivered at a medical facility in Pierce County. A stratification analysis will be performed on this data considering income, parity, system of care, maternal age, smoking, marital status, race, and the impact of these variables on several outcomes: level of prenatal care, birthweight, neonatal mortality rate, infant mortality rate, and postneonatal mortality rate. Prenatal care and birth weight will be separately analyzed as dependent variables to determine their impact on mortality rates. The Mantel-Haentzel test will be the primary statistical tool, but if time permits a mathematical model utilizing logistic regression will be attempted.

Progress: This protocol has been completed and a thesis accepted by the MPH program at the University of Washington. A paper was presented at the Uniformed Services Chapter of the American Academy of Family Physicians in March 1988.

29,848 births and 183 linked deaths were analyzed. The analysis revealed statistically comparable neonatal mortality rates for civilian and military whites and military blacks. Civilian blacks, however, had a rate significantly higher than the civilian whites. There was no significant difference between the civilian and military black communities for percentage of low birthweight and level of prenatal care. The neonatal risk difference for the civilian black cohort was only partially explained by the extraneous variables that were studied. Military health care had an apparent protective effect, especially for low income blacks. This effect was not explained by differences in the level of prenatal care or by the percentage of low birthweight deliveries.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 87/64 Status: Completed

Title: Analysis of EDTA Chelation of Amniotic Fluid to Improve the Efficacy of the Latex Fixation Test for Rapid Detection of Group B Streptococci

Start Date: 17 Apr 87 Est Completion Date: 30 Nov 87

Department: Family Practice Facility: MAMC

Principal Investigator: CPT Mark S. Raney, MC

Associate Investigators: MAJ Charles E. Henley, MC

CPT David R. David, MC

CPT John C. Schilhab, MC

Key Words: Group B streptococci, latex fixation test

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: \$352.00 N/A

Study Objective: To attempt to significantly reduce the unacceptably high incidence of inconclusive results on the latex fixation test for Group B streptococci (GBS) in amniotic fluid.

Technical Approach: When amniotic fluid specimens are submitted for both culture and the latex fixation test for Group B streptococci, they will be tested by two different methods. One method will use chelation with EDTA prior to testing with the Wellcogen Strep B kit. The other method will forego the chelating step and simply test the specimen in accordance with laboratory protocol. For the EDTA chelation method, 50 μ l of amniotic fluid will be placed in 1.5 ml microcentrifuge tube and added to 150 μ l of a 0.1 M solution of EDTA and then the tubes will be vortexed. The specimen will then be heated for five minutes in a boiling water bath and then cooled to room temperature and clarified by centrifugation. Then 20 μ l of the test latex will be placed in one circle on a test card and 20 μ l of controlled latex will be placed in a separate circle. Forty microliters of the supernatant will then be placed next to each drop of latex. Without delay and using separate mixing sticks, the latex reagents will be mixed with the body fluid samples and the mixture spread over as much of the circle as possible. The card will then be slowly rocked to and fro and observed for agglutination for three minutes. The data will be compiled and statistically analyzed to determine if the hypothesis that the incidence of inconclusive results obtained by the Wellcogen Strep B test procedure can be reduced from 37% from a previous study to below 10% in this study. A comparison will be made of the efficacy of the test based on its sensitivity and specificity compared to the culture results to simultaneously determine if the high level of efficacy is maintained.

Progress: Dr. Mark Raney took over this protocol as the principal investigator upon the reassignment of Dr. David. Data collection is complete. Preliminary analysis indicates that the EDTA chelation was ineffective in improving the efficacy of the latex fixation test in amniotic fluid for rapid detection of Group G streptococci.

DETAIL SHEETS
FOR
PROTOCOLS

DEPARTMENT OF MEDICINE

Detail Summary Sheet

Date: 30 Sep 88	Protocol No.: 88/79	Status: On-going
Title: Salicylate Overdose: Quantitation of Renal Excretion with Forced Alkaline Diuresis		
Start Date: 16 Sep 88	Est Completion Date: Jan 90	
Dept/Svc: Medicine	Facility: MAMC	
Principal Investigator: CPT Matthew S. Bachinski, MC		
Associate Investigators: MAJ Howard M. Cushner, MC		
CPT Donna L. Mercado, MC		
CPT Thomas Peller, MC		
CPT Bernard J. Roth, MC		
CPT LeRoy Southmayd, MC		
Key Words: salicylate, overdose, renal excretion, diuresis		
Accumulative MEDCASE	Est Accumulative	Periodic Review
Cost: -0-	OMA Cost: \$1900.00	N/A

Study Objective: To assess the effectiveness of a forced alkaline diuresis in reducing plasma salicylate concentrations in patients who present with acetylsalicylic acid blood levels of ≥ 50 mg/dl and have adequate renal function.

Technical Approach: Patients as stated above will be admitted to the ICU and followed, receiving the standard of care plus: base-line labs for SGOT, SGPT, LDH, bilirubin, calcium, magnesium and phosphorus; history taken to quantify as closely as possible the amount of aspirin ingested and the time of ingestion; IV D5W with 150 mEq NaHCO_3/L at 50-150 cc per hour; weight every 12 hours; chest x-ray each day; calcium and magnesium every 12 hours; labs to include arterial blood gas, electrolytes, BUN, creatinine, and serum salicylate level, every 6 hours; urine collection every 6 hours for dipstick pH, volume measurement, urine salicylate level and sodium determination. IV infusion rate will be adjusted to patient size and age. Pulmonary edema will be monitored by chest x-ray and physical examination; arterial blood gases, electrolytes, calcium, and magnesium will be monitored and adjustments made to maintain chemical homeostasis. Patients will be treated until serum salicylate is < 30 mg/dl. Patients' normal outpatient medications not containing aspirin will be allowed.

Progress: New study. No patients enrolled.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 88/47 Status: On-going

Title: Investigation into Thyroid Function Abnormality Associated with Hexabrix, a New Intravenous Iodine-Containing Contrast Agent

Start Date: 15 Apr 88 Est Completion Date: Jun 88

Dept/Svc: Medicine/Endocrine Facility: MAMC

Principal Investigator: CPT Brenda K. Bell, MC

Associate Investigators: MAJ Jennifer Nuovo, MC

CPT Patrick Gorman, MC

Key Words: Hexabrix, Hypaque 76, cardiac catheterization

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: \$1800.00 N/A

Study Objectives: To look for evidence of thyroid function abnormality following the use of Hexabrix, a new iodine containing intravenous contrast agent, and to compare clinical evidence of thyroid dysfunction, i.e., goiter, nodular thyroid, Hashimoto's thyroiditis, with the evidence of iodine-induced hyper or hypothyroidism.

Technical Approach: Subjects with no evidence of thyroid function abnormality and patients with goiter undergoing cardiac catheterization, with the administration of Hexabrix or Hypaque contrast material, will be studied. Patients will be examined for the presence of goiter or nodular thyroid disease and a baseline thyroid function test, including TSH and T₃ by RIA, will be done. The thyroid function tests will be repeated at three days and at one month after administration of the contrast agent. The amount of contrast agent administered will be used to calculate the milligrams of iodine that the patient was administered.

Progress: MAJ Nuovo was the original principal investigator for this protocol. MAJ Bell was appointed the new principal investigator upon the resignation of MAJ Nuovo.

Twenty-one subjects have been entered in the study, but complete data is available on only four subjects. There is a major problem with patients forgetting the one month thyroid function tests. The investigator is trying to remedy this situation by calling the patients and reminding them of the one month appointment.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 87/118 Status: On-going

Title: Reversion of Oropharyngeal Colonization in Patients
 Discharged From A Critical Care Unit

Start Date: 14 Sep 87 Est Completion Date: Dec 87

Dept/Svc: Medicine/Internal Medicine Facility: MAMC

Principal Investigator: CPT Kenneth A. Bertram, MC

Associate Investigator: LTC Rodney A. Michael, MC

Key Words: oropharyngeal, colonization, reversion, CCU

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: \$4080.00 Sep 88

Study Objective: To determine the time to reversion to normal oropharyngeal microflora after discharge from a critical care unit in a group of patients hospitalized for greater than 72 hours in a critical care setting.

Technical Approach: Sixty adult patients admitted to the ICU will have nasal and oropharyngeal swabs for culture upon admission to the ICU and thereafter at 24, 48, 72, and 120 hours. After discharge from the ICU, swab cultures will also be done at 1, 2, and 4 weeks after discharge and evaluated for the presence of gram-negative bacilli and *Staphylococcus aureus*. The data will be evaluated for total number of gram-negative isolates and *S. aureus* isolates, incidence of colonization by category of patient, incidence of colonization correlated with time in the ICU environment, and time to reversion to normal flora. Chi-square and trend analysis will be used to statistically analyze data.

Progress: Due to a number of unforeseen difficulties, this study has not been implemented. The investigators plan to implement the study in January 1989.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 86/83 Status: Completed

Title: Investigation of Effects of Calcium Channel Blockers on
Production of Testosterone

Start Date: 15 Aug 86 Est Completion Date: Aug 87

Dept/Svc: Medicine/Endocrinology Facility: MAMC

Principal Investigator: CPT Kevin J. Carlin, MC

Associate Investigators: COL Stephen R. Plymate, MC

COL Gary L. Treece, MC

LTC Robert E. Jones, MC

MAJ Daniel H. Knodel, MC

Key Words: testosterone, production, calcium channel blockers

Accumulative MEDCASE

Est Accumulative

Periodic Review:

Cost: -0-

OMA Cost: \$3891.00

Jan 88

Study Objective: To determine the effects of calcium channel blockers on testicular function, using testosterone levels in 10 healthy males before and after administration of medication for one week and to observe subjects for altered testicular function after stimulation with HCG (both on and off med medication).

Technical Approach: Ten healthy males (18-40) will have a history and physical exam plus CXR, EKG, SMA-20, CBC, and UA. Stage I: Off all medication, subjects in AM will have baseline levels of LH by RIA, LH bioactive, testosterone, estradiol, and SHBG drawn. HCG (3000 units IM) will be given and repeat levels of testosterone, estradiol, and SHBG will be drawn at 1, 2, 3, and 72 hours. Subjects will then be started on verapamil, 80 mg po QID. On day 8 the baseline levels will be repeated and subjects will be injected with HCG as previously done. At 1, 2, 3, and 72 hours after administration the blood levels will again be drawn and then medication will be stopped. Stage II: After a two week rest period without medication, the procedures in Stage I will be repeated using diltiazem, 60 mg po QID. Stage III: Again, after a two week rest period with no medication, the procedures will be repeated utilizing nifedipine, 10 mg (2) po qid. There will be a postmedication pill count to monitor compliance with medication. Patients will have post-investigation physical, SMA-20, CBC, and EKG to make sure no ill side effects have occurred.

Addendum June 1987: In order to better delineate the etiology of the lowering of testosterone, the investigators will perform two HCG stimulation tests 10 days apart and draw testosterone levels at baseline, 1, 2, 3, and 72 hours, similar to the original plan but on no medications and using the same subjects.

Progress: Eight subjects were studied on the original protocol and on the addendum to the protocol. The findings from the basic protocol were presented at the 4th Annual Army Regional American College of Physicians Meeting in Oct 87 and the findings from the addendum were presented at the American Society of Andrology in May 88.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 87/42 Status: Completed

Title: Western Washington Tissue Plasminogen Activator -
Emergency Room Trial

Start Date: 16 Jan 87	Est Completion Date: Jan 88
Dept/Svc: Medicine/Cardiology	Facility: MAMC
Principal Investigator: LTC Roger F. Chamusco, MC (new PI Dec 87)	
Associate Investigators:	
COL Theodore Steudel, MC	MAJ Everett W. Newcomb, MC
MAJ Philip W. Berger, MC	MAJ Matthew M. Rice, MC
MAJ Cloyd B. Gatrell, MC	CPT Mary D. Boyer, MC
	Steven Pace, M.D, DAC
MAJ Blake P. Gendron, MC	J. Ward Kennedy, M.D.

Key Words: tissue plasminogen activator, acute myocardial infarction, efficacy, safety, practicality

Accumulative MEDCASE	Est Accumulative	Periodic Review:
Cost: -0-	OMA Cost: -0-	May 88

Study Objective: To evaluate the efficacy, safety, and practicality of administering intravenous recombinant tissue plasminogen activator (rt-PA) emergently to patients with acute myocardial infarction (AMI) in hospital emergency rooms.

Technical Approach: Patients <75 years of age with symptoms of AMI with onset within six hours or presentation lasting more than 20 minutes (unrelieved with nitroglycerin), an electrocardiogram compatible with AMI, and in whom no more than 60 minutes have elapsed since initial evaluation will be infused with rt-PA with an initial bolus of 6 mg IV push. The infusion will be continued using an IV infusion pump to deliver 60 mg rt-PA in the first hour, 20 mg over the second hour, and 5 mg for the next four hours. When the rt-PA infusion is completed, IV heparin will be started at 1000 IU per hour. PTT will be drawn at two hours after start of heparin and infusion rate adjusted to maintain PTT in the 6-80 second range. PTT's will be drawn every 6 hours and adjusted to maintain systemic anticoagulation for at least 96 hours following rt-PA infusion. The patient will be started on aspirin 325 mg/day one day prior to discontinuation of the heparin infusion. Routine CCU care will be followed per the cardiologist's orders. Cardiac angiography will be done at 7-10 days after initial rt-PA treatment and, six weeks following hospitalization, the patient will be offered a nuclear medicine determination of ejection fraction and infarct size, and a repeat two dimensional echocardiogram.

Progress: This protocol originally called for 150 mg total dose of rt-PA and was amended in April 1987 to a lower total dose of 100 mg after two episodes of intracerebral bleed were reported at other institutions. rt-PA has now been approved by the FDA and added to the MAMC Formulary. An additional 13 patients were entered at MAMC in FY 88 for a total of 29 patients entered. Study-wide, the bleeding complication rate was 1.4% at 150 mg rt-PA (intracerebral hemorrhage) and no bleeding complications were reported at 100 mg rt-PA. There was a 6% death rate on treated groups study-wide.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 87/98 Status: On-going

Title: The Effects of Ibuprofen on Airflow in Patients with Chronic Obstructive Lung Disease (COLD)

Start Date: 21 Aug 87 Est Completion Date: Feb 88

Dept/Svc: Medicine/Pulmonary Facility: MAMC

Principal Investigator: LTC William H. Cragun, MC (new PI Jul 88)

Associate Investigator: CPT Marin H. Kollef, MC

Key Words: COLD, airflow, Ibuprofen, placebo

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: \$350.00 Sep 88

Study Objective: To assess the effect of Ibuprofen on airflow in patients with COLD.

Technical Approach: Patients (>35 years) with clinical signs and spirometric evidence of moderate to severe chronic obstructive lung disease will be entered in the study. Baseline physical examination, spirometric data (FEV₁, FVC) and history will be obtained. Patients will undergo a randomized, blinded crossover study with placebo or ibuprofen over four weeks according to the following schema: Week 1: washout of prior ASA/NSAID use; Week 2: start placebo or ibuprofen; Week 3: washout period; Week 4: start crossover placebo or ibuprofen. Spirometry, history, and physical examination will be obtained at the end of each treatment period. Outcome variables will include changes in the FEV₁, FVC, and dyspnea score at the end of weeks 2 and 4.

Progress: Data collection is complete on two subjects at MAMC. The original principal investigator, Dr. Kollef, is now assigned to FAMC and is in the process of getting this protocol approved at FAMC in order to perform a collaborative study.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 87/113 Status: Terminated

Title: Assessment of Calcium Acetate as a Phosphate Binder and Calcium Supplement in Patients with Chronic Renal Failure

Start Date: 18 Sep 87 Est Completion Date: Apr 88

Dept/Svc: Medicine/Nephrology Facility: MAMC

Principal Investigator: MAJ Howard Cushner, MC

Associate Investigators: COL John B. Copley, MC, BAMC

MAJ Jeff Addison, MC, MAMC

MAJ Charles Nolan, MC, Wilford Hall

Key Words: renal failure, chronic, calcium acetate, binder

Accumulative MEDCASE

Est Accumulative

Periodic Review:

Cost: -0-

OMA Cost: \$500.00

Sep 88

Study Objective: To assess the usefulness of calcium acetate as a phosphate binder and calcium supplement in patients with end-stage renal disease.

Technical Approach: Patients 18 to 80 years will have phosphate binding agents discontinued for one week. A serum phosphorus will be drawn pre-dialysis one week after discontinuance of the phosphate binding agent(s). Only those patients who have a serum phosphorus >5.5 mg/dl off phosphate binders will be entered. The patients will be treated with either an aluminum-containing phosphate-binding agent, calcium acetate, or calcium carbonate in a double blinded fashion. Pre-study PA20, C terminal parathyroid hormone level, serum aluminum level, and CBC will be drawn. Every two weeks during the study, a PA 20 will be drawn mid-week pre-dialysis. At 4 and 8 weeks after beginning the study drug, serum aluminum and C terminal PTH levels will be drawn. At the completion of 2 months on the study drug the patients will be switched to one of the other phosphate binding agents and evaluated in an identical fashion. Then the third drug will then be evaluated in an identical fashion. In patients with chronic renal failure, not on dialysis, similar labs will be drawn at similar time periods. Dosage adjustments of study medications will be made in order to achieve a serum calcium of 10-10.5 mg/dl and serum phosphorus 4.5-5.5 mg/dl. A three day dietary history will be obtained at the beginning of each treatment period in order to determine the average phosphorus and calcium intake. A questionnaire will be administered to all patients which includes the following information: was constipation present; complaints about any of the drugs and, if so, what were they; which drug was preferred with respect to the taste and easiness to swallow. Mean and standard deviation for serum calcium, phosphorus, calcium phosphate products, C-PTH, alkaline phosphatase, and serum aluminum levels will be determined and compared between the treatment periods using repeated measures ANOVA to analyze the data.

Progress: This was a collaborative study with BAMC and Wilford Hall Medical Center. The over-all project director at BAMC cancelled the protocol. MAMC did not have the patient population to conduct the protocol at this site alone.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 88/48 Status: Completed

Title: Aluminum Absorption with the Use of Aluminum-Containing Compounds in Combination with Solubilized Calcium Citrate in Dialysis Patients

Start Date: 15 Apr 88 Est Completion Date: Jul 88

Dept/Svc: Medicine/Nephrology Facility: MAMC

Principal Investigator: MAJ Howard Cushner, MC

Associate Investigators: COL John B. Copley, MC

MAJ Jill Lindberg, MC

C.Y. Pak, M.D.

K. Sakhaee, M.D.

Key Words: dialysis, aluminum absorption, aluminum-containing compounds, solubilized calcium citrate

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: \$362.00 N/A

Study Objective: To assess whether citrate in the form of solubilized calcium citrate increases aluminum absorption in dialysis patients.

Technical Approach: Fourteen dialysis patients will be studied. Vitamin D preparations will be discontinued for one week. Serum will be obtained at the end of this week for SMA-20, aluminum level, and PTH. All serum studies will be drawn midweek, predialysis.

Phase 1: Patients will then be given 2 gm of aluminum hydroxide or carbonate per day in 3 divided doses with meals for 2 weeks.

Phase 2: The aluminum preparation will continue for 2 more weeks plus 1.5 gm/day Supercitracal, given on the same schedule.

Phase 3: Aluminum-containing phosphate binders will be discontinued after Phase 2 is completed. The patients will continue taking Supercitracal for one month. Serum will be obtained at the end of each phase for aluminum level, PA 20, and PTH level.

Descriptive statistics will be computed for all serum and urine biochemical variables. Tests for normality (Anderson-Darling) and equal variances (Bartlett) will be performed on variables prior to analysis, based on these assumptions. A correlation matrix of serum and/or urine variables will be calculated at each phase to examine relationships between these variables. Repeated measures ANOVA will be used to assess the effect of the treatment phase on variables of interest. For significant ANOVA statistics, multiple comparisons will be performed using Bonferroni paired t-tests (phase effect) and Student-Newman-Keuls (group effect).

Progress: Ten subjects were evaluated at MAMC and 20 subjects were evaluated at BAMC. The protocol has been completed. Results from the collaborative study at BAMC will be forwarded to Dr. Cushner for combined data analysis.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 88/85 Status: On-going
Title: Free 1,25 (OH)₂D₃ Measurements in Nephrotic Patients with
and without Chronic Renal Failure
Start Date: 16 Sep 88 Est Completion Date: Oct 88
Dept/Svc: Medicine/Nephrology Facility: MAMC
Principal Investigator: MAJ Howard Cushner
Associate Investigators: None
Key Words: nephrotic syndrome, normal renal function, renal
insufficiency, free 1,25 (OH)₂D₃
Accumulative MEDCASE Est Accumulative Periodic Review
Cost: -0- OMA Cost: \$122.00 N/A

Study Objective: To evaluate vitamin D binding protein and free 1,25 (OH)₂D₃ levels in patients with nephrotic syndrome to determine if there is a reduced circulating level of vitamin D binding protein due to urine losses and if there is an alteration in binding of vitamin D with this protein in this disorder.

Technical Approach: Patients with nephrotic syndrome followed in the Nephrology Clinic at MAMC will be identified by chart review. Five patients with nephrotic syndrome and normal renal function, and five patients with nephrotic syndrome and renal insufficiency will be studied. A 27 cc blood sample will be obtained and assayed for total 1,25 dihydroxyvitamin D, percent free 1,25 dihydroxyvitamin D, and vitamin D binding protein. Free total 1,25 vitamin D concentrations will be calculated.

Progress: Three subjects have been studied.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 86/57 Status: Terminated

Title: The Effect of Nonsteroidal Anti-inflammatory Agents
(NSAIDs) on the Template Bleeding Time

Start Date: 18 Apr 86 Est Completion Date: Apr 88

Dept/Svc: Medicine/Hematology Facility: MAMC

Principal Investigator: COL Irwin B. Dabe, MC

Associate Investigator: CPT Michael D. Stone, MC

Key Words: anti-inflammatory agents, nonsteroidal, template
bleeding time, degree, duration

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: -0- Jul 87

Study Objective: To determine the degree and duration of effect of various NSAIDs on the bleeding time when given at clinically used doses for a duration long enough to achieve steady state levels.

Technical Approach: Sixty patients with normal platelet count, renal function, hepatic function, alkaline phosphatase, and total bilirubin will be studied. Persons not receiving NSAIDs will undergo a baseline bleeding time and receive one of the study drugs at the dose and for the duration listed below. A repeat bleeding time will be done two hours after the last dose. The bleeding time will be repeated every 24 hours until normalization. Patients already receiving a NSAID will have a bleeding time done two hours after their last dose. They will discontinue the drug and repeat bleeding times will be done every 24 hours until it normalizes. At that point, drug therapy will be restarted at the previous dose.

Drug doses: Ibuprofen - 800 mg p.o. T.I.D. x 12 doses
Indomethacin - 25 mg p.o. T.I.D. x 12 doses
Sulindac - 200 mg p.o., B.I.D. x 8 doses
Piroxicam - 20 mg p.o., QD x 14 doses

Patients will be assigned to a drug in the order they are entered in the protocol until there are 15 patients in each group.

Progress: No new patients were entered in this study in FY 88. This protocol was terminated due to the difficulty of obtaining subjects that were willing to participate in the study because of the repeat bleeding time studies.

Detail Summary Sheet

Date: 30 Sep 88	Protocol No.: 87/70	Status: On-going
Title: High Dose Cisplatin, VP-16 with or Without Radiation Therapy in Advanced Non-small Cell Lung Cancer		
Start Date: 17 Apr 87	Est Completion Date: Dec 90	
Dept/Svc: Medicine/Hematology	Facility: MAMC	
Principal Investigator: COL Irwin B. Dabe, MC (new PI Jul 88)		
Associate Investigators:		
COL Donald H. Kull, MC	MAJ David M. Dunning, MC	
LTC Lauren K. Colman, MC	MAJ Ruben Sierra, MC	
LTC Howard Davidson, MC	CPT Margaret Barnes, MC	
MAJ Thomas Baker, MC	CPT David R. Bryson, MC	
Key Words: non-small cell lung cancer, high dose cisplatin, VP-16 radiation vs no radiation		
Accumulative MEDCASE	Est Accumulative	Periodic Review:
Cost: -0-	OMA Cost: -0-	N/A

Study Objective: To evaluate proposed treatment schedules with respect to response rates, toxicities, and overall survival.

Technical Approach: Approximately 20 patients will be treated in three groups. Treatment will be determined by extent and location of cancer and by previous therapy.

Group I: Limited non-small cell lung cancer (NSCLC) with prior radiotherapy will be treated with cis-platinum, 100 mg/M², days 1, 8, 29, 36, 57, and 64 plus VP-16, 100 mg/M², on days 1-3, 29-31, and 57-59. There will be no radiotherapy.

Group II: Limited NSCLC, no prior radiotherapy, will be treated with cis-platinum, 100 mg/M², days 1, 8, 29, 36, 57, and 64 plus VP-16, 100 mg/M², days 1-3. They will also receive radiotherapy to the chest for 5-6 weeks starting day 29. Prophylactic whole brain radiotherapy will be given for three weeks starting 3-4 weeks after chest radiotherapy is completed for patients achieving clinical partial or complete remission.

Group III: Extensive NSCLC will be treated with cis-platinum, 100 mg/M², days 1, 8, 29, 36, 57, 64 plus VP-16, 100 mg/M², days 1-3, 29-31, and 57-59.

Response rate will be defined as number of patients who have achieved a complete or partial response divided by the total number of patients evaluable for response (those who completed at least four weeks of the treatment program). Patients will be considered to be evaluable for toxicity if they received at least one dose of chemotherapy.

Progress: Four additional patients were entered in FY 88 for a total of 15 patients entered. One patient had weakness and neuropathy which is slowly improving. Hearing loss is frequent.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 86/28 Status: Terminated

Title: Phase II Study of Ifosfamide and Mesna Alone or as Part of Combination Chemotherapy in Refractory Testicular Cancer

Start Date: 17 Jan 86 Est Completion Date: Jan 88

Dept/Svc: Medicine/Oncology Facility: MAMC

Principal Investigator: LTC Howard Davidson, MC

Associate Investigators: COL John Redmond, MC

MAJ David Dunning, MC

Key Words: testicular, cancer, ifosfamide, mesna, combination

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: -0- Sep 88

Study Objective: To determine the objective response rate and duration of remission of ifosfamide in patients with testicular cancer refractory to cis-diamminedichloroplatinum (CDDP) combination chemotherapy; the objective response rate and duration of remission of Ifosfamide combination chemotherapy for remission reinduction in patients not cured with initial therapy, the toxicity of Ifosfamide in refractory testicular cancer; the toxicity of ifosfamide in combination with cisplatin \pm VP-16, VP-16 alone, or vinblastine \pm bleomycin in refractory testicular cancer.

Technical Approach: After one 5-day course of either treatment A, B, C, D, E, or F (see below) response to therapy will be evaluated. If disease has decreased and/or some symptom relief is noted with no increase in disease, therapy will continue on the same schedule for as long as response is noted for a maximum of 6 courses of therapy. If there is no response after 6 courses, the treatment will be stopped. Patients will receive Ifosfamide alone or in combination based on prior experience with chemotherapy. Treatment will be repeated every 3 weeks for patients who do not demonstrate progression for a maximum of 6 courses. In patients with subsequent resection of residual carcinoma, 2 additional post surgical courses will be done. Treatment A: Ifosfamide - single agent; Treatment B: Ifosfamide + platinum; Treatment C: Ifosfamide + Platinum + VP-16; Treatment D: Ifosfamide \pm Platinum plus Velban; Treatment E: Ifosfamide + VP-16 \pm Bleomycin; Treatment F: Ifosfamide + Velban + Bleomycin. This study is being done in conjunction with the University of Indiana.

Progress: Only one patient was entered in this protocol (FY 86). This patient is now being followed on SWOG 8616.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 86/87 Status: Completed

Title: Radiation Survival of Human Prostate Carcinoma Cells

Start Date: 15 Aug 86 Est Completion Date: Nov 87

Dept/Svc: Medicine/Oncology Facility: MAMC

Principal Investigator: MAJ David Dunning, MC

Associate Investigators: COL Donald Kull, MC

CPT Joseph Hellman, MS

Richard Ostenson, M.D.

Stephen Loop, M.S.

Key Words: cells, carcinoma, prostate, survival, radiation

Accumulative MEDCASE

Est Accumulative

Periodic Review:

Cost: -0-

OMA Cost: \$1943.00

Jun 88

Study Objective: To determine *in vitro* survival following incremental exposure to radiation of several prostate cancer cell lines that have been established and maintained in tissue culture medium.

Technical Approach: Confluent tissue culture flasks or cell suspension will be exposed to incremental doses (100-1400 rads) of radiation using a Co 60 source. Throughout the procedures, cells will be kept on ice to maintain viability. Following radiation treatment, the adherent tumor cells will be trypsinized for 5-10 minutes and then washed several fold in PBS containing 1% FCS to inhibit further enzyme action. Cell numbers will be determined by direct counting in a hemacytometer. Cell viability will be ascertained by trypan blue exclusion. Irradiated suspension cultures and control cultures will be treated in an analogous fashion. Control cultures will consist of TC flasks or suspension cultures harvested at the time of the initiation of the experiment and maintained on ice throughout the radiation period.

Progress: A paper was presented at the 4th Annual Hematology/Oncology Scientific Meeting in October 1987. A manuscript is being prepared for publication.

There were no significant differences in the radiation sensitivity parameters for either the cell suspension or the cell monolayer cultures. By this methodology, measurements of radiation survival could be accurately made to levels as low as 0.01% of the control values. Survival curves determined by direct counting of tumor cells demonstrated a decrement in surviving cell number at all radiation doses tested. These results suggest that prostate tumor cells are less sensitive to radiation than most human adenocarcinomas. An average SF₂ of 0.54 suggests that prostate tumor cells are similar to melanoma in radiosensitivity. These data demonstrate that the tritiated thymidine incorporation assay offers a rapid and reproducible method to determine the radiation sensitivity of prostate adenocarcinoma cell lines with accuracy that compares well with that of more labor-intensive methods.

Detail Summary Sheet

<u>Date: 30 Sep 88</u>	<u>Protocol No.: 88/19</u>	<u>Status: On-going</u>
<u>Title: Effect of Hydrochlorothiazide on Postural Blood Pressure Changes</u>		
<u>Start Date: 11 Dec 87</u>	<u>Est Completion Date: Jun 89</u>	
<u>Dept/Svc: Medicine/Internal</u>	<u>Facility: MAMC</u>	
<u>Principal Investigator: CPT Joel T. Fishbain</u>		
<u>Associate Investigators: LTC Robert Harvey, MC</u>		
<u>MAJ Howard Cushner, MC</u>		
<u>CPT Leroy Southmayd, MC</u>		
<u>Key Words: blood pressure, postural, changes, hydrochlorothiazide</u>		
<u>Accumulative MEDCASE</u>	<u>Est Accumulative</u>	<u>Periodic Review:</u>
<u>Cost: -0-</u>	<u>OMA Cost: \$150.00</u>	<u>N/A</u>

Study Objective: To assess the effect of hydrochlorothiazide on postural change in blood pressure and pulse.

Technical Approach: 50-80 patients diagnosed as hypertensive, confirmed by 5-day blood pressure recordings, will have a base-line history and physical examination. Prior to initiating thiazide, the patients will have a 24-hour urine and a fasting 908, and creatinine clearance will be calculated. Within one day of the urine collection and after five minutes of rest in a prone position, orthostatic changes will be assessed by taking three blood pressure measurements and a one minute pulse rate. These measurements will be repeated after two minutes in a sitting and then a standing position. The patient will be weighed (fasting) and placed on 25 mg of hydrochlorothiazide. The 24-hour urine collection, the 909, and the blood pressure and pulse measurements as described above will be repeated at three weeks and three months. All patients will be given identical encouragement to observe and restrict sodium intake, increase activity at least five days per week, and, when appropriate, lose weight and discontinue smoking. Pretreatment, three week, and three month orthostatic blood pressure and pulse measurements will be compared. Changes in pulse rate, systolic blood pressure, diastolic blood pressure, and mean arterial pressure will be compared using the paired T test. If there are significant differences, the lab values will be studied to determine correlation.

Progress: Approximately 15 patients have been entered in this study. Thus far an occasional patient has been noted to have a drop in systolic blood pressure and an increase or decrease in pulse rate with position changes prior to medication.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 86/54 Status: Terminated

Title: The Natural History of HTLV-III Infection and Disease in
a United States Military Population

Start Date: has not started Est Completion Date: Not known

Dept/Svc: Medicine/Infectious Disease Facility: MAMC

Principal Investigator: COL Peter Gomatos, MC

Associate Investigators: None

Key Words: HTLV-III, natural history, progression, military

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: \$5,920.00** OMA Cost: \$1,940,064.00** Mar and Sep 88

Study Objective: To assess the impact of HTLV-III infection on - fitness for duty by systematically defining the natural disease progression in individuals with documented HTLV-III infections in the general military population; to determine the impact of co-factors, i.e., drug abuse, physical activity, on disease progression; and to form an information base and a study cohort upon which numerous other studies can be built, i.e., drug treatment of HTLV-III.

Technical Approach: Currently, all military health care beneficiaries with serological evidence of HTLV-III infection are referred to an Army medical center for evaluation by an Infectious Disease specialist. These patients will be evaluated by the complete standard battery of testing done for HTLV-III patients, plus patient education and counselling. Each HTLV-III infected individual will be staged according to the Walter Reed Staging Classification. The only additional requirement of individuals enrolled in this study is that information gathered from each individual as a consequence of this study will be centralized in a common data base located at WRAIR. These subjects will have repeat evaluation every 6 months for up to five years with communication continued via letters at three month intervals to maintain contact and provide any new information to the subjects. At a minimum, the occurrence/staging of disease progression will be determined with time interval, age, sex, risk factor, ethnic group, coinfection with EBV, CMV, and HBV representing individual variables.

Progress: This protocol has not received final approval for funding and the principal investigator has been unable to obtain any definitive information on the plans from Medical R&D Command for this study. Therefore, he has determined that he will terminate the protocol. It will be available in the DCI files if the study is funded and there is an interested investigator at MAMC to reactivate the study.

**All funds to be provided by Medical R & D Command.

Detail Summary Sheet

Date: 30 Sep 88	Protocol No.: 85/25	Status: Completed
Title: Efficacy & Safety of Trimethoprim/Sulfamethoxazole vs Ampicillin in the Treatment of Upper Urinary Tract Infections		
Start Date: 18 Jan 85	Estimated Completion Date: Jun 85	
Dept/Svc: Medicine/Infectious Disease	Facility: MAMC	
Principal Investigator: CPT Patrick D. Gorman, MC		
Associate Investigators: COL Peter Gomatos, MC MAJ John W. Gnann, MC CPT Michael Lyons, MC CPT William A. Pearce, MC		
Key Words: Pyelonephritis, intravenous antibiotics		
Accumulative MEDCASE	Est Accumulative	Periodic Review:
Cost: -0-	OMA Cost: -0-	N/A

Study Objective: To compare the safety, clinical efficacy, and bacteriological efficacy of trimethoprim/sulfamethoxazole and ampicillin in the treatment of hospitalized patients with infections of the upper urinary tract.

Technical Approach: Patients with suspected pyelonephritis requiring IV antibiotics will be randomized to trimethoprim/sulfamethoxazole 10 ml (160 mg trimethoprim plus 800 mg sulfamethoxazole) I.V. every 12 hr plus gentamicin 1 mg/kg every 8 hr (adjusted for creatinine) or ampicillin 500 mg I.V. every 6 hr plus gentamicin 1 mg/kg every 8 hours (adjusted for creatinine). Medications will be given for at least 72 hr or until the patient has been afebrile for 24 hours. If urine culture does not reveal *Pseudomonas aeruginosa* or other resistant pathogens, the gentamicin will be discontinued after 24 hours. After the antibiotics are stopped, the patient will receive the corresponding oral preparation to complete a 14 day course. Urine culture and analysis, blood culture, CBC, SGOT, and creatinine will be obtained at predetermined intervals. Symptoms and physical findings will be recorded daily. Studies on urine bacteria isolates will include quantitation, antibiotic disc susceptibility testing, and MIC determination. Specimens will be sent to the University of Washington for ACB determination, *E. coli* serotyping, and piliation studies.

Progress: This protocol was originally closed in March 1987 due to the departure of the investigators, but all data analysis had not been completed. The protocol was reactivated in March 1988 with CPT Gorman listed as the principal investigator because he was the individual who would be completing the data analysis and preparing a paper for presentation, even though he had not been listed on the original protocol.

A paper has been prepared and accepted for presentation.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 86/78 Status: Completed

Title: Evaluation of Prednisone as an Anti-tussive During
Bronchoscopy

Start Date: 18 Jul 86	Est Completion Date: Nov 86
Dept/Svc: Medicine/Pulmonary	Facility: MAMC
Principal Investigator: CPT Bruce S. Grover, MC	
Associate Investigators:	MAJ Thaddeus L. Dunn, MC
COL J. Waylon Black, MC	MAJ Michael C. Witte, MC
MAJ W. Hal Cragun, MC	CPT Marin Kollef, MC
Key Words: bronchoscopy, anti-tussive, prednisone, placebo	
Accumulative MEDCASE	Est Accumulative Periodic Review:
Cost: -0-	OMA Cost: \$50.00 Sep 88

Study Objective: To determine if prednisone given prior to bronchoscopy will help reduce the incidence and severity of coughing during bronchoscopy.

Technical Approach: Thirty adult patients scheduled for bronchoscopy will be randomized. Arm I will receive prednisone the night prior to and at 6 hr prior to the procedure. Arm II will receive a placebo on the same schedule. Spirometry will be done 72 hr prior to, immediately prior to, and immediately after the bronchoscopy. Patients will receive atropine and codeine 20-30 minutes prior to the procedure. Nebulized lidocaine and lidocaine jelly will be administered in one nostril and bronchoscopy will then be initiated in the usual manner. Once the bronchoscope is through the nasal passage, all coughs during the procedure will be recorded with the amount of topical lidocaine used as a cough suppressant noted. At the end of the procedure, the patient will be asked to complete a questionnaire, stating tolerance of the procedure, what he disliked most about the procedure, and whether or not he would undergo the procedure again. Statistical analysis will be done using analysis of variance. The amount of coughing and the degree of patient tolerance will be compared between the prednisone and placebo groups. The bronchoscopy will be divided into 15 min periods and the coughs will be counted as coughs per 15 min period and also as coughs per minute. If there is a significant difference in coughing or patient tolerance, an analysis will be done to determine whether there is a difference in response between the groups with and without bronchodilator response during pulmonary function testing. The data will be analyzed after 30 subjects have been studied to determine if more subjects need to be studied in order to achieve statistical significance.

Progress: No new patients were enrolled in this study in FY 88. Thirty patients had been entered in previous years.

There was no significant difference between treatment and placebo groups in the amount of coughing during bronchoscopy.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 87/02 Status: Terminated

Title: Effect of Testosterone on Bone Density in Males on Chronic Prednisone Treatment for Obstructive Airways

Start Date: Sep 86 Est Completion Date: Mar 88

Dept/Svc: Medicine/Pulmonary Facility: MAMC

Principal Investigator: CPT Bruce Grover, MC

Associate Investigators: COL Gary L. Treece, MC

COL Stanton Brown, MC MAJ Thaddeus Dunn, MC

COL Robert Karl, MC MAJ Michael Witte, MC

COL Stephen Plymate, MC CPT Kevin Carlin, MC

Key Words: bone density, OAD, prednisone, testosterone

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: 200.00 Sep 88

Study Objective: To determine if testosterone therapy can inhibit or reverse the bone loss incurred during long term glucocorticoid therapy in males with obstructive lung disease.

Technical Approach: Subjects: 20-40 males, >21 years

Patients with asthma or COPD currently on glucocorticoids will be evaluated basally with T₄, T₃U, TSH, CBC, SMA 20, PTH, 25 hydroxy vitamin D, testosterone, SSBG, LH, FSH, prealbumin, arterial blood gas, 24-hour urine for Ca Cr, spirometry, maximal inspiratory pressure (MIP), metabolic bone survey, and a bone density measurement of L2-L4 and the femoral head by dual photon bone densitometer. Utilizing a double-blind study, each patient will receive 1500 mg calcium/day and 50,000 U of vitamin D/week. All patients will be maintained on theophylline compounds and inhaled beta agonists. The prednisone dosage will be maintained as low as the respiratory status will allow. Patients will be randomized into two groups. Group 1 will receive depot testosterone, 200 mg IM, every two weeks. Group 2 will receive a placebo injection. Bone density will be measured, utilizing the dual photon bone densitometer, when the patient enters the protocol, and at 3, 6, 9, and 12 months. A repeat metabolic bone survey will be taken at 12 months. Spirometry and MIP will be repeated at 3, 6, 9, and 12 months.

Statistical analysis: Bone density measurements before and after treatment in the treated and placebo groups will be compared using the two-tailed T test. Regression analysis will be used to determine the influence of baseline total and free testosterone on the response to treatment. Semi-quantative evaluation of clinical factors such as patient well being, prednisone requirements, libido, bone pain, and development of new or progression of compression fractures will also be made.

Progress: No patients were entered in the study. After two years of waiting for funding for the dual photon densitometer, which was necessary to perform this study, funding for this equipment still had not been approved. Therefore, the study was terminated.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 88/44 Status: On-going

Title: Redundant Care of Internal Medicine Patients in
Subspecialty Clinics

Start Date: 18 Mar 88 Est Completion Date: May 88

Dept/Svc: Medicine/Internal Facility: MAMC

Principal Investigator: LTC Robert C. Harvey, MC

Associate Investigators: CPT Patrick D. Gorman, MC

CPT Steven C. Hahn, MC

Key Words: multi-clinic/single clinic visits, resources

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: -0- N/A

Study Objective: To evaluate redundant subspecialty clinic visits in the internal medicine patient population and estimate the impact on resources in terms of potential excessive visits.

Technical Approach: This will be a retrospective chart review of patients receiving care in the Internal Medicine Clinic at MAMC. Two groups, defined as multi-clinic and single clinic visits, will be studied. The first group will consist of patients receiving care solely in the Internal Medicine Clinic by a single care provider for the entire case management without involvement of physicians in other areas. Referrals for evaluation or recommendation of care, subspecialty oriented procedures and follow-up, and patients seen for less than one year will be excluded. The second group will consist of patients who receive care in the Internal Medicine Clinic and are also seen in the subspecialty clinics for internal medicine problems. Approximately 300 charts will be reviewed. Demographics, epidemiology (diagnosis, duration, and therapy), number of patient visits for the past four years, length of time as a patient in the Internal Medicine Clinic, and manner of referral will be assessed. Appropriateness of the visit and the reason for overlap between clinics will also be assessed for multi-clinic visit patients. Patients in the two groups will be matched demographically and epidemiologically. At the conclusion of the review, baseline characteristics of the patient population will be described. Appropriate statistical techniques will be applied to determine differences in staff, housestaff, quantity of medical problems or medications, and referral patterns. Categorical data analysis (descriptive and inferential) will be performed as warranted.

Progress: CPT Gorman was the original principal investigator for this protocol. Upon his reassignment in Jul 88, LTC Harvey assumed the role of principal investigator.

Raw data have been collected from the charts of 175 patients.

Detail Summary Sheet

Date: 30 Sep 88	Protocol No.: 88/49	Status: On-going
Title: Methotrexate in the Treatment of Steroid Dependent Chronic Obstructive Pulmonary Disease (COPD)		
Start Date: 15 Apr 88	Est Completion Date: Oct 89	
Dept/Svc: Medicine/Pulmonary	Facility: MAMC	
Principal Investigator: CPT Mary P. Horan, MC		
Associate Investigators:		
COL William P. Andrade, MC	MAJ Samuel G. Joseph, MC	
LTC W. Hal Cragun, MC	CPT Bruce S. Grover, MC	
Key Words: double-blind, crossover, placebo		
Accumulative MEDCASE	Est Accumulative	Periodic Review:
Cost: -0-	OMA Cost: \$770.00	N/A

Study Objective: To demonstrate a statistically significant reduction in the cortisone requirements of COPD patients who cannot successfully be weaned below 10 mg/day despite trials on ≥ 2 occasions.

Technical Approach: In a double-blind, crossover method, patients 40-70 years of age will be studied. At the time of entry each patient will have required 10 mg/day of prednisone, therapeutic levels of theophyllines, and inhaled beta agonist at least three times per day for the preceding year. Patients will be randomly assigned to receive either methotrexate or placebo for 12 weeks (Period 1.) At the end of Period 1, patients will be crossed over to the other drug (Period 2). During the first week of each period, patients will take one pill every 12 hrs x 3 doses/week, and, during weeks 2-12, they will take 2 pills every 12 hrs x 3 doses/week. During the entire study, patients will keep a daily diary, recording cortisone usage and subjective rating of COLD symptoms. Laboratory data on entry will include chest x-ray, spirometry, DL_{CO}, creatinine, SGOT, CBC, differential CBC, and pregnancy test if appropriate. Patients will be seen every three weeks for collection of diaries, directed examination, pulmonary function tests, a review of adverse reactions, and laboratory assessment to include creatinine, SGOT, CBC, and differential CBC. DL_{CO} will be performed at entry and at the end of each 12-week period. Chest x-rays will be obtained upon entry and exit from the study. Trough theophylline levels will be obtained at entry and at the end of each 12 week period and the frequency of inhalant usage will be noted at entry and at the end of each 12 week period. Data analysis will be performed using Student's two-tailed t-test to determine the effect of methotrexate upon cortisone usage. In addition, analysis will be done to compare symptom scores, pulmonary functions, WBC; SGOT; theophylline levels; presence or absence of positive allergy skin tests; prior dosage of steroid as determinant of response; and adverse occurrences.

Progress: No patients have been entered. At the suggestion of the FDA, the protocol is being rewritten to modify the study design as well as the addition of further laboratory evaluations.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 83/81 Status: On-going

Title: Studies on Fatty Acid Activation in Spermatozoa: Kinetics and Localization

Start Date: 16 Sep 83 Est Completion Date: Sep 84

Dept/Svc: Medicine/Endocrine Facility: MAMC

Principal Investigator: LTC Robert E. Jones, MC

Associate Investigators: COL Bruce L. Fariss, MC
COL Stephen R. Plymate, MC

Key Words: Palmitic acid, ATP, Mg++, CoASH, time and protein dependency curves, enzyme location/latency

Accumulative MEDCASE Est Accumulative Periodic Review:
Cost: -0- OMA Cost: \$785.00 Jan 88

Study Objective: To define the kinetic characteristics and cellular localization of the enzyme system responsible for the initiation of saturated fatty acid metabolism in spermatozoa.

Technical Approach: Normal human semen samples will be used to establish a ligase assay. Ligase activity will be measured using a sensitive radioligand/millipore filter procedure that utilizes (3H)-coenzyme A as the radioactive trace. Approximately 0.2 μ C of (3H) will be present in each individual assay. The samples will be centrifuged at 2800g for 10 minutes at room temperature, the seminal plasma supernatant will be discarded, and the sperm pellet will be resuspended in an isotonic buffer. This sperm mixture will be recentrifuged and washed twice prior to use. After the final centrifugation, the pellet will be diluted in a potassium enriched buffer to achieve a sperm density of 2×10^8 /ml. The assay mixture will contain palmitic acid, ATP, Mg++ and CoASH and will be initiated by the addition of the washed sperm preparation. Time and protein dependency curves will be run to determine the length of incubation needed to achieve first order kinetics in the measurement of initial velocities. Both Lineweaver-Burk plots and hyperbolic best-fit will be used to calculate approximate Km values for each substrate. Temperature, pH curves, and rates with alternate substrates will also be run. Enzyme location/latency will be determined by assaying separate cell fractions prepared by sonication and differential centrifugation of the isolated sperm. The effects of sulfhydryl reagents, albumin, and detergents will be studied to assist in estimation of latency.

Progress: The ligase enzyme in sperm has been further studied to include its substrate specificity for polyunsaturated fatty acids and its substrate level regulation. Docosahexaenoic acid (22:6) has a nearly four-fold lower Km and is a noncompetitive inhibitor of palmitic acid (16:0) activation. In contrast, 16:0 is a competitive inhibitor of 22:6 utilization, suggesting that there is a single ligase enzyme in sperm with a single substrate binding site and a regulating site.

Jones, Plymate: Biol Reprod 39:76, 1988
Jones, Plymate: Ann NY Acad Sci 513:571, 1987
Jones, Plymate: J Andrology 7:323, 1986

Detail Summary Sheet

Date: 30 Sep 88	Protocol No.: 85/84	Status: On-going
Title: Purification of Long Chain Fatty Acid: CoASH Ligase From Human Spermatozoa		
Start Date: 23 Aug 85	Est Completion Date: Sep 86	
Dept/Svc: Medicine/ Endocrine	Facility: MAMC	
Principal Investigator: LTC Robert E. Jones, MC		
Associate Investigators: COL Stephen R. Plymate, MC		
MAJ Charles J. Hannan, MSC		
Key Words: cellular location, molecular size, functional relationship, hepatic/mitochondrial forms		
Accumulative MEDCASE	Est Accumulative	Periodic Review:
Cost: -0-	OMA Cost: 708.00	Nov 86

Study Objective: To isolate and purify long chain fatty acid: CoASH ligase (AMP) (E.C. 6.2.1.3).

Technical Approach: Human sperm will be collected and prepared. Ligase will be protected with 5 mM p-aminobenzamidine and extracted with 1.0% Triton X-100. The crude preparation will be delipidated by serial washings with n-butanol, acetone, and ether. The final pellet will be dried under nitrogen and reconstituted in 10 mM phosphate buffer. Affinity chromatography with Blue Sepharose CL-6B will be the principle purification step. Ligase will be eluted from the column with palmitoyl CoA dissolved in phosphate buffer. Fractions will be collected, read at 280 nm to determine the presence of protein, and assayed for ligase activity.

It is possible that several proteins which require nucleotides will be retained on the column; the eluate obtained by adding a palmitoyl CoA solution should contain those enzymes which possess a relatively high affinity for acyl CoA. Ligase acyl CoA:L-glycerol -3-phosphate transferase, palmitoyl carnitine O-acyl transferase and palmitoyl CoA deacylase would fall into the latter category. Ligase differs from the other acyl CoA dependent enzymes by virtue of an approximate 50-100 fold lesser affinity for palmitoyl CoA and an absolute requirement for ATP. By using a concentration gradient of palmitoyl CoA and/or an ATP elution step, these properties should facilitate purification of ligase.

Classical purification procedures for ligase are extremely complicated and involve multiple intermediate steps. On the other hand, affinity chromatography of a related enzyme using a related matrix yielded a 14-fold increase in specific activity with a single pass over the column. Purity and sizing of ligase will be accomplished by isoelectric focusing, polyacrylamide gel electrophoresis, and size exclusion chromatography (either HPLC or Sephadex G200). Protein will be determined with a BioRad kit and ligase specific activity will be calculated after each purification step.

Progress: Technical problems preventing neutralization of acrosomal protease have interfered with purification. The investigators are trying new agents/techniques to solve the purification problem.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 85/85 Status: Completed
Title: Kinetics of Polyunsaturated Fatty Acid (PUFA) Activation
in Human Sperm
Start Date: 23 Aug 85 Est Completion Date: Sep 86
Dept/Svc: Medicine/Endocrinology Facility: MAMC
Principal Investigator: LTC Robert E. Jones, MC
Associate Investigators: COL Stephen R. Plymate, MC
MAJ Charles J. Hannan, MSC
Key Words: PUFA, ligase activity, human sperm, acyl CoA
Accumulative MEDCASE Est Accumulative Periodic Review
Cost: -0- OMA Cost: 700.00 Jan 88

Study Objective: To determine the kinetics and substrate specificities of PUFA as related to acyl CoA synthesis in human sperm.

Technical Approach: Only ejaculates deemed normal by standard criteria will be utilized in this study. Two different techniques for determining ligase activity will be used. The first is a radioligand-millipore filter assay which measures acyl CoA formation via the incorporation of 3H-CoASH. The second measures the rate of 3H-palmitic acid conversion to palmitoyl CoA. The former assay is nonspecific in detecting activation of virtually all saturated or unsaturated medium to long chain (12 carbons or greater) fatty acid while the latter is specific for palmitic acid. The incubation mixture, which has been previously optimized, will be identical for both techniques. Protein will be measured colorimetrically with a BioRad kit, and kinetic constants (K_m , V_{max} , K_i) will be calculated using standard formulae and plots. Two questions will be addressed: what is the PUFA specificity for sperm ligase and are PUFA and saturated fatty acids activated by the same enzyme. The experimental approach is summarized as follows:

Experiment	Assay	Variables	Data Collected
PUFA specificity	3H-CoASH	16:1, 18:1, 18:2, 18:3 20:4, 22:1, 22:6	Km, V_{max}
Double Bond specificity	3H-CoASH	16:1 (cis, trans)	Km, V_{max}
Competition curve	3H-PA	Coincubation of 16:0 (0-10 μ M) with 0, 5, 10 μ M PUFA	Km/ K_i , V_{max}

Progress: Docosaheptaenoic acid (22:6) has a lower K_m for activation than other fatty acids. Examples of selected fatty acids demonstrate competitive inhibition of palmitic acid (16:0) activation whereas 22:6 was a noncompetitive inhibitor of 16:0 activation. In contrast, 16:0 was a competitive inhibitor of 22:6. A pattern of negative cooperativity was observed with coenzyme A and 22:6. The investigators conclude that 22:6 regulates fatty acid utilization in sperm through a complex kinetic mechanism and that there is probably only one ligase enzyme in sperm.

Jones, Plymate: J Andrology 8:40, 1987
 Jones, Plymate: Ann NY Acad Sci 513:571, 1987

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 36/70 Status: Terminated

Title: Hormonal Regulation of Rabbit (*Oryctolagus cuniculus*) Liver Long Chain Fatty Acid:CoASH Ligase (AMP). Effects of Insulin, Glucagon, Glucocorticoids and Thyroid Hormones

Start Date: 20 Jun 86 Est Completion Date: Jul 87

Dept/Svc: Medicine/Endocrine Facility: MAMC

Principal Investigator: LTC Robert E. Jones, MC

Associate Investigator: COL Stephen R. Plymate, MC

Key Words: long chain fatty acid: CoASH ligase, rabbit liver, hormonal regulation, effects

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: \$2388.00 Sep 88

Study Objective: To determine if rabbit liver ligase is modulated by hormonal influences by testing the effects of various hormones on the kinetics of fatty acid activation in cultured hepatocytes.

Technical Approach: Hepatocytes will be obtained and cultured using modifications of a previously approved MAMC protocol. The biomatrix (collagen-coating) will be synthetically generated using commercially available collagen. The wells will be allowed to air dry and will be recoated within 24 hours. After the biomatrix has set the plates will be covered in paraffin film and stored frozen. To guarantee culture plate sterility, the wells will be exposed to 10,000 rads from a cobalt source prior to cell plating. Hormonal testing, in triplicate, will then be done (T_4 , dexamethasone, insulin [without SG-F7 and in CEM 2000 minus insulin], and glucagon) using varying concentrations, including zero concentration. All hormones will be tested at a 50 nM concentration with CEM 2000 and SGF-7. The effects of time exposure will be assessed. After the incubations have been completed, the cells will be harvested by collagenase digestion, identical conditions will be pooled, and the cells counted. Per cent cellular viability will be determined, cells will be centrifuged, washed in sucrose 5mM Tris, and homogenized. The homogenate will be centrifuged to remove cellular debris/plasma membranes and the resulting supernatant will be centrifuged at 10,000 g. The pellet containing mitochondria will be saved and the supernatant with the microsomal fragments will be centrifuged at 105,000 g. Both pellets will be washed and recentrifuged as outlined above. Plasma membranes will be isolated and purity determined by enzymatic analysis. Ligase activity will be measured using a minor modification of the method of Polokoff and Bell (J Lipid Res 1975). One way ANOVA will be used to determine differences within a given hormone treatment group. If a difference is found ($P < 0.05$), a t test or multiple range comparison will be used to identify the specific deviations. A similar approach will be used to study differences between different hormone incubations.

Progress: No work was done on this protocol in FY 88. The decision to terminate the protocol was made in view of the availability of the Hep G2 cell line.

Detail Summary Sheet

Date: 30 Sep 88	Protocol No.: 87/23	Status: On-going
Title: Investigations into the Mechanisms of Phospholipid Synthesis in Human Spermatozoa		
Start Date: 21 Nov 86	Est Completion Date: Dec 87	
Department: Clinical Investigation	Facility: MAMC	
Principal Investigator: LTC Robert E. Jones, MC		
Associate Investigators: COL Stephen R. Plymate, MC		
MAJ Charles J. Hannan, MC CPT Kevin J. Carlin, MC		
Key Words: spermatozoa, phospholipids, palmitic acid, docosa-hexaenoic acid, acyl transferase, Land's pathway		
Accumulative MEDCASE	Est Accumulative	Periodic Review:
Cost: -0-	OMA Cost: \$1600.00	Jan 88

Study Objectives: To determine if sperm can replenish phospholipids after they have been partially hydrolyzed to the lyso-forms by the action of phospholipases A₂ or A₁ and to attempt to identify and characterize sperm acyl transferase.

Technical Approach: Acyl transferase, acyl CoA:1-acyl-sn-glycero-3-phosphocholine O-acyl transferase will be screened by coincubating human sperm with labelled fatty acids, CoASH, ATP, Mg²⁺, and Tris. The reaction will be terminated by delipidating the sperm with CHCl₃: MeOH, and the organic phase will be chromatographed on silica gel TLC plates. These plates will be developed and spots will be scraped and counted. If the labelled fatty acid is found to be contained within a phospholipid region, cofunctioning of ligase and acyl transferase will be assumed to occur. Studies to characterize acyl transferase activity will be performed using an assay based on the liberation of CoASH which reacts with DTNB, resulting in a change in absorption at 414 nm. Either palmitoyl or docosa-hexaenoyl CoA will be used as the acyl donor to lyso-phosphatidyl choline. The conversion of lyso-phosphatidyl choline to phosphatidyl choline will be chromatographed. This assay will be optimized for pH, ionic strength, substrate levels and amount of enzyme before kinetic constants are determined. For carnitine-dependent transacylation, D,L-palmitoyl carnitine and lyso-phosphatidyl choline will be coincubated with washed sperm, delipidated and the products chromatographed as above. If the amount of lyso-phosphatidyl choline declines while phosphatidyl choline increases, a carnitine dependent mechanism will be presumed to exist. Alternatively, carnitine dependency could be screened by using ³H-palmitoyl carnitine to look for labelled phosphatidyl choline formation. The effect of 22:6 on 16:0 incorporation into phospholipids will be assessed by incubating unlabeled 22:6 with ³H-16:0 and following the appearance of 16:0 in phosphatidyl choline. Conversely, the effect of 16:0 on ¹⁴C-22:6 will be studied.

Progress: This protocol has demonstrated that human sperm can incorporate either docosa-hexaenoic acid (22:6) and palmitic acid (16:0) into phosphatidyl choline. The investigators have synthesized the coenzyme A thioester of 22:6 and are characterizing the 1-acyl lysophosphatidyl choline acyl transferase activity in sperm. Presented at the 1988 Meeting, American Society for Andrology, Jones, Plymate: J Androl 9:41, 1988

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 88/26 Status: On-going

Title: Neutral and Polar Lipid Synthesis in Human Spermatozoa:
A Correlation with Morphology and Function

Start Date: 15 Jan 88 Est Completion Date: Jun 89

Dept/Svc: Medicine/Endocrinology Facility: MAMC

Principal Investigator: LTC Robert E. Jones, MC

Associate Investigators: COL Stephen R. Plymate, MC

MAJ Charles J. Hannan, MS

CPT Karl E. Friedl, MS

Key Words: fatty acids, lipid synthesis, ligase activity, sperm

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: \$40,000 OMA Cost: \$2,000.00 N/A

Study Objective: To compare the rates of fatty acid activation to acyl CoA and subsequent disposal into neutral or polar lipids with sperm morphology or an assessment of sperm motility.

Technical Approach: The incorporation of palmitic (16:0) and docosaehaenoic acids (22:6) into neutral or phospholipids will be measured by incubating whole, fresh sperm with ³H-16:0 and ¹⁴C-22:6. Total lipids will be extracted using the method of Bligh and Dyer. The chloroform phase will be taken to dryness under N₂ at 42°C and subsequently reconstituted in a minimal volume of chloroform. The chloroform mixture will be applied to a silicic acid column and subsequently eluted with 20 ml chloroform followed by 20 ml of methanol. The chloroform fractions containing neutral lipids will be combined, evaporated, and repeatedly extracted to remove the free fatty acids. Both the methanol and chloroform eluates will be counted, and an aliquot of each will be chromatographed on silica gel G to ensure complete separation. Incorporation rates will be expressed as nmoles fatty acid incorporated/10⁶ sperm or nmoles phospholipid P/hour. After extracting the sperm with 0.1% Triton X100, ligase activity will be measured. Both 16:0 and 22:6 will be used as substrates in the incubations. Ligase activity will be expressed as nmoles acyl CoA formed/min/mg protein. The seminal plasma concentrations of these compounds will be measured using an enzymatic spectrophotometric technique. These parameters will be considered separately in relationship to ligase activity and lipid synthesis. Semen samples will be handled and analyzed according to the current WHO guidelines. Morphology will be assessed on fixed smears, and motility will be objectively quantified with an automated semen analyzer. With the exception of the sperm density, the semen quality will be blinded to the person performing the biochemical analyses. Incorporation rates and the distribution of the fatty acid labels and ligase activity will be correlated with sperm morphology and motility of the semen sample using either linear regression or chi-square analyses.

Progress: MEDCASE application for BLIC-C funding has been completed for the computer-assisted semen analyzer.

Detail Summary Sheet

Date: 30 Sep 88	Protocol No.: 88/83	Status: On-going
Title: Influence of Calcium on Phosphatidylcholine Synthesis in Human Spermatozoa		
Start Date: 16 Sep 88	Est Completion Date: Sep 89	
Dept/Svc: Medicine/Endocrine	Facility: MAMC	
Principal Investigator: LTC Robert E. Jones, MC		
Associate Investigators: COL Stephen R. Plymate, MC MAJ Charles Hannan, MC		
Key Words: free fatty acids, lyso-phosphatidylcholine		
Accumulative MEDCASE	Est Accumulative	Periodic Review
Cost: -0-	OMA Cost: \$2444.00	N/A

Study Objective: To determine the effects of calcium on the synthesis of phosphatidylcholine from free fatty acids and lyso-phosphatidylcholine (LPC) in freshly ejaculated human spermatozoa.

Technical Approach: Semen samples will be centrifuged at 650g for 15 minutes and washed twice in an isotonic buffer. The sperm pellet will be resuspended at a concentration of 2×10^8 in the isolation buffer. Approximately 1×10^7 sperm will be used per assay. The incubation buffer conditions will be identical to those previously established in the DCI lab. In brief, the incubation mixture contains 20 mM ATP, 20 mM $MgCl_2$, 50 μM LPC, 10 μM fatty acid, 5mM dithiothreitol, 0.1 mM coenzyme A, and 280 mM Tris. The reaction is initiated with the addition of washed spermatozoa. After one hour, the phospholipids are extracted and separated by thin layer chromatography. Enzymatic rates are calculated as nmoles fatty acids incorporated into phosphatidylcholine/ 10^7 sperm/hour. The investigators have shown that there are two types of substrate blanks in this system. The first, a coenzyme A blank, assess ligase and acyl transferase activity and consequently provides data on the activities of these two enzymes while the second, the LPC blank, yields information on the generation of acyl acceptors presumably through the activity of phospholipases. By using either 16:0 or 22:6 as acyl substrates and utilizing the LPC blank, the phospholipase A_1 can be differentiated from A_2 . Because LPC is added to the incubations, the LPC blanks become all the more critical in determining the possibility of calcium control of this pathway. The concentration of calcium in the incubations will be 1.7 mM, and the concentration of A23187, a calcium ionophore, will range from 10-30 μM . If an effect is seen which suggests ligase modulation, ligase activity will be specifically addressed using both whole sperm or a Triton x 100 extract of sperm. The rates of acyl substrate utilization will be compared by an ANOVA, rates obtained with and without LPC will be compared with a Student's t test. Ligase activity will be assessed using kinetic techniques previously described (Biol Reprod 39:76, 1988).

Progress: This protocol has just been approved by the IRB and has not been started.

Detail Summary Sheet

Date: 30 Sep 88	Protocol No.: 88/84	Status: On-going
Title: <i>In Vivo</i> and <i>In Vitro</i> Comparisons for Sex Hormone Binding Globulin (SHBG) Production in Morbid Obesity		
Start Date: 15 Sep 88	Est Completion Date: Sep 89	
Dept/Svc: Medicine/Endocrine	Facility: MAMC	
Principal Investigator: LTC Robert E. Jones, MC		
Associate Investigators: COL Preston L. Carter, MC		
COL Stephen R. Plymate, MC		
MAJ Jonathan Kushner, MC		
1LT Rita C. Hoop, MS		
Key Words: morbid obesity, SHBG, hepatic tissue, L-thyroxine		
Accumulative MEDCASE	Est Accumulative	Periodic Review
Cost: -0-	OMA Cost: \$4750.00	N/A

Study Objective: To determine the molecular basis for the reduction of serum SHBG levels in morbid obesity.

Technical Approach: Subjects: 5 morbidly obese subjects undergoing a vertical banded gastroplasty (VBG) and 5 lean, age and sex matched controls undergoing and elective cholecystectomy.

Three liver biopsies will be obtained intraoperatively. Subcutaneous fat will be obtained along the incision site. One core, which represents the *in vivo* portion of the study, will be immediately frozen and the remaining samples will be dispersed with collagenase/DNase and placed in a short term culture with 10% fetal calf serum and 3 mM L-glutamine supplemented Dulbecco's modified Eagle's media (DMEM). After three days, the media will be removed and replaced with unsupplemented DMEM. L-thyroxine (1 μ M) and insulin (10 nM) will be added to each of the test flasks while the control flask will be treated with vehicle alone. After two days, the spent culture media will be removed and frozen for later SHBG analysis. The cells will be harvested with trypsin, washed, and frozen. Detection of SHBG mRNA will be performed according to the method of White and Bancroft (J Biol Chem 257: 8569, 1982), employing a custom oligonucleotide probe coupled to an enzymatic detection system. Specificity of the probe will be ensured by simultaneously hybridizing matched subcutaneous fat samples and by probing at the hepatocyte lysate with a ³²P labeled completed cDNA probe for human SHBG. The tissue culture media will be assayed for SHBG as previously described (Plymate, et al, J Clin Endocrinol Metab 67:460, 1988). Differences in relative levels of SHBG mRNA (estimated as number of molecules per hepatocyte) between controls and test subjects will be determined using an unpaired t test. The comparisons between media levels of SHBG and cellular levels of SHBG mRNA (L-thyroxine/ insulin supplemented versus controls) will be handled with a paired t test. If multiple comparisons are required, an ANOVA will be used.

Progress: This protocol has just been approved by the IRB (Sep) and has not been started.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 88/37 Status: Completed

Title: Effect of Blood-Sparing Techniques on Blood Volume Loss
and Need for Transfusion in the ICU Patient

Start Date: 18 Mar 88 Est Completion Date: May 88

Dept/Svc: Medicine/Pulmonary Facility: MAMC

Principal Investigator: MAJ Samuel G. Joseph, MC

Associate Investigators: CPT Bruce Grover, MC

LTC W. Hall Cragun, MC CPT Mary P. Horan, MC

MAJ Anthony Sado, MC CPT Marin Kollef, MC

Key Words: phlebotomy, blood loss, pre- and post-education

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: \$200.00 N/A

Study Objective: To determine the effect of blood-sparing techniques on blood volume loss and need for transfusion in ICU patients.

Technical Approach: Twenty-five successive adult patients in the ICU will be analyzed in each of two phases, before and after education of nursing and physician staff regarding these blood-sparing methods. Daily logs will be kept by the bedside and completed by the phlebotomist. Date, time, status of patient, method of withdrawal, amount drawn, source, type of test (ABG, chemistry, CBC, culture, other), HCT, and amount of blood discarded will be annotated for each phlebotomy. Phase two will involve a similar number of successive ICU patients after nursing and physician staffs have undergone in-service training on sparing methods and consequences of excessive phlebotomy and transfusion. Identical daily logs will be used in this phase. Number of phlebotomies, amount of blood drawn, red-cell volume of blood lost and transfused, and need for transfusion will be compared using Student's T Test. Patients remaining in the ICU for less than 48 hours and those with or who develop active bleeding will be excluded.

Progress: 123 subjects were entered in this study. The blood loss group before instruction had an average of 46cc of blood withdrawn, 37% of which was discarded. The no blood loss group had an average of 50cc withdrawn, 47% of which was discarded. The total before instruction group had 48cc per patient withdrawn with 42% discarded. After instruction, the blood loss group had approximately 62cc withdrawn and 9.5% discarded at a P value of $<.03$ and the no blood loss group had 36cc withdrawn with 2.5cc discarded with a P value of $<.0002$ (when compared to the before instruction group). The total amount of blood withdrawn from each patient before and after instruction was not statistically significant; in fact, there was an increase in the blood loss group after instruction. The insignificant change of total amount per patient withdrawn before and after instruction indicates that there may yet be further reduction in total phlebotomy amount and that the key to this may be further awareness on the parts of both housestaff and nursing staff. A paper has been accepted for presentation in October 1988.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 88/71 Status: On-going

Title: Hepatitis B Vaccine (Recombivax) - Abbreviated Schedule
Vaccination Trial

Start Date: 19 Aug 88 Est Completion Date: Mar 90

Dept/Svc: Medicine Facility: MAMC

Principal Investigator: CPT Robert J. Kazragis, MC

Associate Investigators: LTC Ronald H. Cooper, MC

Key Words: hepatitis B, vaccine, conventional vs reduced dose

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: \$3785.00 N/A

Study Objective: To test and compare the efficacy of conventional and reduced dosages of intradermally and intramuscularly administered Recombivax, given in an abbreviated schedule.

Technical Approach: Subjects: 75, male/female, ages 18-45

Evaluations before entry: medical history form and interview; hepatitis B surface antigen and antibody, hepatitis B core antibody, serum alanine and aspartate aminotransaminase levels, and a completed blood count.

The subjects will be randomized to one of three arms:

10 µg dose Recombivax IM at 0, 4, and 7 weeks

2 µg dose Recombivax ID at 0, 4, and 7 weeks

1 µg dose Recombivax ID at 0, 4, and 7 weeks

HBsAg, anti-HBs, and anti-HNc will be followed at days 0, 30, 60, 90, 190, and 260.

Individuals who fail to achieve a protective level of anti-HBs will be revaccinated at one year with 10 µg IM, Recombivax.

Data analysis: Chi-square analysis of geometric mean titers of anti-HBs and comparison of antibody titers and response rates to previously published studies.

Progress: New study - no subjects entered.

Detail Summary Sheet

Date: 30 Sep 89 Protocol No.: 88/78 Status: On-going

Title: The Regression of Left Ventricular Hypertrophy by Echocardiographic Criteria in Patients Treated for Poorly Controlled Hypertension in an Intensive Stepped Care Approach versus the Usual Clinic Setting, Utilizing the Same Antihypertensive Regimen

Start Date: 16 Sep 88 Est Completion Date: Jun 90

Dept/Svc: Medicine/Pulmonary Facility: MAMC

Principal Investigator: CPT Lynn M. Keenan, MC

Associate Investigators:

MAJ Howard M. Cushner, MC MAJ Alice M. Mascette, MC

MAJ Kim Havas, ANC CPT Mark P. Elam, MC

Key Words: hypertrophy, hypertension, intensive/routine setting

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: \$4000.00 N/A

Study Objective: To determine if the regression of left ventricular hypertrophy (LVH) occurs with the treatment of hypertension in patients followed in an intensive setting as opposed to the usual setting and to evaluate whether there is a critical level of blood pressure (BP) control that is necessary in order to achieve regression of LVH in the setting of hypertension.

Technical Approach: Sixty patients ages 30-70 treated at MAMC for poorly controlled hypertension with LVH by echocardiographic criteria will be evaluated by screening history and physical, SMA-20 (to include potassium, CO₂, and chloride), urine analysis and blood pressure. Subjects will be randomized to be followed by their primary care physician using his routine procedures or to be followed intensely with evaluations every four weeks. Blood pressures will be obtained consistently by the same investigator with the same blood pressure cuff with the patient seated at rest for five minutes. All patients will be tapered off previous medications over a period of weeks as hydrochlorothiazide and lisinopril are added. In order to achieve good blood pressure control, lisinopril will be started at 5 mg qd and increased as necessary to 40 mg qd. Hydrochlorothiazide will be started at 25 mg qd and increased to 50 mg qd. If necessary, Catapres will be added. The goal of BP control is systolic BP <140 and diastolic BP <90. Patients will receive follow-up SMA-20 at weeks 1 and 4 and at the end of the study. Blood pressures will be followed by monthly visits in the intensive care group versus less often in the usual care group. Differences in left ventricular wall thickness will be compared with a t test. One statistical significance of regression in left ventricular wall thickness and BP control for the intensive versus usual care patients will be assessed.

Progress: New study - no patients entered.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 88/12 Status: Terminated

Title: Clearance of Bacterial Endotoxin by Continuous
Arteriovenous Hemofiltration (CAVH)

Start Date: 11 Dec 87 Est Completion Date: Dec 87

Dept/Svc: Medicine/Pulmonary Facility: MAMC

Principal Investigator: CPT Marin H. Kollef, MC

Associate Investigators: LTC Rodney Michael, MC

MAJ Howard Cushner, MC

Key Words: endotoxin, bacterial, clearance, CAVH

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: -0- N/A

Study Objective: To determine if CAVH is able to clear endotoxin from gram negative bacteria in the form of lipopolysaccharide from the circulation.

Technical Approach: Five critically ill patients in the Intensive Care Unit with gram negative bacterial sepsis (defined by positive blood cultures) and renal failure requiring CAVH due to hemodynamic instability will be studied. On each day (not more than five days) the patient is receiving CAVH, serum specimens will be drawn from the arterial, venous, and collection chambers/channels of the CAVH device. These specimens will be assayed and quantitatively analyzed for bacterial endotoxin.

Progress: One patient was evaluated for entry in this protocol. The laboratory doing the assay for endotoxin withdrew and no other facility is available to do the assay. Therefore, the protocol was terminated.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 87/01 Status: On-going

Title: Sequential Therapy with Methotrexate and 5-FU in Advanced Colorectal Carcinoma

Start Date: 17 Oct 86 Est Completion Date: Oct 88

Dept/Svc: Medicine/Hematology-Oncology Facility: MAMC

Principal Investigator: MAJ Mark H. Kozakowski, MC**

Associate Investigators: MAJ David Dunning, MC

COL Irwin B. Dabe, MC MAJ Ruben Sierra, MC

LTC Lauren K. Colman, MC CPT Denis Bouvier, MC

LTC Howard Davidson, MC CPT Donna Mercado, MC

MAJ Thomas Baker, MC D. White, M.D.

Key Words: carcinoma, colorectal, methotrexate, 5-FU, sequential

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: -0- N/A

Study Objective: To evaluate a treatment schedule in terms of therapeutic effectiveness: response rate, survival, and toxicity in patients with colorectal carcinoma.

Technical Approach: Patients with histologic evidence of colorectal carcinoma will receive methotrexate, 100 mgs/M² IV, followed by 5-FU, 1250 mgs/M² in an 18 hour IV infusion. Leucovorin will be given orally at a dose of 10 mgs every 6 hours for 6 doses, beginning 24 hours after the methotrexate is given. Beginning with the second course the 5-FU dose will be increased to 1500 mg/M² and will be adjusted thereafter as necessary in response to side effects. This regimen will be given every two weeks (or as soon as there is evidence of hematologic recovery from the prior course) until progression or unacceptable toxicity is encountered. Pre-study evaluation will include history and physical examination, CBC, LFT, BUN, creatinine, CEA, liver CT scan, endoscopy to evaluate intraluminal lesion (if any), bone scan, and CXR. Further evaluation will include CBC, LFT, BUN, and creatinine every 15 days; CEA every four weeks; and evaluation of endoluminal lesions every two months.

Progress: Four patients were entered in this study in FY 88. Of these four patients, there was one minor response, one progressive disease, one stable disease, and one patient was removed from the study due to toxicity (significant mucositis leading to volume depletion and acute renal failure which reversed). Patient entry is complete, but some of the subjects have not completed both phases of the study.

A paper was presented at the ACP/4th Annual Army Regional Meeting in October 1987 and at the Annual Meeting of the American Society for Clinical Oncology in May 1988.

Pro Ann Meet Am Soc Clin Oncol 7:142A, 1988

**MAJ Ruben Sierra, MC, original principal investigator. MAJ Kozakowski was named the new principal investigator for this protocol in August 1988.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 86/17 Status: Terminated

Title: Colon Inflammation in Reiter's Syndrome: Response to Sulfasalazine. Results of a Controlled Study.

Start Date: 15 Nov 85 Est Completion Date: Jul 89

Dept/Svc: Medicine/Rheumatology Facility: MAMC

Principal Investigator: MAJ M. Frank Lyons, MC (new PI, Aug 88)

Associate Investigators: LTC Thomas F. O'Meara, MC

MAJ Robert C. Hays, MC MAJ James Yovanoff, MC

Key Words: colon inflammation, Reiter's syndrome, sulfasalazine

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: \$300.00 Jan 87

Study Objective: Part I: To evaluate the incidence of occult inflammatory lesions of the bowel in patients with Reiter's syndrome, regardless of the presence or absence of gastrointestinal symptoms. Part II: To treat Reiter's patients who are refractory to conventional therapy with sulfasalazine and document subjective and objective changes in the patient's arthropathy. (Double blind study)

Technical Approach: Part I: Patients who fulfill the Amer Rheumatism Assoc criteria for Reiter's syndrome will receive colonoscopy with colonic mucosal biopsies. Baseline data will include stool culture for *Yersinia*, *Shigella*, *Campylobacter*, and stool samples for ova cysts and parasites. Serial stool hematest determinations will be obtained and serum will be drawn for ANA, rheumatoid factor, HLA B27, Westergren sedimentation rate, CRP, serum protein electrophoresis, and quantitative immunoglobulins. Patients cannot have taken laxatives, cathartics, or had enemas for 2 wks prior to colonoscopy. Colon biopsies will be graded by severity of disease and chronicity of disease using established criteria. Part II: Patients who have not responded to standard therapy consisting of ≥ 1 nonsteroidal anti-inflammatory drugs for a 6 mon period prior entry will be treated with sulfasalazine over a 12 wk period. Multiple subjective and objective parameters will be measured to assess the clinical activity of the patient's arthritis. Upon completion of 12 wks of therapy the patients with initially abnormal biopsies will receive repeat colonoscopy with biopsy to assess macroscopic and microscopic evidence of improvement in the inflammatory process. All colonic biopsies will be graded as in Part I. After 3 mon of treatment (or 5 mon if the dose is increased to 4.0 grams), the medication will be discontinued and the patient will be reevaluated at monthly intervals for 2 additional months. Data will be analyzed together and separately for all patients who meet ARA criteria for Reiter's syndrome and the group of patients who had a syndrome consistent with Reiter's without urethritis.

Progress: MAJ Lyons was named the principal investigator for this protocol in Aug 88. No patients were enrolled in this study in a > 2 year time period. After discussing the protocol with Dr. Yovanoff (original PI) and Dr. O'Meara (interim PI) and GI Clinic staff members, it was decided that the time that would be devoted to this protocol could be better spent on other endeavors since it is difficult to get volunteers; therefore, it was terminated.

Detail Summary Sheet

Date: 30 Sep 88	Protocol No.: 88/55	Status: On-going
Title: Double Blind, Multicenter, Placebo Controlled Clinical Trial to Evaluate the Efficacy and Safety of HA-1A Human Monoclonal Antibody in Patients with Severe Gram-negative Sepsis/Gram-negative Septic Shock		
Start Date: 20 May 88	Est Completion Date: May 89	
Dept/Svc: Medicine/Infectious Disease	Facility: MAMC	
Principal Investigator: LTC Rodney A. Michael, MC		
Associate Investigators: MAJ Samuel Joseph, MC		
LTC Ronald H. Cooper, MC	MAJ Anthony Sado, MC	
LTC William Cragun, MC	CPT Mary Horan, MC	
MAJ Bruce Grover, MC	CPT Bernard Roth, MC	
Key Words: Gram-negative sepsis, HA-1A, efficacy, mortality		
Accumulative MEDCASE	Est Accumulative	Periodic Review:
Cost: -0-	OMA Cost: -0-	N/A

Study Objective: To determine: the efficacy of HA-1A monoclonal antibody in reducing the mortality and direct morbidity of gram-negative sepsis; the impact on patient benefit and laboratory parameters/clinical signs associated with sepsis; and the safety and potential for immunogenicity of HA-1A.

Technical Approach: In a multicenter, double-blind, parallel group study, severely ill patients with a clinical diagnosis of severe gram-negative sepsis or gram-negative septic shock will be randomized to receive either a single intravenous infusion of 100 mg of HA-1A human monoclonal IgM antibody or a human albumin placebo. Prior to enrollment, each patient will undergo a physical exam, a medical history will be taken, and an APACHE II score will be calculated. Samples for clinical chemistry, clinical hematology, and urinalysis will be obtained 4 hrs prior to infusion, at 12 and 24 hr, and 3, 5, 7, 14, and 28 days after infusion until death or at least one documented normal set of values is obtained. Blood for bacteriological cultures will be obtained within the 24 hours prior to enrollment and subsequently as dictated by the clinical course. Additional body sites and fluids will be cultured as dictated by clinical status to document all suspected foci of infection. Chest x-rays will be done within 12 hours of infusion, either pre or post infusion. HA-1A antibody concentration will be measured prior to and at 1 and 2 hr and 28 days after infusion. The mortality rate will be the primary efficacy variable (although other efficacy parameters will be measured) and will be estimated in the control group following the entry of 10 confirmed gram-negative placebo patients. This will determine the time of 3 interim analyses and the overall sample size. All statistical tests will be based on 2-sided alternative hypotheses, since no prior assumptions will be made that HA-1A treatment is superior to that of placebo.

Progress: This protocol is awaiting final approval from the HSRRB.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 86/99 Status: Completed

Title: Investigations into Immune Phenomena Associated with
 Thyroid Autoimmune Disease

Start Date: Oct 86 Est Completion Date: Jun 88

Dept/Svc: Medicine/Endocrinology Facility: MAMC

Principal Investigator: MAJ Jennifer A. Nuovo, MC

Associate Investigators: COL Gary Treece, MC
COL Kenneth Burman, MC LTC Robert Jones, MC
COL Stephen Plymate, MC MAJ Daniel Knodel, MC

Key Words: thyroid autoimmune disease, insulin, goiter, cancer

Accumulative MEDCASE Est Accumulative Periodic Review:
Cost: -0- OMA Cost: \$3260.00 Oct 86

Study Objective: To continue work in the area of thyroid immunology screening for evidence of concomitant autoimmunity to insulin and insulin receptors in patients with autoimmune thyroid disease and to observe changes in antibody production during the course of the disease; to look for evidence of thyroid and insulin autoimmunity in these patients and patients with thyroid disease not usually felt to be autoimmune; to further characterize the IgG to insulin found previously in sera of patients with Graves' disease.

Technical Approach: Study A: Measurement of insulin antibodies in the serum of 50 normal subjects (sex- and age-matched to diseased patients); 50 patients with Graves' disease at diagnosis, during therapy, and following definitive therapy; 50 patients with Hashimoto's thyroiditis; 10 patients with thyroiditis; 10 patients with lupus or rheumatoid arthritis; 20 patients with simple goiter and 20 with multinodular goiter; and 50 patients with diabetes mellitus, using an ELISA test that has been modified for detecting insulin antibodies. If blood glucose levels are abnormal, insulin and C-peptide levels will be obtained. Study B: Insulin receptor binding studies will be performed on the subjects and controls listed in Study A. Study C: Immunoglobulin detected by ELISA will be purified by means of insulin affinity columns to determine if the immunoglobulin is a specific anti-insulin antibody. The immunoglobulin adhering to the column will be eluted, dialyzed, and concentrated, and then retested using the ELISA assay to test the ability of the antigen/antibody complex to inhibit insulin binding in previously positive sera.

Progress: One hundred patients with autoimmune thyroid disease were evaluated for the presence of insulin autoantibodies in serum by ELISA. Ten patients were positive for insulin autoantibodies. Of these, nine were negative for insulin antibodies by RIA and all were negative for Islet cell antibodies. ELISA may be a more sensitive test for low titer antibodies against insulin patients with evidence of autoimmune disease.

A paper was presented at the American Diabetes Association International Research Symposium in October 1987.

Detail Summary Sheet

Date: 30 Sep 88	Protocol No.: 87/74	Status: Completed
Title: Association of Risk Factors for Osteoporosis with Suspected Stress Fractures in Active Duty Women		
Start Date: 17 Apr 87	Est Completion Date: Dec 87	
Dept/Svc: Medicine/Endocrine	Facility: MAMC	
Principal Investigator: MAJ Jennifer Nuovo, MC		
Associate Investigator: CPT Karl Friedl, MS		
Key Words: osteoporosis, stress fractures, risk factors		
Accumulative MEDCASE	Est Accumulative	Periodic Review
Cost: -0-	OMA Cost: -0-	N/A

Study Objective: To estimate the size of the subset of active duty women who may have experienced lower extremity stress fractures during exercise and to determine whether or not this group is characterized by any potential risk factor(s) for osteoporosis.

Technical Approach: A questionnaire will be mailed to the work address of all active duty women stationed at Ft Lewis, WA. An identifying postcard will be enclosed for return under separate cover in order to locate initial non-respondents. A second mailing, two weeks after the first, will be made only to soldiers not returning the postcards. The questionnaire will elicit information on age, race, menstruation, children, method of birth control, smoking, weight control, exercise, pain in shins and feet, bone fractures, and family history of fractures or bone malformations. The returned data will be analyzed by frequency and cross tabulation procedures. Women answering yes to questions regarding fractures or pain will be compared to the remaining respondents for differences in the prevalence of amenorrhea, late menarche, parity, gynecologic age, smoking history, above or below normal weight, and exercise habits. Age and ethnic background will be handled as known covariates.

Progress: 2,460 active duty women were surveyed for risk factors for osteopenia and incidence of stress fracture. There were 1500 responses. There was a significant correlation of smoking and low weight with incidence of stress fracture. The other factors that were studied (number of pregnancies, amount of exercise, and medication usage) did not correlate.

A paper is being prepared for submission for publication in the Journal of Obstetrics and Gynecology.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 88/10 Status: Completed

Title: Nasal Polyps, A Manifestation of Allergy?

Start Date: 16 Oct 87		Est Completion Date: Jun 88
Dept/Svc: Medicine/Allergy		Facility: MAMC
Principal Investigator: CPT Jonathan A. Perkins, MC		
Associate Investigators: COL W. Pierre Andrade, MC		
LTC Don B. Blakeslee, MC		
Key Words: polyps, nasal, allergy markers, etiology		
Accumulative MEDCASE	Est Accumulative	Periodic Review:
Cost: -0-	OMA Cost: -0-	N/A

Study Objective: To compare the markers for allergic disease in patients with nasal polyps and control patients with allergic and nonallergic rhinitis without nasal polyps and patients without nasal disease or polyps in order to better understand the underlying etiology of nasal polyposis.

Technical Approach: Patients will be entered into one of 4 groups based on atopy or the presence or absence of nasal polyps. Atopy is defined as (1) a clinical history of allergy, (2) a family history of allergy, (3) one positive skin test, and (4) one positive serum RAST (radioallergosorbent testing). Group I: 10 patients without nasal polyps or known 1-4; Group II: 10 patients with perennial rhinitis without nasal polyps or 2-4 but with 1; Group III: 10 patients with allergic rhinitis without nasal polyps, but with 13 and/or 4; Group IV: 10-20 patients with nasal polyposis scheduled for polypectomy. A personal and a family history of eczema, asthma, rhinitis, hay fever, urticaria, vernal conjunctivitis, sinus disease, and adverse reactions to foods, drugs, or animals will be obtained. Onset of symptoms, occurrence throughout the year, specific substances or settings that exacerbate symptoms, and prior treatment will be determined. Medication(s) taken for other medical problems will be noted. Physical exam will be performed and sinus x-rays will be taken to rule out sinus disease. Prick skin testing (PST) to inhalants will be performed. If PST is negative intradermal skin testing (IDST) will be conducted with 7 common allergens endemic to the Pacific northwest and those suggested by history. Serum RAST will be done only on allergens positive by IDST. Nasal secretions will be tested by RAST to allergens positive by PST. If PST is negative, this fluid will be tested to allergens positive on IDST and those suggested by history. If IDST is negative, serum and nasal secretions in Groups I, II, and IV will be subjected to the 7 allergens used in IDST and allergens suggested by history. Nasal polyp fluid of patients in Group IV will be subjected to the same procedure as nasal secretions. Standard statistical analysis will be conducted using Dunnett's Test for the measurement of variation between groups.

Progress: A paper has been written and presented at the Annual Meeting of the American Academy of Otolaryngology, Sep 88.

Detail Summary Sheet

Date: 30 Sep 88	Protocol No.: 88/30	Status: On-going
Title: Investigation of the Serum-Effusion Albumin Gradient to Aide in the Differential Diagnosis of Pleural Effusions		
Start Date: 19 Feb 88	Est Completion Date: Sep 88	
Dept/Svc: Medicine/Pulmonary	Facility: MAMC	
Principal Investigator: CPT Bernard J. Roth, MC		
Associate Investigators: LTC William Cragun, MC LTC Thomas O'Meara, MC		
Key Words: transudate, exudate, thoracentesis		
Accumulative MEDCASE	Est Accumulative	Periodic Review:
Cost: -0-	CMA Cost: \$303.00	N/A

Study Objective: To evaluate the serum-effusion albumin gradient in patients with pleural effusions of varying etiologies in order to determine its efficacy in distinguishing transudates from exudates.

Technical Approach: A thoracentesis will be performed on patients with radiographic evidence of a pleural effusion. Albumin, total protein, glucose, and LDH levels will be determined on the fluid as well as cell count with cytopspin differential, culture for bacteria, fungi and tuberculosis, and cytology. If the fluid appears milky, triacylglycerol and cholesterol levels will be determined. Total protein, LDH, glucose, and albumin levels will be determined on a simultaneously drawn serum sample. If the fluid is exudative by Light's criteria (effusion-serum protein ratio >0.5 , effusion LDH >200 IU, or effusion-serum LDH ratio >0.6) and etiology is not evident from the above evaluations, a pleural biopsy will be performed, if clinically indicated. The evaluation of each patient will be reviewed and a clinical assignment of likely etiology, transudative versus exudative, will be made. This will be supported by pathology and pulmonary pressures whenever available. The following categories will be established: (1) patients with transudates secondary to congestive heart failure, either prior to or after diuretic therapy; (2) patients with exudates secondary either to infection or malignancy, and (3) miscellaneous (hypoalbuminemia, chylous, pseudochylous, etc.). The discriminating power of the serum-effusion albumin gradient will be compared to that of Light's criteria. A serum-effusion albumin >1.1 will be defined as a transudate.

Progress: Twenty-six subjects were studied. Effusions that were exudative had an albumin gradient <1.3 . Those that were transudative were >1.3 . Using this criteria, effusions can be classified with as good or better precision than with Light's criteria.

A paper was presented to the Washington State Chapter of the American College of Physicians and has been accepted for presentation at the Army Regional Meeting of the American College of Physicians.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: #88/36 Status: On-going

Title: Diurnal Variability of Corticotropin-Releasing Hormone, Corticotropin, and Cortisol in Pregnant Women

Start Date: 18 Mar 88 Est Completion Date: Oct 88

Dept/Svc: Medicine/Endocrinology Facility: MAMC

Principal Investigator: MAJ William R. Sheldon, MC

Associate Investigators: None

Key Words: CRH, ACTH, cortisol, hemoglobin, hematocrit

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: \$1690.00 N/A

Study Objective: To determine if a diurnal variation exists in the secretion of corticotropin releasing hormone (CRH) of placental origin and of adenocorticotropin hormone (ACTH) and cortisol measured simultaneously in maternal blood during the third trimester of pregnancy.

Technical Approach: Six patients in the third trimester of an uncomplicated pregnancy will be studied. Two nonpregnant women with normal menstrual periods and on no medications will be studied in the same manner as the pregnant subjects in order to establish that the normal diurnal variation in ACTH and cortisol can be clearly seen under the experimental conditions. Subjects will be admitted to the hospital the evening prior to the study. At least one hour before the first blood sample is drawn, an IV line will be placed in a forearm vein and infused with 0.9% saline at a rate sufficient to keep the line open throughout the study. Samples of blood will be drawn every two hours starting at 0800 hours and ending at 0600 hours the next morning. The samples will be assayed for hCRH, ACTH, and cortisol, using standard RIA kits. At the end of the study, the hemoglobin and hematocrit will be measured on each subject. Analysis of variance will be used for the statistical analysis of the data.

Progress: Progress has been made in developing the assay for corticotropin-releasing hormone. Unsuccessful attempts have been made to enroll subjects.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 81/56 Status: On-going

Title: The Effect of Nephrosis on Treated Hypothyroidism

Start Date: 20 Mar 81 Est Completion Date: Sep 86

Dept/Svc: Medicine/Endocrinology Facility: MAMC

Principal Investigator: COL Gary L. Treece, MC

Associate Investigators:

COL Bruce L. Fariss, MC MAJ Edward Lelonek, MC

COL Stanton Brown, MC MAJ James S. Little, MSC

COL Stephen R. Plymate, MC MAJ Louis N. Pangaro, MC

COL Poong S. Shim, MC MAJ David Turnbull, MSC

MAJ Lawrence Agodoa, MC CPT Jeffrey Addison, MC

Key Words: Hypothyroidism, treated, L-thyroxine

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: \$2425.00 Sep 88

Study Objective: To document an anticipated increased dosage requirement for patients with treated hypothyroidism who develop the nephrotic syndrome. Related objectives include answers to the questions: (1) does nephrosis unmask hypothyroidism and (2) does nephrosis mask hyperthyroidism?

Technical Approach: SUBJECTS: normals; normals treated with L-Thyroxine for one month; patients with hyperthyroidism; patients with hypothyroidism, primary untreated or treated for one month with L-thyroxine; and patients with the nephrotic syndrome untreated or treated for one month with L-thyroxine. All subjects will have a 24-hr urine for volume, creatinine, total protein, urine protein, electrophoresis, T_4 , and T_3 . Fasting samples will be drawn for SMAC-20, T_4 , T_3 resin, T_3 by RIA, TSH, THAT (an extra tube will be drawn for free T_4 , reverse T_3 , and TBG). A fasting TRH test will be done and blood for TSH will be drawn at 0, 30, and 60 mins post injection. The above procedures will be repeated after at least 30 days on one or more doses of T_4 for the treated groups. Urine protein electrophoresis will not be performed on urine with a total protein of <150 mg for 24 hrs; patients with known cardiovascular disease or >50 years will be excluded from the treated groups; and 24-hr urines will be obtained prior to or at least 72 hours after the TRH test.

Progress: No additional patients were entered in FY 88.

Eight patients have previously been studied and additional patients are being sought. The thyroid function tests will be rerun utilizing the highly sensitive TSH assays. T_3 and T_4 levels have not yet been determined pending the application of a suitable technique.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 82/05 Status: On-going

Title: The Utility of Urinary Free Cortisol to Monitor
Replacement Therapy for Adrenal Insufficiency

Start Date: 20 Nov 81 Est Completion Date: Sep 86

Dept/Svc: Medicine/Endocrinology Facility: MAMC

Principal Investigator: COL Gary L. Treece, MC

Associate Investigators: LTC Robert Jones, MC

MAJ Daniel Knodel, MC

Key Words: adrenal insufficiency, urinary free cortisol, monitor,
hydrocortisone, cortisone

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: \$700.00 Feb 87

Study Objective: To evaluate the possible usefulness of monitoring urinary free cortisol as an objective parameter of therapy that may avoid both under- and over-medicating patients with chronic adrenal insufficiency.

Technical Approach: Ten euthyroid patients with spontaneous or surgically induced adrenal insufficiency will be evaluated. Patients taking Aldactone will not be included unless it can be withdrawn. Patient involvement will be divided into 3 parts. During all 3 parts, the dose of any mineralocorticoid will not be altered. Patients having been on previous maintenance dose of glucocorticoid for at least 3 days and free of acute illness will be asked to collect 2 consecutive 24 hr urines for free cortisol, 17 LH corticosteroids, and creatinine. A fasting plasma cortisol, an ACTH level, and a 2-hr post-dose cortisol will be drawn on one of the days that the urine is being collected. Patients will then be asked to take an amount of glucocorticoid, orally, equivalent to 50% of their maintenance dosage for 7 days, after which blood and urine will be obtained. If a difference should be found in any of the parameters between patients taking hydrocortisone vs cortisone, several patients will be asked to switch to an equivalent amount of the other drug in the maintenance dosage for 7 days after which blood and urine will be obtained. If a difference should be found in any of the parameters between patients taking mineralocorticoid and those not taking such a drug, several patients on mineralocorticoid will be asked to discontinue the drug for 7 days and be restudied. Several patients not taking mineralocorticoid will be asked to take Florinef 0.1 mg/day orally for 7 days and be restudied as above. At the conclusion of the study, the patients will be given their maintenance dose and type of drug(s) unless otherwise clinically indicated.

Progress: No additional patients were entered in FY 88. In previous years, four patients have been entered. Patient recruitment is continuing. The available blood/urine remains frozen for batch analysis when patient recruitment is complete.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 84/40 Status: On-going

Title: Treatment of Graves' Ophthalmopathy with Cyclosporin

Start Date: 16 Mar 84 Est Completion Date: Sep 86

Dept/Svc: Medicine/Endocrinology Facility: MAMC

Principal Investigator: COL Gary L. Treece, MC

Associate Investigators: COL Leonard Wartofsky, MC

COL Stanley Allison, MC LTC Robert E. Jones, MC

COL Francis G. LaPianan, MC CPT Andrew Ahmann, MC

Key Words: Graves' ophthalmopathy, cyclosporin, group study

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: \$200.00 Sep 88

Study Objective: To assess the efficacy of Cyclosporin treatment on the ophthalmopathy of Graves' disease.

Technical Approach: This will be a collaborative study with the Endocrine Services at the other MEDCEN's. The study will be composed of a random cross-over design comparing cyclosporin treatment to the most commonly employed current therapy, high dose oral prednisone. Since responses tend to be seen rapidly the drugs will each be administered for three weeks. Each patient's response to one drug will be compared to his own response to the other drug. A total of 20 patients will be evaluated initially with random alternating allocation to either Group A or Group B:

- Group A: (1) prednisone, 40 mg, T.I.D. x three weeks
(2) full evaluation of response
(3) cyclosporin 5-10 mg/kg/day x three weeks

Group B: Reverse order of Group A.

Clinical assessment will be weekly with ophthalmopathy index and T₄, T₃, etc, at 0, 4, 6, 9, and 12 weeks. TRH will be done at 0, 4, and 9 weeks, and cyclosporin or prednisone levels will be done at 2, 3, 4, 7, 8, and 9 weeks.

Progress: No additional patients were entered in this study at MAMC in FY 88. One patient was entered prior to FY 88. Recruitment is very difficult for this protocol.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 85/24 Status: Completed

Title: Physiological and Biochemical Changes During Thyroid Extract Withdrawal

Start Date: 18 Jan 85 Estimated Completion Date: May 85

Dept/Svc: Medicine/Endocrinology Facility: MAMC

Principal Investigator: COL Gary L. Treece, MC

Associate Investigators: COL Stephen R. Plymate, MC

LTC Anthony P. Zavadil, MC

LTC Robert E. Jones, MC

Key Words: Thyrolar, L-thyroxine, metabolism

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: \$1810.00 Sep 88

Study Objective: To evaluate the physiological and biochemical changes that take place during thyroid extract withdrawal in order to better understand the origin of the symptoms of these patients.

Technical Approach: Nonpregnant patients >21 years of age will fill out a symptom questionnaire and have a complete history and physical exam. A blood sample and a resting metabolic rate will be taken after an overnight fast. Patients will then receive an injection of TRH and have blood samples drawn at 30 and 60 min. Each patient will have systolic time intervals measured in a fasting or late postprandial state. Blood samples will be obtained four hours after ingestion of the daily thyroid hormone preparation on a day other than the day the TRH test is done. Patients will then be switched to L-thyroxine for 6 weeks with appropriate dosage modifications. At the end of the 6 weeks, the patients will have all the above tests performed. Patients will then be treated with the thyroid hormone preparation as determined by patient preference in consultation with the primary physician. Baseline data will be compared with the treatment data using Student's t test. The baseline and treatment data will also be compared with established normals or with age, sex, and weight matched control values.

Progress: The technical portion of the study is completed. Currently, the data are being analyzed for the purpose of submitting an abstract to the 1989 American Thyroid Association Annual Meeting. Twelve subjects were entered in the study.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 87/59 Status: On-going

Title: Symptomatic versus Conventional Treatment of Duodenal
Ulcer Disease Using Ranitidine

Start Date: 20 Mar 87 Est Completion Date: Sep 88

Dept/Svc: Medicine/Internal Medicine Facility: MAMC

Principal Investigator: MAJ Amy M. Tsuchida

Associate Investigators: MAJ Marshall E. McCabe, MC

LTC Thomas F. O'Meara, MC CPT Gregory E. Schlepp, MC

LTC Michael H. Walter, MC Gari Sisk, R.N.

Key Words: ulcer, duodenal, healing, recurrence, Ranitidine

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: -0- May 88

Study Objective: To compare healing and recurrence of duodenal ulcers treated with Ranitidine only when symptomatic to those treated with a conventional ulcer treatment regimen of fixed duration.

Technical Approach: Approximately 100 patients, either sex, >18 years with endoscopically confirmed, symptomatic duodenal ulcers will be randomly assigned to receive either Ranitidine 300 mg once daily for four weeks (control group) or 300 mg once daily for a minimum of one week and thereafter only when needed for pain relief (study group). Initial evaluation on entry will include a history profile. Patients will receive a symptom log on which they will record symptoms, adverse reactions, medication consumption, and tobacco, alcohol, and coffee consumption daily. Patients will be contacted by telephone at one and three weeks to assess symptoms and progress. Patients will return to the clinic at two weeks following entry for a pill count to assess compliance. The subjects will be endoscopically evaluated at the end of the four-week period to assess ulcer healing by a physician blinded to the treatment status.

Patients whose ulcers are healed will undergo repeat endoscopy at eight weeks from entry to assess for ulcer recurrence. Patients with unhealed ulcers at four weeks will undergo an additional four weeks of treatment with Ranitidine, 300 mg orally once daily. They will continue to complete daily symptom logs and have a pill count performed at eight weeks. These patients will undergo repeat endoscopy at eight weeks to evaluate ulcer healing.

Ulcer healing will be the primary parameter of comparison between the two groups and will be analyzed using a chi square analysis. Duration of treatment, demographics, symptoms, and adverse reactions will be analyzed and compared using covariant analysis.

Progress: No patients were entered in this study due to the re-assignment of the principal investigator (Jul 87). At the request of Dr. O'Meara, the interim principal investigator, the protocol was placed in a suspended status until a new principal investigator could be obtained. MAJ Tsuchida agreed in August 1988 to take over the study.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 88/34 Status: On-going

Title: Use of Dipentum in Patients with Ulcerative Colitis Who
Are Sensitive to Azulfidine

Start Date: 19 Feb 88 Est Completion Date: Mar 89

Department/Service: Gastrointestinal Facility: MAMC

Principal Investigator: MAJ Amy M. Tsuchida, MC

Associate Investigators: LTC Michael H. Walter, MC

Key Words: colitis, ulcerative, Dipentum, Azulfidine

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: -0- N/A

Study Objective: To ascertain the efficacy of Dipentum in the treatment of active ulcerative colitis in emergency instances in patients for whom sulfasalazine is contraindicated and to ascertain the potential side effects of Dipentum.

Technical Approach: In an open, uncontrolled trial, patients will have a complete physical, the diagnosis and extent of colitis will be determined, and disease severity classified. Baseline hemoglobin, white blood cell count with differential, including inspection of Heinz bodies, reticulocyte count, mean corpuscular volume, prothrombin time, platelet count, glucose-6-phosphodehydrogenase activity, SGOT, SGPT, glucose, alkaline phosphatase, bilirubin, total protein, albumin, globulin, blood urea nitrogen, serum creatinine and sedimentation rate, and chemical and microscopic urinalysis will be determined and repeated on days 14 and 28. Treatment will be conducted on a graduated dose regimen as follows: Days 1-4, 250 mg, Days 5-8, 250 mg twice a day; days 9-12, 250 mg three times a day; and days 13 and thereafter, 250 mg four times a day. After two weeks of treatment, the investigator may discretionally increase or decrease the dose by up to 50% should conditions warrant such a change. At the completion of a 60 day course of Dipentum, the patient will be examined and colitis activity will be classified as remission, mild, or severe. Patients whose disease state has improved, those whose disease is slightly improved and the physician feels will continue to improve with further therapy, and those who by virtue of Dipentum treatment have been able to reduce the dose of steroids and/or other drugs for ulcerative colitis, will be continued on Dipentum treatment. Patients will return at two weeks after the completion of treatment for a physical examination and a repeat of the laboratory work to determine progress of disease and the presence of any side effects. Patients who continue on Dipentum beyond the 60 days will be examined at bi-monthly intervals. During each office or telephone interview, possible side effects will be elicited. A series of signs and symptoms will be evaluated to include date of onset, cessation, management, and follow-up.

Progress: One patient has been entered in this study on a compassionate use basis.

Detail Summary Sheet

Date: 30 Sep 88	Protocol No.: 87/65	Status: On-going
Title: A Comparison of 7 vs 14 Days Therapy with Trimethoprim/ Sulfamethoxazole in the Treatment of Acute Pyelonephritis		
Start Date: 17 Apr 87	Est Completion Date: May 89	
Dept/Svc: Medicine/Infectious Disease	Facility: MAMC	
Principal Investigator: CPT Paula S. Vogel, MC		
Associate Investigators: LTC Rodney A. Michael, MC		
CPT Patrick D. Gorman, MC		
CPT William A. Pearce, MC		
Key Words: pyelonephritis, trimethoprim-sulfamethoxazole, days		
Accumulative MEDCASE	Est Accumulative	Periodic Review:
Cost: -0-	OMA Cost: -0-	Aug 88

Study Objective: To compare 7 vs 14 days of TMP/SMX treatment in acute pyelonephritis and also to compare the results to those of a previous study of 14 days of TMP/SMX plus gentamicin.

Technical Approach: All patients will initially receive intravenous TMP/SMX every 12 hours for at least six doses and until afebrile. Thereafter, patients will receive oral TMP/SMX twice daily and will continue oral therapy as outpatients. Group A will receive 14 days of therapy and Group B will receive 7 days of therapy. All subjects will have a physical exam and a symptom assessment before the institution of therapy and daily while in the hospital. Urine samples will be obtained before therapy and daily thereafter during the hospital stay. Quantitative aerobic bacterial cultures will be performed on all specimens. Antibody coated bacteria testing will be performed on all initial specimens which grow $\geq 10^3$ cfu/ml of a recognized uropathogen. A dipstick urinalysis will be done on all urine specimens. Vaginal cultures and blood specimens will be obtained upon admission and again on the third day. Patients will return to clinic at one and four weeks following completion of therapy. At each follow-up visit, patients will undergo symptom assessment and a physical exam and urine specimens, cultures of the vagina, and blood samples will be collected. At the one week visit patients will be questioned regarding self-administration of medications and will return the dosing calendar which they were given at discharge. At two weeks following the end of therapy, patients will return to provide a clean-catch midstream urine specimen for culture and urinalysis. Appropriate statistical techniques will be used to compare the baseline characteristics of the patient population and to analyze the adverse effects and clinical laboratory data. Categorical data analysis of the efficacy data will be performed as warranted.

Progress: CPT Patrick Gorman, the original principal investigator, was reassigned in July 1988 and CPT Vogel was approved as the principal investigator for this protocol.

During FY 88, 24 patients were enrolled without complications or untoward reactions.

DETAIL SHEETS
FOR
PROTOCOLS

DEPARTMENT OF NURSING

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 87/75 Status: Completed

Title: Patient Classification in the Emergency Department

Start Date: 15 May 87 Est Completion Date: Jul 87

Department: Emergency Medicine Facility: MAMC

Principal Investigator: 1LT Patrick J. Bennett, ANC

Associate Investigators: None

Key Words: tool, analysis, staffing requirements, validity

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: -0- Sep 88

Study Objective: To assess the cross institutional validity of an emergency department patient classification tool in differentiating between groups of patients by quantity of nursing care consumed.

Technical Approach: Categorization of the amount of nursing care required will be done using a four category scheme that differentiates between groups of patients based on assessment of admission, status of care provider, complexity of care, amount of nursing contact with patient and significant others, patient's physical and psychological status, and priority for care. Consistency of ratings will be assured by having only the principal investigator performing categorizations. Direct nursing care will be defined as nursing functions that involve immediate contact by nurse or medic with patients or significant others. This ranges from data collection and counseling to interventions to simple observation within five feet of patient. The times for direct nursing care will be recorded on a flow sheet that also provides for specification of status of the nursing care provider, medical diagnosis, and total length of stay of patient. Other factors to be evaluated include correlation of estimation of nursing care consumption by primary RN coordinating care to category classification (this will assess the validity of patient classification by nursing estimation as compared with observed direct times). Also evaluated will be the relationship between primary nurses' backgrounds and quantity of total direct care time as well as proportion of RN care times to paraprofessional care times. Medical diagnosis, length of stay, category of care, and nursing backgrounds will also be examined to determine their respective effects on intensity of direct nursing care services.

Progress: The Patient Classification Tool for the Department of Emergency Medicine was developed and tested in a clinical trial, utilizing 45 subjects. Direct nursing care was recorded by minutes and compared to the levels of care, as determined using the tool. Differences between categories of care were significant. This protocol was performed as one of the requirements's for a Master's Degree in Nursing and the principal investigator is in the process of completing his thesis.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 87/78 Status: Completed

Title: The Glasgow Coma Scale: Observer Variability and
Correctness of Scores Obtained with Its Use

Start Date: 15 May 87 Est Completion Date: Jul 87

Department: Nursing Facility: MAMC

Principal Investigator: CPT Luisa M. Janosik, AN

Associate Investigators: Sharon Fought, R.M., M.S.M., Ph.D.
University of Washington

Key Words: Glasgow Coma Scale, scores, variability

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: -0- N/A

Study Objective: To determine interrater reliability of the Glasgow Coma Scale when used by various levels of health care professionals to score a patient examination on videotape.

Technical Approach: Approximately 40 staff members, both nursing and medical, from areas of the hospital which provide care for head-injured patients and use the Glasgow Coma Scale as a standard method of assessing level of consciousness will be studied. Data collection will take place on wards and medical departments on a rotating schedule. Data collection will coincide with two of three shift changes in a 24-hour period on two consecutive days. Each subject will be asked to complete a demographic questionnaire. A videotape of examination of Patient A according to Glasgow Coma Scale criteria will then be shown. Concurrently, subjects will complete Glasgow Coma Scale A. The instructional videotape will then be shown. This tape is approximately 5-8 minutes in length and will demonstrate the correct method of using the Glasgow Coma Scale. Subjects will then view the examination tape of Patient B while completing the corresponding Glasgow Coma Scale form. After data collection has been completed, feedback will be provided to interested units. Data will be analyzed descriptively and statistically. Statistical measurements anticipated for assessment of interrater reliability will include percentage agreement, percentage disagreement, Cohen's kappa, phi, and T-tests.

Progress: Data collection and analysis has been completed. The principal investigator is in the process of writing a thesis as one of the requirements of Master's Degree in Nursing.

Detail Summary Sheet

Date: 30 Sep 88	Protocol No.: 88/51	Status: On-going
Title: Positioning of Premature Infants in Car Seats and Effects on Ventilation		
Start Date: 15 Apr 88	Est Completion Date: Dec 88	
Department: Pediatrics	Facility: MAMC	
Principal Investigator: 1LT Pamela S. Smith, AN		
Associate Investigators: MAJ Jose Garcia, MC 2LT Alice Hofer, AN		
Key Words: BP, pulse, respiration, oxygen saturation, 3 angles		
Accumulative MEDCASE	Est Accumulative	Periodic Review:
Cost: -0-	OMA Cost: \$15.00	N/A

Study Objective: To test the hypothesis that premature infants weighing less than 3 kg are at risk for ventilatory compromise while restrained in infant car seats.

Technical Approach: Approximately 15 infants born before 36 weeks gestation will be studied. Information will be recorded from a routine heelstick spun hematocrit done within 48 hours prior to the data collection. Theophylline levels will be recorded from routine samples on those infants who are on theophylline. A complete nursing assessment will be performed to include temperature, pulse, respiration, BP, height, weight, and chest circumference. The study will begin 30 minutes after the infants have been fed. The infants will have been prefitted for the car seat to prevent excessive handling during the testing phase. The test period will comprise 90 minutes: 30 minutes to collect baseline data, 30 minutes in the car seat, and 30 minutes for recovery. Each infant will be tested at the same hour on three consecutive days, utilizing a different angle of inclination each day (95, 110, 140'). Baseline and recovery data will be collected with the infants in prone position. Data to be collected include pulse, respiration, blood pressure, oxygen saturation, color, activity status, position, and nursing interventions required for apnea or bradycardia episodes. During the testing phase infants will be placed in a car seat, with attention given to maintaining proper position for a patent airway. The child will be placed in the car seat under an Ohio Neonatal Warmer with temperature probe attached. A cardiorespiratory monitor will be attached to the child. and an oximeter probe will be attached to a hand or a foot to monitor oxygen saturation. A polaroid photo will be taken to ensure that the infants are positioned in the same fashion each day. Data throughout the three test phases will be collected in two minute intervals, using a stopwatch for accurate timing. Two investigators will be recording data during the testing in order to verify accuracy. The Freidman test will be used for data analysis.

Progress: Nine infants have been studied. Some of the infants have demonstrated periods of respiratory distress and hypoxia but were able to compensate through various methods.

D E T A I L S H E E T S
F O R
P R O T O C O L S

DEPARTMENT OF OB/GYN

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 87/03 Status: On-going
Title: Prophylactic Tocolysis of Twins
Start Date: 17 Oct 86 Est Completion Date: Dec 88
Department: OB/GYN Facility: MAMC
Principal Investigator: MAJ William K. Brady, MC
Associate Investigator: COL John A. Read, MC
Key Words: twins, tocolysis, prophylactic, terbutaline, bed rest
Accumulative MEDCASE Est Accumulative Periodic Review:
Cost: -0- OMA Cost: \$952.00 Sep 88

Study Objective: To determine if an orally administered tocolytic agent and modified bed rest regimen in patients with twin gestation is superior to bed rest alone as a method for the prevention of preterm labor/delivery, and to determine if an orally administered prophylactic tocolytic agent significantly reduces the incidence of intrauterine growth retardation (IUGR)/discordant growth in twin gestation.

Technical Approach: One hundred patients with known twin gestation at 20-26 weeks gestation confirmed by ultrasound will be entered in a randomized double blind study. All patients will be advised to stop working, abstain from intercourse, and institute maximum bed rest at home (a minimum of 8 hours of bed rest during the day in addition to the normal hours of sleep). All patients will undergo the following baseline laboratory studies: EKG, glycosylated hemoglobin, one hour glucose challenge test, endocervical/vaginal cultures for Group B streptococci, *Chlamydia trachomatis* and *N. gonorrhea* organisms. The one hour glucose and hemoglobin values will be repeated at 32 weeks gestation. All patients will be seen weekly after 20 weeks and a pelvic examination for cervical changes and Bishop's score will be performed. All endocervical cultures will be repeated if weekly external tocometer tracing demonstrates evidence of increased uterine activity compared to the previous week's uterine activity. At delivery, placentas will be weighed and maternal and umbilical artery glycosylated hemoglobin values will be obtained. Study patients will receive terbutaline, 5.0 gm orally every 4 hours while awake (0600-2200 hrs), from the time of entry into the study until 37 weeks gestation. The control group of patients will receive a placebo and will undergo the same laboratory and clinical testing. Chi-square/ Fisher Test and T-test will be used to analyze the data.

Progress: An additional 16 patients were entered in FY 88 for a total of 30 patients entered.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 87/04 Status: Completed

Title: Evaluation of the Latex Fixation Test in Detection of the Group B Streptococcus in the Lower Genital Tract of Women in Labor

Start Date: 17 Oct 86 Est Completion Date: May 87

Department: OB/GYN Facility: MAMC

Principal Investigator: MAJ William K. Brady, MC

Associate Investigators: COL Patrick Duff, MC

Key Words: Latex Fixation Test, Group B Streptococci, women, labor, lower genital tract

Accumulative MEDCASE Est Accumulative Periodic Review:
Cost: -0- OMA Cost: \$900.00 Sep 88

Study Objective: To determine if the Group B streptococci latex fixation test is sufficiently sensitive to identify streptococcal colonization of the lower genital tract in obstetric patients.

Technical Approach: Three hundred women at term who present in labor with intact membranes will undergo sterile speculum examination with duplicate sterile swabs taken from the endocervix and vagina during the admission assessment. One swab will be inoculated immediately onto a blood agar plate for culture. The duplicate swab will be run with the Wellcogen Strep B Latex Fixation Test. Neonates will be evaluated for the first month of life.

Results of the Group B Streptococcus Latex Fixation Test will be compared to the subsequent culture results to determine the reliability of the Group B Streptococcus Latex Fixation Test.

Results of the latex fixation test will be evaluated with respect to sensitivity, specificity, predictive value, and efficiency.

Progress: Approximately 500 patients were entered in this study. A paper was presentation at the Annual Meeting of Infectious Disease Society for Obstetrics and Gynecology in August 1988. A manuscript has been accepted for publication in Obstetrics and Gynecology.

The group B streptococci latex fixation test appears to be a rapid and reliable means of detecting group B streptococci in the lower genital tract of term patients with intact membranes. Use of this method should permit a more selective approach to the intrapartum chemoprophylaxis of women colonized with group B streptococci.

Detail Summary Sheet

Date: 30 Sep 88	Protocol No.: 87/05	Status: On-going
Title: Plasma Fibronectin Concentrations in Obstetric Patients		
Start Date: 17 Oct 86	Est Completion Date: May 87	
Department: OB/GYN	Facility: MAMC	
Principal Investigator: MAJ William K. Brady, MC		
Associate Investigator: COL Patrick Duff, MC		
Key Words: plasma fibronectin, term, uncomplicated, chorioamnionitis, unscheduled cesarean delivery		
Accumulative MEDCASE	Est Accumulative	Periodic Review:
Cost: -0-	OMA Cost: \$520.00	Sep 88

Study Objective: To measure the plasma fibronectin concentration in uncomplicated term patients, term patients with chorioamnionitis, and term patients undergoing unscheduled cesarean delivery.

Technical Approach: In the first phase of the investigation, 25 normal patients will have a blood sample drawn early in labor and again just prior to delivery to determine if the fibronectin concentration changes during labor.

In the second phase, blood samples will be obtained on 25 term women with chorioamnionitis at the time the diagnosis is established to determine what happens to the serum fibronectin concentration in response to intrauterine infection. Fibronectin concentrations in infected patients will be compared to those in uninfected parturients.

In phase 3, plasma samples will be obtained from 100 women prior to cesarean delivery. Fibronectin concentrations in women who remain uninfected will be compared to those who develop post-cesarean endomyometritis.

Plasma fibronectin concentrations will be determined by a turbidimetric immunoassay. Differences in mean plasma fibronectin concentrations will be evaluated by means of the paired and unpaired t test.

Progress: Fifteen additional patients were entered in FY 88 for a total of 45 patients entered. The assays have been completed and the data are being compiled.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 87/69 Status: On-going

Title: Low-Dose Aspirin in the Prevention of Pregnancy-Induced Hypertension and Pre-eclampsia in Primigravida Women.

Start Date: 17 Apr 87 Est Completion Date: Apr 89

Department: OB/GYN Facility: MAMC

Principal Investigator: MAJ William Kim Brady, MC

Associate Investigators: COL William L. Benson, MC

COL Patrick Duff, MC

COL John A. Read, MC

MAJ Jose Garcia, MC

MAJ Charles J. Hannan, MS

MAJ Frederick E. Harlass, MC

Key Words: pre-eclampsia, hypertension, prevention, low-dose aspirin, primigravida women

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: \$5952.00 Jan 88

Study Objective: To investigate the effect of low-dose aspirin taken daily from 22 weeks gestation until delivery, on the development of pregnancy-induced hypertension and pre-eclampsia in normotensive primigravida women.

Technical Approach: Healthy primigravida women will be enrolled in the study at 22 weeks gestation. Pre-entry evaluations will include CBC, platelet count, PT/PTT, and ultrasound to confirm dates. Patients will be randomized to either 81 mg of aspirin per day or a placebo in a double blind fashion to be taken until delivery. There will be approximately 300 women in each group. Patients will receive standard antenatal care with visits every 2 weeks until 36 weeks and weekly visits thereafter. Index of aspirin ingestion will be determined by measuring malondialdehyde levels at 28 weeks and again when the patient presents for delivery. Levels of thromboxane B₂ and 6-keto-prostaglandin F1 alpha will be measured via 24 hr urine collections performed at 28 and 36 weeks gestation. The thromboxane B₂ and 6-keto-prostaglandin F1 alpha urine specimens will be collected and 50 samples from each group of patients will be randomly selected and respective radioimmunoassays will be performed. The thromboxane A₂/prostacyclin balance between the two groups will be compared. Malondialdehyde assays will be run on all samples. Mode of delivery, neonate apgar scores, and routine neonatal laboratory tests will also be compared. Serial ultrasounds with biometric measurements will be performed at 28 and 34-36 weeks to assess fetal growth. Serial umbilical artery doppler FVW studies will be done at entry into the study, at 2 weeks, and again when scheduled ultrasounds are done. This information will be compared to the respective patient's thromboxane/prostacyclin data and clinical outcome.

Progress: The protocol was amended in January 1988 to add the serial ultrasound and umbilical artery doppler FVW studies. No patients have been entered. The investigators are awaiting the arrival of the doppler ultrasound equipment to begin the study.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 85/20 Status: Suspended

Title: Microsurgical Technique

Start Date: 16 Jan 85 Estimated Completion Date: Indefinite

Department: OB/GYN Facility: MAMC

Principal Investigator: MAJ John W. Cassels, MC

Associate Investigators: COL Richard P. Belts, MC

LTC I. Keith Stone, MC

MAJ Leslie W. Yarbrough, VC

Key Words: Residents, proficiency, reproductive tracts, rabbits

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: \$400.00 Sep 88

Study Objective: To develop proficiency with instrument and suture handling when using the operating microscope.

Technical Approach: Residents in the Department of Obstetrics and Gynecology who are rotating through the Infertility Service will be obligated to demonstrate proficiency with microsurgical dissection and reanastomosis of rabbit reproductive tracts. Rabbits will be anesthetized with ketamine and midline laparotomies will be performed. Using the organic operating microscope, dissection and proper realignment of reproductive structures will be accomplished under staff supervision. Sutures and instruments will duplicate those used in the reanastomosis of human oviducts. The rabbits will be recovered from surgery and will at approximately four weeks postoperatively undergo laparotomy excision of the oviducts for histologic examination and methylene blue instillation to determine patency. The animal model will then be terminated.

Progress: Four sessions were conducted in early 1988. No further sessions have been conducted because of personnel turnover.

Dr. Stone, the original principal investigator, PCS'd in August 1988 and Dr. John Cassels took over this protocol as the principal investigator. The protocol will be rewritten to bring it more in line with current format and standards before more procedures are performed.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 88/43 Status: Completed

Title: Visualization and Inspection of the Appendix on Routine Laparoscopy

Start Date: 18 Mar 88 Est Completion Date: Apr 88

Department: OB/GYN Facility: MAMC

Principal Investigator: CPT Jeffrey Christian, MC

Associate Investigators: LTC David Magelssen, MC

Key Words: appendix, visualization, frequency, chart review

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: -0- N/A

Study Objective: To document the frequency with which the appendix is adequately visualized during routine laparoscopy.

Technical Approach: Charts will be reviewed on all patients who undergo laparoscopy at MAMC during the period of 1 February through 30 April 1988. Data collection will include age, race, gravidity and parity, height, weight, prior surgical history, indication for laparoscopy, surgical findings, and whether or not the appendix was visualized and its appearance, if so. In addition, charts for a one year period (July 1986 to June 1987) will be reviewed retrospectively with the same information collected.

Progress: This protocol has been completed and a paper has been accepted for presentation at the Armed Forces District of the American College of OB/GYN in November 1988.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 86/40 Status: On-going

Title: Infection Prevention in Patients Undergoing Radical
Hysterectomy

Start Date: Feb 86 Est Completion Date: Feb 88

Department: OB/GYN Facility: MAMC

Principal Investigator: LTC Gordon O. Downey, MC

Associate Investigators: COL William Benson, MC

COL Roger B. Lee, MC

Key Words: hysterectomy, infection, cefamandole

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: -0- Sep 88

Study Objective: To determine the effectiveness of antibiotics (cefamandole) in preventing infectious morbidity of radical abdominal hysterectomy.

Technical Approach: Approximately 120 patients with gynecologic cancer undergoing radical hysterectomy with bilateral pelvic lymphadenectomy, without active infection or allergy to the study antibiotic will be eligible. Patients will be randomly assigned to receive 2 g cefamandole in 100 cc D5W IV or I.V. placebo (D5W) in the induction room and at two hours from time of skin incision.

Preoperative evaluation will include chest radiograph, CBC, serum electrolytes, serum hepatorenal profile, and urinalysis. CBC, urinalysis, serum electrolytes, and hepatorenal profile will be obtained on postoperative days 2 and 4 and at any other times indicated.

Infection rate, surgical site infections, and febrile morbidity by the fever index among the two groups will be compared.

Progress: LTC Gordon Downey was named the principal investigator on this protocol in August 1988 upon Dr. Lee's retirement.

Two additional patients were entered in the study in FY 88 for a total of four entries.

Detail Summary Sheet

Date: 30 Sep 88	Protocol No.: 87/61	Status: On-going
Title: A Phase III Trial of Intraperitoneal Interferon vs Intraperitoneal Cis-platinum for Minimal Residual Ovarian Carcinoma Following Systemic Chemotherapy (Schering C86-504)		
Start Date: 20 Mar 87	Est Completion Date: Indefinite	
Department: OB/GYN	Facility: MAMC	
Principal Investigator: LTC Gordon O. Downey, MC		
Associate Investigators: COL William L. Benson, MC COL Roger B. Lee, MC		
Key Words: ovarian carcinoma, prior chemotherapy, interferon, cis-platinum, intraperitoneal, efficacy, toxicity		
Accumulative MEDCASE	Est Accumulative	Periodic Review:
Cost: -0-	OMA Cost: -0-	N/A

Study Objective: To confirm the response rate seen with i.p. Intron in minimal residual ovarian carcinoma; to compare the efficacy of i.p. platinum versus i.p. Intron in inducing responses in this group of patients; and to compare toxicities of the different treatment arms.

Technical Approach: This is a randomized, multi-institutional, phase III clinical trial for patients with ovarian carcinoma with approximately 40 patients entered in each arm. Prior to randomization, patients shall have had maximal surgical debulking followed by 4-12 cycles of conventional chemotherapy utilizing cis-platinum, and second-look operation. Patients with minimal residual disease and positive cytology will be eligible. Patients will be entered in the study no later than two weeks following second-look operation, and a Tenckhoff or Port-A Cath or similar catheter will be placed surgically as soon as possible following randomization. Treatment with intraperitoneal therapy will begin no later than one month following second-look surgery. Patients will be randomized to receive Intron or platinum and all patients will be treated with 12 weeks of therapy. The patients will undergo an exploratory laparotomy at the conclusion of the final therapy unless there is gross measurable disease by physical examination, CT scan, or ultrasound exam which obviates the need for laparotomy. An assessment of disease status will be done at selected points of patient follow-up. Patients will be evaluable for efficacy after receiving one month of therapy. All patients entered will be evaluable for toxicity.

Progress: No patients have been entered in this study.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 86/66 Status: Completed

Title: A Comparison of Cefazolin Versus Cefotetan as Single-Dose Prophylaxis for Prevention of Postcesarean Endometritis

Start Date: Sep 86 Est Completion Date: Indefinite

Department: OB/GYN Facility: MAMC

Principal Investigator: COL Patrick Duff, MC

Associate Investigators: COL John A. Read, MC

MAJ Andrew Robertson, MC

Key Words: endometritis, postcesarean, prophylaxis, cefazolin cefotetan, single-dose

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: \$1000.00 Dec 87

Study Objective: To evaluate the efficacy of two single-dose antibiotic regimens as prophylaxis for prevention of postcesarean endomyometritis.

Technical Approach: Utilizing a double blind format, 200 patients having cesarean delivery will be studied. Patients who already are infected at the time of surgery or who are allergic to either of the study drugs will be excluded from the investigation. Upon entry into the study, patients will be randomized to receive either cefotetan (2 gm) or cefazolin (2 gm). The drugs will be administered intravenously after delivery of the fetus.

Postoperatively, patients will be evaluated for evidence of infection-related morbidity. Measures of morbidity will include standard febrile morbidity, fever index, endometritis, UTI, wound infection, development of serious sequelae of primary infection (bacteremia, septic shock, pelvic abscess, septic pelvic thrombophlebitis), and duration of hospitalization.

Patients also will be evaluated in the outpatient clinic six weeks after surgery to determine if late sequelae of infection have developed. Differences in treatment effect will be evaluated by means of the the chi-square test (discrete data) and independent sample t-test (continuous data).

Progress: This protocol was shown as completed in the Annual Research Progress Report for FY 87. On continuing review, the reviewer checked the completed box on the form by mistake. The protocol was reinstated and in March 1988 was amended to allow the principal investigator to study 200 more patients.

Approximately 600 patients were studied. This is the largest study comparing a limited-spectrum to an extended-spectrum antibiotic for prophylaxis that has been reported in the literature. Data analysis is complete and a manuscript is being prepared for submission for publication.

Detail Summary Sheet

Date: 30 Sep 88	Protocol No.: 87/49	Status: On-going
Title: A Comparison of Cefazolin Versus Cefotetan as Single Dose Prophylaxis in Vaginal Hysterectomy		
Start Date: 27 Feb 87	Est Completion Date: Apr 88	
Dept/Svc: OB/GYN	Facility: MAMC	
Principal Investigator: COL Patrick Duff, MC		
Associate Investigators: LTC Keith Stone, MC CPT Timothy J. Boley, MC		
Key Words: hysterectomy, cefazolin, cefotetan, prophylaxis		
Accumulative MEDCASE	Est Accumulative	Periodic Review:
Cost: -0-	OMA Cost: \$600.00	Sep 88

Study Objective: To evaluate the efficacy of a single dose of two cephalosporins as prophylaxis for vaginal hysterectomy.

Technical Approach: This will be a randomized double blind study with 100 patients included in each arm. Study patients will be given either cefotetan or cefazolin intravenously immediately prior to the vaginal incision. Preoperative evaluation will include CBC and urine culture. Each patient will undergo the standard vaginal preparation with povidone-iodine prior to surgery. Postoperatively, patients will be evaluated for evidence of febrile morbidity, pelvic cellulitis, urinary tract infection, bacteremia, septic shock, and pelvic abscess. Other parameters to be considered include duration of hospitalization and fever index. Patients will also be evaluated two to four weeks postoperatively. Differences in treatment effect will be evaluated by means of the chi-square test (discrete data) and independent sample t-test (continuous data).

Progress: Eighty-eight patients were entered in this study in FY 88 for a total of 137 entries.

COL Patrick Duff assumed the role of principal investigator for this protocol upon the departure of Dr. Boley in July 1988.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 87/115 Status: On-going

Title: Treatment of Bacterial Vaginosis in Pregnancy

Start Date: 18 Sep 87 Est Completion Date: Oct 88
Department: OB/GYN Facility: MAMC
Principal Investigator: COL Patrick Duff, MC
Associate Investigators: David A. Eschenbach, Univ Washington
Key Words: vaginosis, bacterial, pregnancy, treatment
Accumulative MEDCASE Est Accumulative Periodic Review:
Cost: -0- OMA Cost: -0- Aug 88

Study Objective: To determine if treatment of bacterial vaginosis during pregnancy will decrease the incidence of preterm delivery and/or the incidence of postpartum infection.

Technical Approach: Women with bacterial vaginosis will be identified by screening Gram stains of vaginal discharge. Subjects will be entered between the 15th and 25th weeks. Once the woman consents, a second Gram stain will be done and a vaginal swab taken for isolation of group B streptococci, *Ureaplasma urealyticum*, *Mycoplasma hominis*, *Lactobacillus sp*, and *Gardnerella vaginalis*. Subjects will then be randomized to either amoxicillin or placebo in a double-blind fashion. Subjects will take the drug or placebo orally three times per day for 14 days. Subjects will complete a questionnaire on demographic, lifestyle, and pregnancy history questions. At one month from the beginning of treatment, subjects will have a repeat Gram stain and will be asked to obtain a self-administered Gram stain if they develop signs and symptoms of bacterial vaginosis before presentation for delivery. At the time of delivery, the subjects will have a repeat Gram stain and a summary of labor and delivery will be abstracted from their charts to a standardized data form. At one month postpartum, the subjects will complete a questionnaire concerning medication compliance and side effects, and at six weeks postpartum they will be telephoned to obtain information on symptoms of postpartum endometritis and the recurrence of bacterial vaginosis. The major comparisons of interest will be the rates of prematurity, premature rupture of membranes, and postpartum endometritis among women treated with amoxicillin compared to women who received placebo. Analysis will be done by multivariate logistic regression to allow for adjustments for multiple potential confounding factors.

Progress: After studying approximately 100 patients, there was no statistically significant difference between the response of patients who received amoxicillin and those who received placebo, with approximately 50-55% of the patients in each group experience resolution of their infection.

This protocol was revised in August 1988 to compare topical 2% clindamycin cream with a placebo. Patients are now being enrolled in this revised protocol.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 88/35 Status: On-going
Title: Comparison of Endometrial Biopsy Specimens Using a Plastic
Curette (Pipelle) versus a metal Curette (Novak)
Start Date: 15 Mar 88 Est Completion Date: Aug 88
Department: OB/GYN Facility: MAMC
Principal Investigator: CPT Katherine S. Foley, MC
Associate Investigators: COL William L. Benson, MC
COL James L. Kelley, MC
CPT Mark Brissette, MC
CPT Neil W. Rawlins, MC
Key Words: hysterectomy, fragmentation, adequacy, accuracy
Accumulative MEDCASE Est Accumulative Periodic Review:
Cost: -0- OMA Cost: -0- N/A

Study Objective: To compare the reliability of Pipelle curettes and Novak curettes when used to perform endometrial biopsies.

Technical Approach: Sixty gynecological patients scheduled for vaginal or abdominal hysterectomy will be randomly assigned to have a biopsy with either the Pipelle or the Novak curette. The biopsies will be performed in the operating room after the administration of anesthesia. Specimens will be processed in the usual fashion. Specimens from the hysterectomy will be used as controls. An OB/GYN staff member and two pathologists will grade the specimens from the biopsies and the hysterectomy without the knowledge of the biopsy instrument used.

Student's t test will be used to analyze the weight and degree of fragmentation. Chi square analysis will be used to determine the diagnostic accuracy and adequacy of the specimen.

Progress: Eight patients have been entered in this study.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 88/28 Status: On-going

Title: The Urethral Cytology of Patients with Urethral Syndrome

Start Date: 19 Feb 88 Est Completion Date: May 88
Department: OB/GYN Facility: MAMC
Principal Investigator: LTC David J. Magelssen, MC
Associate Investigator: CPT Kevin P. Sargeant, MC
Key Words: urethral syndrome, present/absent, cytology
Accumulative MEDCASE Est Accumulative Periodic Review:
Cost: -0- OMA Cost: \$30.00 N/A

Study Objective: To determine if demonstrable differences in urethral cytology exist between gynecologic patients with the urethral syndrome and those without it.

Technical Approach: The study population will consist of 25 to 30 women being followed in the urogynecologic clinic. Patients having symptoms referable to the urinary tract (frequency, urgency, dysuria, dyspareunia, low back pain, chronic pelvic pain) and sterile urine cultures will be eligible. They will be divided into two groups: patients with urinary tract symptoms and sterile urine cultures and patients seen in the clinic but not having symptoms referable to the urinary tract. A wool-tipped Calgi swab will be dipped in normal saline and then introduced into the urethra and used to swab the urethral tract. The swab will then be placed in Saccomanno's fixative and transported to Cytology for examination. The results will be collected from the lab, divided into normal cytology versus any unusual or abnormal features and evaluated for statistical significance using the chi-square test.

Progress: CPT Kevin Sargeant was the original principal investigator for this protocol. LTC Magelssen assumed the role of principal investigator upon the reassignment of CPT Sargeant in July 1988.

Twenty-two patients have been entered in the study. Cytologic findings have been reviewed of patients' urethras who have urethral syndrome symptomatology. Preliminary data is inconclusive as to whether these patients have evidence of inflammatory urothelium when compared to controls. The study is on-going but has temporarily been placed on hold due to inadequate cytologic technician support.

Detail Summary Sheet

Date: 30 Sep 88	Protocol No.: 83/02	Status: Terminated
Title: Randomized Trial of Ambulation vs Oxytocin for Labor Enhancement		
Start Date: 15 Oct 82	Est Completion Date: Oct 86	
Department: OB/GYN	Facility: MAMC	
Principal Investigator: COL John A. Read, MC		
Associate Investigators: COL Edward E. Dashow, MC LTC Frederick H. Coleman, MC		
Key Words: ambulation, oxytocin, labor enhancement		
Accumulative MEDCASE	Est Accumulative	Periodic Review:
Cost: -0-	OMA Cost: -0-	Dec 87

Study Objective: To compare the efficacy of ambulation vs oxytocin in cases of dysfunctional labor or so called dystocia.

Technical Approach: Patients who have failed to progress in labor for one hour, ≥ 4 cm dilated, and requiring augmentation of labor will be studied. Membranes shall have been ruptured and direct internal fetal monitoring in use, showing no evidence of fetal distress. Patients should not have received analgesia or sedations for at least one hour and should not be drowsy or exhausted. Patients will be placed on the fetal monitor in the right or left lateral decubitus position. There will be a 30 minute observation period during which time uterine activity will be quantified: uterine activity units on line, Montevideo units; contraction frequency; intensity and baseline tonus; fetal heart rate pattern and variability; and progress in effacement, dilation, and station.

Group I: Using either a cable or 2-channel telemetry the patient will assume the vertical position. Exams will be conducted at one and two hours, noting the parameters stated above. If after 2 hours no progress has occurred, the patient will be returned to bed and oxytocin utilized. If good progress is being accomplished, the patient may continue ambulation if she chooses.

Group II: Continuous IV infusion of oxytocin will begin at 0.5 mU/min and increased every 15 min until contractions are every 2 1/2-3 min and >50 mmHg in intensity. Patient will be in the right or left lateral decubitus position and the parameters noted above will be measured. If at the end of two hours there is no progress and other conditions are met, the patient will be given the option to ambulate.

Length of labor, time from study entry to delivery, type delivery, 1 and 5 min Apgar scores, cord blood gases, maternal pain perception, newborn weight and neonatal problems will also be noted.

Progress: No patients were entered on this protocol due to time and equipment constraints. Upon continuing review in December 1987, the principal investigator made the decision to terminate the protocol since it appeared that no work could be done on the study in the foreseeable future.

Detail Summary Sheet

Date: 30 Sep 88	Protocol No.: 87/73	Status: On-going
Title: Effect of Continuous versus 13 Day Provera Supplementation to Premarin Treatment on Serum Lipids in Postmenopausal Women		
Start Date: 15 Apr 87	Est Completion Date: Sep 88	
Dept/Svc: OB/GYN	Facility: MAMC	
Principal Investigator: CPT Michael Yancey, MC		
Associate Investigators: LTC Keith Stone, MC		
MAJ Charles Hannan, MS		
CPT Karl Friedl, MS		
Thomas Kettler, B.S., DAC		
Key Words: postmenopausal, lipids, provera, premarin		
Accumulative MEDCASE	Est Accumulative	Periodic Review
Cost: -0-	OMA Cost: \$8670.00	N/A

Study Objective: To determine if there are any significant differences in the effect of continuous progestogen treatment compared to a standard regimen of intermittent progestogen treatment in postmenopausal women receiving estrogen therapy.

Technical Approach: Sixty non-smoking, postmenopausal women will be entered into 3 groups, all of which will receive conjugated estrogens plus either 13 day Provera treatment at 10 mg qd, continuous Provera at 5 mg qd, or continuous Provera at 10 mg qd. Fasted blood samples will be drawn one week apart, prior to the initiation of treatment and again on days 13 and 26 of each treatment cycle in the 1st, 3rd, and 6th months. Post-heparin lipase activities will also be measured in blood samples obtained 10 min after infusion of 30 IU heparin/kg body weight. If significant decreases in HDLC exceeding a 25% change are detected in the first 10 women in any group after the first 3 months of treatment, the study will be terminated at that point. Serum lipid analysis will include total cholesterol, triglyceride, HDL-cholesterol, and HDL2-cholesterol and enzymatic methods, and apolipoprotein A-I and A-II will be measured by RIA kits. Hepatic triglyceride lipase and lipoprotein lipase activities will be measured by hydrolysis of 3H-triolein and differentiated by protamine sulfate inhibition. Provera will be measured by an in-house assay which uses antibody and labeled 6a-methyl-17a-hydroxyprogesterone acetate. SHBG will be measured by SHBG DHT-binding assay. Estrogens and insulin may also be measured by specific RIAs after review of the results from other assays. Individual variables will be initially tested in 3-way analysis of variance and significant differences will then be pinpointed with a multiple range test. Univariate correlations will be examined for SHBG and HDLC, serum Provera and each of the lipid variables. Covariates including age, body weight, adiposity, and former smoking, drinking, and exercise histories may also be considered.

Progress: Sixty-one subjects were enrolled. Subject enrollment is complete and data analysis is in progress.

Detail Summary Sheet

Date: 30 Sep 88	Protocol No.: 88/24	Status: On-going
Title: Randomized Trial of Spontaneous Vaginal Versus Outlet Forceps Delivery in Term Pregnancies		
Start Date: 15 Jan 88	Est Completion Date: Jun 88	
Department: OB/GYN	Facility: MAMC	
Principal Investigator: CPT Michael K. Yancey, MC		
Associate Investigators: COL William L. Benson, MC		
MAJ Jose Garcia, MC		
MAJ Frederick Harlass, MC		
Key Words: maternal/neonatal morbidity, spontaneous/forceps delivery, cranial ultrasound, cord gases		
Accumulative MEDCASE	Est Accumulative	Periodic Review:
Cost: -0-	OMA Cost: \$480.00	N/A

Study Objective: To compare two methods of vaginal delivery in a prospective randomized fashion in order to determine if there is any increase in maternal or neonatal morbidity with either method relative to the other.

Technical Approach: Patients with a term gestation (37-42 weeks), who have had an uncomplicated course of labor and no evidence of fetal distress, will be studied. Data collection will include duration of second stage of labor, infant birth weight, Apgar scores, cord gases, the presence of maternal or fetal birth trauma, estimates of blood loss, and pre and postdelivery hematocrits. Evaluation of neonates will include a detailed examination of the infants plus a cranial ultrasound.

Approximately 600 patients will be randomly assigned to either spontaneous or low forceps delivery. Cord blood samples will be obtained shortly after cord clamping. Cord gases will be recorded and the nursery staff will be notified of any abnormal findings. The data sheet, which will consist of a checklist of pertinent physical findings, will accompany the infant to the nursery. The cranial ultrasound will be performed within 24-72 hours following birth. The maternal hematocrit will be evaluated by routine methods on admission to the hospital and on the third postpartum day. The remainder of the information will be obtained from a review of the maternal in-patient record.

Data will be compared utilizing the Student's t test or chi-square analysis, as appropriate.

Progress: 140 subjects have been enrolled.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 88/54 Status: On-going

Title: Intraoperative Autotransfusion During Cesarean Section

Start Date: 20 May 88 Est Completion Date: Dec 88
Department: OB/GYN Facility: MAMC
Principal Investigator: CPT Michael K. Yancey, MC
Associate Investigator: COL Patrick Duff, MC
Key Words: Haemonetic cell-saver, goats, pulmonary emboli
Accumulative MEDCASE Est Accumulative Periodic Review:
Cost: -0- OMA Cost: \$1275.00 N/A

Study Objective: To explore the potential use for autologous intraoperative blood transfusion in obstetrical cases in which the blood has been contaminated with amniotic fluid debris.

Technical Approach: Phase I. Washed and unwashed blood specimens that have been contaminated with amniotic fluid debris from five patients who underwent cesarean section will undergo analysis. Parameters will include microscopic analysis of buffy coat smears, utilizing stains for mucin, fat, and fetal squamous cells, microbiologic cultures, and fetal erythrocyte counts. Descriptive statistics will document the content of the specimens.

Phase II. Group I: Five pregnant goats will be used as controls. A Swan-Ganz catheter will be placed in the right jugular vein. An arterial transducer will be placed in the right carotid artery, and a small venous catheter will be placed in the left saphenous vein. A cesarean section will be performed on each animal. Amniocentesis will be performed and as much amniotic fluid removed as possible. Blood contaminated with amniotic fluid will be suctioned from the abdominal cavity and reinfused back into the animal after it has been diluted with an equal volume of amniotic fluid, which will be determined by a drop in hematocrit to 50% of a venous sample. ECG, mean arterial pressure, pulmonary capillary wedge pressure, and central venous pressure will be continuously monitored. After 48 hours, the animals will be given euthanasia and necropsied. Histological specimens will then be obtained to determine the presence or absence of pulmonary emboli.

Group II: Five pregnant goats will be used in this group. The procedures will be identical to those of Group I except the blood and amniotic fluid will be filtered with a Haemonetics cell-saver prior to reinfusion.

The analysis of patient samples will be descriptive. The animal data will be evaluated in terms of the principal outcome measure: presence of pulmonary emboli.

Progress: This study has not been implemented.

DETAIL SHEETS
FOR
PROTOCOLS

DEPARTMENT OF PEDIATRICS

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 88/72 Status: On-going

Title: Antibiotic Prophylaxis of Recurrent Otitis Media

Start Date: 19 Aug 88 Est Completion Date: Aug 89
Dept/Svc: Pediatrics Facility: MAMC
Principal Investigator: LTC Thomas R. Babonis, MC
Associate Investigators: COL Thomas S. Charbonnel, MC
COL Dan C. Moore, MC
COL Marvin S. Krober, MC
COL Michael R. Weir, MC
LTC Janet Rowe, MC
CPT Amy M. Taylor, MC
Key Words: otitis media, prophylaxis, recurrent, children
Accumulative MEDCASE Est Accumulative Periodic Review:
Cost: -0- OMA Cost: -0- N/A

Study Objective: To determine relative efficacy of low dose sulfisoxazole, high does sulfisoxazole, or erythromycin in prophylaxis for recurrent otitis media.

Technical Approach: Children 12 months to 12 years of age with a history of 3 or more episodes of acute otitis media in the previous 6 months or 5 or more episodes in the previous 12 months will be considered for entry. Children with immune deficiency, cleft palate, ventilating tubes, serious otitis media, and other chronic illnesses will be excluded. The subjects will be evaluated by history, physical examination and tympanogram. Physical examination will include ears, pneumatic otoscopy, nose, throat, palate, lymph nodes. Subjects will be randomly assigned to receive either sulfisoxazole, 35 mg/kg/day as a single dose; sulfisoxazole, 75 mg/kg/day in two doses; erythromycin ethylsuccinate, 20 mg/kg/day in two doses, or placebo in two doses. After 3 months, the subjects will again be randomly assigned to receive one of the 3 remaining medications. These assignments will be made before the study begins using paired random numbers. All subjects will be seen at monthly intervals with otoscopy, tympanometry, side effects to medication, and history of ear problems during the preceding month recorded. Outcome measurements will include the incidence of symptomatic ear infections, and abnormal otoscopy and tympanograms on each treatment regimen. The presence of risk factors will be correlated with the overall effectiveness of prophylaxis. Data analysis: Each population will be compared in a 2x2 chi square as initial vs final and the results combined. Then a 2x4 chi square comparing each medication will be used to determine differences between medications; 2x2 chi square tables will be used for post hoc tests. The units will be months with otitis vs months without otitis.

Progress: Four patients have been entered.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 88/09 Status: Completed

Title: Body Positioning: The Effect on the Physiological
Status of Preterm Infants Recovering from
Respiratory Distress Syndrome

Start Date: 16 Oct 87 Est Completion Date: May 88

Department: Pediatrics Facility: MAMC

Principal Investigator: Kristie F. Bjornson, P.T., DAC

Associate Investigator: MAJ Jose Garcia, MC

Key Words: preterm infants, respiratory distress syndrome,
body positioning

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: -0- N/A

Study Objective: To compare the effect of different body positions on the physiological status of preterm infants as they recover from respiratory distress syndrome.

Technical Approach: Six preterm infants of appropriate size for gestational age will be studied in the supine, prone, and right side-lying positions (20 minutes in each position) for 9 sessions. Baseline data will be recorded for 5 minutes before the first position change. The order of the position changes for each day will be randomly assigned. Photographs will be made of each position at each session to maintain consistency in positioning. The time interval between sessions will be a minimum of 24 hours to decrease the effect of handling and the maximum interval will be 3 days in order to decrease the effect of maturation. Utilizing a momentary time-sampling technique, the mean arterial pressure (MAP), heart rate, respiratory rate, oxygenation percent, color, behavioral state, behavioral stress cues, and environmental factors which might affect the physiological responses will be recorded at 1-minute intervals. Demographic data, including birth date, age, gestational age, apgars, birth weight, current weight, race, sex, type of delivery, and maternal complications will be recorded. Physiological data noted before and after the 3 position changes will be temperature, ventilation rate, and FiO_2 . Data for each variable will be plotted using a line graph. The 3 positions across the 9 sessions will be graphed for visual analysis and to discern clinical significance. As an adjunct to visual analysis, the data will be analyzed using repeated measures ANOVA. Variability of MAP and heart rate will be analyzed in terms of median variability per session. Behavioral data will be analyzed descriptively in relation to each body position.

Progress: Visual analysis showed no consistent level differences for MAP, heart rate, and respiratory rate across positions. Oxygen saturation was consistently highest in the prone position, with supine and side-lying lower at no consistent level. No consistent differences in variability by ranges were documented for MAP and heart rate. Variability within subjects from session to session was noted and appeared within acceptable clinical limits. Prone positioning appeared to be effective in achieving higher oxygen saturation in ventilated preterm infants. A thesis is being prepared to submit as a requirement to obtain a Master of Science.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 87/66 Status: Terminated

Title: A Study of Fecal Overload in Adolescents

Start Date: 17 Apr 87 Est Completion Date: 31 Jan 88

Dept/Svc: Pediatrics/ Adolescent Facility: MAMC

Principal Investigator: COL Thomas S. Charbonnel, MC

Associate Investigators: COL Robert D. Karl, MC

LTC Dan C. Moore, MC

CPT Scott McClean, MC

Key Words: fecal, overload, adolescents

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: -0- Sep 88

Study Objective: To determine if fecal overload is a common cause of abdominal pain in adolescents; to determine if the scoring method of plain abdominal film devised by Barr, et al, is an accurate and easy way for a primary care physician to diagnose this condition, given minor suggestive findings in the history and physical; and to determine if treatment of this condition is effective in eliminating the symptom of abdominal pain.

Technical Approach: Inclusion criteria: children having at least four episodes of abdominal pain lasting at least one minute over a two month or longer period of time, plus one or more of the following: constipation, frequency of stools less than every other day, straining during defecation, large stools, rectal or abdominal pain during defecation, blood either on stool or on wiping paper, hard or pellet-like stools, diet severely lacking in fiber, intermittent crampy character to the pain, palpation of fecal material in the abdomen, large amount of stool in the rectum, or anal fissures.

A history and physical exam will be obtained. A flat plate abdominal film will be obtained and read according to the scoring system devised by Barr, et al. If the score is ≥ 10 , the patient will be entered in the study. Sixty subjects will be randomized to either Ducolax (two 5 mg tablets at bedtime) or a placebo. Patients will be followed up in two to three weeks. Relief of symptoms will be evaluated by questioning. A repeat abdominal film will be obtained and read in the same manner as the pretreatment film. The treatment will be judged successful and appropriate, if the symptoms are gone and the score falls below 10 or in the case of those initially having a score of 10-12, a drop of 4 or more points.

Progress: Four patients were entered on this protocol in approximately 18 months. The number of patients meeting the criteria for entry was not as large as anticipated. Most of the patients refused to participate when presented with the possibility of receiving a placebo. Therefore, the protocol was terminated.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 84/73 Status: Terminated

Title: Prophylactic Intravenous Immunoglobulin in High Risk Neonates

Start Date: 17 Aug 84 Est Completion Date: Sep 87

Department: Pediatrics Facility: MAMC

Principal Investigator: CPT Glenn D. Jordan, MC

Associate Investigators: LTC C. Gilbert Frank, MC
MAJ Jose Garcia, MC

Key words: immunoglobulin, neonates, high risk, prophylactic

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: -0- Sep 88

Study Objective: To evaluate the effectiveness of intravenous immunoglobulin (IVIG) with high titer to known disease producing types of Group B streptococci (GBS) in preventing GBS disease in the high risk neonate.

Technical Approach: This will be a double-blind multi-institution study with prescreened IVIG and control drug (5% albumin) supplied to each institution in a prerandomized fashion. Subjects will be neonates >2000 grams or 34 weeks at birth and >12 hours of age. Infants of mothers with immune deficiency syndrome will be excluded. The drugs will be used as a single infusion, 500 mg/kg. All infants will have constant temperature, heart rate, respiratory rate, and blood pressure (if on umbilical arterial catheter) monitoring. If umbilical arterial catheter is not present, BP will be obtained before, midway through, and at the completion of the infusion. Fifteen minutes post-infusion a whole blood sample for serum total of IgG and GBS antibodies will be obtained. At 1, 2, and 8 weeks, another blood sample will be taken for antibody studies, a history will be recorded, and routine development assessment will be done.

Progress: CPT Jordan became the principal investigator on this study upon the reassignment of MAJ Garcia in July 1988.

Upon continuing review in September 1988, after Dr. Jordan had had more time to review the records for this study, he decided that this protocol should be terminated due to insufficient patient entry. Over a four-year period only three children had entered the study, with one child expiring prior to completion of the study, secondary to intraventricular hemorrhage.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 86/68 Status: Terminated

Title: Antenatal Phenobarbital: Prophylactic Efficacy for the
 Prevention of Neonatal Intracerebral Hemorrhage (ICH)

Start Date: Sep 86 Est Completion Date: May 89

Dept/Svc: Pediatrics Facility: MAMC

Principal Investigator: CPT Glenn D. Jordan, MC

Associate Investigators: MAJ Jose Garcia, MC

LT Fred Guyer, M.D., USPHS

Key Words: intracerebral hemorrhage, prophylactic, phenobarbital

Accumulative MEDCASE

Est Accumulative

Periodic Review:

Cost: -0-

OMA Cost: \$50.00

Oct 87

Study Objective: To assess the putative benefit of antenatal administration of phenobarbital in ICH prophylaxis.

Technical Approach: Mother-infant dyads <30 weeks gestation who present with either premature labor or ruptured membranes will be studied in a randomized, double-blind, placebo-controlled trial. Subjects will be given an initial dose of either 1000 mg, I.V. over 60 minutes or a placebo. Subsequent patient management will be in accordance with standard patient care. If the delivery does not occur within 24 hours of initial drug administration, a maintenance dose of the drug will be given every 24 hours until delivery or until labor is successfully arrested. After delivery each infant will receive a cranial ultrasound on at least three occasions (within 12 hours of birth, at 72 hours, and at 7 days). A sample of cord blood will be obtained at delivery and samples of each infant's blood will be drawn on days 3 and 7 for serum drug levels. Length of time pre- and postadministration of phenobarbital to delivery will be analyzed. Data from mothers on steroids will be analyzed separately.

Progress: CPT Jordan was named the principal investigator on this protocol upon the reassignment of MAJ Garcia in July 1988.

Upon continuing review, Dr. Jordan stated that recent literature has suggested some question on the safety of postnatal administration of phenobarbital and requested that the protocol be terminated until this area had been further studied.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 87/50 Status: On-going

Title: Antibody Response to Measles-Mumps-Rubella Vaccine in
Children with Concurrent Upper Respiratory Infection

Start Date: 27 Feb 87 Est Completion Date: Mar 88

Department: Pediatrics Facility: MAMC

Principal Investigator: COL Marvin S. Krober, MC

Associate Investigators: Dr. Marchetti, University of Hawaii
Catherine Yokan, M.D., DAC
Carl Stracener, M.D., DAC

Key Words: vaccine, measles-mumps-rubella, concurrent URI,
antibody response, safety, efficacy

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: -0- Sep 88

Study Objective: To determine whether or not afebrile upper respiratory infections interfere with successful immunization with combined measles-mumps-rubella vaccine (MMR).

Technical Approach: Fifty children with upper respiratory infections and 50 well controls between 15 and 24 months of age will be entered in the study when they present for routine MMR immunization. Pertinent history and physical findings will be recorded and the children will be given the standard MMR. Blood will be drawn and repeat samples obtained at eight weeks. The paired samples will be assayed for serologic response to the immunization. Patients shown to be immune on the initial sample will be excluded from further analysis. For those initially susceptible, antibody responses will be compared in geometric mean titers and in percent of vaccine failures (no rise in titer) to determine whether or not upper respiratory infections resulted in a failure of response or a diminution of response.

Progress: Samples have been obtained from 27 patients and stored frozen. All samples will be assayed and data will be evaluated after an additional 25 patients have been enrolled in the study.

Detail Summary Sheet

Date: 30 Sep 88	Protocol No.: 87/51	Status: On-going
Title: Optimum Penicillin Dosage for Treatment of Streptococcal Pharyngitis		
Start Date: 27 Feb 87	Est Completion Date: Feb 88	
Department: Pediatrics	Facility: MAMC	
Principal Investigator: COL Marvin Krober, MC		
Associate Investigators: COL Thomas Charbonnel, MC COL Conrad L. Stayton, MC COL Michael Weir, MC CPT Nicholas Themelis, MC		
Key Words: streptococcal pharyngitis, penicillin, efficacy, compliance, hematuria		
Accumulative MEDCASE	Est Accumulative	Periodic Review:
Cost: -0-	OMA Cost: \$500.00	/A

Study Objective: To determine the relative efficacy of different dosage regimens of penicillin in the treatment of streptococcal pharyngitis; to ascertain compliance on the different regimens; and to find the incidence of hematuria after illness.

Technical Approach: Children between the ages of 3 and 18 years with clinical symptoms of sore throat and with throat culture or streptococcal latex agglutination rapid screening test positive for Group A beta hemolytic streptococci will be entered in the study. Approximately 300 children will be randomized to receive penicillin VK in one of three regimens: 1000 mg once daily, 500 mg twice daily, or 250 mg four times daily. Throat cultures and urine specimens will be obtained at two days. A urine sample will be obtained on the last day of a 10 day treatment plan. Two to three days after the treatment has been completed, the children will be examined and the throat will again be cultured and the urine checked for presence of blood and penicillin. Pill counts will be used as a second measure of compliance. Subjects will have a final examination and throat culture done two weeks after completing antibiotic treatment. Comparison will be made between the three treatment groups in: percentages with persistent positive throat cultures; percentages with recurrence of positive culture with or without symptoms; amount of unused medicine; percentage still taking penicillin at ten day follow-up (as evidenced by presence of penicillin in the urine sample); and percentage with hematuria.

Progress: 93 patients have been randomly assigned to receive penicillin VK once, twice, or four times daily. A review of the data on the first 75 patients entered revealed no difference in the percentages of treatment failures in each of the three treatment groups ($P < 0.05$). Data will be reanalyzed for power and statistical significance after 75 admissions to the study.

COL Krober was named the principal investigator on this protocol upon the departure of COL Stayton in July 1988.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 88/25 Status: On-going

Title: Ceftriaxone for Outpatient Management of Suspected
Occult Bacteremia

Start Date: 15 Jan 88 Est Completion Date: Jul 89

Department: Pediatrics Facility: MAMC

Principal Investigator: COL Marvin S. Krober, MC

Associate Investigator: MAJ Edward M. Eitzen, MC

Key Words: bacteremia, occult, ceftriaxone, outpatient

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: 3000.00 N/A

Study Objective: To determine if ceftriaxone given in a single injection per day will clear existing bacteremia and eradicate established subclinical focal infections.

Technical Approach: Subjects (approximately 400) will be sick febrile children 3 months to 3 years of age with fever $\geq 39.5^{\circ}\text{C}$ of unknown origin and WBC $\geq 15,000$. Children with a temperature $\geq 40.3^{\circ}\text{C}$, rectally, will be entered regardless of WBC value. Only children who have no evidence of a specific viral infection will be considered. Children who have clinical evidence of focal infection warranting early antimicrobial treatment, CSF analysis consistent with meningitis, symptoms of a nonspecific upper respiratory illness, and antibiotic therapy or DPT immunization within the preceding 48 hr will be excluded. All children who meet the criteria will have a urinalysis and urine cultures and chest x-rays. Patients will be randomized to receive oral Augmentin, 40 mg/kg/day, in divided doses or ceftriaxone in a single IM injection, 75 mg/kg/day. A comprehensive data form, including all pertinent clinical, laboratory, and demographic information will be completed at the time the child is entered in the study. Patients will be re-evaluated within 24 hours with particular attention to the development of focal infection and/or therapeutic adverse reactions. If the patient is still sick and febrile at 24 hours, blood cultures will be repeated and each patient will continue to receive the initial treatment. Each patient will subsequently be seen daily with the blood culture repeated and treatment continued until the patient is afebrile and clinically improved for 24 hr. All patients who have positive blood cultures will be re-examined and repeat blood cultures will be obtained. Subsequent management will be determined by the examining pediatrician. Preliminary analysis will characterize age, gender, race, magnitude of fever, and duration of fever prior to therapy. Evaluations will consist of the presence of focal infection and persistence of bacteremia on follow-up (chi square analysis) and decrement in body temperature and functional status (Wilcoxon rank sum test). The functional status of the patient will be quantified via a scoring system of behavioral characteristics: irritability, consolability, and presence or absence of social smile.

Progress: Ten patients were entered, three of whom were truly bacteremic. The study will be continued, in cooperation with nine other medical center, until 300 Patients have been studied.

Detail Summary Sheet

Date: 30 Sep 88	Protocol No.: 87/16	Status: On-going
Title: Higher Cortical Functioning in School Aged Children with Headache		
Start Date: 21 Nov 86	Est Completion Date: Jan 89	
Department: Pediatrics	Facility: MAMC	
Principal Investigator: MAJ William McClintock MC		
Associate Investigator: CPT Barry S. Anton, MSC, USAR		
Key Words: headache, muscle contraction, migraine, siblings		
Accumulative MEDCASE	Est Accumulative	Periodic Review:
Cost: -0-	OMA Cost: -0-	Jan 88

Study Objective: To determine if subtle deficits in higher cortical functioning may contribute to migraine headache.

Technical Approach: Three groups of school aged children between the ages of six and twelve years will be studied.

- Group 1: Ten children with muscle contraction headaches (intermittent - at least one headache every two months for one year).
- Group 2: Ten children with migraine headaches (intermittent - at least one headache every two months for one year).
- Group 3: Ten siblings of children from group 1 or group 2 with no history of headache or other medical condition (controls).

Subjects in the two experimental groups will have no history of progressive neurologic disease or other serious medical condition. A complete history (including onset of headache, frequency, cause, intensity, location and character of pain, associated symptoms, and relief factors), family history of headache, physical exam (blood pressure, cardiovascular exam, HEENT exam, fundoscopic exam, listening for bruits), neurological examination (cranial nerve exam, musculo-skeletal exam, sensory and motor exam, gait, reflex and cerebellum) will be conducted on each patient. In addition, neurophysiological assessment of each patient will be undertaken. The neuropsychological examination will include the following standardized test instruments: Wechsler Intelligence Scale for Children (Revised), Wide Range Achievement Test - Revised, Trail Making Test, Bilateral Name Writing, Word Fluency Test, Bilateral Finger Agnosia, Token Test for Children, Grooved Pegboard, Digit Symbol Test (oral and written), and Child Behavior Checklist. Tests will be given to all children in the same sequence. In order to assess current medical status and screen for medical disorders that might affect neuropsychological test results, medical records of all subjects will be thoroughly reviewed. A parent of each child will be asked to complete a problem check list and a detailed medical history questionnaire.

Progress: Nine patients with migraine and four patients with tension headache have been tested.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 87/100 Status: On-going

Title: Thyroid Size in Children and Adolescents

Start Date: 21 Aug 87 Est Completion Date: Dec 88
Department: Pediatrics Facility: MAMC
Principal Investigator: LTC Dan Moore, MC
Associate Investigators: None
Key Words: thyroid, size, children, manually, ultrasound
Accumulative MEDCASE Est Accumulative Periodic Review:
Cost: -0- OMA Cost: -0- Sep 88

Study Objective: To establish normal dimensions ± 2 standard deviations (SD) for thyroid lobe length and width in children and adolescents. A goiter would then be defined as thyroid gland exceeding 2 SD of these dimensions.

Technical Approach: During the course of a routine physical examination, thyroid glands of 300 normal children and adolescents aged 6-20 years (20 at each age, 10 of each sex) will be measured in the following manner. With the neck extended, the thyroid isthmus is located with the index finger. The medial aspect of each lobe is followed to the apparent tip of each lobe. The upper tip of each lobe is located as the patient swallows with the index finger over each tip. The apparent inferior border of each lobe is located as the patient swallows with the index finger over the inferior portion of the gland. The lateral borders of the gland will be located with the index fingers placed medial to the sternocleidomastoid muscle as the gland moves as the patient swallows. The length will be measured as the distance from the apparent tip of each lobe to the apparent inferior border of each lobe. The width will be measured as the distance from the lateral borders of the gland. Means and SD will be calculated for length of each lobe and mid-isthmus width. For validation of measurement accuracy, 30 patients (2 each age, 1 each sex) will have the same measurements determined by thyroid ultrasound.

Progress: Ninety patients have been entered. At present, the Department of Radiology can not do the ultrasounds due to their workload.

Detail Summary Sheet

Date: 30 Sep 88	Protocol No.: 88/06	Status: On-going
Title: Comparison of Growth Response of Two Commercially Available Recombinant Preparations of Growth Hormone		
Start Date: 16 Oct 87	Est Completion Date: Oct 92	
Department: Pediatrics	Facility: MAMC	
Principal Investigator: LTC Dan C. Moore, MC		
Associate Investigator: None		
Key Words: growth response, Humatrope, Protropin		
Accumulative MEDCASE	Est Accumulative	Periodic Review:
Cost: -0-	OMA Cost: -0-	Sep 88

Study Objective: To compare two commercially available growth hormone preparations in equal doses to determine if there is a significant difference in growth response and antigenicity.

Technical Approach: This is a randomized, double-blind study of prepubertal children, who have never received growth hormone, with <5 cm/yr growth velocity and <10 ng/ml peak growth hormone after administration of 2 pharmacologic stimuli (Arm I); and prepubertal children who have been on growth hormone for at least two years who are beyond the typical catch-up growth phase (Arm II). Baseline data will include age, sex, pretreatment growth velocity, height, weight, growth hormone antibodies, bone age, serum T₄, and concurrent hormone therapy. Patients will be randomized to receive either Humatrope or Protropin, 0.06 mg/kg/dose sq 3 times a week for 6 months. After 6 months, the alternate hormone preparation will be given in the same dosage. At 6 and 12 months, data collection will include height, weight, growth velocity, bone age, growth hormone antibodies, T₄, pubertal stage, and change in concurrent hormone therapy. At 12 months, the patients will be continued on the hormone which has been most effective. A minimum of 35 children will be studied in each arm of the study.

The initial response to growth hormone will be compared using a logistic regression with manufacturer as dependent and all other data as independent variables. The coefficients of the independent variables will provide information about the relative weight of each variable. Failure to show a difference will not show comparability, but will indicate that very large samples are necessary to show a difference. Repeated measures ANOVA will be used to compare the crossover aspect of the study. Group differences may or may not be significant; a significant interaction term is indicative of preparation differences at the dose used. Paired and unpaired t-test will be used as post-hoc tests. A difference in annualized growth velocity of >0.5 cm/yr will be considered as a difference in effectiveness.

Progress: One patient has been entered in this study.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 88/18 Status: On-going

Title: Attitudes Towards Body Weight and Eating in Children

Start Date: 11 Dec 87 Est Completion Date: Dec 88
Department: Pediatrics Facility: MAMC
Principal Investigator: LTC Dan C. Moore, MC
Associate Investigators: None
Key Words: children, body weight, eating, attitudes, 10-12 yrs
Accumulative MEDCASE Est Accumulative Periodic Review:
Cost: -0- OMA Cost: -0- N/A

Study Objective: To determine the degree to which female children ages 10-12 years are concerned about weight and body size.

Technical Approach: A minimum of 300 female children ages 10-12 seen in the Pediatric Clinic will be asked to participate. After assent, the subjects' weight and height will be recorded and they will complete a questionnaire before leaving the clinic. The questionnaire will elicit information the subject's satisfaction with and self perception of height, weight, and appearance; desire to gain or lose weight; dieting history; eating habits; and worries about becoming too fat or thin. Responses will be analyzed descriptively, then analyzed by ANOVA, test or proportions, and Duncan's multiple range (SPSS) to detect significant differences by height, weight, or age in feelings about weight, body shape, and eating/weight loss behaviors.

Progress: 126 subjects have been entered. Preliminary data indicate that a significant proportion of preteen girls are concerned about body weight and eating. Some have already experienced behaviors usually associated with eating disorders in adolescents. Overall, 59.8% of preteen girls were dissatisfied with their current weight. In regard to eating behaviors, 17.6% had already experience binge eating and 23.4% had thought about it; 3.7% had experienced self-induced vomiting. Fasting for 24 hours to lose weight had occurred in 10.3% and 29.2% had thought about it; 16.8% thought about food a lot and 65.4% worried about getting too fat; 11.3% worried about getting too thin.

The investigators will continue to enroll subjects until approximately 300 have been entered.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 88/07 Status: On-going

Title: Quantitation of Dysmorphic Features for Syndrome
Identification

Start Date: 16 Oct 87 Est Completion Date: Oct 89

Department: Pediatrics Facility: MAMC

Principal Investigator: LTC Glenn C. Tripp, MC

Associate Investigators: COL Michael Weir, MC

Gentry Yeatman, M.D.

Key Words: syndrome, identification, dysmorphic features,
image analysis, computerized

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: \$40,000.00 OMA Cost: -0- Sep 88

Study Objective: By careful measurement of facial features and ratios of these features of normal and syndromic children or photographs of them, to explore the limits of normal and attempt to identify clearly significant syndromic deviations.

Technical Approach: Initial data will be obtained from measurements of facial photographs of children without a pre-existing diagnosis of a malformation syndrome. Initial sampling will include 100 randomly selected children from each of the following groups: 6 and 18 months and 3.5 and 6.5 years. Samples will be representative of the major ethnic groups. These data will subsequently be compared to known craniofacial malformation syndromes for patients seen clinically and from case reports and series. The study will also use a computer-based image analysis system for normal patients, syndromic patients, and literature reports of syndromes. The images will be digitalized and distances and areas will be recorded. Where available, absolute sizes will be recorded, but ratios of suspect features to apparently normal features will be the principal data element. The focus of the data analysis will be to identify cut points to distinguish normal features from borderline and from clearly abnormal features. Features explored will involve location, size, and shape of facial/cranial features and may be expanded to hand and foot segment/lower segment ratios.

Dimensions and ratios will be compared across ethnic groups by ANOVA. If no differences occur, groups will be combined. Similar analysis will be used to compare syndromes with the normal groups.

Progress: Problems with photographic equipment and digitalizing equipment selection has predominated work so far. At present, the investigators are collecting initial photographs of the children at stated ages to norm midface measurement ratios.

Detail Summary Sheet

<u>Date: 30 Sep 88</u>	<u>Protocol No.: 87/99</u>	<u>Status: Terminated</u>
<u>Title: Rapid Detection of Infectious Mononucleosis by Enzyme Immunoassay</u>		
<u>Start Date: 21 Aug 87</u>	<u>Est Completion Date: Aug 88</u>	
<u>Department: Pediatrics</u>	<u>Facility: MAMC</u>	
<u>Principal Investigator: COL Michael R. Weir, MC</u>		
<u>Associate Investigators: COL Thomas Charbonnel, MC</u>		
<u>COL Marvin S. Krober, MC</u>		
<u>Key Words: mononucleosis, detection, rapid, enzyme immunoassay</u>		
<u>Accumulative MEDCASE</u>	<u>Est Accumulative</u>	<u>Periodic Review:</u>
<u>Cost: -0-</u>	<u>OMA Cost: -0-</u>	<u>Sep 88</u>

Study Objective: To evaluate the performance characteristics (reliability, accuracy, ease of use) of the Ventrescreen Mono Test for use in detecting infectious mononucleosis heterophil antibodies in finger tip blood and venipuncture samples.

Technical Approach: Approximately 100 patients suspected of having infectious mononucleosis will, after a thorough history and physical examination, be entered in the study. A fingerstick capillary tube blood sample will be obtained and used for the performance of the Ventrescreen Mono Test at the time of entry. Venous blood samples will be obtained from a single venipuncture at the time of entry as follows: 3 cc for CBC with differential; 3 cc for rapid slide testing for heterophil antibodies in the conventional manner; 1 cc for the performance of the Ventrescreen Mono Test; and 6 cc to be evaluated for viral capsid antigen IgM and VCA IgG.

The Ventrescreen Mono Test will be compared to the conventional heterophil antibody rapid slide test using a standard two-by-two table. Any samples with a discrepancy will undergo Epstein-Barr virus serology. Five samples in positive agreement and five samples in negative agreement will undergo EBV serology as controls.

Progress: Fifteen patients were entered in the study. This rate of patient entry was too slow to satisfy the needs for meaningful results in a reasonable period of time. The mono kits are no longer available. Therefore, the protocol was terminated.

Detail Summary Sheet

Date: 30 Sep 88	Protocol No.: 84/62	Status: Completed
Title: Screening of Infants for Movement Deficits		
Start Date: 18 May 84	Est Completion Date: May 85	
Activity: Student Program, HSC	Facility: MAMC	
Principal Investigator: Catherine Yokan, M.D., DAC		
Associate Investigators:	LTC Jane K. Sweeney, AMSC	
COL Carl Plonsky, MC	Lynette S. Chandler, Ph.D.	
LTC Glenn Tripp, MC	Margo B. Holm, Ph.D.	
Key Words: movement deficits, infants, Chandler Movement Assessment of Infants - Screening Test		
Accumulative MEDCASE	Est Accumulative	Periodic Review:
Cost: -0-	OMA Cost: -0-	Oct 87

Study Objective: To establish norms for the Chandler Movement Assessment of Infants Screening Test (CMAI-ST); to establish inter-rater reliability, test-retest reliability, and predictive validity for the CMAI-ST.

Technical Approach: Fifty infants will be examined in age groups of 2, 4, 6, and 8 months, plus or minus one week. The infants will be examined in only one of those time frames in order to establish norms. Thirty infants from the 200 will be observed by two examiners simultaneously to determine inter-rater reliability. An additional 30 infants will be examined during two time frames to establish test-retest reliability. The outcome of the CMAI-ST will be correlated with physician assessment at the regularly scheduled 12-month exam to establish predictive validity. Half of the children from each group will be male and half will be female and distinct races will be represented to match the population of infants of military personnel. A Denver Prescreening Development Questionnaire will be completed by the parents. The high risk profiles of the 30 infants tested twice for test/retest reliability will be compared with those infants tested once. Only those twice-tested infants who maintain a high risk profile or increase their apparent degree of involvement will be considered at risk. All once-tested infants will be evaluated on their original profile. Pearson-product-movement correlations will be calculated to determine the predictive validity of twice-tested and once-tested infants. Percent of false positives and false negatives from each group will also be calculated.

Progress: Dr. Yokan was named the principal investigator on this study upon the reassignment of LTC Sweeney. The study has been completed. 266 children were entered in this study and norms were established for the CMAI-ST for 2-12 month old infants. The test is most effective with children from 5-12 months of age when given by evaluators who have not had advanced training in movement of infants. On the basis of the data on the DPDQ, it would appear that a high risk score of from 1-3 is acceptable on the CMAI-ST and that infants receiving a ≤ 4 should be referred for rescreening or for assessment by a movement specialist. The CMAI-ST is being used within a battery of tests to screen infants in several organizations in Pierce County, Washington.

DETAIL SHEETS
FOR
PROTOCOLS

DEPARTMENT OF PSYCHIATRY

Detail Summary Sheet

Date: 30 Sep 88	Protocol No.: 88/50	Status: Terminated
Title: Cross-Sequential Investigation of Neuropsychological Functioning in HIV Seropositive Patients		
Start Date: 15 Apr 88	Est Completion Date: Dec 89	
Department: Psychiatry	Facility: MAMC	
Principal Investigator: Timothy S. Clark, Ph.D.		
Associate Investigators: LTC Anthony C. Zold, MS MAJ Lloyd I. Cripe, MS MAJ Kenneth Hoffman, MC Gordon Winslow, M.A.		
Key Words: patients, controls, neuropsychological instruments		
Accumulative MEDCASE	Est Accumulative	Periodic Review:
Cost: -0-	OMA Cost: -0-	N/A

Study Objective: To describe the neuropsychological correlates of HIV infections across stages of the Walter Reed Classification System; to establish an epidemiological database for dementia among HIV seropositive patients; to develop and evaluate a predictive model for deterioration of cognitive and intellectual functioning using early neuropsychological and physical markers; and to develop a diagnostic battery of neuropsychological measures for the early detection and monitoring of decline in HIV dementia.

Technical Approach: The study will consist of two elements. Element A will compare the performance of 30 HIV seropositive patients with 30 matched controls. After consent has been obtained, results of HIV seropositive patients' comprehensive examination done as part of clinical practice will be entered in the data base. Control data will be acquired from a focused battery of tests which will be administered to volunteers. Element A patients will receive a detailed clinical interview including history and a comprehensive battery of questionnaires, personality, and neuropsychological instruments. Control subjects will receive a brief interview to insure the absence of neurologic history and a focused battery of neuropsychological measures. Element B involves reevaluation of patients at six-month intervals using a focused battery of measures. In addition, the control group will be reevaluated once six months later using the same focused battery to determine test-retest reliability of the battery.

Data will be analyzed using appropriate nonparametric statistics. Results of Element A will include comparison of patient and control groups using Mann Whitney U as well as other relevant statistics. Results of Element B will involve test-retest reliability statistics and tests of repeated measures.

Progress: This protocol was approved in April 1988 with stipulations by the IRB. It was terminated in September 1988 due to insurmountable problems with the logistics and in meeting the regulatory requirements.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 88/08 Status: Terminated

Title: The Relationship Between Conflict and Social Development
in Latency Aged Children

Start Date: 16 Oct 87 Est Completion Date: Jun 88

Department: Psychiatry Facility: MAMC

Principal Investigator: CPT Frederick N. Garland, MS

Associate Investigators: LTC Timothy Davis, MS

LTC Anthony Zold, MS

Linda Christensen, M.A.

Key Words: children, conflict, social development, facial cues

Accumulative MEDCASE

Est Accumulative

Periodic Review:

Cost: -0-

OMA Cost: -0-

N/A

Study Objective: To compare accuracy in identifying affective facial cues and to compare perceptual, cognitive and affective perspective-taking skills between physically abused and non-abused children and to determine the influence of perspective-taking skills on parents' perceptions of behavioral problems in the home.

Technical Approach: 30 abused children and a matched sample of non-abused children will be studied in 2 age groups (4-6 and 7-9 years) making the study a 2x2 (abuse & age) factorial design. Parents will complete the Child Behavior Checklist (Achenback and Edelbrock, 1987). The tasks will be presented to the children in one of six counterbalanced presentation orders. The Affective Judgment Task requires the child to accurately sort 30 photographs of adult facial expressions into six categories of affect. The Affective Perspective Taking Test requires the child to infer affect from 6 common situations (such as someone else being stung by a bee or receiving a gift) and also infer someone else's affect from 4 situations in which the child's affect is likely to be different from theirs in order to assess the child's relative freedom from egocentric thinking in making inferences about another's emotional state. The Cognitive Perspective-Taking Task requires the child to infer what someone would know about a situation if they did not have as much information as the child. The Perceptual Perspective-Taking Task requires the child to shift his perspective in a spatial plane and infer the visual array as perceived by a person at a different vantage point. The Slosson Intelligence test will be administered following the experimental tasks. A 2x2 (group and age) multivariate analysis of covariance (intelligence) will be performed. Dependent measures will include performance on the Affective Judgement Task and the 3 perspective-taking tasks. Univariate analysis of covariance will be conducted with between group t-test comparisons as appropriate. Scheffe's method will be used to correct for experiment-wise error in posthoc comparisons. The Child Behavior Checklist will be compared in a 2x2 (group and age) ANOVA in order to assess general adjustment.

Progress: 50 controls and 10 clinical subjects were tested. The current number of 10 clinical subjects is not sufficient for analysis. The project was terminated at MAMC because there was no one to take over the study. Dr. Garland will seek approval from the IRB to continue this study at DDEAMC.

Detail Summary Sheet

Date: 30 Sep 88	Protocol No.: 88/77	Status: On-going
Title: Self-Report of Attention Deficit Hyperactivity Disorder (ADHD)		
Start Date: 16 Sep 88	Est Completion Date: 30 Jun 89	
Department: Psychiatry	Facility: MAMC	
Principal Investigator: CPT Jeffrey E. Hansen, MS		
Associate Investigators: Thomas Clingan, M.D., DAC		
Key Words: ADHD, self-report, instrument, development		
Accumulative MEDCASE	Est Accumulative	Periodic Review
Cost: -0-	OMA Cost: -0-	N/A

Study Objective: To develop a children's self-report instrument for ADHD.

Technical Approach: The experimental group will consist of 30 male ADHD children. In order to control for the frequently reported overlap between ADHA and conduct problems, there will be a control group comprised of 10 male children with conduct problems who were not assessed to have ADHA and a second control group of 15 normal children. All children will be between 9 and 12 years of age and have an IQ score of at least 80. Experimental and control groups will be matched on the basis of IQ.

The Hansen Self-Report Scale (HSRS) will be administered to all children. This is a scale constructed by the principal investigator. To represent the construct of ADHD, items were chosen to parallel as closely as possible the specific DSM III-R criteria for ADHD. The 20 item-HSRS was arranged in a true-false format. Most of the items were taken from the previously validated Revised Conners Teacher Rating Scale (CTRS) [Conners; 1969; 1973], the Revised Parent Symptom Questionnaire (PSQ) [Conners 1973 and 1978] and the Child Behavior Checklist (Achenbach and Edelbroch, 1983), and rewritten for administration to children.

Parents of all children will be administered the PSQ and teachers will be administered the CTRS. The ADHD children will be administered the Slosson Intelligence Test (SIT) and the HSRS and then seen by a pediatrician, who is blinded to the results of these tests. The pediatrician will conduct an intake/assessment and collect the PSQ from the parents and the CTRS from the school. Normal subjects will not be seen the pediatrician but will be given the SIT and the HSRS.

The following statistical procedures will be used to analyze the data:

Multiserial correlation: concurrent validity, construct validity, internal reliability.

Multiple Sample Chi Square: Differences between groups.

Progress: This is a new study and no subjects have been entered.

DETAIL SHEETS
FOR
PROTOCOLS

DEPARTMENT OF RADIOLOGY

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 87/92 Status: Terminated

Title: Magnetic Resonance Investigational Study Protocol

Start Date: 19 Jun 87 Est Completion Date: Jun 88
Department: Radiology Facility: MAMC
Principal Investigator: CPT James D. Winthrop, MC
Associate Investigators: COL Robert D. Karl, MC
MAJ Craig S. Hammes, MC
Key Words: magnetic resonance imaging, software, surface coils
Accumulative MEDCASE Est Accumulative Periodic Review:
Cost: -0- OMA Cost: -0- /A

Study Objective: To estimate the sensitivity (the incidence of true positive results) and specificity (the incidence of true negative results) of magnetic resonance (MR) as a diagnostic procedure.

Technical Approach: Included in the study will be in-patients and outpatients with suspected medical disorders, where definitive diagnosis is likely, who have had or are scheduled for other imaging modalities. Patients with mechanical or electrically activated implants such as cardiac pacemakers, neurostimulators, or biostimulators will be excluded. Patients with aneurysm clips will be excluded unless the physician is certain that the clips are not magnetically active.

The subject accrual period will be ongoing until all supplements related to the the MR system configuration and intended clinical indication are attained.

Prior to performing the imaging study, the investigators will review the patient's medical history and existing physical exam results, verify eligibility, and record the results on a study form. Subjects will serve as their own controls. Investigators will determine the subjects' final clinical diagnoses by compiling the results of other diagnostic procedures. These results will be compared to the MR results. Efficacy will be measured by comparing the accuracy (estimating sensitivity and specificity) of MR to the final clinical diagnosis. Short-term safety exposure to MRI will be assessed by compiling complication and adverse reaction results.

Statistical analysis will include a description of the subject's baseline characteristics, identification of complications and adverse reactions, and summarization of the efficacy parameters. Analysis of the efficacy parameters will include a comparison of the MR results to the final clinical diagnosis and other diagnostic results.

Progress: Successful clinical imaging had been completed in 157 patients before this protocol was suspended in November 1987, pending the addition of a consent form as required by HSHN-I, HSC. All aspects of the MRI were then released by the FDA and the protocol was terminated.

DETAIL SHEETS
FOR
PROTOCOLS

DEPARTMENT OF SURGERY

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 87/07 Status: On-going

Title: General Surgery Stapling Familiarization Lab (Swine Model)

Start Date: 17 Oct 86 Est Completion Date: Oct 87

Dept/Svc: Surgery/General Facility: MAMC

Principal Investigator: COL Charles A. Andersen, MC

Associate Investigators: COL Preston L. Carter, MC

COL Richard A. Hall, MC

COL Stanley C. Harris, MC

MAJ Stephen B. Smith, MC

Key Words: familiarization lab, stapling, general surgery, swine

Accumulative MEDCASE Est Accumulativ Periodic Review:

Cost: -0- OMA Cost: \$500.00 Sep 88

Study Objective: To familiarize residents in General Surgery with the proper use of surgical stapling devices.

Technical Approach: For each laboratory session, two animals will be anesthetized (ketamine HCl 20 mg/kg body weight and atropine .088 mg/kg body weight, IM) as a pre-anesthetic. The animals will then be intubated endotracheally and surgical anesthesia will be induced and maintained using a mixture of Halothane and nitrous oxide.

Once a surgical level of anesthesia has been achieved, the abdominal cavity will be entered via a midline incision. A demonstration of stapling techniques (under the direct supervision of staff surgeons and representatives from the staple manufacturer) will be performed on the animal by the surgical residents. After the demonstration, all animals will be euthanatized without being allowed to recover from anesthesia.

Progress: This protocol, which was suspended in June 1987 pending revisions required by HSC, has now been revised and approved, and the protocol placed in an on-going status. A training session utilizing this protocol is planned for mid-October.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 86/88 Status: Completed

Title: Method of Determining in Dogs the Vascularity of Transposed Patellar Tendons Used in ACL Reconstructions

Utilizing Fluorescein Dye, with Correlation to Viability

Start Date: 15 Aug 86 Est Completion Date: Aug 87

Dept/Svc: Surgery/Orthopedics Facility: MAMC

Principal Investigator: CPT Brian Barnard, MC

Associate Investigator: CPT Robert Arciero, MC

Key Words: patellar tendons, vascularity, fluorescein dye, dogs

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: \$400.00 Sep 88

Study Objective: To determine whether the patellar tendon graft utilized in ACL reconstructions is vascularized at the time of transposition and whether the transposed graft maintains its circulation, i.e., remains viable.

Technical Approach: Preoperatively, the animals will be weighed and examined for general physical abnormalities as well as examination of the knees to include ROM, ligamentous laxity, thigh circumference, and x-rays. Six experimental and six control animals will be studied. After being anesthetized, a midline incision will be made under tourniquet control to identify the patella-patellar tendon complex. The central 1/3 of the PT will be harvested with an attached wedge of bone taken proximally from the patella and distally from the proximal tibia. The attachment of the fat pad to the PT graft will be reinforced and the free ends of the graft will be tagged with sutures placed through drill holes in the bone. The intercondylar notch will be exposed and the ACL will be resected from its femoral and tibial attachments. Bony canals will be created to allow isocentric placement of the graft. At this point the tourniquet will be deflated and fluorescein will be injected. After 10 minutes, photos will be obtained of the graft using the fluorescence camera. The patellar bone wedge will be passed into the femoral canal and fixated. The tibial component will be passed and prior to final fixation, an exam of the knee to include ROM and stability will be performed. When no instability is detected, yet motion is not impeded, the graft will be secured. The defect in the patellar tendon and the skin will be closed and the surgical site covered with a cast with the knee bent at 45°. The cast will be kept on for 7-10 days. The animals will be sacrificed on a weekly basis beginning at the third postop week in order to obtain 2 control and 2 study knees per week. Before sacrifice, the animals will be anesthetized and examined to check for knee motion and laxity. After sacrifice, the hind limb will be disarticulated at the hip, decalcified, and sectioned for radiographic and histologic examination.

Progress: This protocol has been completed and a paper has been submitted for publication.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 84/51 Status: Terminated

Title: Orchiectomy and Observation in the Treatment of Clinical Stage I Nonseminomatous Germ Cell Tumor of the Testis (NSGCTT)

Start Date: 18 May 84 Est Completion Date: May 89

Dept/Svc: Surgery, Urology Facility: MAMC

Principal Investigator: COL William Belville, MC

Associate Investigators: COL Alfred S. Buck, MC

COL Victor J. Kiesling, MC

COL Freidrich H. Stutz, MC

Key Words: NSGCTT, treatment, orchiectomy, observation

Accumulative MEDCASE

Est Accumulative

Periodic Review:

Cost: -0-

OMA Cost: -0-

Sep 88

Study Objective: To determine the efficacy of orchiectomy alone in the treatment of clinical Stage I NSGCTT. The factors that pre-dispose to relapse with Stage I disease will be analyzed.

Technical Approach: At present, clinical Stage I NSGCTT is treated by radical orchiectomy and radical retroperitoneal lymph node dissection. To avoid the ejaculatory impotence associated with the radical retroperitoneal lymph node dissection, the investigators propose to follow orchiectomy patients monthly for two years and then quarterly for two years with no further treatment unless relapse occurs. Subjects must have histologically confirmed carcinoma (not pure seminoma nor pure choriocarcinoma) at the testis. Postorchiectomy evaluation must have been completed within four weeks of the diagnosis of the primary tumor. Patients with involvement of the spermatic cord or evidence of epididymal invasion; or with evidence of tumor outside the testis by any other diagnostic means, or with a second malignancy (except a squamous or basal cell skin cancer) will be excluded. Patients who after careful counselling elect to undergo a radical retroperitoneal lymph node dissection will be followed as per protocol. Preorchiectomy evaluation will include complete history, physical, WBC and platelet count, HGB, bilirubin, alkaline phosphatase, SGOT, SGPT, serum calcium, BUN, creatinine, uric acid, chest x-ray, and serum tumor markers to include α -fetoprotein, β -HCG, and LDH. Post-orchiectomy evaluation will include bipedal lymphangiogram, abdominal and chest CT, excretory urography, and normal serum tumor markers which have returned to normal at a rate predicted by the known serum half-life of the respective marker. Follow-up will include history, physical exam, SMAC 20, CBC with platelet count, chest x-ray or CT, and serum tumor markers. During the first two years of follow-up, the patient will undergo abdominal CT every three months, and then annually for two additional years.

Progress: One patient was entered in this study in FY 87. This protocol was terminated by the principal investigator because of a change in accepted surgical technique (marked by decreased surgical morbidity) plus reports of delayed metastasis coupled with difficulty in enrolling patients renders the protocol obsolete.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 86/86 Status: On-going

Title: An 18-Month Double-Blind, Multicenter Study to Compare the Efficacy and Safety of the Antiandrogen RU 23908 in Combination with Leuprolide with that of Leuprolide in Patients with Carcinoma of the Prostate (Stage D₂), Followed by an Extended Treatment Period to Evaluate the Long-Term Safety and Tolerance of RU 23908

Start Date: 15 Aug 86 Est Completion Date: Sep 88

Dept/Svc: Surgery/Urology Facility: MAMC

Principal Investigator: COL William D Belville, MC

Associate Investigator: COL Irwin B. Dabe, MC

Key Words: prostate, carcinoma, RU 23908, leuprolide

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: -0- Sep 88

Study Objectives: To compare the safety and efficacy of the antiandrogen RU 23908 in combination with leuprolide to that of leuprolide plus placebo in the treatment of patients with prostatic carcinoma (Stage D₂). Difference in time to progression, survival, clinical response, pain, performance, and long-term safety of RU 23908 will be assessed in the same patient population.

Technical Approach: This is a multicenter study with two parts. Part A is a randomized, double-blind, parallel comparison between the combination of leuprolide plus antiandrogen RU 23908 and leuprolide plus placebo. Patients 18-85 years of age presenting with newly diagnosed stage D₂ carcinoma of the prostate and a life expectancy of at least 3 months will be eligible. Patients who have undergone orchiectomy, received previous hormonal or systemic chemotherapy, with rapidly progressing fatal illness other than carcinoma of the prostate, who have undergone previous hypophysectomy or adrenalectomy, or with another neoplasm, sensitivity to any contrast agent in a radiological evaluation, or severe hepatic or renal dysfunction will be excluded. Patients will be treated for 18 months. Patients who do not respond to treatment will be unblinded. Those receiving RU 23908 will be given the option to continue or to receive other treatment. Patients receiving placebo will be withdrawn from the the study.

Progress: The consent form for this study was amended in March 1988 to add the risk of interstitial pneumonitis as a side effect of RU 23908 since a 3.1% incidence of this complication was reported study-wide.

The study was closed to patient entry in September 1988 since the required number of subjects had been enrolled. Seven subjects were enrolled at MAMC with no complications. Monitoring of subjects is still in progress.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 87/57 Status: Completed

Title: Urinary Retention as an Indicator of Prostate Carcinoma

Start Date: 20 Mar 87 Est Completion Date: Jan 88

Dept/Svc: Surgery/ Urology Facility: MAMC

Principal Investigator: COL William D. Belville, MC

Associate Investigators: COL Victor J. Kiesling, MC

LTC John A. Vaccaro, MC

CPT Rodney Davis, MC

Key Words: carcinoma, prostate, urinary retention, indicator

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: -0- N/A

Study Objective: To determine the incidence of adenocarcinoma of the prostate in males who present with acute urinary retention.

Technical Approach: Fifty consecutive patients ≥ 18 years of age presenting with acute urinary retention will be evaluated. A record will be maintained on each subject to include documentation of the results of the findings on physical examination of the prostate and the examiner's initial clinical impression of a benign or malignant gland. Following initial evaluation and stabilization, all patients will undergo standard transperineal needle biopsy of the prostate. Biopsy material will be evaluated for the presence or absence of malignancy. The results of the prostate biopsy will be correlated with the initial examiner's clinical impression and any subsequent prostatic tissue obtained by a definitive surgical procedure.

Progress: Three additional patients were entered in FY 88 for a total of 42 patients studied. The data clearly show that urinary retention is not associated with prostate carcinoma given a normal prostate exam. The findings are in sharp contrast to accepted dogma.

A manuscript has been submitted to the Journal of Urology for consideration for publication.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 88/74 Status: Terminated

Title: A Multicenter Fixed-Dose Study of the Safety and Efficacy of Low Doses of Terazosin in the Treatment of the Symptoms of Benign Prostatic Hypertrophy

Start Date: 16 Sep 88 Est Completion Date: Feb 89

Dept/Svc.: Facility: MAMC

Principal Investigator: COL William D. Belville, MC

Associate Investigators: David Silverman, M.D.

McKay L. Platt, M.D.

Key Words: hypertrophy, prostatic, treatment, Terazosin

Accumulative MEDCASE Est Accumulative Periodic Review

Cost: -0- OMA Cost: \$40.00 N/A

Study Objective: To evaluate the safety and efficacy of four dosage levels of terazosin versus placebo in the treatment of the symptoms of benign prostatic hypertrophy (BPH).

Technical Approach: The study will be divided a 4-week, single-blind, placebo lead-in period, and a 12-week, double-blind treatment period including an initial 24-hour controlled environment observation period. Study visits will occur at 2-week intervals. During the lead-in period, each patient will be evaluated to determine if the selection criteria have been met and to obtain baseline values for the variables to be analyzed. At the final visit of the placebo lead-in period, qualifying patients will be randomly assigned in equal proportions to the following 5 treatment groups: placebo, and 0.5, 1, 2, or 5 mg of terazosin. The first 2 doses of 0.5 mg of terazosin or placebo will be administered during the observation period while the patient is confined in a controlled environment. Placebo patients will continue to receive placebo for the entire 12-week, double-blind period. Following the lead-in period, terazosin patients will be treated at 1-week intervals with successive doses of 0.5, 1, 2, and 5 mg until the randomly assigned fixed-dosage level is reached. Patients will then be maintained at the fixed-dosage level for the remainder of the study. At the final study visit, all terazosin patients will have received terazosin for 12 weeks and will have received the fixed dosage for at least 9 weeks. All study medication will be administered once daily.

Response to treatment will be measured objectively by uroflowmetric determinations at each visit. This will include measurement of peak and average flow rates as well as an assessment of the pattern of flow. Residual urine volumes will be determined at the end of the lead-in period and at the end of the treatment period. The subjective evaluation will be based on a patient diary in which the presence of symptoms will be recorded; a patient self-assessment form; the investigator's symptom evaluation; and the investigator's global assessment of the patient's overall clinical condition.

Progress This study was terminated by the sponsoring company due to a lack of funds.

Detail Summary Sheet

Date: 30 Sep 88	Protocol No.: 87/85	Status: Terminated
Title: <u>Vocal Function Following Carbon Dioxide Laser Surgery</u>		
Start Date: 19 Jun 87	Est Completion Date: Dec 93	
Dept/Svc: <u>Otolaryngology/Surgery</u>	Facility: <u>MAMC</u>	
Principal Investigator: <u>LTC Don B. Blakeslee, MC</u>		
Associate Investigators: <u>Kenton L. Yockey, MA/CCC</u> <u>Guity Nevissi, M.D.</u>		
Key Words: <u>vocal function, surgery, carbon dioxide laser</u>		
Accumulative MEDCASE	Est Accumulative	Periodic Review:
Cost: -0-**	OMA Cost: -0-**	Sep 88

Study Objective: To determine if vocal fold dysfunction is directly related to the depth of the surgically created ulcer of the vocal fold.

Technical Approach: Phase I: Direct laryngostroboscopy will be performed on 12 dogs. The recurrent laryngeal nerves and the external branches of the superior laryngeal nerves will be stimulated and phonation will be videorecorded for 8-12 seconds. A surgical wound will be created by removing a 4x4 mm segment from the midportion of a vocal cord by CO₂ laser dissection with the nonoperated cord serving as the control. The wound will be observed under magnification and photographed to confirm the accuracy of the resection, and the specimen will be histologically examined to verify the exact segments removed. After a six-week healing period, the larynges will be re-examined and laryngeal form and function will be restudied. Function studies will include symmetry of wave form, measurement of subglottic pressure, air flow, sound pressure, and electroglottography. Fundamental frequency, jitter, shimmer, noise-to-harmonics ratio, and intensity will be analyzed on a PM pitch analyzer. The animals will then be euthanized and one vocal fold from each larynx will be removed for histologic examination to include gross anatomy of the body and the cover, fibroblast activity, foreign body, and inflammatory reaction.

Phase II: 24 adult patients with vocal dysfunction secondary to vocal fold lesions, who have failed appropriate medical management, will undergo preoperative studies utilizing the GLIMPES station, which uses a videocamera in conjunction with a microphone, an electroglottograph, an intraoral pressure tube, a transducer, and an accelerometer and its associated electronics to record fundamental frequency, jitter, shimmer, noise-to-harmonics ratio, and intensity. The patient will then undergo excision of the vocal fold lesion by CO₂ laser with specimens obtained for histopathology. The depth of of each incision will be documented and recorded. Each patient will be studied again using the GLIMPES station at 3, 6, and 12 months after surgery.

Progress: This protocol was terminated due to design problems and a lack of funding. It had been submitted for a joint

**VA/DoD grant which was denied.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 87/38 Status: Completed

Title: Bioreactivity of Blood Vessel Prostheses After
Implantation

Start Date: 16 Jan 87 Est Completion Date: Jan 89

Dept/Svc: Surgery/General Facility: MAMC

Principal Investigator: CPT Jon C. Bowersox, MC

Associate Investigators: COL Charles A. Andersen, MC
John B. Sharefkin, M.D.

Key Words: bioreactivity, prostheses, blood vessel, fibronectin

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: \$1386.00 N/A

Study Objective: To quantitate the levels of fibronectin on the luminal surfaces of blood vessel grafts; to determine the distribution of fibronectin; and to measure the extent of vascular endothelial cell spreading and attachment on the graft surfaces.

Technical Approach: Fibronectin assay by ELISA: Specimens will be incubated in a polycarbonate immunoassay chamber, first with rabbit anti-human fibronectin antibody and then with alkaline phosphatase-conjugated goat anti-rabbit IgG. Samples will then be incubated with nitrophenylphosphate and an ELISA reader used to determine relative concentrations of the reaction product. Positive controls of the enzymatic detection system will be prepared by reacting the phosphate substrate directly with secondary antibody conjugate. A standard curve will be constructed from serial dilutions of human fibronectin incubated with either nonimplanted graft material or NIH reference standard polyethylene. This assay will also be performed using monoclonal antibodies against the human fibronectin cell-binding domain. Cell attachment studies: Human saphenous vein endothelial cells (SVEC) in near confluent monolayers will be exposed to ³H-thymidine in M199 for 24 hours and the resulting radiolabeled cells harvested. Specific radio-labeling activity will be determined by quantitating equal cell aliquots with a hemacytometer and a scintillation counter. All samples will be standardized so that equal aliquots can be incubated with graft material, after which samples of both the attached cells and the reaction supernatant will be quantitated with a scintillation counter. Cell spreading: SVEC will be prepared as described above except that ³H-thymidine uptake will be omitted. Following incubation with the graft material, cells will be fixed, stained with Wright's stain, and quantitated by light microscopy. Immunohistochemical examination of graft surfaces: Prepared sections of the graft material will be subjected to antibody staining. After incubating the specimens first with rabbit anti-human fibronectin and then with rhodamine-conjugated goat anti-rabbit IgG, they will be examined by epi-illumination light microscopy.

Progress: The results of this study were published in the Surgical Forum and CPT Bowersox was awarded the Henry Harkins Award for the best resident research paper at the Washington State Chapter of the American College of Surgeons Annual Meeting.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 87/39 Status: Terminated

Title: Effects of Cell Attachment Peptides on Endothelial Cell Binding to Synthetic Blood Vessel Grafts

Start Date: 16 Jan 87 Est Completion Date: Jun 88

Dept/Svc: Surgery/General Facility: MAMC

Principal Investigator: CPT Jon C. Bowersox, MC

Associate Investigator: COL Charles Andersen, MC

Key Words: cell attachment peptides, endothelial cell binding, synthetic blood vessel grafts

Accumulative MEDCASE Est Accumulative Periodic Review:
Cost: -0- OMA Cost: \$1220.00 N/A

Study Objective: To determine the effects of the cell attachment peptides on endothelial cell seeding (attachment and retention).

Technical Approach: Crosslinking cell attachment peptides to graft material: The synthetic cell attachment peptides arginine glycine aspartic acid (RGD) and RGD + serine-cysteine (RGDCS) will be used in this study. A reaction will be started by dissolving RGDCS in DMSO containing 10 mM SADP (N-succinimidyl-4-azidophenyl-1, 3 dithiopropionate). After 30 minutes, the reaction will be terminated and DMSO removed by dialysis. PTFE and Dacron graft material will be cross reacted with RGDCS-SADP and activated by exposure to light. The efficiency of the crosslinking reaction will be determined by using ³H-RGDCS peptides prepared by borohydride reduction.

Determining endothelial cell attachment efficiency to grafts: Graft material prepared as described above will be placed in immunoassay chambers and cell attachment will be quantitated using human saphenous vein endothelial cells. To determine the specificity of the attachment reaction for cell attachment peptides, RGD and RGDCS will be added to the attachment medium containing the endothelial cells.

The major difficulty in completing this study will lie in effectively crosslinking attachment peptides to graft materials. Heterobifunctional crosslinking reagents are the most versatile class of linkers available; if the initially chosen molecule is ineffective, additional crosslinkers will be utilized.

The reactivity of these grafts toward platelets and fibrin will be compared with those coated with the intact fibronectin molecule.

Progress: This study was terminated due to scheduling conflicts for the laboratory studies.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 87/58 Status: Completed

Title: Patency of Double J Ureteral Stents

Start Date: 20 Mar 87 Est Completion Date: Mar 88
Dept/Svc: Surgery/Urology Facility: MAMC
Principal Investigator: MAJ Charles W. Fox, Jr, MC
Associate Investigators: COL William Belville, MC
COL Stanton F. Brown, MC
COL Robert D. Karl, MC
COL Victor J. Kiesling, MC
LTC John A. Vaccaro, MC
Key Words: ureteral stents, patency, cystography (nuclear and retrograde), lasix renography
Accumulative MEDCASE Est Accumulative Periodic Review:
Cost: -0- OMA Cost: \$35.00 N/A

Study Objective: To establish the lasix diuretic renogram half disappearance time for renal units which have indwelling double J silicone ureteral catheters; to compare the ability of standard retrograde cystography and nuclear cystography in determining patency of double J silicone ureteral catheters in obstructed renal units; and to correlate the half time of disappearance of radionuclide with patency evaluations done by standard retrograde cystography and nuclear cystography.

Technical Approach: Twenty patients requiring an indwelling ureteral catheter will undergo retrograde cystography, nuclear cystography, and lasix renography prior to placement of the catheter. Patients will receive post-instrumentation antibiotics to decrease the risk of infection. The same tests will be repeated at 2 weeks post-catheter placement and every 4 weeks after that until the catheter is removed. Four weeks following removal, patients will be studied again.

The Nuclear Medicine Service will calculate the half life on lasix renography and evaluate the nuclear cystogram for demonstration of reflux into the renal pelvis which would be listed as a positive test. The Urology Service will interpret the retrograde cystogram. A positive test will be demonstration of reflux into the renal pelvis.

Progress: 36 additional patients were studied in Fy 88 for a total of 50 patients studied. A paper is to be presented at the Kimbrough Urological Conference in November 1988 and to the Northwest Urologic Conference in December 1988.

The prospective comparison of retrograde cystography, nuclear cystography, and lasix renography to detect indwelling ureteral stent patency has shown that the lasix renogram is the most sensitive test. Stent obstruction occurred in 8% of stents followed; 44% of the stents in place longer than three months were obstructed.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 86/50 Status: Terminated

Title: Ultrasonic Imaging of Veins Throughout Pregnancy and
Early Post-Partum

Start Date: Mar 86 Est Completion Date: Sep 88

Dept/Svc: Surgery/Vascular Surgery Facility: MAMC

Principal Investigator: Nancy N. Greenfield, R.N., M.S., DAC

Associate Investigators: COL William L. Benson, MC

Linda K. Bickerstaff, M.D., DAC

Key Words: DVT, pregnancy, early post-partum, ultrasound

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: \$16,990.00 OMA Cost: -0- Sep 88

Study Objective: To map out changes occurring in the veins throughout normal pregnancy and identify patients at risk for or having deep venous thrombosis (DVT).

Technical Approach: Thirty patients aged 18-30, assumed to have a normal uncomplicated pregnancy with no history of DVT or a complicated pregnancy in the past, will be studied. Fifteen patients will be first pregnancy and 15 patients will be in a second or later pregnancy. Ultrasonic imaging of the deep venous system - from the common femoral vein as far distal as can be imaged (an attempt will be made to image the calf vessels) will be done. Recording of the images will be made on video. These studies will be done serially at 3, 6, 7, 8, and 9 months and again 6 weeks post-partum.

Progress: The equipment was unable to give the resolution necessary for study purposes. The study was attempted on other equipment, which was unable to visualize values below common femoral vein. Therefore, the study was terminated.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 87/55 Status: Completed

Title: Technetium-99m Stannous Pyrophosphate Myocardial
Scintigraphy in the Diagnosis of Rabbit Myocardial
Contusion

Start Date: 20 Mar 87 Est Completion Date: May 87

Dept/Svc: General Surgery Facility: MAMC

Principal Investigator: CPT Robert L. Hall, MC

Associate Investigators: COL Robert C. Karl, MC

LTC James Jones, MC

CPT George Hodges, MC

CPT Mark R. Nyreen, MC

Key Words: myocardial contusion, diagnosis, scintigraphy,
99m technetium stannous pyrophosphate

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: \$131.00 Sep 88

Study Objective: To determine if 99m technetium pyrophosphate scintigraphy will accurately diagnose acute myocardial contusion in the rat model.

Technical Approach: Ten large adult SPF Sprague-Dawley rats will be anesthetized and connected to a 3-lead ECG. While anesthetized, the rats will receive a controlled mediastinal-directed blow sufficient to induce cardiac injury yet allow the rat to survive. Prior studies on four rats will have determined the exact procedures to be used to give consistent injuries. Technetium pyrophosphate will be injected intravenously into the rat. Two hours after injection, the rat will undergo nuclear scanning. After completion of the scan, a thoracotomy will be performed and the heart and great vessels will be harvested. The harvested heart will be inspected for gross evidence of injury. Histopathological findings will be identified and noted. The accuracy of the nuclear medicine scan will be determined by comparing the scan results with confirmed pathological evidence of injury. Four additional rats will serve as controls and undergo all procedures except the injury.

It is anticipated that the results derived from this protocol will be clear cut and will lead to obvious conclusions. However, if instances arise where the data suggest ambiguity as to whether subtle or minor changes occurred compared to controls, then the potential implications of such changes will be analyzed to determine if it would be of interest in the context of the project to examine them by detailed mathematical statistical analysis.

Progress: Eight rabbits were studied. The study has been completed and the principal investigator is preparing a paper for submission for publication.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 85/21 Status: On-going

Title: Advanced Trauma Life Support Course

Start Date: 16 Jan 85 Estimated Completion Date: Indefinite

Dept/Svc: Surgery/General Facility: MAMC

Principal Investigator: COL Stanley C. Harris, MC

Associate Investigator: MAJ Leslie W. Yarbrough, VC

Key Words: residents, venous cutdown, cricothyroidotomy, tube
thoracostomy, peritoneal lavage, pericardiocentesis,
goat model

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: \$1600.00 Sep 88

Study Objective: To provide training to general surgery, emergency medicine, and family practice residents and, specifically, to teach proper management of the initial one hour following major trauma.

Technical Approach: During a laboratory session involving goat surgery, each student in the group will be directly involved in a hands-on performance of a venous cutdown, a cricothyroidotomy, a tube thoracostomy, peritoneal lavage, and pericardiocentesis. This course will be conducted 3-4 times/year at MAMC.

Progress: Three ATLS courses were presented with approximately 16 students per class.

Detail Summary Sheet

Date: 30 Sep 88	Protocol No.: 87/31	Status: Terminated
Title: Stapedius Reflex for Evaluation of the Perforated Tympanic Membrane		
Start Date: 1 Jun 87	Est Completion Date: Dec 87	
Dept/Svc: Surgery/Otolaryngology	Facility: MAMC	
Principal Investigator: CPT Michael A. Jaindl, MC		
Associate Investigators: LTC Carl M. Loovis, MS CPT Robert Wright, MS		
Key Words: tympanic membrane, perforated, stapedius reflex		
Accumulative MEDCASE	Est Accumulative	Periodic Review:
Cost: \$6895.00	OMA Cost: -0-	N/A

Study Objective: To examine the stapedius reflex in patients with perforations of the tympanic membrane and correlate size of perforation with presence of reflex.

Technical Approach: Patients who have been identified with a tympanic membrane perforation or PE tube in place will be examined and the location and size of the perforation documented. A pure tone audiogram and stapedius reflex testing will then be performed. The stapedius reflex testing will be done using a Model 310 audiometer with test frequencies of 1, 5, and 10 KHz and probe tones of 200 and 500 Hz and 1 KHz. The amplitude of each response will be recorded. The strength of the test signal will be increased and the resultant reflex amplitude will be observed and recorded in order to document presence or absence of rollover. Finally, a continuous test signal will be presented to test for reflex decay. Any patient with evidence of rollover or reflex decay will be included in the study and referred for further noninvasive tests to rule out presence of an acoustic or cerebellopontine angle tumor.

The data will be analyzed to attempt to correlate size of perforation with presence and amplitude of stapedius reflex. Calculations will be presented that demonstrate the acoustics of the stapedial reflex as generally understood today. Calculations will also be presented that support the observation that a stapedius reflex can be measured in the presence of a perforation depending on the size of the perforation. Chi square analysis will be used to correlate reflex amplitude and size of perforation.

All patients with perforations will be followed. If the perforation closes, the patient will be reevaluated using the same procedure to document presence of stapedius reflex.

Progress: The digital audiometry equipment was received, tested, and calibrated. Testing on volunteer subjects was started. However, the equipment was found to be too sensitive at high frequencies to adequately access tympanic membrane movement due to transients and artifacts. The project was terminated. Further investigation will require a different protocol.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 88/01 Status: Completed

Title: Effect of Post-Operative Nutritional Support on Plasma Fibronectin

Start Date: 16 Oct 87 Est Completion Date: Feb 88

Dept/Svc: Surgery/General Facility: MAMC

Principal Investigator: CPT Linda K. James, MC

Associate Investigators: MAJ Stephen B. Smith, MC

CPT Jon C. Bowersox, MC

Key Words: fibronectin, plasma, nutritional support, post-op

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: \$600.00 N/A

Study Objective: To determine if the decrease in circulating plasma fibronectin observed after surgery may be prevented by immediate post-operative, peripherally administered, parenteral nutritional support.

Technical Approach: Patients age 18 and older, without evidence of active malignancy or signs of infection will be studied. Inclusion into the study will be limited to patients admitted with a diagnosis of small bowel obstruction. Patients on total parenteral nutrition administered through a central venous catheter will be excluded. Patients will be randomized to either post-operative hydration with D₅ and appropriate electrolytes or standard parenteral post-operative nutrition beginning at 0300 on post-operative day 1. Admission fibronectin levels will be measured and serial assays will be done on post-operative days 1, 3, 5, and 7 or until the patient is tolerating a regular diet. Twelve to 15 patients per group will be studied.

Preoperatively, the means of the two groups will be compared using the unpaired Student's t test to ensure they are the same. A paired t test will be used to determine if subsequent values are different from the admission or preoperative fibronectin values (and other parameters such as weight, WBC, etc).

Progress: This study was completed and a paper was presented at the Gary P. Wratten symposium and at the Northwest Chapter of the American College of Surgeons.

The data show that plasma fibronectin levels fall 20-30% with surgery in both groups of patients. In patients receiving PPN, there is a return to preoperative fibronectin levels by post-operative day three, with a rebound increase in fibronectin levels to 135% of preoperative values after that time. In contrast, patients receiving D₅ and electrolyte solutions only had prolonged depression of fibronectin levels below preoperative values. Thus, PPN appears to be a reasonable alternative to central venous hyperalimentation in restoring plasma fibronectin levels in surgical patients and may provide a means for reducing the morbidity associated with postoperative malnutrition without the risks and cost associated with central venous access.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 88/57 Status: Suspended

Title: Evaluation of Ankyloglossia: A Prospective Study

Start Date: 20 May 88 Est Completion Date: Apr 91
Dept/Svc: Surgery/ Otolaryngology Facility: MAMC
Principal Investigator: CPT Ray E. Jensen, MC
Associate Investigators:
COL Gerald R. Aaron, DC MAJ Robert J. Newman, MC
LTC Don B. Blakeslee, MC Mark J. Stephan, M.D., DAC
MAJ Jose D. Masi, MC Kenton L. Yockey, M.A., DAC
Key Words: natural history, criteria for intervention & treatment
Accumulative MEDCASE Est Accumulative Periodic Review:
Cost: -0- OMA Cost: -0- N/A

Study Objective: To better define the natural history of congenital ankyloglossia in order to establish appropriate criteria for intervention and treatment.

Technical Approach: This will be a non-randomized prospective study of congenital ankyloglossia to include objective diagnosis with management based on multi-disciplinary input from otolaryngology, speech pathology, dentistry, and pediatrics. Electron microscopy will be included for completeness. Hereditary patterns will be investigated and reported when available. Indications will be speech disorders, swallowing problems, dental problems, and cosmetic/functional abnormalities all directly related to ankyloglossia. Consultations will be obtained on all patients from speech pathology, developmental pediatrics, and dentistry. Speech recordings will be obtained pre and post-treatment.

Twenty-five patients <3 years will be entered and observed. Twenty-five patients ≥ 3 years will be entered and considered for surgical repair if indicated. Periodic review of subject files will take place as needed to direct appropriate management and case gathering. Follow-up for surgical patients will be at two weeks post-operation and at 1 and two years for all patients. After a two to three year period, cases will be compiled and an attempt made to draw conclusions from the gathered data. Type of data analysis will be based on type of data obtained.

Progress: This protocol has been suspended until the principal investigator provides the revisions required by the Institutional Review Board.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 86/94 Status: On-going

Title: A Prospective Evaluation of Testicular Shielding in Preventing Hypogonadism in Prostate Cancer Patients Receiving External Beam Radiotherapy

Start Date: Sep 86 Est Completion Date: May 87

Dept/Svc: Surgery/General Facility: MAMC

Principal Investigator: COL Victor J. Kiesling, MC

Associate Investigators: COL Donald H. Kull, MC
COL Stephen R. Plymate, MC
MAJ Pushpa M. Patel, MC
CPT Christopher P. Evans, MC

Key Words: prostate cancer, hypogonadism, testicular shielding

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: \$1500.00 Sep 88

Study Objective: To assess a possible protective effect on testicular function of a lead testicular shield during the radiation treatment period.

Technical Approach: Twenty prostate cancer patients >18 years will be randomized into two groups to wear a lead gonadal shield during radiation therapy or to wear no shield during the therapy. Patients with prior radiation or hormonal therapy will be excluded. Prior to entry blood will be drawn for basal FSH, LH, testosterone, TeBG, prolactin, and estradiol levels. An LHRH stimulation test will be done with 30 and 60 minute levels drawn. Blood will again be drawn during mid-course of therapy and at 1 and 12 weeks post-therapy for these same determinations. Comparison of group results will be performed by standard statistical methodology.

Progress: COL Victor Kiesling took over the protocol as principal investigator upon the reassignment of Dr. Evans.

Three additional patients were entered in FY 88. Radiotherapy and pre and post LHRH stimulation tests have been completed on all subjects. Several prospective candidates for this study have refused enrollment during FY 88 due to the logistics problem of returning for the LHRH stimulation tests. The investigators will continue to attempt to enroll subjects with a projected goal of 20 subjects.

Detail Summary Sheet

Date: 30 Sep 88	Protocol No.: 88/31	Status: On-going
Title: Photodynamic Therapy of Human Prostate Cancer in Vitro		
Start Date: 19 Feb 88	Est Completion Date: Aug 88	
Dept/Svc: Surgery/Urology	Facility: MAMC	
Principal Investigator: COL Victor J. Kiesling, MC**		
Associate Investigators: COL William Belville, MC		
CPT Thomas A. Rozanski, MC		
Richard Ostenson, M.D., ALVAMC		
Stephen Loop, M.S., ALVAMC		
Key Words: cell line, prostate, ALVA-31, HPD, phototherapy		
Accumulative MEDCASE	Est Accumulative	Periodic Review:
Cost: -0-	OMA Cost: \$1205.00	N/A

Study Objective: To study the effect of photodynamic therapy on the primary human prostate tumor cell line ALVA-31, using the hematoporphyrin derivative (HPD) as the photosensitizing agent.

Technical Approach: Tumor cells from a primary human prostate cancer cell line which originated from a radical prostatectomy specimen and which has been maintained in continuous culture for over 3 years will be used in this study. Tumor cells will be suspended in media and placed on a 96-well plate using 10,000 cells/well. HPD will be diluted with tissue culture media into various concentrations, ranging from 0.3 to 40.0 µg/ml. The cells will be incubated with the HPD for varying periods of time prior to light exposure with a 750 watt halogen-tungsten lamp. Light passes through a plate of heat absorbing glass and a red filter prior to irradiating the cells. Each plate will be set up with 3 treatment groups: cells exposed to light only without prior HPD treatment; cells treated with HPD and kept covered during the light exposure; and cells treated with HPD and exposed to light. Following light exposure, the tumor cells will be incubated with tritiated thymidine, used as a measure of cell growth. This process measures the effect of HPD phototherapy on the viability of the prostate tumor cells. Preliminary studies, using 8 different doses of HPD and incubating cells with HPD for 2 hr prior to light exposure at 30 sec and 2 and 6 min demonstrated an obvious dose-response relationship to both increasing the dose (concentration) of HPD and increasing the duration of light exposure. These experiments will be repeated as well as devising a more complete response curve with the above mentioned variables.

Progress: Using tritiated thymidine uptake, a dose response relationship in cell toxicity with respect to time of light exposure and to increasing concentration of HPD was demonstrated in the ALVA 31 human prostate tumor cell line. Repeat confirmatory studies are pending acquisition of more HPD which is presently not available. Preliminary results were presented by Dr. Rozanski at the Kimbrough Urological Society in November 1987 and at the Northwest Urological Society in December 1987.

**Replaced CPT Rozanski as the principal investigator, Jul 88.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 79/64 Status: On-going

Title: Implantation of Intraocular Lenses

Start Date: 16 Mar 79 Est Completion Date: Indefinite

Dept/Svc: Surgery/Ophthalmology Facility: MAMC

Principal Investigator: LTC Thomas H. Mader, MC

Associate Investigators: MAJ Kevin J. Chismire, MC

COL Stanley C. Allison, MC MAJ Leslie P. Fox, MC

COL Stanley C. Sollie, MC MAJ Paul H. Ryan, MC

LTC John C. Goodin, MC MAJ Anthony R. Truxal, MC

LTC Christopher G. Knight, MC MAJ Lawrence J. White, MC

MAJ Bruce D. Bellin, MC CPT Lawrence E. Hannon, MC

Key Words: intraocular lenses, implantation

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: \$200.00 Sep 88

Study Objective: To become proficient in intraocular lens implantation and to gain investigator status with FDA requirements, in order to provide a new technique in ophthalmic surgical care for our patients.

Technical Approach:

1. Obtain appropriate instruments to accomplish the procedure.
2. Obtain research investigator status with companies that have FDA approval to supply the lenses.
3. Implant lenses in 10 rabbits as a training experience for surgical nurses and assistants in this procedure.
4. Implant lenses in appropriately selected patients in order to provide visual rehabilitation.
5. To eventually establish this as a routine procedure in the military medical armamentarium of ophthalmic care.

Progress: Approximately 250 IOL's were implanted in FY 87 with no adverse reactions. IOL's have withstood the test of time and most are now considered safe for most patients. Most IOL's are no longer considered investigational. However, the protocol will remain open in order to use updated lenses that are still investigational.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 86/29 Status: Terminated

Title: The Clinical Study of Intraocular Lens Implant and the Use of Viscoat, Phase II

Start Date: 17 Jan 86 Est Completion Date: Jan 88

Dept/Svc: Surgery/Ophthalmology Facility: MAMC

Principal Investigator: LTC Thomas M. Mader, MC

Associate Investigators: MAJ Kevin J. Chismire, MC

MAJ Leslie P. Fox, MC

MAJ Lawrence J. White, MC

Key Words: IOL, Viscoat, adverse effects, other surgeries

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: -0- Sep 88

Study Objective: To collect data for reports of potential adverse reactions or complications which may have been undetected in a pilot study with a smaller patient population and to evaluate certain indications including corneal transplant surgery, retinal detachment surgery, glaucoma filtering surgery, and other more specific procedures.

Technical Approach: Viscoat is a sterile non-pyrogenic, viscoelastic solution used to maintain anterior chamber depth which exhibits IOL coating properties and effectively protects the ocular tissue, as shown in Phase I of this study of 200 consecutive patients. In Phase II, additional investigators will be added to the study and non-consecutive patients will be used to provide a sufficient number of patients in certain surgical procedure categories, such as corneal transplant, glaucoma surgery, and retinal detachment. The preoperative condition of each patient will be recorded with particular reference to corneal abnormalities, previous anterior segment disease, and intraocular pressure level. Intraoperative conditions will be evaluated and recorded as to the ocular status before Viscoat is injected. Viscoat will be introduced and the amounts introduced aspirated from the eye will be recorded, along with the effectiveness in facilitating anterior segment surgery. At 1-3 and 4-15 days postoperatively, the corneal appearance, anterior segment inflammation (iritis), and intraocular pressure level will be examined and recorded. In order to monitor the safety of Viscoat, a table will be generated that summarizes the occurrence of both adverse reactions and postoperative complications.

Progress: Approximately 150 patients have been treated with Viscoat with no adverse reactions. The Ophthalmology staff was of the opinion that Viscoat did not satisfactorily coat intraocular lenses or lend itself to easy aspiration from the human eye as compared with sodium hyaluronate. Therefore, the study was terminated.

Detail Summary Sheet

Date: 30 Sep 88	Protocol No.: 87/21	Status: On-going
Title: Home Intravenous Hyperalimentation in Treatment of Lymphoma		
Start Date: Nov 86	Est Completion Date: Sep 87	
Dept/Svc: Surgery/General	Facility: MAMC	
Principal Investigator: CPT Robert Martindale, MC		
Associate Investigators:		
Pamela Charney, R.D.	COL Charles A. Andersen, MC	
LTC Howard Davidson, MC	COL John Redmond, MC	
MAJ Lauren K. Colman, MC	COL Irwin B. Dabe, MC	
Key Words: lymphoma, hyperalimentation, intravenous, home		
Accumulative MEDCASE	Est Accumulative	Periodic Review:
Cost: -0-	OMA Cost: -0-	Jan 88

Study Objective: To determine if addition of home intravenous hyperalimentation in patients treated with aggressive, curative-intent chemotherapy regimens for lymphoma can reduce the incidence of chemotherapy complications, specifically mucositis, weight loss and infection; and to study whether patients treated with hyperalimentation are able to stay closer to full intended doses.

Technical Approach: Ten subjects ranging from 18-75 years will be studied. Chemotherapy medications will already have been determined. Patients will receive Nystatin Swish and Swallow or Mycellex Troches, generic mylanta, Benydryl, and Lidocaine Gel mouthwash, and Septra. An I.V. hyperalimentation solution based on metabolic requirements as determined by the BEE method with the addition of appropriate stress factor will start within one week of first chemotherapy. TPN will be given according to the same schedule as chemotherapy. TPN will be temporarily withheld if a patient's weight gain is >5 pounds above entry weight. Patients will be given either the total estimated caloric requirement or one half the total estimated and adjusted weekly as needed. Hyperalimentation will be given at night so as not to itself deter patients from oral alimentation. Body weight changes, TLC, albumin values, number of days hospitalized, number of days with fever, number of days with severe stomatitis, and percentage of full dose chemotherapy in patients who receive MACOP-B will be compared to those same values and parameters in a historical control group of seven patients who received MACOP-B. For patients who receive m-BACOD or PROMACE-Cytabom, the control group will be historical controls as reported in Phase II SWOG studies of each of the regimens. Analysis will be performed by calculating means of each parameter in the two groups compared, then using chi-square analysis.

Progress: Three patients were entered in the study in FY 87 with no adverse effects reported. No additional subjects have been entered in FY 88 due to funding restraints.

Detail Summary Sheet

Date: 30 Sep 88	Protocol No.: 88/40	Status: On-going
Title: Clinical and Radiographic Evaluation of Base Wedge Osteotomies of the First Metatarsal		
Start Date: 18 Mar 88	Est Completion Date: Mar 89	
Dept/Svc: Surgery/Podiatry	Facility: MAMC	
Principal Investigator: CPT Ernest L. Mollohan, MS		
Associate Investigators: MAJ Richard O. Jones, MS		
Key Words: periosteum, stripping/nonstripping, x-rays		
Accumulative MEDCASE	Est Accumulative	Periodic Review:
Cost: -0-	OMA Cost: -0-	N/A

Study Objective: To assess the effects on bone healing of stripping or not stripping the periosteum when performing base wedge osteotomies of the first metatarsal, utilizing ASIF fixation.

Technical Approach: A minimum of 100 patients with signs and symptoms within the realm of diagnosis of hallux abducto valgus, requiring surgical intervention, will have base wedge osteotomies of the first metatarsal performed. Patients will be randomized to have the periosteum stripped or not stripped prior to ASIF fixation. All patients will be placed in below the knee casts with crutch ambulation. Periosteum will be cut with sharp dissection in all cases, whether for complete exposure of metatarsal shaft or for measuring wedge osteotomy. Axial, lateral, and medial oblique x-rays will be obtained at 2, 6, 12, and 26 weeks postsurgery. Radiographs will be compared for boney union.

Progress: Sixty patients have been entered in the study.

Detail Summary Sheet

Date: 30 Sep 88	Protocol No.: 86/85	Status: On-going
Title: Device for Intraoperative Identification of Recurrent Laryngeal Nerve		
Start Date: 15 Aug 86	Est Completion Date: Indefinite	
Dept/Svc: Surgery/Otolaryngology	Facility: MAMC	
Principal Investigator: LTC David W. Moore, MC**		
Associate Investigators: COL Charles A. Andersen, MC		
LTC Donald B. Blakeslee, MC		
MAJ Peter Greenman, MC		
CPT Dale B. Smith, MC		
Key Words: laryngeal nerve, identification, balloon device		
Accumulative MEDCASE	Est Accumulative	Periodic Review:
Cost: -0-	OMA Cost: -0-	Aug 88

Study Objective: To determine the effectiveness of using an endolaryngeal monitoring device to assist in identification of laryngeal nerves and the prevention of intraoperative nerve damage.

Technical Approach: This protocol will be implemented if animal studies in #86/84 (CPT Dale Smith, principal investigator) are successful. Patients requiring general anesthesia for surgical procedures involving risk of injury to laryngeal nerves will undergo a pre-op laryngeal exam and voice analysis. Intubation with a double-cuffed endotracheal tube will be done at surgery. The upper most cuff (sensing balloon) will lie at the level of the true vocal cord and will be intermittently inflated while connected to a Hewlett-Packard arterial pressure monitor through a pressure transducer. Electrical stimulation of the laryngeal nerves with resultant true vocal cord motion will be confirmed by graphic display. Post-operative laryngeal exam will be conducted and any anatomic or vocal impediment will be noted. Patients will be followed until normal laryngeal function returns. Statistical analysis will be done of change in operative morbidity using the device. Possible correlation between required stimulation amperage, graphic pattern, and type and duration of laryngeal impediment will be studied. Further analysis will attempt to correlate the findings in the swine study with this human clinical trial.

Progress: 14 patients were entered in FY 88 for a total of 35 patients studied. The device, to date, has proven reliable, safe, and effective.

A paper was presented at the American Academy of Otolaryngology Head and Neck Surgery Meeting in September 1988.

**LTC Moore replaced Dr. Smith as the principal investigator, Aug 88.

Detail Summary Sheet

Date: 30 Sep 88	Protocol No.: 87/42	Status: Terminated
Title: Efficacy of Behavioral Testing as a Screening Device for Military Children at High Risk for Hearing Loss		
Start Date: 27 Feb 87	Est Completion Date: Jan 89	
Dept/Svc: Surgery/Audiology	Facility: MAMC	
**Principal Investigator: MAJ Reynaldo M. Perez, MS		
Associate Investigators: LTC Carl F. Loovis, MS		
CPT Randy Bennett, MC		
CPT Robert Wright, MS		
Key Words: hearing loss, children, behavioral testing		
Accumulative MEDCASE	Est Accumulative	Periodic Review:
Cost: -0-	OMA Cost: \$200.00	N/A

Study Objective: To devise a time efficient, effective, and practical procedure for the early identification of childhood hearing loss and to develop a behavioral screening method that is simple, accurate, and brief enough to act as a primary filter.

Technical Approach: Thirty infants 4.5-12 months will be tested. The subjects will be infants with congenital prenatal infections, elevated bilirubin, low birth weight, with suspected craniofacial abnormalities, *H. influenza* meningitis, other NICU graduates, or those whose parents have expressed concern. Screening for narrow band and speech detection will be performed using a conventional 2-channel clinical audiometer. Screening for speech will be performed using a monitored live voice peaked on a VU meter uttering the child's name alternately with the nonsense syllables "pa-pa-pa". The screening level criterion for a "pass" for narrow band will be 40 db and 30 db KHz for threshold estimate for speech. Response authentication will be performed by an examiner in the control booth and an observer seated facing the mother and child. Infants will be given a tympanometric exam on each visit and any child with middle ear pressure in excess of negative 100 mm H₂O in either ear will be screened out. The subjects will return at a later date for auditory brainstem response testing. A questionnaire will be filled out by a parent to establish whether there is parental concern about deafness. Subjects will be divided into 2 categories, "pass" or "fail" behavioral screening criteria. All will be evaluated by ABR, a definitive means of establishing the integrity of the basal portion of the cochlea. A matrix will be developed, plotting "pass/fail" according to the two different measures. A statistical value for specificity and sensitivity will be determined to evaluate the effectiveness of the behavioral procedure in predicting hearing loss as determined by the ABR. Trends pointing to the greater predictability of hearing loss by etiology using the behavioral technique will be sought.

Progress: Four infants were entered in FY 88 for a total of 11 infants studied. Due to the transitory nature of the targeted population, it has proven to be extremely difficult to enroll subjects for this study; therefore, it was terminated.

**MAJ Perez replaced LTC Loovis as the principal investigator in December 1987.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 88/56 Status: On-going

Title: Idiopathic Hematuria with Hypercalciuria in Adults:
Incidence, Pathogenesis, and Treatment

Start Date: 20 May 88 Est Completion Date: May 89

Dept/Svc: Surgery/Urology Facility: MAMC

Principal Investigator: CPT Leonard G. Renfer, MC

Associate Investigators: COL Victor J. Kiesling, MC
MAJ Howard M. Cushner, MC

Key Words: hematuria, hypercalciuria, HCTZ vs no treatment

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: 2000.00 N/A

Study Objective: To identify that proportion of patients with idiopathic hematuria that have hypercalciuria and to monitor the response of the hematuria to hydrochlorothiazide (HCTZ) in both normocalciuric and hypercalciuric patients.

Technical Approach: Patients \geq 18 years of age with idiopathic hematuria will be studied for hypercalciuria. Specifically, patients with hematuria >2 RBC/hpf on spun sample will undergo IVP/cytoscopy/urine C&S. If these studies fail to identify the source of persistent hematuria, the patients will undergo the following studies: 24-hr urine specimen for calcium, protein, creatinine, and uric acid, SMA-20, complete blood count with ESR, PTT/PT, and sickle index (if patient is black).

Patients with normal studies will be divided into control and treatment groups. The treatment group will be treated with HCTZ, 50 mg b.i.d., for 8 weeks. Seven days prior to the initiation of therapy, the patient will begin testing urine dipstick for blood daily and continue for the remainder of the study period. Clinic follow-up for both controls and treatment groups will be at 2, 4, and 8 weeks after initiation of therapy as well as 2 and 4 weeks after termination of therapy. A repeat 24 hr urine collection to assess for response of calcium excretion, the SMA-20 for serum electrolytes, and a separate spot urine sample for urine calcium/urine creatinine ratio will also be performed at each visit.

Patients with the diagnosis of hypercalciuria will be randomized into control and treatment groups with treatment and monitoring as for the subjects with normal studies.

Control groups will receive no treatment, but have follow-up and diagnostic tests as described for the treatment group.

Progress: Four patients were entered in the study in FY 88.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 86/100 Status: Completed

Title: Effects of Androgen Depletion on Human Prostate Tumor Cell Growth in the Athymic Balb/c Mouse

Start Date: Sep 86 Est Completion Date: Sep 87

Dept/Svc: Surgery/Urology Facility: MAMC

Principal Investigator: CPT Thomas A. Rozanski, MC

Associate Investigators:

COL William D. Belville, MC Richard Ostenson, M.D.

COL Stephen R. Plymate, MC Stephen Loop, M.S.

Key Words: prostate tumor, androgen depletion, cell growth, mouse

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: \$7021.00 Oct 87

Study Objective: To study the effects of androgen depletion on prostate tumor growth using the athymic Balb/c mouse and human prostate tumor cell line ALVA-31 as the model.

Technical Approach: Surgical castration will be performed under light halothane anesthesia with aseptic technique. GnRH will be used in doses of 25 to 100 µg and administered as daily intraperitoneal injections or implanted slow-release microcapsules. Flutamide will be administered intraperitoneally on a daily basis. Varying doses will be used to determine optimal effect. Tumor cells will be injected subcutaneously into the posterior flank and volume measured 3 times/wk. Approximately 40 animals will be studied at a time and various hormone manipulations will be compared using normal or castrated animals as controls (8/group). Serum hormone levels will be measured in order to assure castration levels of testosterone, along with monitoring of various other hormone levels before, during, and after treatments. Testosterone and GRH receptors will be isolated from tumor nodules by radioactive iodine binding and dextran/charcoal techniques. Biochemical studies will attempt to characterize the receptors and determine relationships between receptor numbers and activity before and after hormonal manipulations.

Progress: Approximately 200 mice were injected with ALVA-31 prostate tumor cells and treated with various hormonal manipulations, including orchiectomy, intraperitoneal leuprolide, and combination therapy. All three significantly slowed the growth of the tumors; however, combination therapy was better at reducing tumor growth than either method alone.

An abstract from this study won the Best Resident Research Award at both the Kimbrough Urologic Seminar in October 1986 and the Northwest Urologic seminar in November 1986. It was also presented at the meeting of the Western Section of the American Urologic Association in March 1988.

Detail Summary Sheet

Date: 30 Sep 88	Protocol No.: 86/84	Status: Completed
Title: Intraoperative Monitoring of Recurrent Laryngeal Nerve Function in Swine		
Start Date: 15 Aug 86	Est Completion Date: May 87	
Dept/Svc: Surgery/Otolaryngology	Facility: MAMC	
Principal Investigator: CPT Dale B. Smith, MC		
Associate Investigators: LTC Donald B. Blakeslee, MC		
MAJ Edward Woody, MC		
MAJ Leslie W. Yarbrough, MC		
CPT Margaret Richardson, MC		
Key Words: recurrent laryngeal nerve, intraoperative, swine		
Accumulative MEDCASE	Est Accumulative	Periodic Review:
Cost: -0-	OMA Cost: \$800.00	N/A

Study Objective: To demonstrate the effectiveness and sensitivity of an endolaryngeal monitoring device to allow documentation of true vocal cord function during intraoperative electrical stimulation of the recurrent laryngeal nerve and to correlate histologic damage with intraoperative stimulation patterns and post-op recovery rates by the introduction of various stages of nerve damage.

Technical Approach: Five 10-20 kg pigs will be anesthetized and intubated with a 7.0 mm customized double-ballooned endotracheal tube. The sensing balloon will be inflated between the vocal cords and connected to a Hewlett-Packard monitor. Various system settings will be investigated to identify the most suitable balloon inflation volume, graphic sensitivity, and stimulator amperages. Once these parameters are identified, the laryngeal innervation will be exposed using surgical approaches commonly used in human cases. Various degrees of nerve damage will be induced in a unilateral recurrent laryngeal nerve (RLN) by pressure loaded calipers and confirmed by histologic examination of identically damaged nerves which are motor to the strap muscles in the area. Stimulation of the damaged RLN will be recorded graphically, immediately after nerve damage and in the reopened surgical wound on post-op days seven and ten. Additional histologic specimens from damaged strap nerves will be harvested at these times. The wounds will then be allowed to undergo complete healing. The pigs will undergo sedation and endoscopic laryngeal exams and squeal recordings to monitor the laryngeal recovery. The frequency of these exams will be dictated by the speed of recovery.

Progress: Eight animals have been studied. The degree of injury was correlated with perioperative nerve stimulation patterns. The piglet proved an adequate model for laryngeal research. The investigators had planned to study additional animals, but a decision was made to report the protocol as completed when the principal investigator was reassigned.

An abstract was presented at the Annual Meeting of the Otolaryngology, Head and Neck Surgery Meeting in September 1987 and a paper has been submitted for publication.

Detail Summary Sheet

Date: 30 Sep 88	Protocol No.: 87/89	Status: On-going
Title: The Effect of a Veterans Administration Geriatric Assessment and Rehabilitation Unit on Elderly Surgery Patients from an Army Medical Center		
Start Date: 19 Jun 87	Est Completion Date: Dec 90	
Dept/Svc: Surgery/General	Facility: MAMC	
Principal Investigator: MAJ Stephen B. Smith, MC		
Associate Investigators: David Silverman, M.D., ALVAMC Kenneth Mostow, ALVAMC		
Key Words: geriatric, surgery, assessment, rehabilitation		
Accumulative MEDCASE	Est Accumulative	Periodic Review:
Cost: -0-**	OMA Cost: -0-**	Sep 88

Study Objective: To determine if frail, elderly surgery patients treated in the Geriatric Assessment and Rehabilitation Unit (GARU) at American Lake VA Medical Center (ALVAMC) will have better outcomes with improved cost-benefit and cost-effectiveness than those receiving the standard care at Madigan Army Medical Center (MAMC).

Technical Approach: The study population will consist of 160 elderly (>65) patients who have had surgery at MAMC with one or more medical or functional problems that will interfere with discharge. Persons with severe dementia or terminal phase disease will be excluded. The patients will be enrolled five days after surgery and randomly assigned to either remain at MAMC and receive the usual care or be transferred to ALVAMC and treated at the newly created GARU. The GARU utilizes an interdisciplinary team trained in geriatrics to provide specialty care to frail elderly patients at risk of institutionalization. Before randomization, study patients will be interviewed to obtain baseline data regarding demographic background, medical and social history, and physical and mental function. A relative or close friend will be interviewed to confirm this information. The patients will be reassessed to include patient and proxy interview at discharge and at 3 and 12 months after discharge. Standardized and validated instruments will be used to measure changes in the physical and mental functioning of both groups to include the Personal Self-Maintenance Scale, the Instrumental Activities of Daily Living Scale, the Kahn-Goldfarb Mental Status Questionnaire, and the Yesavage Depression Scale. Data will also be collected to determine the cost of the health care provided to both groups from their admission for surgery until one year after discharge. Data analysis will be performed primarily with descriptive statistics. Means and standard deviations will be calculated for pre- and post-test variables, such as placement location at discharge and changes in functional and mental status. Death rates and cost will also be analyzed.

Progress: Five patients were entered in the study in FY 88. Most of the effort expended on the project consisted of developing detailed procedures and of familiarizing personnel with the project and gaining their support.

**Funded by a joint VA/DoD grant.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 88/41 Status: On-going

Title: Urinary D-Lactate as an Indicator of Bowel Ischemia

Start Date: 18 Mar 88 Est Completion Date: Aug 88

Department/Service: Surgery/General Facility: MAMC

Principal Investigator: CPT Barbara L. Tylka, MC

Associate Investigators: COL Charles A. Andersen, MC

CPT Jon C. Bowersox, MC

Key Words: ischemia, bowel, urinary D-lactate levels

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: \$400.00 N/A

Study Objective: To determine whether urinary D-lactate levels can be used as non-invasive indicators of bowel ischemia in critically ill patients.

Technical Approach: Patients ≥ 18 years of age with hypovolemia, Ogilvie's syndrome, or a hemodynamically significant cardiac event requiring pressor support will be studied. Daily urine samples will be collected for analysis of urinary D-lactate until discharge from the ICU or CCU or death. The D-lactate concentration will be determined via the enzymatic conversion of D-lactate to pyruvate by the enzyme D-lactate dehydrogenase. To correct for variations in urine concentration, the urine creatinine will also be measured and results expressed as the D-lactate/creatinine ratio. If operative intervention is deemed necessary on clinical grounds, the bowel will be examined at surgery or, in the event of death, at autopsy for evidence of ischemia. The determination of ischemia will be made by the operating surgeon and any resected specimens will be examined by the pathologist. Subjects discharged from the ICU or CCU without operative intervention will be considered to not have experienced any clinically significant bowel ischemia and will form the control population. Based on previous studies, it is estimated that 20-30 patients, with a minimum of 10 with clinically proven bowel ischemia, will be required to determine a difference in urinary D-lactate levels between control and ischemic populations. Results will be analyzed by Student's paired t-test.

Progress: Three controls and three patients with bowel ischemia have been entered.

Detail Summary Sheet

<u>Date:</u> 30 Sep 88	<u>Protocol No.:</u> 86/16	<u>Status:</u> On-going
<u>Title:</u> Teaching Program for Practical Microsurgery		
<u>Start Date:</u> 15 Nov 85	<u>Estimated Completion Date:</u> Open-ended	
<u>Dept/Svc:</u> Surgery/Orthopaedic	<u>Facility:</u> MAMC	
<u>Principal Investigator:</u> LTC Bruce R. Wheeler, MC		
<u>Associate Investigators:</u> COL Thomas Griffith, MC		
COL Richard A Camp, MC	LTC Robert J. Kenevan, MC	
COL Jackie Finney, MC	MAJ Stephen D. Clift, MC	
<u>Key Words:</u> microsurgery, teaching program, laboratory animals		
<u>Accumulative MEDCASE</u>	<u>Est Accumulative</u>	<u>Periodic Review:</u>
<u>Cost:</u> -0-	<u>OMA Cost:</u> \$690.00	Jan 88

Study Objective: To perfect the techniques needed to perform clinical microsurgery and to establish formal training programs in clinical microsurgery at MAMC for use of those surgeons desiring to develop this expertise.

Technical Approach: A schedule of one or two afternoons per week will be set aside for teaching sessions. Sessions will begin with lectures, followed by practical exercises in anatomy and step-by-step instruction in the surgical techniques. Staff and residents from the Orthopaedic, Plastic Surgery, and Thoracic Surgery Services will train in the following procedures:

- (1) reimplantation of extremities
- (2) re-anastomosis of peripheral vessels and nerves
- (3) repair of avulsion wounds
- (4) graft transplants
- (5) free cutaneous, myocutaneous and composite tissue transfer for traumatic lesions and reconstructive procedures
- (6) re-anastomosis of facial nerve lesions

The training will begin with small vessels and nerves in cadaver specimens of small laboratory animals. When the anatomy of the area is learned as well as the use of the microsurgical instruments and the operating microscope, then microsurgical procedures in living rats, guinea pigs, and rabbits can be learned.

Progress: Two microvascular workshops were conducted in FY 88.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 85/65 Status: On-going

Title: Biologic Ingrowth Total Hip Replacement

Start Date: 24 May 85 Estimated Completion Date: Jul 89

Dept/Svc: Surgery/Orthopedics Facility: MAMC

Principal Investigator: MAJ William J. Wilson, MC

**Associate Investigators: COL Thomas J. Parr, MC

MAJ Jonathan P. Bacon, MC

MAJ Charles Morrow, MC

Key Words: hip replacement, biologic ingrowth, non-cemented

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: -0- Aug 87

Study Objective: To evaluate the use of a new total hip prosthesis undergoing FDA evaluation for approval as an uncemented device.

Technical Approach: Patients (50-60) \geq 21 years of age will be entered into the study at each of approximately 15 clinical centers. The patient's age, weight, general medical condition and history, extent of injury, expected activity level, and mental alertness will be given full consideration before surgical intervention. Contraindications to use of the device are overt infection, inadequate neuromuscular status, poor prognosis for good wound healing, marked bone loss or osteoporosis, and revision procedures for which an adequate press fit of the prosthesis can not be achieved. The surgeon must evaluate each patient and document these evaluations preoperatively, at surgery, and at 1,3,6, 12,18, and 24 months. Preoperative patient assessment includes routine blood work and radiography. The surgery will be carried out per standard SOP for hip replacement surgery. In order to assess bone-prosthesis contact, AP and lateral radiographs will be made to profile the undersurface of the femoral collar. These same radiographs will be made at the 1, 3, 6, 12, 18, and 24 month evaluations. Evaluation of the device will be based on the incidence and severity of complications. The results will be presented according to a number of baseline and operative factors (e.g., primary diagnosis, age, sex, bone quality, operative complications) to determine if there are particular subgroups of the target population at high risk for certain complications. The incidence of complications will be compared to published results on follow-up of patients with cemented and non-cemented prostheses to determine if the risk of complications is equivalent to the published results. The Harris Hip Score and the Charnley Modified D'Aubigne Scale will be used to evaluate the effectiveness of the device.

Progress: Patient entry has been completed and the investigators are continuing to collect follow-up data.

**MAJ Wilson replaced MAJ Morrow as the principal investigator in August 1988.

DETAIL SHEETS
FOR
PROTOCOLS

DIRECTORATE OF NUTRITION CARE

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 87/43 Status: Completed

Title: Advance Liquid Diet Evaluation

Start Date: 27 Feb 87 Est Completion Date: Mar 89

Unit: Directorate of Nutrition Care Facility: MAMC

Principal Investigator: LTC Annetta J Cooke, SP

Associate Investigators: Dianne Engell, Ph.D.

USA NATICK Research Center

Key Words: diet, liquid, dental, acceptability, cost

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: -0- N/A

Study Objective: To determine whether commercially produced dental liquid products are acceptable to patients who are placed on a dental liquid diet for jaw injuries and other dental problems.

Technical Approach: This is a multi-institutional study. The study population will be 75 patients (total) who will be on a liquid diet because of a dental problem or jaw injury. The test diet has been developed by the Food Engineering Directorate at the US Army Research, Development, and Engineering Center. It is a three-meal/day diet containing approximately 2500-3100 calories /day. Protein, carbohydrate and fat make up, respectively, 12%, 25%, and 43% of the daily caloric intake, depending on the consumption of supplements such as juices and milk. The subjects will be tested for four days. They will receive the test diet and the current hospital diet on alternate days. A repeated measures design will be used so that each patient will evaluate both diets and thus serve as his own control. The two conditions will be counterbalanced; half the patients will receive the test diet first and half will receive the current diet first. The participants will complete a questionnaire three times a day to cover all meal and snack periods to rate products on acceptability, appearance, flavor, consistency, texture, ease of sipping, variety, and portion size. A questionnaire will be developed specifically for each meal. On the days the subjects receive the test liquid items, they will also fill out a second questionnaire to estimate the amount of each new meal and between-meal product they have consumed. To validate the intake estimate, dietitians will measure the amount of each product before and after the patient has consumed as much as he wants. Dietitians will be asked to evaluate the products on characteristics such as ease of preparation, time requirements, and variety of products.

Progress: Ten patients were entered in the protocol at MAMC. The data has been forwarded to NATICK for group analysis.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 88/22 Status: Completed

Title: Nutrition and Physical Endurance Appraisal
Start Date: 4 Jan 88 Est Completion Date: Jun 88
Unit: Directorate of Nutrition Care Facility: MAMC
Principal Investigator: LTC Annetta J. Cooke, ASPC
Associate Investigators: COL Stephen R. Plymate, MC
CPT Karl E. Friedl, MS
Key Words: Army Physical Fitness Test, fasting, non-fasting
Accumulative MEDCASE Est Accumulative Periodic Review:
Cost: -0- OMA Cost: \$3150.00 N/A

Study Objective: To determine if there is a significant relationship between a soldier's ability to perform physical tasks and the amount of time that has transpired since his last meal.

Technical Approach: The study population will be divided into 3 groups of 30. Each group will perform each of the protocols described below with a 7-day rest period between protocols. Protocol 1: Patients will fast 12 hours prior to performing the Army Physical Fitness Test (APFT). Just prior to the APFT, the subjects will be weighed, pulse will be taken, and blood samples to measure free fatty acids, free amino acids, cholesterol, triglycerides, lactate, glucose, insulin, and cortisol will be taken. Subjects will be asked to identify any physical injury or event which might impact on their performance. Subjects will be asked to do as many sit-ups and push ups as they can and to run the two mile run as fast as they can. A questionnaire will be completed by the subjects at the conclusion of the APFT, regarding usual eating and exercise habits, tobacco and alcohol consumption, dieting history and conclusions regarding which protocol on which they performed best. Protocol 2: Subjects will consume a breakfast of their own choosing 60-90 mins before the APFT. A blood sample will be drawn prior to breakfast and subjects will fill out a questionnaire regarding food selection and the quantity eaten. The remainder of the protocol will be the same as Protocol 1. Protocol 3: The same as Protocol 2 except that the breakfast will be fed 4 hours prior to performing the APFT. Data from the APFT will be collected using actual repetitions performed and minutes for the run and will be analyzed comparing individual scores on the 3 protocols as well as by groups. A nutritional analysis will be conducted on each person's meal to determine if there is a correlation between intake of calories or percentage of carbohydrate, protein and fat and the subject's performance. Blood chemistries will be used to provide objective assessment of the metabolic state of the individuals.

Progress: Eighty subjects were studied. No definitive findings were found regarding time of meal consumed and performance. However, there appears to be some correlation between the amount of carbohydrate consumed and performance at the 2-hour time period. A paper was presented at the AMSC Research Course in August 1988 and was reported through the U.S. Army Development and Employment Agency as Report #A-216.

D E T A I L S H E E T S
F O R
P R O T O C O L S

P R E V E N T I V E M E D I C I N E S E R V I C E

Detail Summary Sheet

<u>Date: 30 Sep 88</u>	<u>Protocol No.: 88/80</u>	<u>Status: On-going</u>
<u>Title: Health Promotion and Disease Prevention Needs Assessment of the Army Retirees in the Pacific Northwest</u>		
<u>Start Date: 16 Sep 88</u>	<u>Est Completion Date: Dec 88</u>	
<u>Service: Preventive Medicine</u>	<u>Facility: MAMC</u>	
<u>Principal Investigator: CPT Cynthia A. Brandt, MC</u>		
<u>Associate Investigators: LTC K. Mills McNeill, MC</u>		
<u>CPT Margot R. Krauss, MC</u>		
<u>Key Words: retirees, disease prevention, health promotion</u>		
<u>Accumulative MEDCASE</u>	<u>Est Accumulative</u>	<u>Periodic Review</u>
<u>Cost: -0-</u>	<u>OMA Cost: \$520.00</u>	<u>N/A</u>

Study Objective: To identify and quantify the health promotion and disease prevention needs of the Army retiree personnel as measured by the prevalence of health risk behaviors as well as preventive behaviors.

Technical Approach: This is a descriptive cross-sectional study utilizing a self-administered mailed questionnaire. Questionnaires will be mailed to a randomly selected sample of 400 Army retirees residing within the "catchment area" defined as a 40 mile radius of MAMC. An equivalent number of subjects will be selected from zip codes not in this area. The age range is expected to be from approximately 40 to 85 years of age. Patients who would require surrogate respondents will be excluded.

The questionnaire will contain questions to elicit demographic data as well as data concerning hospital usage, general health of the subject, diet and alcohol use, daily activities, and safety and preventive measures such as seat belt use and immunizations

Descriptive statistics will include prevalence of behavioral risk factors of the total sample with 95% confidence intervals, comparison will be made to general population data available, and comparison of the "catchment area" group with the other geographical groups of retirees, to identify differences in the core users of Madigan as regards behavioral risk factors. Secondary analysis may include looking for evidence of a cohort effect, a relationship of the year entered service and behavioral risk factors, or length of service and behavioral risk factors.

Progress: The questionnaire has been pretested on 10 volunteers.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 88/04 Status: Terminated

Title: Reactogenicity of Intradermally Administered Rabies Human Diploid Cell Vaccine

Start Date: 16 Oct 87 Est Completion Date: Mar 88

Service: Preventive Medicine Facility: MAMC

Principal Investigator: MAJ Arlene L. Burke, MC

Associate Investigators: MAJ Wayne M. Lednar, MC
CPT Dustin Frazier, MC

Key Words: rabies, vaccine, human diploid cell, intradermally

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: \$850.00 N/A

Study Objective: To determine the comparative reactogenicity and immunogenicity of Merieux human diploid cell rabies vaccine (HDCV) administered intradermally at the volar aspect of the forearm and the lateral aspect of the deltoid and to compare the Rapid Fluorescent Focus Inhibition Test (RFFIT) method of determining immunogenicity and the new Enzyme Linked Immunosorbent Assay (ELISA) method.

Technical Approach: Two groups of 60 Special Forces soldiers with no previous exposure to rabies vaccine, who will be receiving the HDCV as part of their standard preventive medicine care, will be studied. Subjects will be randomized to receive the vaccine intradermally, either in the volar aspect of the forearm or the lateral aspect of the deltoid. Baseline titers will be drawn prior to administration of the vaccine. Subjects will complete a questionnaire to provide information on present medications and vaccination history. HDCV will be given intradermally on days 0, 7, 21, and 28. The same NIH lot will be used throughout the study. Special Forces nursing personnel will be especially trained to administer the vaccine. If leakage occurs at the vaccination site, the subject will be revaccinated and removed from the study. Subjective signs and symptoms of reactogenicity will be assessed by questionnaire seven days after each dose is administered and the principal investigator will evaluate the vaccine reactions in order to provide objective findings of reactogenicity. Post-vaccine series titers will be drawn on day 90. All serology samples will be analyzed by both the RFFIT and ELISA methods for testing antibody titers and the results compared. The Student's t test will be used to analyze the actual titers. The investigators will then compare, by site, the geometric means of the actual titers by T test as the final step in the comparison process.

Progress: This study was delayed due to logistical problems and then terminated when the principal investigator was reassigned.

Detail Summary Sheet

Date: 30 Sep 88	Protocol No.: 86/21	Status: On-going
Title: Data Collection for the Selected Cancers Among Vietnam Veterans Study		
Start Date: 15 Nov 85	Est Completion Date: Jun 89	
Service: Preventive Medicine	Facility: MAMC	
Principal Investigator: CPT Margot R. Krauss, MC		
Associate Investigators: COL Frederick J. Erdtmann, MC Linda S. Heuser, M.A., Hutchinson CRC Thomas L. Vaughan, M.D., Hutchinson CRC		
Key Words: cancer, vietnam veterans, Agent Orange		
Accumulative MEDCASE	Est Accumulative	Periodic Review:
Cost: -0-	OMA Cost: -0-	Sep 88

Study Objective: To evaluate the risk associated with exposure to Agent Orange among veterans of the Armed Forces in Vietnam.

Technical Approach: This is a multicenter study, funded by the U.S. Centers for Disease Control. Males diagnosed between 1 Oct 85 and 30 Nov 88 with birth dates between 1929 and 1953 as having soft tissue sarcomas (excluding Kaposi's sarcoma), certain bone and cartilage sarcomas, lymphomas, nasal cancers, nasopharyngeal cancers, and primary liver cancers will be studied. Subjects must be identified within one month of diagnosis and interviewed within three months of diagnosis. The patient or the next-of-kin will be sent a letter and a fact sheet explaining the study and requesting participation. This letter will be followed by a telephone call and a time for a telephone interview will be scheduled. The vital status of all interviewed patients will be checked every six months and a physician will interview the next-of-kin on those patients who have died since being interviewed. This interview will be done in order to compare the information provided by the next-of-kin with that originally obtained from the patient. The interview will obtain information about patients' jobs, medical illnesses, personal habits, and other information related to general health. Tissue blocks and/or a set of six slides will be requested from pathologists and sent to a pathology panel for independent review. If the patient is a Vietnam veteran, information will also be obtained from military records about previous chemical exposures in Vietnam. The CDC will also request information about chemical exposure from the military. Controls will be matched for age and vital status. Controls will be contacted in the same manner as other subjects. Once an interview is edited for completeness, it will be sent to the CDC where requests for information from military records and data analysis will be done.

Progress: The investigators are still entering patients. Approximately 250 patients have been entered study-wide.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 88/05 Status: Completed

Title: Evaluation of an Office-Based Sexually Transmitted Disease Prevention Education Program

Start Date: 16 Oct 87 Est Completion Date: Dec 87

Service: Preventive Medicine Facility: MAMC

Principal Investigator: CPT Margot R. Krauss, MC

Associate Investigators: MAJ Wayne M. Lednar, MC
Jeanie Onitsuka, B.S.N., M.H.S.

Key Words: sexually transmitted disease, program, office-based

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: \$630.00 Sep 88

Study Objectives: To assess the baseline knowledge of soldiers regarding sexually transmitted diseases (STD) and to compare the knowledge and intent to make changes in sexual behavior after a typical clinic visit (which includes physician provided education) and a visit which includes an educational videotape which consists of a motivational program targeted for a young adult population using peer models.

Technical Approach: Approximately 300 male active duty soldiers with urethritis will be studied. Before entering the waiting room they will complete a questionnaire designed to determine what they know about STD. On randomly selected days, a videotape entitled "Sex, Drugs, and Aids" will be playing in the waiting room at 0830, 0930, and 1030 hours. The clinic opens at 0730 and stops accepting new patients at 1000 hours. Generally, the patients start being seen by the physicians at 0800 hours. The initial questionnaire should take approximately 15 minutes to complete. The videotape runs approximately 18 minutes. This should provide the opportunity for most of the patients to see the film. After seeing the physician, the subjects will be asked to fill out a second questionnaire similar to the first one which will also collect data on whether the physician discussed STD with the soldier, if the soldier saw the videotape, how much of the videotape the soldier saw, if the videotape helped the soldier understand AIDS better, and any affect watching the videotape had on motivating the soldier to change his sexual habits. Six months after the study, a review of the log of clinic visits will be performed to determine how many visits to the clinic have occurred in the six months prior to the study and how many in the six months after the study. The questionnaires will be analyzed using paired analysis techniques. The two educational approaches will be analyzed by chi square analysis.

Progress: Approximately 600 subjects were studied. The data indicate that education during a clinic visit for STD treatment can have a significant impact on increasing knowledge about STD and HIV infection.s A paper has been submitted for consideration for publication at the Prevention 89 Meeting.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 87/84 Status: Terminated

Title: Effects of an Employee Fitness Program on Back Injuries and Absenteeism

Start Date: 19 Jun 87 Est Completion Date: Dec 89

Service: Preventive Medicine Facility: MAMC

Principal Investigator: MAJ Wayne M. Lednar, MC

Associate Investigators: Richard A. Deyo, M.D., M.P.H.

Seattle V.A. Medical Center

Key Words: employee fitness, back injuries, absenteeism

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0-** OMA Cost: -0-** Aug 88

Study Objective: To determine if a worksite exercise program can improve aerobic fitness, reduce recurrences of back pain, back-related absenteeism, and overall work loss; to determine the factors that influence the individual decision to participate in and comply with an exercise regimen; to determine the overall costs of a work-based exercise program; and to determine the net cost or savings from the employer's perspective.

Technical Approach: The program will be implemented as a randomized controlled trial at MAMC and two V.A. facilities. Approximately 750 employees with prior back problems will be enrolled. Patients will be randomized to a supervised and individualized exercise program, conducted at the worksite, including back and general aerobic conditioning, or to a control group that receives no exercise. The baseline evaluation will include a questionnaire which will elicit demographic data, job information, physical activity, days of limited activity, and back pain history. Physiologic and psychological status will be determined at entry, 5 wk, 6 mth, and 1 yr with functional status determined at entry, 6 mth, and 1 yr. A sub-study will be conducted to address the problem of compliance and develop compliance-enhancing techniques. This substudy will consist of interviewing subjects who decline to enter the exercise study regarding their reasons for not participating, interviewing subjects who drop out of the study about their reasons for dropping out, and having a sample of 120 potentially eligible subjects evaluate the questionnaire. The resulting compliance-enhancing strategies will be implemented in year two of the study. Costs will be assessed by asking patients to maintain a diary of cost for medical care, by having the subjects complete the medical costs section of Fries' Health Assessment Questionnaire at six months and one year, and by maintaining a record of health care costs and continuation-of-pay compensation paid by the employer for the subjects. Costs of the exercise program and costs of time excused from work will also be included.

Progress: This joint VA/DoD protocol was funded for only 10% of the requested funds and MAMC was not awarded any of these funds; therefore, the protocol was terminated.

**to be funded by joint VA/DoD grant

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 87/116 Status: Completed

Title: A Clinical Efficacy Study Comparing Gram Stain and Culture to Enzyme Immunoassay for the Diagnosis of Gonococcal Urethritis in Men

Start Date: 18 Sep 87 Est Completion Date: Dec 87

Service: Preventive Medicine Facility: MAMC

Principal Investigator: CPT LeRoy Southmayd, MC

Associate Investigators: MAJ Charles Hicks, MC, WRAMC

COL Edmund C. Tramont, MC, WRAIR CPT Jeff Lennox, MC, WRAMC

LTC John W. Boslego, MC, WRAIR Michael Goerss, M.D., MAMC

LTC Rodney Michael, MC, MAMC Carrie Gilreath, MAMC

Key Words: urethritis, gonococcal, diagnosis, gram stain, culture, enzyme immunoassay

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: -0- N/A

Study Objective: To evaluate the efficacy of the enzyme immunoassay system (EIA) for the diagnosis of gonorrhea.

Technical Approach: 300 males, 18-65 years, with a clinical diagnosis of acute urethritis will be enrolled in the study. A medical history, including recent antimicrobials, and physical exam will be obtained. Two urethral swab specimens will be obtained. Culture, gram stain and EIA will be done on one specimen and EIA only will be done on the second specimen. To avoid experimental bias, the test sequence will be alternated according to odd/even numbers. The EIA test will be performed so that the EIA results will be available for all patients within two hours of initial registration, thus being available within a reasonable time for theoretical application toward diagnosis. Cultures will be processed per the usual routine. Cultures will be considered positive when there is growth of typical *N. gonorrhea* colonies which are oxidase positive, show characteristic gram staining, and are positive with Phadebact tests. A positive gram stain will be defined as the presence of GNID or GNED with characteristic morphology. EIA definitions: true positive - a positive EIA with either a positive gram stain, a positive culture, or a known GC contact; true negative: a negative EIA with a negative gram stain and a negative culture; false positive: a positive EIA with a negative gram stain, a negative culture, and no recent GC contact; and false negative: a negative EIA with either a positive gram stain or a positive culture. Sensitivity, specificity, and positive and negative predictive values will be calculated from the EIA subsets in the standard manner. EIA results will be compared independently to both culture and gram stain.

Progress: Approximately 200 subjects were entered in this group study with WRAMC and WRAIR. EIA was easily incorporated into the routine of a busy STD clinic, and the test was simple to learn and perform. Results were available within 45 minutes. EIA may prove to be a useful alternative to gram stain and/or culture. A paper has been accepted for presentation at the Interscience Conference on Antimicrobial Agents and Chemotherapy in Oct 88.

D E T A I L S H E E T S
F O R
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1ST SPECIAL FORCES GROUP

FT LEWIS, WA

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 88/29 Status: On-going
Title: Special Operations Medical NCO Sustainment Training
Start Date: 19 Feb 88 Est Completion Date: Feb 91
Unit: 1st Special Forces Group Facility: MAMC
Principal Investigator: CPT Dustin Frazier, MC
Associate Investigators: CPT Jeffrey S. Macintire, VC
Key Words: venous cutdown, needle thoracentesis tube thoracostomy,
pericardiocentesis, cricothyroidotomy, peritoneal lavage
Accumulative MEDCASE Est Accumulative Periodic Review:
Cost: -0- OMA Cost: -0-* N/A

Study Objective: To provide annual Advanced Trauma Life Support-type surgical training for 18D Special Forces medical sergeants as required by Special Operations Command Regulation 350-9.

Technical Approach: Having received formal training at the 18D MOS qualification course, medical NCO's will be afforded the opportunity to conduct sustainment training on no less than an annual basis in accordance with SOCOM Reg 350-9.

Combat Trauma Management Lab The purpose of this lab is to refresh skills in aseptic emergency surgical techniques. Personnel will be divided into groups of 4 with each group under the supervision of an instructor. Each soldier will perform each of the following surgical exercises:

venous cutdown	needle thoracentesis
tube thoracostomy	pericardiocentesis
cricothyroidotomy	peritoneal lavage

These procedures will be performed in the manner described in the Academy of Health Sciences Advanced Trauma Life Support Program.

One adult goat will be used per group. Four people will be in each group. All procedures will be done under general anesthesia. All animals will be euthanized at the end of the training procedure by lethal injection of T-61 veterinary euthanasia solution.

Progress: The purpose of this protocol is to provide an opportunity for Special Operations medics to practice ATLS skills in the event they are unable to attend the annual instruction provided locally by the Academy of Health Sciences. To date, the protocol has not had to be utilized.

D E T A I L S H E E T S
F O R
P R O T O C O L S

ACTIVE DUTY STUDENTS
STUDENT DETACHMENT, HSC

and

ACTIVE DUTY STUDENTS
UNITED STATES AIR FORCE

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 87/95 Status: Completed

Title: Early Mobilization: Its Effects on Grade Two and Single Ligament Grade 3 Lateral Ankle Injuries

Start Date: 17 Jul 87 Est Completion Date: Dec 87

Unit: Student Detachment, Health Services Cmd Facility: MAMC

Principal Investigator: MAJ Joseph R. Dettori, AMSC

Associate Investigators: LTC Bruce Wheeler, MC
CPT Bradley D. Pearson, PT

Key Words: ankle, injuries, lateral, grade 2, early mobilization

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: \$1160.00 N/A

Study Objective: To determine if the management of Grade 2 and single ligament Grade 3 ankle sprains in active duty personnel by early ankle mobilization can return soldiers back to full duty quicker than delayed ankle mobilization and to determine if cheaper forms of early ankle mobilization management (ace wraps) are as successful as more expensive forms of early mobilization management such as air splints.

Technical Approach: Patients will be randomized to a control group (plaster immobilization) and two experimental groups (ace wrap and air splint). Subjects will undergo an initial assessment to include ankle arthrography to delineate the extent of injury. Group 1 will receive plaster immobilization (controls) and will perform isometric exercises in the cast hourly, for one week. Group 2 will receive an ace wrap and perform active range of motion (AROM), with the wrap removed, at least three times per day and resistive exercises with rubber tubing three times per day plus ice and elevation throughout the day, as permitted, for one week. Group 3 will receive an air splint and therapy the same as in Group 2. Phase two will consist of three treatments in the Physical Therapy clinic over a one week period. All three groups will perform strengthening exercises for 10 minutes, proprioceptive exercise on a balance board for ten minutes, single legged toe raises (maximum of 20), and home exercise instruction for AROM with resistive exercises with rubber tubing and toe raises. Phase III will consist of five treatment sessions over a period of two weeks. Each group will participate in functional ankle exercises and home exercises with rubber tubing and AROM. The measures to be utilized in this study will be swelling, AROM, gait, strength, height/weight, point tenderness, anterior drawer test, pain, work status, ability to run, and ability to complete the functional ankle program without pain. All data except for muscle strength will be collected prior to intervention and weekly thereafter. A final measurement to include muscle strength will be performed at the end of Phase 3.

Progress: This study has been completed. A thesis has been submitted to the University of Washington as one of the requirements for a doctorate in physical therapy. A paper is being prepared for submission for publication and a paper was presented at the Mary Lipscomb Hamrick AMSC Research Course, August 1988.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 88/45 Status: Completed

Title: The Needs of Family Members of Cancer Patients

Start Date: 18 Mar 88 Est Completion Date: May 88
Unit: Air Force Institute of Technology Facility: MAMC
Principal Investigator: CPT Jamie Sue Iversen, AFNC
Associate Investigators: None
Key Words: emotional, cognitive and physical needs, questionnaire
Accumulative MEDCASE Est Accumulative Periodic Review:
Cost: -0- OMA Cost: -0- N/A

Study Objective: To identify the cognitive, emotional, and physical needs of family members of adult cancer patients and to compare the results of this study with the needs of relatives of cancer patients in a study conducted by Tringali (1986).

Technical Approach: This will be a descriptive study of 50 family members (spouse or adult child) of patients ≥ 21 years of age, diagnosed as having cancer of any body system or organ. A convenience sample will be utilized and there will be no control for location or type of malignancy. A questionnaire completed by the family member will provide demographic information on the family member and on the patient. This information will include age of family member, sex, relationship to the patient, education level, and information on the patient's age, sex, diagnosis, disease site, date of diagnosis, and treatment modalities. The questionnaire contains a list of 53 need statements developed by Tringali (1986). They are grouped into cognitive, emotional, and physical categories, and space will be provided for the family member to write in needs that have not been identified. Demographic data will be analyzed by measures of central tendency in order to describe how the variables are distributed. The data obtained on the need statements will be analyzed by the use of descriptive statistical methods. The mean score and standard deviation for each need statement will be calculated. A frequency distribution will also be performed on the need statements. Relationships between variables will be done where appropriate. This study will be a replication of Tringali's study except that the study site and sample will be changed. The results of this study will be compared to the results obtained in Tringali's study to determine if the results from that study will be similar in a different population of families of cancer patients.

Progress: Twenty-eight family members of cancer patients were studied. The finding in this study and the Tringali study were similar. In this study, 27 of 53 need statements were rated as most important; in Tringali's study 20 need statements were rated in the same class. The majority of needs in both studies were cognitive followed by emotional needs. Only one physical need was rated as a most important need. A thesis has been submitted as one of the requirements for a Master of Nursing Degree.

D E T A I L S H E E T S
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CHILDRENS CANCER STUDY GROUP PROTOCOLS

Detail Summary Sheet

Date: 30 Sep 88	Protocol No.: 86/65	Status: On-going
Title: CCG 105: Treatment of Newly Diagnosed Acute Lymphoblastic Leukemia in Children with an Intermediate Prognosis		
Start Date: 16 May 86	Est Completion Date: Indefinite	
Department: Pediatrics	Facility: MAMC	
Principal Investigator: Edythe A. Albano, M.D.		
Associate Investigators: LTC Allen R. Potter, MC		
MAJ Kip R. Hartman, MC		
Key Words: leukemia, lymphoblastic, intermediate prognosis		
Accumulative MEDCASE	Est Accumulative	Periodic Review:
Cost: -0-	OMA Cost: -0-	Oct 87

Study Objective: To minimize therapy in good prognosis patients without altering their prognosis and to improve the proportion of all patients cured of leukemia in each category, without seriously compromising the quality of their life span.

Technical Approach: Patients defined as having intermediate prognosis ALL will be randomized to one of four treatment arms, which differ substantially during the first six months of therapy and then share the same maintenance program. The treatment will not be less than two years. Regimen 1 A will utilize vincristine, daunomycin, prednisone, L-asparaginase, and IT methotrexate for induction; consolidation will utilize cyclophosphamide, 6-mercaptopurine, cytosine arabinoside, IT methotrexate, and cranial radiation; interim maintenance will use 6-mercaptopurine and methotrexate; delayed intensification will be vincristine, dexamethasone, adriamycin, L-asparaginase, cyclophosphamide, 6-thioguanine, cytosine arabinoside, and IT methotrexate; maintenance will consist of vincristine, prednisone, 6-mercaptopurine, and methotrexate. Regime 1B will utilize vincristine, prednisone, L-asparaginase, and IT methotrexate for induction; 6-mercaptopurine, IT methotrexate, and cranial radiation for consolidation; 6-mercaptopurine and methotrexate for interim maintenance; delayed intensification and maintenance will be the same as Regimen 1A. Regimen 1C will have induction, consolidation, and maintenance as in Regimen A but with no interim maintenance and delayed intensification. Regimen 1D will have induction, consolidation, and maintenance as in Regimen 1B but without interim maintenance and delayed intensification. Regimens 2A, 2B, 2C, and 2D will correspond to Regimens 1A, 1B, 1C, and 1D, respectively, but with no cranial radiation, and maintenance will be with IT methotrexate.

Progress: No patients have been entered in this protocol.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 86/44 Status: Completed

Title: CCG-107: Treatment of Newly Diagnosed Acute Lymphoblastic Leukemia and Acute Undifferentiated Leukemia in Infants Less than 12 Months of Age

Start Date: 21 Mar 86 Est Completion Date: Indefinite

Department: Pediatrics Facility: MAMC

Principal Investigator: Edythe A. Albano, M.D.

Associate Investigators: LTC Allen R. Potter, MC

MAJ Kip R. Hartman, MC

Key Words: leukemia, lymphoblastic, acute, undifferentiated

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: -0- Sep 88

Study Objective: To subdivide childhood acute lymphoblastic leukemia into homogeneous subgroups (stages) in which specific biologic and therapeutic hypotheses can be tested; to minimize therapy in good prognosis patients without altering their prognosis; and to improve the proportion of all patients cured of leukemia in each category, without seriously compromising the quality of their life span.

Technical Approach: Patients <12 months with newly diagnosed acute lymphoblastic leukemia will receive intensive induction therapy consisting of vincristine, daunomycin, prednisone, L-asparaginase, IT cytosine arabinoside, and IT methotrexate. Following remission induction, patients will receive consolidation therapy consisting of 3 very high dose, protracted (24 hr), systemic infusions of methotrexate with high dose citrovorum factor rescue, and IT cytosine arabinoside. Consolidation therapy will also include 6 mercaptopurine and vincristine. This phase will be followed by an interim maintenance therapy of 6-mercaptopurine and methotrexate. Four months following diagnosis, patients will receive intensification with dexamethasone, vincristine, daunomycin, L-asparaginase, and IT methotrexate for 4 weeks (reinduction) and 6-thioguanine, vincristine, methotrexate, and tapered dexamethasone with citrovorum factor rescue for 3 weeks (reconsolidation). Maintenance therapy (96 weeks) consists of 6-mercaptopurine and methotrexate with periodic vincristine/prednisone pulses as well as IT methotrexate

Progress: No subjects entered at MAMC.

Detail Summary Sheet

Date: 30 Sep 88	Protocol No: 87/93	Status: On-going
Title: CCG 134P: Therapy of Acute Lymphoblastic Leukemia In High Risk Patients		
Start Date: 17 Jul 87	Est Completion Date: Jul 92	
Department: Pediatrics	Facility: MAMC	
Principal Investigator: Edythe A. Albano, M.D.		
Associate Investigator: MAJ Kip R. Hartman, MC		
Key Words: ALL, high risk, chemotherapy		
Accumulative MEDCASE	Est Accumulative	Periodic Review:
Cost: -0-	OMA Cost: -0-	Sep 88

Study Objective: To improve the treatment results for children with acute lymphoblastic leukemia (ALL) who possess poor prognostic features; to prevent the development of central nervous system (CNS) leukemia in these patients using a treatment regimen which includes both systemic high dose chemotherapy and intrathecal chemotherapy, but avoids cranial radiation; and to determine whether there is a difference in the outcome of poor prognosis patients with and without lymphomatous features treated on an identical treatment regimen.

Technical Approach: Previously untreated high risk patients with acute lymphoblastic leukemia will be treated. The induction phase of therapy will be 28 days in length and consist of treatment with vincristine, L-asparaginase, prednisone, daunomycin, and allopurinol. CNS therapy will consist of intrathecal cytosine arabinoside, methotrexate, and a high dose, protracted, systemic methotrexate infusion. Consolidation therapy will begin 7-10 days following completion of induction therapy and will last 35 days and will consist of vincristine, prednisone, and 6-mercaptopurine. CNS prophylaxis during consolidation will include both I.V. high dose methotrexate and intrathecal Ara-C. A 12-week intensification phase will begin 7-10 days after the last day of consolidation and will consist of cyclophosphamide, L-asparaginase, vincristine, daunomycin, and prednisone. CNS treatment will include periodic intrathecal methotrexate and cytosine arabinoside as well as systemic high dose Ara-C. Maintenance therapy will begin 7-10 days after the last day of consolidation and will consist of prednisone, vincristine, 6-mercaptopurine, L-asparaginase, and daunomycin. CNS treatment will include periodic intrathecal chemotherapy with methotrexate and Ara-C as well as systemic high dose methotrexate and high dose Ara-C. The chemotherapy will be given over a 24 week cycle, which will be repeated 4 times, after which all chemotherapy ceases. The first year off study, patients will have a physical exam and CBC every month and bone marrow and lumbar puncture every 4 months. The second year, they will have physical exam and CBC every 3 months and bone marrow and lumbar puncture every 6 months. The third and subsequent years off study, patients will receive routine follow-up per institutional guidelines.

Progress: Two patients have been entered in this study; one of them in FY 88. The study is closed to further patient entry.

Detail Summary Sheet

Date: 30 Sep 88	Protocol No.: 88/63	Status: On-going
Title: CCG 144: Treatment of Acute Lymphoblastic Leukemia in Average Risk Patients		
Start Date: 15 Jul 88	Est Completion Date: Jul 93	
Department: Pediatrics	Facility: MAMC	
Principal Investigator: Edythe A. Albano, M.D.		
Associate Investigator: MAJ Kip R. Hartman, MC		
Key Words: chemotherapy, protracted intravenous, intrathecal		
Accumulative MEDCASE	Est Accumulative	Periodic Review:
Cost: -0-	OMA Cost: -0-	N/A

Study Objective: To compare the efficacy of high dose, protracted intravenous methotrexate infusions versus intrathecal methotrexate as CNS preventive therapy for children with average risk lymphoblastic leukemia and to determine if there is a difference in the hematologic remission duration achieved using these different treatment approaches.

Technical Approach: Newly diagnosed average risk patients will be randomly allocated to receive one of two forms of CNS preventive therapy; either high dose protracted systemic methotrexate infusions or intrathecal methotrexate administered periodically during induction, consolidation, and maintenance. Systemic therapy will be identical for all patients. To insure similarity in the two treatment groups, patient randomization will be stratified to the prognostically significant variables of age and initial white blood cell count. Approximately 80 randomized patients will be required. It is anticipated that the required number of patients will be accrued within a 12-18 month period.

The induction phase for both arms will 28 days in length and will include chemotherapy in both groups with vincristine, l-asparaginase, prednisone, daunomycin, and allopurinol as well as the methotrexate and citrovorum factor rescue.

Consolidation (35 days in length) will begin 10 days after induction therapy is completed and will include vincristine, prednisone, and 6-mercaptopurine in addition to the methotrexate.

Maintenance therapy will begin 10 days after the consolidation phase is completed and will be divided into 6 cycles of therapy, each 22 weeks in length. In addition to the methotrexate, chemotherapy will include prednisone, vincristine, 6-mercaptopurine, and l-asparaginase, daunomycin given on a staggered schedule.

Patients who have an M₃ bone marrow after completing at least 28 days of therapy or who manifest progressive disease will be removed from the study.

Progress: One patient has been entered in this study and is still in the treatment phase.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 88/14 Status: On-going

Title: CCG 213: Treatment of Newly Diagnosed Acute Non-lymphoblastic Leukemia for Children Greater than One Month but Less than 21 Years of Age

Start Date: 11 Dec 87 Est Completion Date: Jan 94
Department: Pediatrics Facility: MAMC
Principal Investigator: Edythe A. Albano, M.D.
Associate Investigator: MAJ Kip R. Hartman, MC
Key Words: ANLL, chemotherapy, sub-protocol/AMOL, chemotherapy
Accumulative MEDCASE Est Accumulative Periodic Review:
Cost: -0- OMA Cost: -0- N/A

Study Objective: To improve the duration of complete remission in children with acute non-lymphocytic leukemia (ANLL).

Technical Approach: Induction will consist of two or three 14-day cycles of Denver Therapy (VP 16-213, daunomycin, Ara-C, 6-thioguanine, and dexamethasone) followed by two or three 14-day cycles of DNM/Ara-C (daunomycin and Ara-C) or given in the reverse order depending on randomization. If bone marrow is M1, ANC ≥ 750 , and platelet count $\geq 75,000$ after two cycles, the patient will start the alternate regimen. Patients with M1 marrow after the first regimen of induction or M1 or M2A marrow at any time after completion of induction will have a bone marrow transplant if a suitable donor is available and the patient/family wishes to pursue this course of action. At the end of induction, patients with remission and no donor will be entered in a consolidation phase which will consist of 2 cycles of high-dose Ara-C and L-asparaginase, followed by two cycles of 6thioguanine, vincristine, ara-C 5-azacytidine, and cyclophosphamide, and then one cycle of VP 16-213, daunomycin, Ara-C, dexamethasone, and 6-thioguanine. Those with remission and no donor will then be randomized to no further therapy or eighteen 28-day cycles of 6-thioguanine, vincristine, Ara-C, 5-azacytidine, and cyclophosphamide. Those who have failed therapy will be taken off study. Intrathecal Ara-C prophylaxis will be given on day 0 of each cycle except for the regimen using high-dose Ara-C.

Children ≤ 2 years of age with acute monoblastic/monocytic leukemia will also be treated on this protocol using a 4-week induction phase of chemotherapy, followed by a four week consolidation phase of chemotherapy plus radiation therapy for CNS prophylaxis or involvement. The maintenance phase will consist of four 3-month chemotherapy courses plus radiation therapy for CNS prophylaxis or involvement. Drugs to be used are VM-26, VP-16, cyclophosphamide, intrathecal Ara-C, vincristine, prednisone, daunomycin, and 6-thioguanine. Patients will be taken off study if they are not in complete remission by Week 8 of the study.

Progress: One patient has entered this study. The patient has completed therapy and is being followed.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 86/31 Status: On-going

Title: CCG 323P: Cyclic Combination Chemotherapy for Newly Diagnosed Stage III Neuroblastoma Age 2 Years or Older at Diagnosis and Newly Diagnosed Stage IV Neuroblastoma All Ages

Start Date: 17 Jan 86 Est Completion Date: Indefinite

Department: Pediatrics Facility: MAMC

Principal Investigator: Edythe A. Albano, M.D.

Associate Investigators: LTC Allen R. Potter, MC

MAJ Kip R. Hartman, MC

Key Words: neuroblastoma, Stages III & IV, chemotherapy, cyclic

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: -0- Jan 87

Study Objective: To evaluate the effect of melphalan in newly - diagnosed untreated Stage IV neuroblastoma; to evaluate the effect on the toxicity in Stage III neuroblastoma age 2 years and older and in Stage IV neuroblastoma of alternating cycles of vincristine/cyclophosphamide-DTIC and intravenous melphalan; and to continue to evaluate front-end prognostic factors other than age at diagnosis in Stage III neuroblastoma 2 years of age and older and Stage IV.

Technical Approach: After satisfying the eligibility criteria as listed in the protocol, patients with Stage III neuroblastoma age 2 years and older at diagnosis or with Stage IV (except IV-S) neuroblastoma, all ages, will be treated with two courses of cyclophosphamide and DTIC for 22 weeks. After a total of 22 weeks of therapy, if the patient has a complete remission, partial remission, or stable disease with no progression, alternating cycles of melphalan and vincristine/cyclophosphamide/DTIC chemotherapy will be continued for the full 105 weeks. Patients with progressive disease after a minimum of four chemotherapy pulses (12 weeks) will be removed from the study and will be candidates for alternative therapy. Patients experiencing progressive disease prior to week 22 may receive XRT at the discretion of the PI and radiotherapist and continue on therapy to week 22.

Progress: No new patients were entered in this study in FY 88. The protocol has been closed to patient entry.

Two patients entered in previous years are still in the treatment phase of the study.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 87/112 Status: On-going

Title: CCG 461: Intergroup National Wilms' Tumor Study 4

Start Date: 18 Sep 87 Est Completion Date: Sep 97

Department: Pediatrics Facility: MAMC

Principal Investigator: Edythe A. Albano, M.D.

Associate Investigator: MAJ Kip R. Hartman, MC

Key Words: Wilms' tumor, chemotherapy, favorable histology, clear cell carcinoma, stages I-IV

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: -0- Sep 88

Study Objective: To gain a better understanding of the Wilms' tumor by gathering detailed information regarding gross and histologic morphology and to correlate this information with treatment and clinical outcome; to test treatment hypotheses by randomized, prospective clinical trials according to stage and histological grade of disease; to refine methods of treatment according to histology and stage; to identify children and families at high risk for cancer, and to study the late consequences of successful treatment given for Wilms' tumor.

Technical Approach: Hypothesis: simplified yet intensified treatment using agents known to be effective will prove to be better or at least no worse than regimens on previous protocols. Intensification will be achieved through shortening the interval between drug cycles, in the process giving more therapy up front and giving as much, if not more, of the drugs over the same time interval, except for vincristine in Stage II/FH (favorable histology). Simplification will be achieved through administering all drugs in single injections at each cycle rather than five daily doses of actinomycin-D and three daily doses of adriamycin as in previous protocols. After surgery, Stage I/FH and anaplastic tumors and Stage II/FH will receive actinomycin-D and vincristine in either the standard schedule or on a pulsed, intensive schedule. Stage III/FH will receive actinomycin D, vincristine, and doxorubicin on a standard schedule plus radiation therapy. High risk (clear cell sarcoma, all stages, and Stage IV/FH) patients will receive pulsed, intensive chemotherapy with actinomycin-D, vincristine, and dactinomycin plus radiotherapy if the primary tumor would qualify as Stage II were there no metastasis.

Progress: No patients entered in this study at MAMC.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 87/76 Status: On-going

Title: CCG-521: Treatment of Newly Diagnosed Advanced Hodgkins Disease (Pathologic Stages III₁ AS_{macro}, III₁A Macromediastinum, III₂A, IIIB, IVA, IVB)

Start Date: 15 May 87 Est Completion Date: May 92

Department: Pediatrics Facility: MAMC

Principal Investigator: Edythe A. Albano, M.D.

Associate Investigator: MAJ Kip R. Hartman, MC

Key Words: Hodgkins, newly diagnosed, chemotherapy, radiotherapy

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: -0- Sep 88

Study Objective: To improve the proportion of patients with advanced Hodgkin's Disease who are cured; to compare the relapse free survival and survival in advanced Hodgkin's disease in children utilizing an eight-drug (twelve cycle MOPP/ABVD) combination chemotherapy regimen versus a four drug (six cycle ABVD) chemotherapy regimen followed by low dose (2100 cGy rad) regional radiation therapy; and to compare the concurrent and long term toxicity of the two regimens.

Technical Approach: Patients <21 years with newly diagnosed Hodgkin's disease, pathologically staged as III₁ AS_{macro}, III₁A macromediastinum, III₂A, IIIB, IVA, or IVB will be randomized to either Regimen A or Regimen B.

The drugs used in Regimen A are mustard, vincristine, prednisone, procarbazine (MOPP) and adriamycin, bleomycin, vinblastine, and DTIC (ABVD). Six courses of therapy will be given. Each course consists of alternating 28-day cycles of MOPP and ABVD. Each cycle of MOPP consists of two pulses of chemotherapy of mustard and vincristine given seven days apart and a fourteen day administration of prednisone and procarbazine. Each cycle of ABVD consists of two pulses of chemotherapy given two weeks apart. Treatment will be terminated at the end of the six courses of chemotherapy or upon disease progression.

Regimen B will consist of six cycles of ABVD. Each cycle consists of two pulses of chemotherapy given two weeks apart. All patients will receive six cycles of chemotherapy unless progressive disease is noted or unacceptable toxicity occurs. Regional irradiation of 2100 cGy in 12 fractions will then be given.

Progress: No patients have been entered in this study at MAMC.

Detail Summary Sheet

Date: 30 Sep 88	Protocol No.: 86/45	Status: On-going
Title: CCG 631: Intergroup Rhabdomyosarcoma Study - III NCI Protocol #: INTERG-0032		
Start Date: 21 Mar 86	Est Completion Date: Feb 92	
Department: Pediatrics	Facility: MAMC	
Principal Investigator: Edythe A. Albano, M.D.		
Associate Investigators: LTC Allen R. Potter, MC MAJ Kip R. Hartman, MC		
Key Words: rhabdomyosarcoma, chemotherapy, radiotherapy		
Accumulative MEDCASE	Est Accumulative	Periodic Review:
Cost: -0-	OMA Cost: -0-	Sep 88

Study Objective: To compare various forms of treatment of rhabdomyosarcoma and to determine: if various combinations of vincristine, dactinomycin, adriamycin, cyclophosphamide, cis-platin, and VP-16, with or without radiation therapy, will improve survival rates in both favorable and unfavorable histology tumors that - have been completely or grossly, but incompletely, removed; if patients with localized orbit and head tumors will do well with vincristine and dactinomycin therapy limited to one year; patients with localized prostate, bladder, vagina, or uterus tumors can be treated successfully with cis-platin, adriamycin, vincristine, cyclophosphamide, and dactinomycin to avoid radical surgery and preserve the involved organ. Other objectives are to use second and third operations to see if the tumor is gone and, if not, to see if any remaining tumor can be surgically removed; to add other combinations of drugs when only partial response is obtained from the initial treatment; to use XRT and IT drugs to treat tumors extending or at risk of extension into the brain or spinal cord; and to do various studies of drug sensitivity and tumor typing on the removed tumor tissue to find new drugs for treatment and new ways of diagnosing cancer.

Technical Approach: Patients will be categorized as: Group I: localized disease, completely resected; Group II: total gross resection with evidence of regional spread; Group III: incomplete resection with gross residual disease; and group IV: distant metastatic disease present at onset. Patients will then be subcategorized into groups according to favorable or unfavorable histology and location of disease and treated with one of 8 regimens containing various combinations of actinomycin-D, adriamycin, cisplatin, cyclophosphamide, cytosine arabinoside, DTIC, hydrocortisone, leucovorin, vincristine sulfate, methotrexate, and VP-16, with or without the addition of radiation therapy and surgery.

Progress: No patients have been entered at MAMC.

Detail Summary Sheet

Date: 30 Sep 88	Protocol No.: 88/13	Status: On-going
Title: CCG 921: Unfavorable Medulloblastoma and Intracranial Primitive Neuroectodermal Tumors (PNET), Malignant Ependymoma, Ependymoblastoma, Pineoblastoma, and Central Neuroblastoma		
Start Date: 11 Dec 87	Est Completion Date: Jan 94	
Department: Pediatrics	Facility: MAMC	
Principal Investigator: Edythe A. Albano, M.D.		
Associate Investigator: MAJ Kip R. Hartman, MC		
Key Words: blastomas, intracranial primitive neuroectodermal tumors, children, chemotherapy, radiotherapy		
Accumulative MEDCASE	Est Accumulative	Periodic Review:
Cost: -0-	OMA Cost: -0-	N/A

Study Objective: To define a more effective treatment for high risk medulloblastoma and other primitive neuroectodermal tumors of childhood.

Technical Approach: Patients <21 years old will have resection, intraoperative staging, and histopathologic assessment. If extent of disease evaluation demonstrates residual tumor $>1.0 \times 1.5$ cm² in Stage T₁₋₂ tumors or Stage T₃₋₄ tumors and/or neuraxis or metastatic extension of tumor (M₁₋₄), patients will be randomized to receive either Control Regimen A or Experimental Regimen B.

Regimen A: Standard radiation therapy plus vincristine once a week for 8 weeks followed by a 28-day rest period and then vincristine, prednisone, and CCNU maintenance chemotherapy given every 42 days for eight courses.

Regimen B: 8-drugs-in-1-day chemotherapy (cisplatin, procarbazine, CCNU, vincristine, cyclophosphamide, methylprednisolone, hydroxyurea, and cytosine arabinoside) for 2 courses on days 0 and 14. A rest period of 14 days will be followed by an extent-of-disease evaluation, then standard craniospinal radiation, and then 8-drugs in-1-day maintenance every 42 days for up to 8 courses. Patients will be followed for toxicity, time, sites of relapse, and survival for five years.

The end-point of this study will be time to disease recurrence or progression, as defined by both neuroradiological and clinical assessments, and overall survival.

Progress: No patients have been entered in this study at MAMC.

Detail Summary Sheet

Date: 30 Sep 88	Protocol No.: 87/67	Status: On-going
Title: CCG-8602: Idarubicin for Remission Induction in Patients with Leukemia in Children in Second or Subsequent Marrow Relapse		
Start Date: 17 Apr 87	Est Completion Date: May 91	
Department: Pediatrics	Facility: MAMC	
Principal Investigator: Edythe A. Albano, M.D.		
Associate Investigator: MAJ Kip R. Hartman, MC		
Associate Investigators: None		
Key Words: leukemia, marrow relapse, idarubicin		
Accumulative MEDCASE	Est Accumulative	Periodic Review:
Cost: -0-	OMA Cost: -0-	Sep 88

Study Objective: To refine the determination of the maximal tolerated dose of intravenous idarubicin given by a weekly x 3 and by a daily x 3 schedule in children with leukemia; to determine the pharmacokinetics of intravenous idarubicin and idarubicinol in children with acute leukemia treated with two schedules, weekly x 3 and daily x 3; and to determine the effects of drug scheduling of idarubicin on remission induction rates for children with acute lymphoblastic leukemia and acute non-lymphoblastic leukemia.

Technical Approach: This is a randomized Phase II study employing two different dosing schedules of idarubicin, given IV. Children who have had a second or subsequent marrow relapse will be treated with a weekly x 3 schedule or a daily x 3 schedule. Since the maximal tolerated dose (MTD) has been reported as both 40 mg/m² and as 30 mg/m², when given IV in equally divided doses daily for three days, the MTD for dosing on the daily schedule will be further refined and the MTD for a weekly schedule in children determined. A dose intermediate between the reported MTD's will be selected to evaluate first. If toxicity is acceptable, the dosages of drug given each week or each day will be escalated after three evaluable patients have been treated. Subsequent escalations in dose will also require acceptable toxicity in three evaluable patients. The dose will not be escalated in individual patients. Each patient will receive only one dosage throughout their treatment. Once the MTD for each schedule is determined, the dose will be used in six additional patients to confirm acceptable toxicity. If acceptable toxicity is confirmed, additional patients will be entered at this dose level to assess remission induction rates. Remission induction rates will be determined at 21 days from initiation of therapy. If remission is not obtained following the three doses of idarubicin, if the leukemia has not responded, and if toxicity from the first course was acceptable, patients will be treated with a second course of the drug, using the same dose and schedule. Remission status will again be evaluated 21 days from the start of the second course of treatment. For patients attaining a complete remission, maintenance therapy will be at the discretion of the investigator caring for the patient.

Progress: No patients have been entered at MAMC.

Detail Summary Sheet

<u>Date: 30 Sep 88</u>	<u>Protocol No.: 87/68</u>	<u>Status: On-going</u>
<u>Title: CCG 8603: Phase I Study of the Combination of 5 Days Intravenous 5-Fluorouracil (NSC-19893) and 6 days of High Dose Oral Leucovorin (NSC-3590) in Pediatric Patients</u>		
<u>Start Date: 17 Apr 87</u>	<u>Est Completion Date: May 91</u>	
<u>Department: Pediatrics</u>	<u>Facility: MAMC</u>	
<u>Principal Investigator: Edythe A. Albano, M.D.</u>		
<u>Associate Investigator: MAJ Kip R. Hartman, MC</u>		
<u>Key Words: IV 5-FU, oral high dose leucovorin, combination</u>		
<u>Accumulative MEDCASE</u>	<u>Est Accumulative</u>	<u>Periodic Review:</u>
<u>Cost: -0-</u>	<u>OMA Cost: \$3000.00</u>	<u>Sep 88</u>

Study Objective: To determine the maximally tolerated dose of 5-fluorouracil (5-FU) administered as a daily x 5 bolus dose in combination with high dose oral folinic acid (leucovorin) in pediatric patients with cancer; to investigate the effects of 5-FU in combination with high dose folinic acid on the inhibition and recovery of thymidylate synthase in leukemic cells; and to determine the pharmacokinetics of oral folinic acid in pediatric patients.

Technical Approach: Patients with leukemia and solid tumors, ages 1-21 years, will be studied. Leucovorin will be administered orally at 0, 1, 2, and 3 hours daily for six days, commencing 24 hours prior to the first dose of 5-FU. Patients will be treated by IV bolus infusion over 15 minutes of 5-FU for five days (days 2-6), within one hour after the fourth dose of leucovorin each day. Second and subsequent courses will be administered no more frequently than three weeks or when the patient has recovered from the toxic effects of the therapy. The daily dose for leucovorin will be 500 mg/m² divided into four equal doses. The starting dose of 5-FU will be 300 mg/m²/day.

The maximum tolerated dose (MTD) will be investigated for leukemia and solid tumors separately. For each of these two disease categories, three evaluable patients will be required at each dose level examined. Dose escalation will proceed at 25% of the previous dose until a dose is reached at which there is evidence of Grade III or IV toxicity which is attributable to the treatment. Three patients will then be enrolled at the penultimate dose and evaluated. If there is no evidence of life threatening toxicity among these three patients, this dose will be considered the MTD. If evidence of such toxicity is noted, the dose level will be reduced in single steps by the original increments and three evaluable patients enrolled. The first dose at which no life threatening toxicities are noted will be considered the MTD.

Progress: No patients have been enrolled at MAMC.

DETAIL SHEETS
FOR
PROTOCOLS

FRED HUTCHINSON CANCER RESEARCH CENTER GROUP PROTOCOLS

Detail Summary Sheet

Date: 30 Sep 87 Protocol No.: 83/47 Status: On-going

Title: FHCRC #152: Combined Modality Treatment for Non-Hodgkin's Lymphomas of Intermediate and High-Grade Malignancy

Start Date: 18 Feb 83 Est Completion Date: Jan 85

Dept/Svc: Medicine/Oncology Facility: MAMC

Principal Investigator: LTC Howard Davidson, MC

Associate Investigators:

COL Irwin B. Dabe, MC	MAJ Thomas M. Baker, MC
COL Friedrich H. Stutz, MC	MAJ Alfred H. Chan, MC
LTC James E. Congdon, MC	MAJ Timothy J. O'Rourke, MC

Key Words: non-Hodgkin's lymphoma, intermediate, high-grade

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: -0- Sep 88

Study Objective: To compare in patients with extensive (stage III and IV), aggressive (intermediate and high-grade malignancy) non-Hodgkin's lymphoma (NHL) the response rate, duration, and survival after treatment with: (1) combined cyclophosphamide, adriamycin, vincristine, and prednisone (CHOP) chemotherapy combined with total body irradiation (TBI), or (2) CHOP chemotherapy combined with upper and lower hemibody irradiation (HBI); and to determine the response rate, duration and survival of patients with limited (stage I, II, and certain stage III and IV), aggressive NHL treated with CHOP chemotherapy with local radiotherapy.

Technical Approach: After appropriate tests to determine the extent of the lymphomas, patients will receive 4 cycles of multi-agent chemotherapy to include Cytosan, adriamycin, Oncovin and prednisone. At the end of 4 cycles of chemotherapy, given 4 wks apart, patients will be restaged to determine the extent of remaining disease. If there is at least a 50% reduction in the observed disease, the patients will proceed to Phase II consisting of radiation therapy. All patients will receive prednisone every other day by mouth and vincristine IV every other week. Those patients with disease involving <50% of the body will receive limited radiation therapy to sites of known lymphoma involvement.

Those patients with extensive disease will be randomized to receive either low dose total body radiation or low dose sequential hemibody radiation therapy. At the completion of Phase II, all patients will receive 4 more cycles of CHOP with the intervals lengthened to 8 weeks. At the end of Phase III, if there is no evidence of remaining disease, patients will be taken off therapy and observed.

Progress: This study has been closed to patient entry. Two patients are being followed at MAMC. Group-wide results show a complete remission of 75% in limited disease and 56% in extensive disease. Survival to three years is 50% in HBI arm (mostly Stage IVB patients).

D E T A I L S H E E T S

F O R

P R O T O C O L S

GYNECOLOGY ONCOLOGY GROUP PROTOCOLS

Detail Summary Sheet

Date: 30 Sep 88	Protocol No.:	Status: On-going
Title: GOG #26A: Master Protocol for Phase II Drug Studies in Treatment of Advanced, Recurrent Pelvic Malignancies		
Start Date: 20 Nov 81	Est Completion Date: Indefinite	
Department: OB/GYN	Facility: MAMC	
Principal Investigator: LTC Gordon O. Downey, MC		
Associate Investigators: COL William Benson, MC, COL Roger B. Lee, MC		
Key Words: advanced malignancy, refractory to prior therapy		
Accumulative MEDCASE	Est Accumulative	Periodic Review:
Cost: -0-	OMA Cost: -0-	Aug 88

Study Objective: To implement a master protocol to screen for activity and efficacy of new agents or combinations in patients with advanced or recurrent pelvic malignancies, resistant to higher priority methods of treatment.

Technical Approach: A "rejection" type design will be used with a fixed sample size of 25 evaluable patients/disease site/drug or combination studied. The design allows replacement of ineffective regimens by newer agents or combinations. Sections relating to specific agents will be sequentially incorporated into this protocol as these agents are studied. Continuing review will be done for each separate protocol.

To be eligible, patients must have histologically confirmed, advanced, recurrent, persistent, metastatic, or local gynecologic cancer with documented disease progression; lesions that are measurable and can be followed for tumor response; abdominal, pelvic, or other masses which can be defined in at least two dimensions by palpation or by x-ray; a GOG performance Grade 0, 1, or 2 (Karnofsky scale 30-100); free of clinically significant infection; off previous chemotherapy for at least 3 weeks; recovered from effects of recent surgery, radiotherapy, or chemotherapy; passed the nadir blood counts from previous therapy and a granulocyte count $\geq 1500/\text{mm}^3$, platelet count $\geq 100,000/\text{mm}^3$, BUN ≤ 25 mg%, creatinine ≤ 1.5 mg%, bilirubin ≤ 1.1 mg, SGOT ≤ 5 IU. Patients receiving myelosuppressive agents will have adequate bone marrow function as described above. Exception to the general requirement for normal liver function will be secondary to documented metastatic tumor to the liver or as noted in the section dealing with that particular agent. Patients with all primary disease sites of gynecologic malignancies are eligible. Each disease site will be accumulated as a separate study sample. For a particular drug study, the allowable disease site(s) may be further qualified. Ascites and pleural effusion alone are not considered measurable for purposes of the study. A steady rise in the titers of alpha-fetoprotein and beta-HCG will be taken as evidence of disease progression in germ cell tumors of the ovary.

Progress: One new patient was entered in this group of protocols in FY 88. In previous years 15 patients have been entered. Of these, 10 died of the disease and three had disease progression. Other available data regarding individual protocols is recorded with each protocol.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 82/07 Status: On-going

Title: GOG #26C: A Phase II Trial of Cis-Platinum
Diamminedichloride

Start Date: 20 Nov 81 Est Completion Date: Indefinite

Department: OB/GYN Facility: MAMC

Principal Investigator: LTC Gordon O. Downey, MC

Associate Investigators: COL William Benson, MC

COL Roger B. Lee, MC

Key Words: advanced malignancy, refractory to prior therapy

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: -0- Sep 88

Study Objective: To determine the efficacy of cis-platinum diamminedichloride in patients whose advanced malignancies have been resistant to higher priority methods of treatment.

Technical Approach: All patients with measurable gynecological cancer, who have failed higher priority therapies, will be offered cis-platinum as a Phase II drug to determine its efficacy. The drug is given at 50 mg/M² intravenously every three weeks as toxicity permits. Patients who respond or who demonstrate disease will continue to receive the agent until progression has occurred.

Progress: No new patients were entered in FY 88. Three patients were entered in previous years. Group-wide data indicate that cis-platinum has marked activity as first-line chemotherapy of squamous cell carcinoma of the cervix, endometrial cancer, and mixed mesodermal sarcomas of the uterus, and is active as second-line therapy of advanced ovarian adenocarcinoma and mixed mesodermal sarcoma of the uterus at the dose and schedule tested. The drug appears to be inactive as second-line therapy against endometrial carcinoma and vulvar carcinoma, and is inactive as first or second-line therapy of leiomyosarcoma of the uterus. It may have limited activity in the therapy of cervical adenocarcinomas.

Detail Summary Sheet

Date: 30 Sep 88	Protocol No.: 83/18	Status: On-going
Title: GOG #26D: A Phase II Trial of VP-16 in Patients with Advanced Pelvic Malignancies		
Start Date: 19 Nov 82	Est Completion Date: Indefinite	
Department: OB/GYN	Facility: MAMC	
Principal Investigator: LTC Gordon O. Downey, MC		
Associate Investigators: COL William Benson, MC COL Roger B. Lee, MC		
Key Words: pelvic malignancies, advanced, resistant		
Accumulative MEDCASE	Est Accumulative	Periodic Review:
Cost: -0-	OMA Cost: -0-	Nov 86

Study Objective: To determine the efficacy of VP-16 in patients whose advanced malignancies have been resistant to higher priority methods of treatment.

Technical Approach: All patients with measurable gynecological cancer who have failed higher prior therapies will be offered VP 16 as a Phase II drug to determine its efficacy. The drug will be given as 100 mg/M² intravenously on days 1, 3, and 5, every four weeks. Patients who respond or demonstrate disease will continue to receive the agent until progression has occurred.

Progress: No patients were entered in this study at MAMC in FY 88. One patient was entered at MAMC in FY 87.

Group-wide, VP-16 appears to have minimal activity against ovarian adenocarcinoma and insignificant activity against squamous cell carcinoma of the cervix and endometrial adenocarcinoma at the dose and schedule tested. VP-16 appears to be inactive in advanced or recurrent non-squamous cell carcinoma of the cervix. Insufficient numbers of cases have been entered into other tumor categories to indicate any trends.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 83/19 Status: Completed

Title: GOG #26E: A Phase II Trial of Glactitol 1,2:5,6-Dianhydro
in Patients with Advanced Pelvic Malignancies

Start Date: 19 Nov 82 Est Completion Date: Indefinite

Department: OB/GYN Facility: MAMC

Principal Investigator: LTC Gordon O. Downey, MC

Associate Investigators: COL William Benson, MC

COL Roger B. Lee, MC

Key Words: pelvic malignancies, advanced, resistant

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: -0- Nov 86

Study Objective: To determine the efficacy of glactitol 1,2:5,6-dianhydro in patients whose advanced malignancies have been resistant to higher priority methods of treatment.

Technical Approach: All patients with measurable gynecological cancer who have failed higher prior therapies will be offered glactitol 1,2:5,6-dianhydro as a Phase II drug to determine its efficacy. The drug will be given as 60 mg/M² slow I.V. push - weekly. If no toxicity has occurred after 4 doses, the dosage will be increased to 75 mg/M² weekly. Patients will continue to receive the agent until progression occurs.

Progress: No patients entered at MAMC.

Detail Summary Sheet

Date: 30 Sep 88	Protocol No.: 83/20	Status: Completed
Title: GOG #26G: A Phase II Trial of ICRF-159 in Patients with Advanced Pelvic Malignancies		
Start Date: 19 Nov 82	Est Completion Date: Indefinite	
Department: OB/GYN	Facility: MAMC	
Principal Investigator: LTC Gordon O. Downey, MC		
Associate Investigators: COL William Benson, MC COL Roger B. Lee, MC		
Key Words: pelvic malignancy, advanced, resistant, ICRF-159		
Accumulative MEDCASE	Est Accumulative	Periodic Review:
Cost: -0-	OMA Cost: -0-	Nov 86

Study Objective: To determine the efficacy of ICRF-159 in patients whose advanced malignancies have been resistant to higher priority methods of treatment.

Technical Approach: All patients with measurable gynecological cancer who have failed higher prior therapies will be offered ICRF-159 as a Phase II drug to determine its efficacy. The drug will be given by mouth as 1.5 gm/M², in three divided doses, one every 6 hours, on day 1, repeated weekly as marrow recovery permits. Patients will continue to receive the agent until progression occurs.

Progress: No patients entered in FY 88. One patient was entered in FY 83, exhibited no response to ICRF and died from disease in FY 84.

Group-wide results thus far show that ICRF appears to have moderate activity in squamous cell carcinoma of the cervix and no significant activity in epithelial tumors of the ovary, endometrial carcinoma, and non-squamous cell carcinoma of the cervix at the dose and schedule tested despite induction of significant myelosuppression.

Detail Summary Sheet

Date: 30 Sep 88	Protocol No.: 83/52	Status: Completed
Title: GOG #26L: A Phase II Trial of Tamoxifen (NSC 180793) in Patients with Advanced Epithelial Ovarian Carcinoma, Part II		
Start Date: 18 Mar 83	Est Completion Date: Jul 88	
Department: OB/GYN	Facility: MAMC	
Principal Investigator: LTC Gordon O. Downey, MC		
Associate Investigators: COL William Benson, MC COL Roger B. Lee, MC		
Key Words: epithelial ovarian carcinoma, advanced, resistant		
Accumulative MEDCASE	Est Accumulative	Periodic Review:
Cost: -0-	OMA Cost: -0-	Mar 87

Study Objective: To determine the efficacy of tamoxifen in patients whose advanced malignancies have been resistant to higher priority methods of treatment.

Technical Approach: All patients with measurable gynecological cancer who have failed higher prior therapies will be offered - tamoxifen as a Phase II drug to determine its efficacy. The drug will be given as 20 mg PO b.i.d. until adverse effects prohibit further therapy. A minimum trial will be defined as receiving a minimum of eight weeks of therapy.

Progress: No patients entered in this study at MAMC in FY 88. In previous years, two patients had been entered. Both expired from their disease.

Group-wide, tamoxifen did not reveal any activity in patients - with advanced or recurrent adenocarcinoma or adenosquamous carcinoma of the endometrium of unknown hormonal receptor status, progressing after heavy pretreatment with hormonal therapy with progestational agents and/or chemotherapy.

Tamoxifen shows definite activity as second-line treatment for epithelial ovarian carcinoma, with overall response rate of approximately 18% and a 10% complete response rate. Durations of response range from 7 to 12 months. Toxicity is minimal. An additional 38% of patients exhibit stable disease, although durations are considerably shorter.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 83/24 Status: On-going

Title: GOG #26N: A Phase II Trial of Dihydroxyanthracenedione (DHAD) in Patients with Advanced Pelvic Malignancies

Start Date: 19 Nov 82 Est Completion Date: Indefinite

Department: OB/GYN Facility: MAMC

Principal Investigator: LTC Gordon O. Downey, MC

Associate Investigators: COL William Benson, MC
COL Roger B. Lee, MC

Key Words: pelvic malignancies, advanced, DHAD

Accumulative MEDCASE Est Accumulative Periodic Review:
Cost: -0- OMA Cost: -0- Sep 88

Study Objective: To determine the efficacy of DHAD in patients whose advanced malignancies have been resistant to higher priority methods of treatment.

Technical Approach: All patients with measurable gynecological cancer who have failed higher prior therapies will be offered DHAD as a Phase II drug to determine its efficacy. The drug will be given as 12 mg/M² I.V. every three weeks. Patients will continue to receive the agent until progression or adverse effects prohibit further therapy.

This protocol was closed to uterus/MMT patient entry in Aug 87.

Progress: No new patients were entered in FY 88 at MAMC. In previous years three patients had been entered. All died of their disease.

Group-wide data indicate minimal activity of DHAD in patients with ovarian cancer who have previously received doxorubicin. In patients with previously treated advanced carcinoma of the cervix, this drug also shows minimal activity. DHAD has minimal activity in patients with nonsquamous carcinoma of the cervix.

Detail Summary Sheet

Date: 30 Sep 88	Protocol No.: 82/30	Status: On-going
Title: GOG #26-O: A Phase II Trial of Aziridinylbenzoquinone (AZQ) in Patients with Advanced Malignancies		
Start Date: 19 Feb 82	Est Completion Date: Indefinite	
Department: OB/GYN	Facility: MAMC	
Principal Investigator: LTC Gordon O. Downey, MC		
Associate Investigators: COL William Benson, MC COL Roger B. Lee, MC		
Key Words: malignancies, advanced, AZQ		
Accumulative MEDCASE	Est Accumulative	Periodic Review:
Cost: -0-	OMA Cost: -0-	Feb 87

Study Objective: To determine the efficacy of AZQ in patients whose advanced malignancies have been resistant to high priority methods of treatment.

Technical Approach: All patients with measurable gynecological cancer who have failed higher prior therapies will be offered AZQ as a Phase II drug to determine its efficacy. The drug will be given as 30 mg/M² given every three weeks. Patients will continue to receive the agent until progression or adverse effects prohibit further therapy.

Progress: No patients entered in FY 88. One patient entered at MAMC during FY 84 with no response to AZQ; death by cancer of cervix.

Group-wide data thus far indicate that AZQ has little if any activity as a salvage agent in either epithelial ovarian cancer or squamous cell carcinoma of the cervix.

Detail Summary Sheet

Date: 30 Sep 88	Protocol No.: 83/26	Status: On-going
Title: GOG #26Q: A Phase II Trial of Aminothiadiazole in Patients with Advanced Pelvic Malignancies		
Start Date: 19 Nov 82	Est Completion Date: Indefinite	
Department: OB/GYN	Facility: MAMC	
Principal Investigator: LTC Gordon O. Downey, MC		
Associate Investigators: COL William Benson, MC COL Roger B. Lee, MC		
Key Words: pelvic malignancies, advanced, aminothiadiazole		
Accumulative MEDCASE	Est Accumulative	Periodic Review
Cost: -0-	OMA Cost: -0-	Nov 88

Study Objective: To determine the efficacy of aminothiadiazole in patients whose advanced malignancies have been resistant to high priority methods of treatment.

Technical Approach: All patients with measurable gynecological cancer who have failed higher prior therapies will be offered aminothiadiazole as a Phase II drug to determine its efficacy. The drug will be given as 125 mg/M² I.V. once a week. Patients will continue to receive the agent until progression or adverse effects prohibit further therapy.

Progress: No entries in FY 88. One patient was entered in FY 85 and died from squamous cell carcinoma of the cervix.

Group-wide data indicate that aminothiadiazole used in this dose and schedule has minimal activity in previously treated patients with ovarian carcinoma, squamous cell carcinoma of the cervix, carcinoma of the endometrium, and nonsquamous cell carcinoma of the cervix.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 84/25 Status: Completed

Title: GOG #26R: A Phase II Trial of Progesterone in the Treatment of Advanced or Recurrent Epithelial Ovarian Cancers that Have Failed Combination Chemotherapy

Start Date: 20 Jan 84 Est Completion Date: Nov 88

Department: OB/GYN Facility: MAMC

Principal Investigator: COL Roger B. Lee, MC

Associate Investigator: COL William Benson, MC

Key Words: epithelial ovarian, advanced, recurrent, progesterone

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: -0- N/A

Study Objective: To determine the efficacy of progesterone in patients whose advanced malignancies have been resistant to higher priority methods of treatment.

Technical Approach: All patients with measurable gynecological cancer, who have failed higher priority therapies, will be offered C.T. Provera as a Phase II drug to determine its efficacy. The drug is given at 50 mg (1 tablet) t.i.d. until progression of disease.

Progress: One patient was entered on the protocol in FY 87 and died of the disease. No other patients were entered at MAMC. The study was closed to patient entry on 1 Feb 88.

Detail Summary Sheet

Date: 30 Sep 88	Protocol No.: 84/64	Status: On-going
Title: GOG 26-S: A Phase II Trial of Teniposide in Patients with Advanced Pelvic Malignancies		
Start Date: 15 Jun 84	Est Completion Date: Jun 89	
Department: OB/GYN	Facility: MAMC	
Principal Investigator: LTC Gordon O. Downey, MC		
Associate Investigators: COL William Benson, MC COL Roger B. Lee, MC		
Key Words: pelvic malignancies, advanced, Teniposide		
Accumulative MEDCASE	Est Accumulative	Periodic Review:
Cost: -0-	OMA Cost: -0-	Jul 87

Study Objective: To determine the efficacy of Teniposide in patients whose advanced malignancies have been resistant to high priority methods of treatment.

Technical Approach: Teniposide will be administered at a dosage of 100 mg/M² every week. The patients will be followed for toxicities to the drug and the drug dosages will be modified according to the severity of the toxicities. Response to the drug will be followed. Progression of disease and/or excessive toxicities will terminate the study for the patient.

Progress: No new patients entered in FY 87. Two patients were entered at MAMC in previous years. One patient has died of disease and the other has progression of disease.

Group-wide data show that teniposide produced only modest activity in previously treated patients with epithelial ovarian cancer at the dose and schedule used. Teniposide displays only modest activity in patients with squamous cell carcinoma of the cervix.

Detail Summary Sheet

<u>Date: 30 Sep 88</u>	<u>Protocol No.: 85/87</u>	<u>Status: On-going</u>
<u>Title: GOG 26 U: A Phase II Trial of Ifosfamide (NSC #109724) and the Uroprotector, Mesna (NSC #25232), in Patients With Advanced Pelvic Malignancies</u>		
<u>Start Date: 20 Sep 85</u>	<u>Est Completion Date: Indefinite</u>	
<u>Department: OB/GYN</u>	<u>Facility: MAMC</u>	
<u>Principal Investigator: LTC Gordon O. Downey, MC</u>		
<u>Associate Investigators: COL William Benson, MC</u>		
<u>COL Roger B. Lee, MC</u>		
<u>Key Words: ifosfamide, mesna, advanced pelvic malignancies</u>		
<u>Accumulative MEDCASE</u>	<u>Est Accumulative</u>	<u>Periodic Review:</u>
<u>Cost: -0-</u>	<u>OMA Cost: -0-</u>	<u>Aug 88</u>

Study Objective: To determine the efficacy of ifosfamide plus mesna in patients whose advanced malignancies have been resistant to higher priority methods of treatment.

Technical Approach: All eligible patients who have failed higher priority therapies will be offered ifosfamide plus mesna as a Phase II drug regimen to determine its efficacy. Ifosfamide will be given at a dosage of 1.8 g/M² daily for five days and mesna will be given 400 mg/M² t.i.d every four weeks. Patients will be followed for toxicities to the drug and the drug dosage will be modified according to the severity of the toxicities. Response to the drug will be followed; progression of disease and/or excessive toxicities will terminate the study for the patient.

Progress: No patients entered at MAMC.

Group-wide data indicate that ifosfamide is an active Phase II drug in relapsed epithelial ovarian carcinoma although nephrotoxicity is a limiting factor in this patient population. Ifosfamide possesses minimal activity in previously treated squamous carcinoma of the cervix.

Detail Summary Sheet

Date: 30 Sep 88	Protocol No.: 85/88	Status: Completed
Title: GOG 26V: A Phase II Trial of N-Methylformamide in Patients with Advanced Pelvic Malignancies		
Start Date: 20 Sep 85	Est Completion Date: Indefinite	
Department: OB/GYN	Facility: MAMC	
Principal Investigator: COL Roger B. Lee, MC		
Associate Investigator: COL William Benson, MC		
Key Words: pelvic malignancies, advanced, N-Methylformamide		
Accumulative MEDCASE	Est Accumulative	Periodic Review:
Cost: -0-	OMA Cost: -0-	N/A

Study Objective: To determine the efficacy of N-Methylformamide in patients whose advanced malignancies have been resistant to higher priority methods of treatment.

Technical Approach: All eligible patients who have failed higher priority therapies will be offered N-Methylformamide as a Phase II drug to determine its efficacy. N-Methylformamide will be given at a dosage of 800 mg/M² daily X 5 for five days every four weeks. Patients will be followed for toxicities to the drug and the drug dosage will be modified according to the severity of the toxicities. Response to the drug will be followed; progression of disease and/or excessive toxicities will terminate the study for the patient.

Progress: No patients entered at MAMC. The protocol was closed to patient entry on 1 Feb 88.

Detail Summary Sheet

<u>Date: 30 Sep 88</u>	<u>Protocol No.: 86/75</u>	<u>Status: On-going</u>
<u>Title: GOG 26W: A Phase II Trial of Echinomycin (NSC #526417) in Patients with Advanced Pelvic Malignancies</u>		
<u>Start Date: 20 Jun 86</u>	<u>Est Completion Date: Indefinite</u>	
<u>Department: OB/GYN</u>	<u>Facility: MAMC</u>	
<u>Principal Investigator: LTC Gordon O. Downey, MC</u>		
<u>Associate Investigators: COL William Benson, MC</u>		
<u>COL Roger B. Lee, MC</u>		
<u>Key Words: malignancies, pelvic, advanced, echinomycin, Phase II</u>		
<u>Accumulative MEDCASE</u>	<u>Est Accumulative</u>	<u>Periodic Review:</u>
<u>Cost: -0-</u>	<u>OMA Cost: -0-</u>	<u>Jul 87</u>

Study Objective: To screen for activity of new agents or drug combinations in patients with advanced malignancies. Its intent is to determine the efficacy of chemotherapeutic agents in patients whose advanced malignancies have been resistant to high priority methods of treatment.

Technical Approach: Echinomycin will be administered at a dosage of 1500 mcg/m every 4 weeks. An adequate trial is defined as receiving one dose of drug and alive at four weeks. Patients receiving one dose of drug and demonstrating progression \leq 4 weeks from study entry will be considered evaluable for response and toxicity. Each patient will remain on study and continue to receive drug until disease progression or adverse effects prohibit further therapy.

Progress: No patients entered at MAMC.

Detail Summary Sheet

<u>Date: 30 Sep 88</u>	<u>Protocol No.: 88/58</u>	<u>Status: On-going</u>
<u>Title: GOG 26X: A Phase II Trial of Gallium Nitrate (NSC #15200)</u> <u>in Patients with Advanced Pelvic Malignancies</u>		
<u>Start Date: 20 May 88</u>	<u>Est Completion Date: Indefinite</u>	
<u>Department: OB/GYN</u>	<u>Facility: MAMC</u>	
<u>Principal Investigator: LTC Gordon O. Downey, MC</u>		
<u>Associate Investigators: COL William Benson, MC</u> <u>COL Roger B. Lee, MC</u>		
<u>Key Words: pelvic malignancy, advanced, gallium nitrate</u>		
<u>Accumulative MEDCASE</u>	<u>Est Accumulative</u>	<u>Periodic Review:</u>
<u>Cost: -0-</u>	<u>OMA Cost: -0-</u>	<u>N/A</u>

Study Objective: To screen for activity of new agents or drug combinations in patients with advanced malignancies. Its intent is to determine the efficacy of chemotherapeutic agents in patients whose advanced malignancies have been resistant to high priority methods of treatment.

Technical Approach: Gallium nitrate will be given as a slow intravenous infusion over 30-60 minutes at a dose of 750 mg/m². The dose will be repeated once every three weeks.

Patients will be hydrated with at least three liters of fluid the day prior to treatment. An additional 500 cc normal saline will be infused in the two hours prior to administration of gallium nitrate. Hydration of three liters of fluid orally or intravenously will be continued during the first 24 hours after therapy.

Patients receiving concurrent radiotherapy are ineligible for this study.

An adequate trial will be defined as receiving one course of therapy and living three weeks. Each patient will continue receiving gallium nitrate until disease progression or death or until adverse effects prohibit further therapy.

Progress: No patients have been entered at MAMC.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 87/62 Status: On-going

Title: GOG 26Y: A Phase II Trial of Vinblastine (NSC 049842) in
Patients with Advanced Pelvic Malignancies

Start Date: 20 Mar 87 Est Completion Date: Indefinite

Department: OB/GYN Facility: MAMC

Principal Investigator: LTC Gordon O. Downey, MC

Associate Investigators: COL William Benson, MC

COL Roger B. Lee, MC

Key Words: pelvic malignancy, advanced, vinblastine

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: -0- Sep 88

Study Objective: To screen for activity of new agents or drug combinations in patients with advanced malignancies. Its intent is to determine the efficacy of chemotherapeutic agents in patients whose advanced malignancies have been resistant to high priority methods of treatment.

Technical Approach: Vinblastine will be administered at a dosage of 9 mg/m², I.V. push, on day 1 every three weeks with dose escalation to 12 mg/m² if minimal or no toxicity. An adequate trial is defined as receiving one course of therapy and alive for evaluation at three weeks. Patients will remain on study until progression of disease or adverse effects prohibit further therapy.

Progress: No patients entered at MAMC.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 88/59 Status: On-going

Title: GOG 26Z: A Phase II Trial of Leuprolide Acetate
(IND #29308) in Patients with Advanced Epithelial
Ovarian Carcinoma

Start Date: 20 May 88 Est Completion Date: Indefinite

Department: OB/GYN Facility: MAMC

Principal Investigator: LTC Gordon O. Downey, MC

Associate Investigators: COL William Benson, MC

COL Roger B. Lee, MC

Key Words: carcinoma, ovarian, epithelial, leuprolide acetate

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: \$7200.00 N/A

Study Objective: To screen for activity of new agents or drug combinations in patients with advanced malignancies. Its intent is to determine the efficacy of chemotherapeutic agents in patients whose advanced malignancies have been resistant to high priority methods of treatment.

Technical Approach: Patients must have biopsy-proven epithelial ovarian cancer according to the criteria of Scully (Human Pathology 1:73, 1970). Patients with tumors of low malignant potential are not eligible. Patients must have a life expectancy of at least two months.

Leuprolide acetate will be administered at a dosage of 1 mg as a daily subcutaneous injection until disease progression.

A minimum trial will be defined as receiving a minimum of eight weeks of therapy. Patients who develop bowel obstruction, toxic side effects, or refuse therapy in these first eight weeks will not be considered fully evaluable for response. Patients will receive therapy until progression or until adverse effects prohibit further therapy.

Progress: One patient entered at MAMC in FY 88.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 88/67 Status: On-going
Title: GOG 26-DD: A Phase II Trial of Amonafide (NSC #308847) in
Patients with Advanced Pelvic Malignancies
Start Date: 19 Aug 88 Est Completion Date: Indefinite
Department: OB/GYN Facility: MAMC
Principal Investigator: LTC Gordon O. Downey, MC
Associate Investigators: None
Key Words: malignancy, pelvic, advanced, chemotherapy, amonafide
Accumulative MEDCASE Est Accumulative Periodic Review:
Cost: -0- OMA Cost: -0- N/A

Study Objective: To screen for activity of new agents or drug combinations in patients with advanced malignancies. Its intent is to determine the efficacy of chemotherapeutic agents in patients whose advanced malignancies have been resistant to high priority methods of treatment.

Technical Approach: Patients must have normal renal and hepatic function. Patients will be entered as nonrandomized cases. Amonafide will be administered as a slow intravenous infusion over an hour at an initial dose of 300 mg/m² daily for five days. A serial dose escalation up to 450 mg/m² will be used in patient without toxicity after each cycle of therapy until a Grade 1 hematologic toxicity occurs.

All patients will receive therapy until disease progression or until adverse effects prohibit further therapy.

Progress: No patients entered at MAMC.

Detail Summary Sheet

Date: 30 Sep 88	Protocol No.: 88/67	Status: On-going
Title: GOG 26-EE: A Phase II Trial of Didemnin B (NSC #325319) in Patients with Advanced Pelvic Malignancies		
Start Date: 16 Sep 88	Est Completion Date: Indefinite	
Department: OB/GYN	Facility: MAMC	
Principal Investigator: LTC Gordon O. Downey, MC		
Associate Investigators: None		
Key Words: malignancy, pelvic, advanced, chemotherapy, didemnin-B		
Accumulative MEDCASE	Est Accumulative	Periodic Review:
Cost: -0-	OMA Cost: -0-	N/A

Study Objective: To screen for activity of new agents or drug combinations in patients with advanced malignancies. Its intent is to determine the efficacy of chemotherapeutic agents in patients whose advanced malignancies have been resistant to high priority methods of treatment.

Technical Approach: Patient must demonstrate a normal prothrombin time to be eligible for this protocol. Didemnin B will be administered at a dosage of 4.2 mg/m² every four weeks. The dosage will be calculated using the GOG standard monogram. Prophylaxis against nausea and vomiting using metoclopramide, diphenhydramine, and dexamethasone will be required. Dose modifications will be will be permitted.

An adequate trial is defined a receiving one dose of drug and alive at four weeks. Patients receiving one dose of Didemnin B and demonstrating progression more than or equal to four weeks from study entry will be considered evaluable for response and progression. Toxicity, however, may be assessed as soon as drug is given. Each patient should remain on study and continue to receive drug until disease progression or adverse effects prohibit further therapy.

Progress: No patients entered at MAMC.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 88/68 Status: On-going

Title: GOG 26-FF: A Phase II Trial of Taxol (NSC #125973) in
Patients With Advanced or Recurrent Ovarian Carcinoma

Start Date: 19 Aug 88 Est Completion Date: Indefinite

Department: OB/GYN Facility: MAMC

Principal Investigator: LTC Gordon O. Downey, MC

Associate Investigators: None

Key Words: carcinoma, ovarian, Taxol, efficacy

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: -0- N/A

Study Objective: To screen for activity of new agents or drug combinations in patients with advanced malignancies. Its intent is to determine the efficacy of chemotherapeutic agents in patients whose advanced malignancies have been resistant to high priority methods of treatment.

Technical Approach: Patients who meet the criteria listed in the master protocol (26A) will be administered Taxol as a 24-hour continuous infusion at an initial dose of 170 mg/m²/24 hours, once every three weeks. The dose will be reduced to 135 mg/m²/24 hours for high-risk patients (those who have received pelvic radiation in addition to first line chemotherapy). Dexamethasone, diphenhydramine, and ranitidine will be given prior to Taxol administration to prevent allergic reaction. Vital signs, including blood pressure, pulse, respiration, and temperature will be taken every 15 minutes during the initial two hours of infusion and then every hour thereafter until one hour after completion of the infusion. Cardiac monitoring is required during the infusion. An adequate trial is defined as receiving one course of therapy and alive for evaluation at three weeks. Each patients should remain on study until progression of disease or adverse effects prohibit further therapy.

Progress: No patients entered at MAMC.

Detail Summary Sheet

Date: 30 Sep 88	Protocol No.: 81/12	Status: On-going
Title: GOG #33: A Clinical Pathologic Study of Stages I and II Carcinoma of the Endometrium		
Start Date: 21 Nov 80	Est Completion Date: Nov 83	
Department: OB/GYN	Facility: MAMC	
Principal Investigator: LTC Gordon C. Downey, MC		
Associate Investigators: COL William Benson, MC COL Roger B. Lee, MC		
Key Words: carcinoma, lymph node, aortic, pelvic, metastases		
Accumulative MEDCASE	Est Accumulative	Periodic Review:
Cost: -0-	OMA Cost: -0-	Sep 88

Study Objectives: To determine the incidence of pelvic and aortic lymph node metastases associated with Stages I and II adenocarcinoma of the endometrium and the relationship of the node metastases to other important prognostic factors. These findings will then be used as a guide for treatment protocols.

Technical Approach: Patients will receive standard treatment; this protocol is only for data collection purposes. Patients with histologically proven endometrial carcinoma, clinical FIGO Stages I (grades 2 and 3) and Stage II (all grades) who have undergone total abdominal hysterectomy, bilateral salpingo-oophorectomy, selective pelvic and para-aortic lymphadenectomy, and peritoneal cytology sampling are eligible. The following histologic types of endometrial carcinoma are acceptable: adenocarcinoma, adenocarcinoma with squamous metaplasia, adenoacanthoma, and adenosquamous carcinoma. Patients who have received preoperative radiotherapy are ineligible. Pathologic evaluation will include: (a) peritoneal washing will be evaluated for malignant cells; (b) the uterus will be evaluated in regard to location of tumor, depth of myometrial invasion, differentiation of tumor, size of uterus; (c) the adnexae will be evaluated for presence of metastasis (d) the lymph nodes (total number indicated) will be evaluated as to metastasis and location and number of lymph nodes involved. After surgery, all patients will be entered into the appropriate protocol or receive appropriate treatment if no protocol is available.

Progress: This protocol is closed to patient entry. No patients were entered in FY 88. In previous years, eight patients were entered on the protocol. Three patients are still being followed on this study.

This protocol was reactivated in October 1986. It was mistakenly closed in FY 84 when it was closed to patient entry. However, the GOG continues to collect data on the patients who have survived; therefore, it must remain open and be reviewed periodically.

Preliminary group-wide data indicate that this study could define the surgical procedure required for optimal evaluation of endometrial cancer.

Detail Summary Sheet

Date: 30 Sep 88	Protocol No.: 81/24	Status: Completed
Title: GOG #34: A Randomized Study of Adriamycin as an Adjuvant After Surgery and Radiation Therapy in Patients with High Risk Endometrial Carcinoma Stage I and Occult Stage II		
Start Date: 6 Jan 81	Est Completion Date: Jan 84	
Department: OB/GYN	Facility: MAMC	
Principal Investigator: LTC Gordon O. Downey, MC		
Associate Investigators: COL William Benson, MC COL Roger B. Lee, MC		
Key Words: carcinoma, endometrial, adriamycin, adjuvant		
Accumulative MEDCASE	Est Accumulative	Periodic Review:
Cost: -0-	OMA Cost: -0-	Sep 88

Study Objective: To study differences in morbidity and patient survival as functions of various tumor growth patterns as well as treatment in the high risk Stage I and, optionally, high risk Stage II occult endometrial carcinoma.

Technical Approach: Patients with primary, previously untreated, histologically confirmed invasive carcinoma of the endometrium, Stage I or II occult, all grades, with one or more of the following high risk criteria are eligible: (1) all lesions with equal to or greater than 1/2 myometrial involvement; (2) positive pelvic and/or para-aortic nodes; (3) microscopic evidence of cervical involvement but no gross clinical involvement of the cervix; (4) adnexal metastasis. Surgery will be followed in 2-6 weeks by "tailored" radiation therapy, pelvic and/or para-aortic, depending on node positivity. Prior to the initiation of radiation, therapy patients will be randomized to no further therapy or to adriamycin beginning 2-4 weeks after radiation therapy.

Progress: No new entries in FY 88. Eight subjects were entered in previous years. The protocol is closed to patient entry. All MAMC patients have completed the 5-year follow-up period.

Detail Summary Sheet

Date: 30 Sep 88	Protocol No.: 81/79	Status: On-going
Title: GOG #40: A Clinical-Pathologic Study of Stages I and II Uterine Sarcomas		
Start Date: 15 May 81	Est Completion Date: Indefinite	
Department: OB/GYN	Facility: MAMC	
Principal Investigator: LTC Gordon O. Downey, MC		
Associate Investigators: COL William Benson, MC COL Roger B. Lee, MC		
Key Words: sarcoma, uterine, pathologic study		
Accumulative MEDCASE	Est Accumulative	Periodic Review:
Cost: -0-	OMA Cost: -0-	Jul 87

Study Objective: To determine the incidence of pelvic and aortic lymph node metastases associated with Stages I and II uterine sarcomas, the relationship of these node metastases to other important prognostic factors such as mitotic index of the tumor, and the complication rate of the procedures. These findings will then be used as a guide for treatment protocols.

Technical Approach: Patients with histologically proven uterine sarcoma clinical Stages I or II who undergo total abdominal hysterectomy, bilateral salpingo-oophorectomy, selective pelvic and para-aortic lymphadenectomy, peritoneal cytology sampling and omentectomy (optional) as described in the protocol are eligible. Patients who have had prior preoperative adjuvant pelvic radiation or chemotherapy will be ineligible. The following pathologic evaluation will be done:

- a. Peritoneal cytology will be evaluated for malignant cells.
- b. The uterus will be evaluated at least in regard to:
 - (1) location of tumor; (2) depth of myometrial invasion;
 - (3) differentiation of tumor; (4) size of uterus;
 - (5) number of mitoses per 10 HPF; (6) histologic type of tumor.
- c. The adnexa will be evaluated for presence of metastasis.
- d. The lymph nodes will be evaluated as to metastasis and location and number of involved lymph nodes.

After surgical staging, patients may be transferred to an appropriate treatment protocol if all criteria are met. If no protocol is available, further treatment will be at the discretion of the physician.

Progress: No new patients were entered at MAMC in FY 88. Six patients have been entered in previous years.

Group-wide data show that lymphatic node metastasis is low while recurrence rate is 47%. Adverse prognostic factors include lymphatic node metastasis, adnexal spread, tumor size, myometrial invasion, and lymphatic-vascular space involvement. Histologic grade appears more significant than mitotic index. The type of heterologous element is not significant. There have been four serious adverse effects with two postoperative deaths.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 81/35 Status: Completed

Title: GOG 41: Surgical Staging of Ovarian Carcinoma

Start Date: 16 Jan 81 Est Completion Date: Jan 86

Department: OB/GYN Facility: MAMC

Principal Investigator: LTC Gordon O. Downey, MC

Associate Investigators: COL William Benson, MC
COL Roger B. Lee, MC

Key Words: surgical staging, ovarian carcinoma, intraperitoneal structures, retroperitoneal lymph nodes, direct examination, cytologic sampling, biopsy

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: -0- Sep 88

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 treatment 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 other 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 complete 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 protocol was closed to patient entry in FY 84. Sixteen patients were entered at MAMC. The GOG has ceased to collect data on these patients.

This study demonstrates the value of omentectomy, lymph node excisions, and diaphragm biopsy in epithelial ovarian tumors. Still to be determined is the value of these procedures in sex cord-stromal and germ cell tumors. Results of this study will be used as a guide in future treatment protocols.

Detail Summary Sheet

Date: 30 Sep 88	Protocol No.: 81/25	Status: On-going
Title: GOG #44: Evaluation of Adjuvant Vincristine, Dactinomycin, and Cyclophosphamide Therapy in Malignant Germ Cell Tumors of the Ovary After Resection of all Gross Tumor, Phase III		
Start Date: 17 Dec 80	Est Completion Date: Jun 83	
Department: OB/GYN	Facility: MAMC	
Principal Investigator: LTC Gordon O. Downey, MC		
Associate Investigators: COL William Benson, MC COL Roger B. Lee, MC		
Key Words: germ cell, ovary, adjuvant, chemotherapy		
Accumulative MEDCASE	Est Accumulative	Periodic Review:
Cost: -0-	OMA Cost: -0-	Sep 88

Study Objective: To evaluate the effect of combined prophylactic vincristine, dactinomycin, and cyclophosphamide (VAC) chemotherapy in patients with endodermal sinus tumor, embryonal carcinoma, immature teratoma (Grades 2 and 3), choriocarcinoma, and malignant mixed germ cell tumors of the ovary, Stages I and II, after total removal of all gross tumor; to evaluate the role of serum markers, especially alpha-feto-protein and human chorionic gonadotropin (beta-HCG), when these are present in predicting response and relapse; to determine the role of restaging laparotomy in determining response, predicting relapse, and planning further therapy.

Technical Approach: Patients with histologically confirmed malignant germ cell tumors of the ovary, Stage I or II, if previously untreated and completely resected, (excluding patients with pure dysgerminoma) will be eligible. Patients with Grade 2 or 3 immature teratoma are eligible. After adequate recovery from required surgery, patients will receive 6 courses of VAC chemotherapy. If progression is noted during chemotherapy, patients will be transferred to the appropriate protocol. Patients with no evidence of disease after 6 courses will then undergo a restaging laparotomy. Those showing evidence of progression will be transferred. If laparotomy reveals no evidence of disease, patients will receive an additional 3 courses of VAC and then be followed on no further therapy.

Progress: No new entries in FY 88. Two patients were entered at MAMC in previous years. The protocol is closed to patient entry.

Group-wide data show that VAC is an active regimen. Six to nine courses will prevent recurrence in the majority of women with malignant germ cell tumors of the ovary.

Detail Summary Sheet

Date: 30 Sep 88	Protocol No.: 81/43	Status: Completed
Title: GOG #48: A Study of Progestin Therapy and a Randomized Comparison of Adriamycin vs Adriamycin Plus Cyclophosphamide in Patients with Advanced Endometrial Carcinoma After Hormonal Failure (Phase III Study)		
Start Date: 20 Feb 81	Est Completion Date: Feb 86	
Department: OB/GYN	Facility: MAMC	
Principal Investigator: LTC Gordon O. Downey, MC		
Associate Investigators: COL William Benson, MC COL Roger B. Lee, MC		
Key Words: carcinoma, endometrial, progestin, chemotherapy		
Accumulative MEDCASE	Est Accumulative	Periodic Review:
Cost: -0-	OMA Cost: -0-	Sep 88

Study Objective: To evaluate the response of advanced or recurrent endometrial carcinoma to oral progestins in patients who have received no prior hormonal therapy for cancer; and to compare a combination of adriamycin and cyclophosphamide to adriamycin alone as therapy for advanced or recurrent endometrial carcinoma which no longer responds to or has failed to respond to progestins in patients who have received no prior cytotoxic drugs.

Technical Approach: Patients with primary stage III or IV, recurrent or residual endometrial adenocarcinoma, adenoacanthoma, or adenosquamous carcinoma, whose potential for cure by radiation therapy or surgery alone or in combination is very poor, are eligible. Patients who have received previous chemotherapy are ineligible. Patients will be randomized to: (1) Adriamycin, 60 mg/M² IV, q 3 wks x 8 courses. Responders will have follow-up only. Those with progression will be transferred to Protocol #26 or (2) Adriamycin, 60 mg/M² IV, q 3 wks x 8 courses plus cyclophosphamide 500 mg/M² IV q 3 weeks x 8 courses. Responders will receive follow-up only. Those with progression will be transferred to Protocol #26. Patients with no prior hormonal therapy will be placed on C.T. Provera for a minimum of 12 weeks. Those with progression of disease at any time after 12 weeks will be randomized as above.

Progress: No patients were entered in FY 88. The protocol has been closed to patient entry. Five subjects were entered at MAMC. Four patients died from disease and one is alive with disease.

Group-wide data show that the combination of adriamycin plus cyclophosphamide appears to offer no advantage over adriamycin alone in the management of endometrial carcinoma. Progestins appear to be less active than previously thought in the treatment of endometrial carcinoma.

Detail Summary Sheet

Date: 30 Sep 88	Protocol No.: 81/70	Status: Completed
Title: GOG #49: A Surgical-Pathologic Study of Women with Invasive Carcinoma of the Cervix Stage I _B and Randomly Assigned Radiation Therapy Versus No Further Therapy in Selected Patients, Phase III		
Start Date: 20 Mar 81	Est Completion Date: Mar 86	
Department: OB/GYN	Facility: MAMC	
Principal Investigator: LTC Gordon O. Downey, MC		
Associate Investigators: COL William Benson, MC COL Roger B. Lee, MC		
Key Words: carcinoma, cervix, radiation versus no further therapy		
Accumulative MEDCASE	Est Accumulative	Periodic Review:
Cost: -0-	OMA Cost: -0-	Sep 88

Study Objective: To determine by observations of the 5-year survival and disease free interval, the validity of current FIGO staging of the histopathologic prognostic factors of size of lesion, location of lesion, depth of invasion of tumor in millimeters, histology and grade, growth pattern, and site and number of positive lymph nodes in Stage I_B carcinoma of the cervix; to rapidly accumulate prospectively significant surgical pathologic data which would expedite development of further protocols; to determine morbidity of primary radical surgical therapy; to determine if radiation therapy will improve survival in selected patients with positive nodes.

Technical Approach: Patients with primary, previously untreated histologically confirmed invasive Stage I_B carcinoma of the cervix will be eligible. Patients must have undergone exploratory laparotomy, peritoneal fluid sampling, bilateral pelvic and para-aortic lymphadenectomy and radical hysterectomy to be eligible for the randomized portion of the study. Those with negative pelvic nodes will receive no further therapy and be followed for 5 years. Patients with positive pelvic nodes, unilateral metastasis, ≤ 3 positive pelvic nodes, no parametrial involvement, and clear vaginal margins will be randomized to receive no further therapy (follow-up for 5 years) or whole pelvic radiation with follow-up of 5 years. Those with positive para-aortic nodes on paraffin section will be entered on other GOG protocols as appropriate.

Progress: This protocol has been closed to patient entry. No patients were entered at MAMC in FY 88. Eight patients were previously entered on this protocol at MAMC. All patients have either expired (3), been lost to follow-up (1) or have completed the five year follow-up period.

Group-wide, no significant advantage was demonstrated for CAP over CP in this patient population when using an equitoxic dose schedule.

Detail Summary Sheet

Date: 30 Sep 88	Protocol No.: 81/105	Status: On-going
Title: GOG #52: A Phase III Randomized Study of Cyclophosphamide Plus Adriamycin Plus Platinol Versus Cyclophosphamide Plus Platinol in Patients with Optimal Stage III Ovarian Adenocarcinoma		
Start Date: 21 Aug 81	Est Completion Date: Aug 86	
Department: OB/GYN	Facility: MAMC	
Principal Investigator: LTC Gordon O. Downey, MC		
Associate Investigators: COL William Benson, MC COL Roger B. Lee, MC		
Key Words: adenocarcinoma, ovarian, chemotherapy		
Accumulative MEDCASE	Est Accumulative	Periodic Review:
Cost: -0-	OMA Cost: -0-	Aug 88

Study Objective: To determine, in optimal Stage III ovarian adenocarcinoma, if the addition of adriamycin to cyclophosphamide plus cis-platinum improves progression-free interval, frequency of negative second-look laparotomy and survival. This protocol replaces GOG #25.

Technical Approach: Eligible patients are those more than six weeks post-operative with proven primary Stage III ovarian adenocarcinoma confined to the abdominal cavity and its peritoneal surfaces with residual tumor masses after surgery no larger than 1 cm in diameter. Patients with prior chemo- or radiotherapy are ineligible. Patients will be randomized to cyclophosphamide plus Platinol every three weeks for eight courses or to cyclophosphamide and Platinol plus adriamycin every three weeks for eight courses. After eight courses those with less than clinically complete response will go off study and be followed for survival; those with clinically complete response will have second-look surgery to validate the complete response or to remove residual tumor masses. Patients will then be followed for approximately five years for survival rates.

Progress: No patients were entered in FY 88. Six patients were entered in previous years. The study has been closed to patient entry. Three patients died of the disease, one has been lost to follow-up, and two are currently being followed on this protocol.

Group-wide data show that no significant advantage can be demonstrated for CAP over CP in this patient population when using an equitoxic dose schedule.

Detail Summary Sheet

<u>Date: 30 Sep 88</u>	<u>Protocol No.: 81/116</u>	<u>Status: Completed</u>
<u>Title: GOG 54: The Treatment of Women with Malignant Tumors of the Ovarian Stroma with Combination Vincristine, Dactinomycin, and Cyclophosphamide--Phase III; and a Phase II Evaluation of Adriamycin in Malignant Tumors of the Ovarian Stroma Refractory to Primary Chemotherapy</u>		
<u>Start Date: 18 Sep 81</u>	<u>Est Completion Date: Sep 88</u>	
<u>Department: OB/GYN</u>	<u>Facility: MAMC</u>	
<u>Principal Investigator: LTC Gordon O. Downey, MC</u>		
<u>Associate Investigators: COL William Benson, MC</u>		
<u>COL Roger B. Lee, MC</u>		
<u>Key Words: ovarian stroma, malignant tumors, primary, refractory</u>		
<u>Accumulative MEDCASE</u>	<u>Est Accumulative</u>	<u>Periodic Review:</u>
<u>Cost: -0-</u>	<u>OMA Cost: -0-</u>	<u>Aug 88</u>

Study Objective: To evaluate the effectiveness of combined vincristine, dactinomycin, and cyclophosphamide (VAC) in treatment of malignant tumors of the ovarian stroma in patients with residual, recurrent or advanced disease; to confirm completeness of response to VAC treatment with restaging laparotomy; to evaluate response to adriamycin in patients who fail primary treatment with VAC; to evaluate the endometrium histologically to learn more about the relationship between stromal tumors and endometrial cancer.

Technical Approach: Eligible patients must have histologically confirmed malignant tumors of the ovarian stroma not amenable to cure by further surgery or radiation therapy. Patients who have received chemotherapy at any time or those who have received radiotherapy <4 weeks prior to entry are ineligible for study. Patients will have undergone an exploratory laparotomy with removal of as much tumor as prudent. Chemotherapy will commence at 4 weeks or no later than 6 weeks following surgery. Patients must have recovered from surgery. All patients will receive VAC for a minimum of 3 cycles or a maximum of 10 cycles. Patients who exhibit a complete response or a partial response after 10 cycles which makes remaining disease resectable will undergo a restaging laparotomy. If all residual disease is resected at restaging laparotomy, patients will receive adriamycin. If there is no evidence of disease at restaging laparotomy, patients will receive intermittent cyclophosphamide. If progression is observed during cyclophosphamide therapy, the patient will be removed from study. Patients who exhibit progression of disease after 3 cycles of VAC will receive adriamycin. If further progression is observed on adriamycin, the patient will be removed from the study. All patients will be followed for 5 years or until death.

Progress: No patients entered during FY 88. Previously, two patients were entered. No further data are being collected on this study. Group-wide data show that objective responses of stromal tumors to VAC chemotherapy do occur. There are too few patients with any particular cell type to permit definitive conclusions regarding sensitivity of a particular cell histology to VAC.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 81/44 Status: Completed

Title: GOG #55: Hormonal Contraception and Trophoblastic Sequelae
After Hydatidiform Mole, Phase III

Start Date: 20 Feb 81 Est Completion Date: Jun 83

Department: OB/GYN Facility: MAMC

Principal Investigator: LTC Gordon O. Downey, MC

Associate Investigators: COL William Benson, MC
COL Roger B. Lee, MC

Key Words: hydatidiform mole, contraception, hormonal

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: -0- Sep 88

Study Objective: To determine whether the administration of estrogen progesterone oral contraceptives following the evacuation of a hydatidiform mole and prior to the HCG titer reaching undetectable levels affects the incidence of trophoblastic sequelae requiring chemotherapy.

Technical Approach: Patients with a histologically verified diagnosis of hydatidiform mole evacuated by suction evacuation of the uterus with uterine conservation are eligible. All patients must have a pelvic ultrasound and arterial blood gases performed within 2 weeks of evacuation. Patients will be randomly assigned to Regimen 1: hormonal contraception - oral contraception to be commenced as soon as the patient has been randomized and will continue for at least 12 weeks; or Regimen 2: mechanical contraception - a. sheath and foam preparation; b. IUD inserted once the uterus has become involuted, again used with foam; c. diaphragm used with contraceptive cream or foam. The principal investigator will choose the method of mechanical contraception and it will be commenced as soon as the patient has been randomized and will continue for at least 12 weeks. At the end of 12 weeks, all patients will be evaluated for development or nondevelopment of trophoblastic sequelae. Further birth control will be at the discretion of the patient and the investigator. All patients will remain on the study for a minimum of six months after primary evacuation of the molar pregnancy.

Progress: No new patients were entered in FY 88. In previous years, seven patients have been entered. Data are being analyzed by GOG; no conclusions at this point.

Detail Summary Sheet

Date: 30 Sep 88	Protocol No.: 82/08	Status: On-going
Title: GOG #56: A Randomized Comparison of Hydroxyurea Versus Misonidazole as an Adjunct to Radiation Therapy in Patients with Stage II _B , III, and IV _A Carcinoma of the Cervix and Negative Para-Aortic Nodes (Phase III)		
Start Date: 20 Nov 81	Est Completion Date: Jul 86	
Department: OB/GYN	Facility: MAMC	
Principal Investigator: LTC Gordon O. Downey, MC		
Associate Investigators: COL William Benson, MC COL Roger B. Lee, MC		
Key Words: cervix, negative para-aortic nodes, chemotherapy		
Accumulative MEDCASE	Est Accumulative	Periodic Review:
Cost: -0-	OMA Cost: -0-	Sep 88

Study Objective: To determine whether hydroxyurea or misonidazole is superior as a potentiation of radiation therapy in advanced cervical cancer; and to compare the toxicity of hydroxyurea versus misonidazole when given concurrently with radiotherapy.

Technical Approach: All patients with invasive squamous cell carcinoma of the cervix, Stages II_B through IV_A will undergo preoperative clinical staging. This will include traditional staging as permitted by FIGO rules. Extended clinical staging utilizing lymphangiography, computerized transaxial tomography, and/or sonography is required. Subsequently, patients will undergo a para-aortic lymphadenectomy and peritoneal exploration. Selected patients may be excluded from this procedure if percutaneous needle biopsy provides histologic proof of metastasis to the aortic nodes. All patients with cancer confined to the pelvis are eligible for treatment. They will receive pelvic irradiation and will be randomly assigned to receive concomitant hydroxyurea or misonidazole. Patients with metastasis outside the pelvis are not eligible for treatment.

Progress: No new entries at MAMC in FY 88. In previous years, five patients have been entered. One died of the disease and four are being followed. The protocol has been closed to patient entry.

Although it is inconclusive from group-wide data analysis that hydroxyurea with radiotherapy is superior to misonidazole with radiotherapy, it appears that hydroxyurea is the more appropriate potentiator in patients with bulky cervix cancer.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 82/31 Status: Completed

Title: GOG #57: A Randomized Comparison of Multiple Agent Chemotherapy with Methotrexate, Dactinomycin, and Chlorambucil versus the Modified Bagshawe Protocol in the Treatment of "Poor Prognosis" Metastatic Gestational Trophoblastic Disease (Phase II)

Start Date: 19 Feb 82 Est Completion Date: Feb 87

Department: OB/GYN Facility: MAMC

Principal Investigator: LTC Gordon O. Downey, MC

Associate Investigators: COL William Benson, MC

COL Roger B. Lee, MC

Key Words: gestational trophoblastic disease, multiple agent chemotherapy, modified Bagshawe protocol

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: -0- Sep 88

Study Objective: To evaluate the effectiveness and toxicity of the Modified Bagshawe Protocol (MBP) in patients with "poor prognosis" metastatic gestational trophoblastic disease (MGTD); and to compare the effectiveness and toxicity of the MBP with standard triple agent chemotherapy with methotrexate, dactinomycin, and chlorambucil (MAC).

Technical Approach: Patients who have a histologic diagnosis of gestational trophoblastic disease and an elevated HCT titer, who are considered "poor prognosis" on the basis of the criteria set forth in the protocol, will be randomized to either a drug combination of MAC or to a modified Bagshawe Protocol.

Progress: No entries at MAMC in FY 88. One patient was entered previously. The protocol is closed to patient entry and the MAMC patient has completed the five year follow-up period.

Group-wide results indicate that the standard MAC regimen is more effective and less toxic than MBP.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 81/117 Status: Completed

Title: GOG #59: A Randomized Comparison of Extended Field Radiation Therapy and Hydroxyurea Followed by Cisplatin or no Further Therapy in Patients with Cervical Squamous Cell Carcinoma Metastatic to High Common Iliac and/or Para-aortic Lymph Nodes--III

Start Date: 18 Sep 81 Est Completion Date: Jul 86

Department: OB/GYN Facility: MAMC

Principal Investigator: COL Roger B. Lee, MC

Associate Investigator: COL William Benson, MC

Key Words: cervical squamous cell carcinoma, iliac, para-aortic lymph nodes, chemotherapy, radiation therapy

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: -0- Aug 88

Study Objective: To determine if cis-diamminedichloroplatinum, cisplatin, given in an adjuvant setting will decrease the risk of geographic failure or improve the survival rate or progression-free interval in patients who have squamous carcinoma of the cervix with metastases to high common iliac and/or para-aortic lymph nodes, proven by either histologic or cytologic means; to evaluate the role of scalene fat pad biopsy in this group of patients before initiation of extended field irradiation therapy; to accumulate clinical/surgical pathologic data on this high risk group of patients to expedite development of further protocols.

Technical Approach: Patients with primary, previously untreated, histologically confirmed, invasive squamous cell carcinoma of the uterine cervix, all clinical stages, with metastasis to high common iliac or para-aortic lymph nodes proven by cytologic or histologic means will be eligible. Patients will undergo preoperative clinical staging, utilizing lymphangiography, computerized axial tomography, and/or sonography as well as traditional methods. Subsequently, patients will undergo a para-aortic lymphadenectomy and peritoneal exploration. Selected patients may be excluded from this procedure if percutaneous needle biopsy provides cytologic proof of metastasis to extrapelvic nodes. Patients with paraaortic metastasis and negative scalene node biopsies are eligible for treatment. They will receive pelvic and para-aortic irradiation and hydroxyurea and will be randomly assigned to receive cisplatin or no further therapy. An adequate trial will be defined as completion of the prescribed radiation therapy, completion of one course of cisplatin and survival of 4 weeks, or survival of 8 weeks after radiation therapy for the no-further-treatment regimen.

Progress: No entries at MAMC in FY 88. Previously one patient has been entered. The protocol is closed to patient entry, and data collection is complete on this patient. Group-wide data indicate that scalene node biopsy is of limited value. Even in this young patient population with favorable performance status, post radiation systemic therapy was not feasible.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 81/118 Status: Completed

Title: GOG #60: A Phase III Randomized Study of Doxorubicin Plus Cyclophosphamide Plus Cisplatin versus Doxorubicin Plus Cyclophosphamide Plus Cisplatin Plus BCG in Patients with Advanced Suboptimal Ovarian Adenocarcinoma, Stages III & IV

Start Date: 18 Sep 81 Est Completion Date: Sep 84

Department: OB/GYN Facility: MAMC

Principal Investigator: COL Roger B. Lee, MC

Associate Investigator: COL William Benson, MC

Key Words: adenocarcinoma, ovarian, chemotherapy

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: -0- Aug 88

Study Objective: To determine if the addition of BCG to doxorubicin plus cyclophosphamide plus cisplatin improves remission rate, remission duration, or survival in suboptimal Stages III and IV ovarian adenocarcinoma; to determine the frequency and duration of true complete remission using these regimens as judged at second-look laparotomy.

Technical Approach: Eligibility: Patients with established sub-optimal Stage III or Stage IV ovarian epithelial cancer. Patients must have optimal surgery for ovarian cancer, with at least an exploratory laparotomy and appropriate tissue for histologic evaluation. Patients with measurable or nonmeasurable disease will be evaluated. Patients with histologically confirmed serous adenocarcinoma, mucinous adenocarcinoma, clear-cell adenocarcinoma, endometrioid adenocarcinoma, undifferentiated carcinoma, or mixed epithelial carcinoma will be eligible. Patients who have received previous chemotherapy or radiotherapy will be ineligible. Patients will be randomized to receive either doxorubicin, cyclophosphamide, and cisplatin every 3 weeks for 8 courses; or the above regimen plus BCG (days 8 & 15 for 8 courses). Patients with complete response will have a second look laparotomy and will be taken off therapy if complete response is confirmed. Patients who have partial response of stable disease will be considered for a second look if, in the opinion of the investigator, significant tumor reduction may have been achieved. If residual tumor is detected, patients will be taken off study and placed on GOG #61. Patients with progressive disease at any time will be removed from the chemotherapy on this study, but will be followed.

Progress: No patients were entered in FY 88. Six patients were entered in previous years; five died of the disease and one was lost to follow-up. No group-wide data available.

Detail Summary Sheet

Date: 30 Sep 88	Protocol No.: 82/09	Status: Completed
Title: GOG #61: Phase III Randomized Study of Cis-Platinum Plus Cyclophosphamide versus Hexamethylmelamine After Second-Look Surgery in Nonmeasurable Stage III Ovarian Adenocarcinoma Partially Responsive to Previous Regimens Containing Cis-Platinum and Cyclophosphamide.		
Start Date: 20 Nov 81	Est Completion Date: Nov 86	
Department: OB/GYN	Facility: MAMC	
Principal Investigator: LTC Gordon O. Downey, MC		
Associate Investigators: COL William Benson, MC COL Roger B. Lee, MC		
Key Words: adenocarcinoma, ovarian, chemotherapy		
Accumulative MEDCASE	Est A umulative	Periodic Review:
Cost: -0-	OMA Cost: -0-	Sep 88

Study Objective: To determine in nonmeasurable but residual Stage III ovarian adenocarcinoma, partially responsive after treatment with regimens containing cis-platinum and cyclophosphamide, if the progression-free interval and survival are improved by continuing cyclophosphamide plus cis-platinum or by changing treatment to hexamethylmelamine.

Technical Approach: With the increasing use of second-look laparotomy after combination chemotherapy for ovarian cancer, more Stage III patients are being identified who show a partial response or stable disease when compared with the original findings. The GOG has two studies involving cyclophosphamide and cis-platinum, but not hexamethylmelamine (Protocols #47 and #52), in which partial responders (as judged at second look) currently go off study. We propose to randomize such patients to more cyclophosphamide plus cis-platinum or to hexamethylmelamine. This additional treatment will be given for a finite period of 12 months since we do not propose a third look that might provide an endpoint for treatment but probably would not benefit most patients as there is no promising third line treatment if residual disease were found and it is unlikely that debulking surgery would be of consistent benefit at this point and it may be difficult to do adequate biopsies after two prior laparotomies. Also, some of these patients may progress slowly even though they do not respond to the additional treatments.

Progress: No new entries in FY 88. Four patients were entered at MAMC in previous years; all died of the disease.

At this time, no conclusions can be drawn from the group-wide data because of inadequate number of patient entered.

Detail Summary Sheet

Date: 30 Sep 88	Protocol No.: 82/36	Status: On-going
Title: GOG #63: A Clinical-Pathologic Study of Stages II _B , III, and IV _A Carcinoma of the Cervix		
Start Date: 19 Mar 82	Est Completion Date: Mar 88	
Department: OB/GYN	Facility: MAMC	
Principal Investigator: LTC Gordon O. Downey, MC		
Associate Investigators: COL William Benson, MC COL Roger B. Lee, MC		
Key Words: carcinoma, cervix, stages II _B , III, IV _A , pathologic		
Accumulative MEDCASE	Est Accumulative	Periodic Review:
Cost: -0-	OMA Cost: -0-	Sep 88

Study Objective: To evaluate the sensitivity and specificity of non-invasive procedures such as sonography, computerized transaxial tomography and lymphangiography in detection of metastases; to better understand the significance of various surgical and pathologic factors involved in staging and therapy for advanced cervical cancer. The accumulated clinical/surgical/pathological data may then play a role in modification or design of future protocols; to determine by observations of five-year survival and disease-free interval, the validity of current FIGO staging in comparison to histopathologic prognostic factors such as size of lesion, location of lesion, histology, grade, pelvic lymph node metastases, and aortic lymph node metastases, in patients with Stages II_B, III, and IV_A carcinoma of the cervix.

Technical Approach: All eligible patients with invasive carcinoma of the cervix, Stages II_B through IV_A, will undergo preoperative clinical staging, including traditional staging as permitted by FIGO rules. Extended clinical staging utilizing sonography, lymphangiography, and computerized transaxial tomography are mandatory. When these tests reveal an aortic nodal metastasis, the patient will have a fine needle biopsy; however, if the tests are negative, the patient will have an aortic lymphadenectomy. Patients who have a positive fine needle biopsy or positive aortic lymphadenectomy will undergo scalene node biopsy before consideration for a GOG treatment protocol. It is anticipated that all patients will be considered for entry into a GOG protocol for which they are suitable when such protocols are available.

Progress: No entries at MAMC in FY 88. In previous years five subjects had been entered. Data is still being collected on one patient.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 83/40 Status: Completed

Title: GOG 66: Ultrastructural, Staging, and Therapeutic Considerations in Small Cell Carcinoma of the Cervix, Phase II

Start Date: 18 Feb 83 Est Completion Date: Jun 86

Department: OB/GYN Facility: MAMC

Principal Investigator: LTC Gordon O. Downey, MC

Associate Investigators: COL William Benson, MC

COL Roger B. Lee, MC

Key Words: cervix, small cell carcinoma, ultrastructural, staging, therapeutic

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: -0- Sep 88

Study Objective: To determine the incidence of neuroendocrine carcinoma of the cervix in cases which are histologically classified as small cell carcinomas, and to determine the response rate to combination chemotherapy in patients with Stage IV_B small cell carcinoma of the cervix or progressive local disease after radiation therapy.

Technical Approach: Eligible patients: Those with histologic diagnosis of small cell carcinoma of the cervix. Patients who have small cell carcinoma mixed with large cell keratinizing carcinoma or large cell nonkeratinizing carcinoma or adenocarcinoma are eligible, providing that the small cell elements comprise 50% of the tumor. Only patients with primary Stage IV_B disease or recurrent disease after local therapy are eligible for chemotherapy. Chemotherapy patients must have measurable disease by palpation or by an appropriate x-ray or ultrasound procedure. Patients with disease localized to the pelvis and regional lymph nodes will receive standard therapy according to the discretion of the investigator. Patients with disease beyond the pelvis or abdominal nodes with no previous irradiation will receive vincristine, 2 mg, doxorubicin, 50 mg/M², and cyclophosphamide, 750 mg/M², IV every 21 days. Patients with previous irradiation will receive vincristine, 2 mg, doxorubicin, 40 mg/M², and cyclophosphamide, 600 mg/M², IV, every 21 days. These regimens will be repeated every three weeks if toxicity permits. Doxorubicin will be discontinued at a cumulative dose of 400 mg/M². Patients in whom tumor progression occurs on this regimen will be treated with VP-16, 100 mg/M² (no previous irradiation) or 80 mg/M² (previous irradiation) IV on days 1, 3, and 5, every four weeks to time of progression. Patients will be followed until expiration or for five years. In the unusual instance of Stage IV_B on the basis of brain metastasis alone, patients will be given whole brain irradiation to a dose of 3000 rads in 10 fractions.

Progress: No entries at MAMC. This protocol is closed to patient entry. No conclusions have been reached at the group level.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 83/63 Status: Completed

Title: GOG 70: A Randomized Comparison of Single Agent
Chemotherapy (Methotrexate and Methotrexate with
Folinic Acid Rescue) in "Good Prognosis" Metastatic
Gestational Trophoblastic Disease

Start Date: 20 May 83 Est Completion Date: Indefinite
Department: OB/GYN Facility: MAMC
Principal Investigator: LTC Gordon O. Downey, MC
Associate Investigators: COL William Benson, MC
COL Roger B. Lee, MC

Key Words: trophoblastic, gestational, single agent chemotherapy
Accumulative MEDCASE Est Accumulative Periodic Review:
Cost: -0- OMA Cost: -0- Sep 88

Study Objective: To judge the relative efficacy of scheduling variation in the chemotherapeutic management of good prognosis metastatic gestational trophoblastic disease and to ascertain the relative toxicities of the two regimens.

Technical Approach: Eligible patients: those with metastatic gestational trophoblastic disease who are good prognosis with duration of disease <4 months from antecedent pregnancy, antecedent molar pregnancy, ectopic pregnancy, or abortion, serum beta-HCG titer <42,000 mIU/ml, no liver or brain metastasis, and no prior chemotherapy.

Regimen I: methotrexate 0.4 mg/kg IM, up to 25 mg daily x 5; repeat every 12 days (7 day window).

Regimen II: methotrexate, 1 mg/kg IM, days 1, 3, 5, and 7. Folinic acid, 0.1 mg/kg, IM, days 2, 4, 6, and 8. Repeat every 14 days (6 day window).

An adequate trial is defined as receiving one course. After the first normal titer (three consecutive weekly normals), each patient will receive one more full course. If remission is obtained, therapy will be discontinued. If the titer should re-elevate prior to three consecutive weekly normals, then chemotherapy will continue until the above criteria are fulfilled. All patients will receive chemotherapy as outlined until there is documented remission, severity of toxicity requires a change, or non-response.

Progress: No new entries at MAMC in FY 88. In previous years, two patients have been entered. Both patients responded to treatment.

The protocol has been closed to patient entry, and data are no longer being collected by the GOG.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 83/41 Status: On-going

Title: GOG 71: Treatment of Patients with Suboptimal Stage IB Carcinoma of the Cervix: A Randomized Comparison of Radiation Therapy and Post-Treatment Para-Aortic and Common Iliac Lymphadenectomy, Versus Radiation Therapy, Para-Aortic and Common Iliac Lymphadenectomy and Adjunctive Extrafascial Hysterectomy, Phase III

Start Date: 18 Feb 83 Est Completion Date: Jun 86

Department: OB/GYN Facility: MAMC

Principal Investigator: LTC Gordon O. Downey, MC

Associate Investigators: COL William Benson, MC
COL Roger B. Lee, MC

Key Words: cervix, carcinoma, radiation, lymphadenectomy, hysterectomy

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: -0- Sep 88

Study Objective: To evaluate the role of adjunctive extrafascial hysterectomy in the treatment of suboptimal Stage IB carcinoma of the cervix, the survival and patterns of failure in bulky IB cervix cancer, and the prognostic value of pretreatment endometrial sampling in suboptimal Stage IB carcinoma of the cervix; and to study the toxicity of a combined radiation and surgical therapeutic program.

Technical Approach: Eligible patients: patients with primary, untreated, histologically confirmed invasive carcinoma of the uterine cervix, FIGO Stage IB, as confirmed by cervical biopsy and endometrial sampling.

Regimen I: Following recovery from radiation therapy, patients will undergo para-aortic and common iliac nodal sampling, abdominal washings, and intra-abdominal exploration.

Regimen II: Following recovery from radiation therapy, patients will undergo para-aortic and common iliac nodal sampling, abdominal washings, and intra-abdominal exploration plus total extrafascial hysterectomy.

All patients will be followed for five years. Patients found to have more extensive disease (i.e., positive para-aortic nodes, intra-abdominal metastasis) will be treated at the discretion of the physician and will be followed for five years.

Progress: One patient entered at MAMC.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 84/33 Status: On-going

Title: GOG 72: 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

Start Date: 17 Feb 84 Est Completion Date: Dec 88

Department: OB/GYN Facility: MAMC

Principal Investigator: LTC Gordon O. Downey, MC

Associate Investigators: COL William Benson, MC

COL Roger B. Lee, MC

Key Words: tumor, ovarian, natural history, melphalan, cisplatin

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: -0- Sep 88

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 5 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 cis-platin treatment (once every three weeks for eight weeks) or follow-up. If there is no evidence of response after three courses of cis-platin, 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: No new patients entered in FY 88. Four patients have been entered in previous years.

Detail Summary Sheet

Date: 30 Sep 88	Protocol No.: 84/26	Status: On-going
Title: GOG #73: A Clinicopathologic Study of Primary Malignant Melanoma of the Vulva Treated by Modified Radical Hemivulvectomy		
Start Date: 20 Jan 84	Est Completion Date: Nov 38	
Department: OB/GYN	Facility: MAMC	
Principal Investigator: LTC Gordon O. Downey, MC		
Associate Investigators: COL William Benson, MC COL Roger B. Lee, MC		
Key Words: melanoma, vulva, hemivulvectomy, clinicopathologic		
Accumulative MEDCASE	Est Accumulative	Periodic Review:
Cost: -0-	OMA Cost: -0-	Sep 88

Study Objective: To determine the relationship of histopathologic parameters (including microstaging of primary malignant melanoma of the vulva) to FIGO staging, nodal status, and ultimate prognosis and to ultimately recommend appropriate therapy for malignant melanomas of the vulva based on histopathologic and microstaging data.

Technical Approach: Patients receiving primary surgical therapy for primary malignant melanoma of the vulva with at least a modified radical hemivulvectomy will be studied. Patients with a history of primary cutaneous melanoma other than of genital tract origin or patients who have received previous chemotherapy or radiotherapy are ineligible. The primary parameters to be studied are maximum diameter of primary lesion, depth of invasion, initial surgical management (including lymph node dissection), nodal status, FIGO staging, microstaging, progression-free interval, and survival probability. The data will be used in an attempt to identify possible prognostic factors. Specific statistical goals will be defined as experience is gained.

Progress: No entries at MAMC.

Detail Summary Sheet

Date: 30 Sep 88	Protocol No.: 84/27	Status: On-going
Title: GOG #74: Early Stage I Vulvar Carcinoma Treated With Ipsilateral Superficial Inguinal Lymphadenectomy and Modified Radical Hemivulvectomy		
Start Date: 20 Jan 84	Est Completion Date: Nov 88	
Department: OB/GYN	Facility: MAMC	
Principal Investigator: LTC Gordon O. Downey, MC		
Associate Investigators: COL William Benson, MC COL Roger B. Lee, MC		
Key Words: carcinoma, vulvar, lymphadenectomy, hemivulvectomy		
Accumulative MEDCASE	Est Accumulative	Periodic Review:
Cost: -0-	OMA Cost: -0-	Sep 88

Study Objective: To document the rates and patterns of recurrence of patients with early Stage I vulvar carcinoma treated with ipsilateral superficial inguinal lymphadenectomy and modified radical hemivulvectomy and to document the survival and recurrence-free interval in the same group of patients.

Technical Approach: Patients who present with primary, untreated, squamous cell carcinoma of the vulva, with no capillary space involvement, and with a lesion measured in vivo ≤ 2 cm, and with histologic evidence of invasion below the basement membrane ≤ 5 mm, will be eligible for further evaluation and entry into this protocol. If the frozen section on the superficial inguinal lymph nodes reveals no evidence of cancer, the patient will go on to have a modified radical hemivulvectomy. If the patient has positive lymph nodes on frozen section, she can be treated with radical vulvectomy and bilateral groin dissection per GOG Protocols 36 and 37. If the final pathology section shows metastatic carcinoma to nodes, the patient can be treated with radical vulvectomy and bilateral groin dissection, per protocols 36 and 37, the surgery to be carried out within six weeks of the time of the initial groin dissection. The patient will be followed every three months for two years and every six months for three additional years. The principal parameters employed to examine the therapeutic effect of hemivulvectomy will be progression-free interval, survival time, and observed adverse effects.

Progress: No entries at MAMC.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 84/28 Status: Completed

Title: GOG #75: Postoperative Pelvic Radiation in Stages I and
II Mixed Mesodermal Sarcomas of the Uterus

Start Date: 20 Jan 84 Est Completion Date: Nov 88

Department: OB/GYN Facility: MAMC

Principal Investigator: LTC Gordon O. Downey, MC

Associate Investigators: COL William Benson, MC
COL Roger B. Lee, MC

Key Words: sarcomas, uterus, radiation, postoperative

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: -0- Sep 88

Study Objective: To determine if pelvic postoperative radiation therapy will decrease local and regional recurrence rates and improve median progression free interval in patients with Stages I and II mixed mesodermal sarcomas of the uterus.

Technical Approach: Patients with clinical Stage I or II mixed mesodermal sarcomas of the uterus undergoing a simple extrafascial abdominal hysterectomy, bilateral salpingo-oophorectomy, or selective pelvic or para-aortic lymphadenectomy will be randomized to receive postoperative radiation therapy or no further treatment. The principal parameters employed to examine the therapeutic effect of postoperative pelvic radiation are local and regional recurrence rates, the duration of progression-free interval, observed survival time and the incidence and severity of observed adverse effects. The patients will be followed until death or for at least ten years.

Progress: No entries at MAMC.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 87/11 Status: On-going

Title: GOG 76A: Master Protocol for Phase II Drug Studies in Treatment of Advanced or Recurrent Squamous Cell Carcinoma of the Cervix

Start Date: 17 Oct 86 Est Completion Date: Indefinite

Department: OB/GYN Facility: MAMC

Principal Investigator: LTC Gordon O. Downey, MC

Associate Investigators: COL William Benson, MC
COL Roger B. Lee, MC

Key Words: master protocol, phase II, carcinoma, cervix, squamous cell, advanced, recurrent

Accumulative MEDCASE Est Accumulative Periodic Review:
Cost: -0- OMA Cost: -0- Aug 88

Study Objective: To identify new active drugs in the control of advanced or recurrent squamous cell carcinoma of the cervix so that combinations of cytotoxic drugs can be formed which might lead to an improved complete remission rate.

Technical Approach: In order for attractive new cytotoxic or other chemotherapeutic agents receive as fair a trial as possible, this study constitutes a Phase II design in a population of patients who have had no prior cytotoxic drug therapy. A rejection type design will be used involving an average sample size of 25 evaluable patients per drug studied, allowing for agents found to be ineffective to be rapidly replaced by other agents. The study will be done in a non-randomized fashion.

Patients with histologically confirmed advanced, persistent, or recurrent squamous cell carcinoma of the cervix with documented disease progression after local therapy who are considered incurable will be eligible. All patients must have measurable disease consisting of abdominal, pelvic, or other masses which can be defined in at least two dimensions by palpation, x-ray, or ultrasound. Patients with another malignancy (prior or concomitant) other than the skin (excluding melanoma) will be ineligible.

Patients who receive one or more courses of the drug and live for at least three weeks will be evaluable for response. Patients who receive one or more courses of the drug, regardless of subsequent survival, will be evaluable for adverse effects.

Each drug will be studied on a separate protocol. Specific details for treatment with each drug will be given in the protocol dealing with the particular agent to be studied.

Progress: One patient has been entered on the cis-platin/5FU protocol (76G) in FY 87 and one patient was entered in the mitomycin-C protocol (76J) in FY 88.

Continuing review will be done on individual protocols.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 87/12 Status: Completed

Title: GOG 76D: A Phase II Trial of Dibromodulcitol (DBD, NSC #104800) in Patients with Advanced Squamous Cell Carcinoma of the Cervix

Start Date: 17 Oct 86 Est Completion Date: Indefinite

Department: OB/GYN Facility: MAMC

Principal Investigator: LTC Gordon O. Downey, MC

Associate Investigators: COL William Benson, MC

COL Roger B. Lee, MC

Key Words: carcinoma, squamous cell, cervix, dibromodulcitol

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: -0- Aug 88

Study Objective: To identify new active drugs in the control of advanced or recurrent squamous cell carcinoma of the cervix so that combinations of cytotoxic drugs can be formed which might lead to an improved complete remission rate.

Technical Approach: Dibromodulcitol, 180 mg/m² p.o., will be taken in a single dose days 1-10 and repeated every four weeks until progression of disease or adverse effects prohibit further therapy.

Progress: No patients have been entered at MAMC.

DBD has activity in untreated squamous cervix cancer. DBD has substantial marrow toxicity (predominantly thrombocytopenia) at the dose and schedule tested, even among patients with no prior chemotherapy. A study has been initiated to determine an appropriate dose for the combination of cisplatin and DBD.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 87/91 Status: On-going

Title: GOG 76 F: A Phase II Trial of Gallium Nitrate (NSC 15200)
Patients with Advanced Squamous Cell Carcinoma of the
Cervix

Start Date: 15 May 87 Est Completion Date: Indefinite

Department: OB/GYN Facility: MAMC

Principal Investigator: LTC Gordon O. Downey, MC

Associate Investigators: COL William Benson, MC

COL Roger B. Lee, MC

Key Words: carcinoma, cervix, squamous, gallium nitrate

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: -0- Sep 88

Study Objective: To identify new active drugs in the control of advanced or recurrent squamous cell carcinoma of the cervix so that combinations of cytotoxic drugs can be formed which might lead to an improved complete remission rate.

Technical Approach: Gallium nitrate will be given as a slow IV infusion of 30-60 minutes at a dose of 750 mg/m² once every three weeks until progression or adverse effects prohibit further therapy.

Progress: No patients have been entered at MAMC.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 87/80 Status: Completed

Title: GOG 76 G: A Phase II Trial of Cisplatin/5-Fluorouracil
Carcinoma of the Cervix

Start Date: 15 May 87 Est Completion Date: Indefinite

Department: OB/GYN Facility: MAMC

Principal Investigator: COL Roger B. Lee, MC

Associate Investigator: COL William Benson, MC

Key Words: carcinoma, cervix, cisplatin, 5-FU

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: -0- May 88

Study Objective: To identify new active drugs in the control of advanced or recurrent squamous cell carcinoma of the cervix so that combinations of cytotoxic drugs can be formed which might lead to an improved complete remission rate.

Technical Approach: Patients will be initially treated with a 50 mg/m^2 infusion of cis-platin on day 1. Subsequent to that, they will receive a 24-hour infusion, days 1-5, of 5-FU at a dose of 1000 mg/m^2 per day. The regimen will be repeated every 21 days until progression or adverse effects prohibit further therapy.

Progress: One patient has been entered at MAMC. This patient had progression of disease and was removed from the protocol.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No. 88/52 Status: On-going

Title: GOG 76J: A Phase II Trial of Mitomycin-C (NSC#26980)
in Patients with Advanced Squamous Cell Carcinoma
of the Cervix

Start Date: 15 Apr 88 Est Completion Date: Indefinite

Department: OB/GYN Facility: MAMC

Principal Investigator: LTC Gordon O. Downey, MC

Associate Investigators: COL William Benson, MC

COL Roger B. Lee, MC

Key Words: carcinoma, cervix, squamous cell, mitomycin-C

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: -0- N/A

Study Objective: To identify new active drugs in the control of advanced or recurrent squamous cell carcinoma of the cervix so that combinations of cytotoxic drugs can be formed which might lead to an improved complete remission rate.

Technical Approach: Patients will receive mitomycin-C, 20 mg/M², intravenously every six weeks for two doses and then 10 mg/M² every six weeks thereafter except for those patients at high risk for myelosuppression. In patients at high risk for myelosuppression, no treatment course will start until the WBC is >3000/mcl and the platelets are >100,000/mcl. The dose level will be reduced in these patients according to nadir counts, length of time myelosuppression is prolonged, and previous radiotherapy history.

A dose reduction will be mandated in all patients in whom the adverse effects exceed a grade 2 level. Should serum creatinine - exceed 2.0 mg/dl, drug therapy will be discontinued.

An adequate trial is defined as at least one drug course. Patients who receive at least one drug dose and follow-up adequate to permit assessment of response will be considered fully evaluable. Patients whose follow-up is inadequate to permit response assessment will be considered evaluable for toxicity only. The drug will be continued until there is documentation of disease progression or unacceptable adverse effects.

Progress: One patient has been entered in the study at MAMC.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 84/74 Status: On-going

****Title:** GOG 78: 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

Start Date: 17 Aug 84 Est Completion Date: Jul 89

Department: OB/GYN Facility: MAMC

Principal Investigator: LTC Gordon O. Downey, MC

Associate Investigators: COL William Benson, MC

COL Roger B. Lee, MC

Key Words: ovary, embryonal carcinoma, choriocarcinoma, endodermal sinus tumor, vinblastine, bleomycin, cisplatin

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: -0- Aug 88

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 alphafetoprotein 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 evaluable 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: No entries at MAMC.

Detail Summary Sheet

Date: 30 Sep 88	Protocol No.: 85/89	Status: Completed
Title: GOG 79: Single Agent Weekly Methotrexate (NSC #740) Therapy in the Treatment of Nonmetastatic Gestational Trophoblastic Disease		
Start Date: 20 Sep 85	Est Completion Date: Indefinite	
Department: OB/GYN	Facility: MAMC	
Principal Investigator: LTC Gordon O. Downey, MC		
Associate Investigators: COL William Benson, MC COL Roger B. Lee, MC		
Key Words: trophoblastic, gestational, methotrexate, weekly		
Accumulative MEDCASE	Est Accumulative	Periodic Review:
Cost: -0-	OMA Cost: -0-	Aug 88

Study Objective: To determine the efficacy of weekly methotrexate therapy for nonmetastatic gestational trophoblastic disease; to ascertain the toxicity of this regimen; and to demonstrate the cost effectiveness of this regimen.

Technical Approach: Patients with nonmetastatic gestational trophoblastic disease with antecedent molar pregnancy or postabortal status and no prior chemotherapy who meet the criteria listed in the protocol will receive initial treatment with methotrexate, 30 mg/M², IM, based on ideal or actual weight, once a week. If there is no toxicity after three weekly courses, the dosage will be escalated by 5 mg/M². If there is not toxicity at the escalated level after three weekly courses, 5 mg/M² escalations of the weekly dosage for three consecutive weeks will be given until a maximum dose of 50 mg/M² is achieved. All patients will receive chemotherapy until remission, severity of toxicity requires a change in therapy, or nonresponse. Nonresponders will go off study and be treated with Dactinomycin. Dosage will be modified according to toxicity encountered. An adequate trial is defined as three one week courses

Progress: No entries at MAMC in FY 88. Two patients were entered on this protocol in FY 86 with no adverse side effects.

Group-wide data indicate that the 30 mg/M² regimen with escalation every three weeks by 5 mg/M² increments to a maximum dose of 50 mg/M² proved to be highly effective (81% complete response), safe, and cost-efficient as compared to a regimen of 40 mg/M² more rapidly escalating every two weeks by 5 mg/M² to 50 mg/M² which demonstrated no greater effectiveness (73% complete response) and no shortened time to response and with no more toxicity. Second-line salvage with five-day methotrexate appeared less effective in the second study compared to dactinomycin in the this study.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 86/08 Status: On-going

Title: GOG 81/A: Master Protocol for Hormonal Treatment of
Advanced or Recurrent Carcinoma of the Endometrium

Start Date: 18 Oct 85 Est Completion Date: Oct 93

Department: OB/GYN Facility: MAMC

Principal Investigator: LTC Gordon O. Downey, MC

Associate Investigators: COL William Benson, MC
COL Roger B. Lee, MC

Key Words: carcinoma, endometrium, advanced, recurrent, hormonal
therapy, medroxyprogesterone acetate, master protocol

Accumulative MEDCASE Est Accumulative Periodic Review:
Cost: -0- OMA Cost: -0- Aug 88

Study Objective: To determine the relative efficacy of two dose schedules of oral MPA in the management of advanced or recurrent endometrial carcinoma; to examine the relationship between the levels of estrogen and progesterone receptors in the neoplasm and subsequent response to progestin therapy; and to determine if patients who respond to therapy with progestins will respond to therapy with anti-estrogens when they relapse on progestins.

Technical Approach: This is a master protocol established in order to study patients being treated with medroxyprogesterone acetate (MPA) for advanced or recurrent endometrial carcinoma. The protocol will be divided into sections to study MPA in patients with various estrogen and progesterone receptors:

- 81B: positive estrogen and progesterone receptors
- 81C: negative estrogen and progesterone
- 81D: positive for either estrogen or progesterone
receptors but not both
- 81E: unknown estrogen and progesterone receptors

Section 81F will study Tamoxifen salvage in patients responsive to MPA in sections B-E. The treatment regimens in each section will be the same with only the receptor studied being different.

Treatment I: medroxyprogesterone acetate 200 mg p.o. daily
Treatment II: medroxyprogesterone acetate 1000 mg p.l. daily

Progress: No patients at MAMC have been entered in any of the sections to this protocol.

Group-wide, 193 patients are presently evaluable for response on the combined trials. Sufficient activity is evident in each regimen to warrant completion of the study. Treatment comparisons will be undertaken in final analysis.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 86/09 Status: On-going

Title: GOG 81/B: A Phase I-II Trial of Medroxyprogesterone Acetate (MPA) in Patients with Advanced or Recurrent Endometrial Carcinoma Positive for Estrogen and Progesterone Receptors

Start Date: 18 Oct 85 Est Completion Date: Indefinite

Department: OB/GYN Facility: MAMC

Principal Investigator: LTC Gordon O. Downey, MC

Associate Investigators: COL William Benson, MC

COL Roger B. Lee, MC

Key Words: endometrial carcinoma, medroxyprogesterone acetate, positive estrogen and progesterone receptors

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: -0- Aug 88

Study Objective: To determine the relative efficacy of a high versus a low dose schedule of oral medroxyprogesterone acetate in treatment of advanced or recurrent endometrial carcinoma and to determine the response rate to progestins in patients positive for estrogen and progesterone receptors.

Technical Approach: Patients will be randomized to:

Treatment I: medroxyprogesterone acetate 200 mg p.o. daily
or

Treatment II: medroxyprogesterone acetate 1000 mg p.o. daily

Therapy will continue until evidence of disease progression. A course will be considered as every 4 weeks. Each patient will have a serum sample drawn after one month on therapy to document compliance and absorption. Treatment will be continued until there is evidence of disease progression or the patient experiences unacceptable adverse effects.

Progress: No entries at MAMC.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 86/10 Status: On-going

Title: GOG 81/C: A Phase I-II Trial of Medroxyprogesterone Acetate (MPA) in Patients with Advanced or Recurrent Endometrial Carcinoma Negative for Estrogen and Progesterone Receptors

Start Date: 18 Oct 85 Est Completion Date: Indefinite

Department: OB/GYN Facility: MAMC

Principal Investigator: LTC Gordon O. Downey, MC

Associate Investigators: COL William Benson, MC
COL Roger B. Lee, MC

Key Words: carcinoma, endometrial, medroxyprogesterone acetate, negative estrogen and progesterone receptors

Accumulative MEDCASE Est Accumulative Periodic Review:
Cost: -0- OMA Cost: -0- Aug 88

Study Objective: To determine the relative efficacy of a high versus a low dose schedule of oral medroxyprogesterone acetate in treatment of advanced or recurrent endometrial carcinoma and to determine the response rate to progestins in patients negative for estrogen and progesterone receptors.

Technical Approach: Patients will be randomized to:

Treatment I: medroxyprogesterone acetate 200 mg p.o. daily
or
Treatment II: medroxyprogesterone acetate 1000 mg p.o. daily

Therapy will continue until evidence of disease progression. One course will be considered as every four weeks. Each patient will have a serum sample drawn after one month on therapy to document compliance and absorption. Treatment will be continued until evidence of disease progression or the patient experiences unacceptable adverse effects.

Progress: No entries at MAMC.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 86/11 Status: On-going

Title: GOG 81/D: A Phase I-II Trial of Medroxyprogesterone Acetate (MPA) in Patients with Advanced or Recurrent Endometrial Carcinoma Positive for Either Estrogen or Progesterone Receptors but Not Both

Start Date: 18 Oct 85 Est Completion Date: Indefinite

Department: OB/GYN Facility: MAMC

Principal Investigator: LTC Gordon O. Downey, MC

Associate Investigators: COL William Benson, MC

COL Roger B. Lee, MC

Key Words: carcinoma, endometrial, medroxyprogesterone acetate, positive for either estrogen or progesterone receptors but not both

<u>Accumulative MEDCASE</u>	<u>Est Accumulative</u>	<u>Periodic Review:</u>
<u>Cost: -0-</u>	<u>OMA Cost: -0-</u>	<u>Aug 88</u>

Study Objective: To determine the relative efficacy of a high versus a low dose schedule of oral medroxyprogesterone acetate in treatment of advanced or recurrent endometrial carcinoma and to determine the response rate to progestins in patients positive for either estrogen or progesterone receptors.

Technical Approach: Patients will be randomized to:

Treatment I: medroxyprogesterone acetate 200 mg p.o. daily
or

Treatment II: medroxyprogesterone acetate 1000 mg p.o. daily

Therapy will continue until evidence of disease progression. A course will be considered as every 4 weeks. Each patient will have a serum sample drawn after one month on therapy to document compliance and absorption. Treatment will be continued until evidence of disease progression or the patient experiences unacceptable adverse effects.

Progress: No entries at MAMC.

Detail Summary Sheet

Date: 30 Sep 88	Protocol No.: 86/12	Status: On-going
Title: GOG 81/E: A Phase I-II Trial of Medroxyprogesterone Acetate (MPA) in Patients with Advanced or Recurrent Endometrial Carcinoma with Unknown Estrogen or Progesterone Receptors		
Start Date: 18 Oct 85	Est Completion Date: Indefinite	
Department: OB/GYN	Facility: MAMC	
Principal Investigator: LTC Gordon O. Downey, MC		
Associate Investigators: COL William Benson, MC COL Roger B. Lee, MC		
Key Words: carcinoma, endometrial, medroxyprogesterone acetate, estrogen or progesterone receptors, unknown		
Accumulative MEDCASE	Est Accumulative	Periodic Review:
Cost: -0-	OMA Cost: -0-	Aug 88

Study Objective: To determine the relative efficacy of a high versus a low dose schedule of oral medroxyprogesterone acetate in the management of advanced or recurrent endometrial carcinoma; to examine the relationship between the levels of estrogen and progesterone receptors in the neoplasm and subsequent response to progestin therapy; and to determine whether patients who respond to therapy with progestins will respond to therapy with anti-estrogens when they relapse on progestins.

Technical Approach: Patients will be randomized to:

Treatment I: medroxyprogesterone acetate 200 mg p.o. daily
or
Treatment II: medroxyprogesterone acetate 1000 mg p.o. daily

Therapy will continue until evidence of disease progression. A course will be considered as every 4 weeks. Each patient will have a serum sample drawn after one month on therapy to document compliance and absorption. Treatment will be continued until evidence of disease progression or the patient experiences unacceptable adverse effects.

Progress No entries at MAMC.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 86/13 Status: On-going

Title: GOG 81/F: A Phase I-II Trial of Tamoxifen Citrate in Patients with Advanced or Recurrent Endometrial Carcinoma Responsive to Progestins

Start Date: 18 Oct 85 Est Completion Date: Indefinite

Department: OB/GYN Facility: MAMC

Principal Investigator: LTC Gordon O. Downey, MC

Associate Investigators: COL William Benson, MC

COL Roger B. Lee, MC

Key Words: carcinoma, endometrial, tamoxifen citrate, progestins

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: -0- Aug 88

Study Objective: To determine whether patients with endometrial carcinoma who have responded to medroxyprogesterone acetate and then progressed will respond to a second hormonal manipulation in the form of tamoxifen citrate.

Technical Approach: Patients must have developed progression of disease on MPA after initial response and must have been off MPA for at least three weeks with no evidence of disease response to withdrawal of MPA unless there is rapid progression, in which case tamoxifen will begin immediately.

Patients will receive tamoxifen, 20 mg p.o., daily. Treatment will be continued until there is evidence of disease progression. An adequate trial is defined as at least one month of therapy.

Progress: No entries at MAMC.

Detail Summary Sheet

Date: 30 Sep 88	Protocol No.: 85/90	Status: On-going
Title: GOG 83: A Clinico-Pathologic Study of Simultaneous Endometrial and Ovarian Carcinomas		
Start Date: 20 Sep 85	Est Completion Date: Indefinite	
Department: OB/GYN	Facility: MAMC	
Principal Investigator: LTC Gordon O. Downey, MC		
Associate Investigators: COL William Benson, MC		
COL Roger B. Lee, MC		
Key Words: carcinoma, ovarian, endometrial, simultaneous		
Accumulative MEDCASE	Est Accumulative	Periodic Review:
Cost: -0-	OMA Cost: -0-	Aug 88

Study Objective: To determine the natural history of patients with synchronous adenocarcinoma presenting in both the endometrium and the ovary; to obtain estimates of mortality at five years; to determine whether histologic criteria or pattern of spread can be used to distinguish subsets of patients with differing prognoses; to determine whether these criteria would be appropriate to direct therapy in different patients to that appropriate for Stage III endometrial carcinoma, Stage I or II ovarian carcinoma with endometrial metastases, or Stage I or II endometrial and ovarian carcinoma.

Technical Approach: Patients will have had no prior pelvic radiation or chemotherapy and will have no previous or concomitant malignancy except of skin (excluding melanoma). Surgery will be carried out as specified in the protocol to include TAH, BSO, pelvic and para-aortic lymphadenectomy, omentectomy, peritoneal cytology, pelvic cytology, pelvic and peritoneal biopsy, and washing, scraping, and biopsy of the right hemidiaphragm. Since no further treatment by protocol is available, further treatment will be at the discretion of the investigator. All patients will be followed for five years. Principal parameters employed to examine the natural history of these patients will be survival time, histologic type, histologic grade, and depth of myometrial invasion.

Progress: No entries at MAMC.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 87/25 Status: Completed

Title: GOG 84: Evaluation of a Shortened Course of Vincristine, Dactinomycin and Cyclophosphamide (VAC) as Adjuvant Therapy for Immature Teratoma of the Ovary, Stage I, Grade 2, Completely Resected (Phase II)

Start Date: 21 Nov 36 Est. Completion Date: Indefinite

Department: OB/GYN Facility: MAMC

Principal Investigator: LTC Gordon O. Downey, MC

Associate Investigators: COL William Benson, MC

COL Roger B. Lee, MC

Key Words: ovary, immature teratoma, VAC, shortened course, adjuvant therapy, post-surgery

Accumulative MEDCASE Fst Accumulative Periodic Review:

Cost: -0- OMA Cost: -0- N/A

Study Objective: To evaluate vincristine, dactinomycin, and cyclophosphamide (VAC) given in a shortened course as adjuvant chemotherapy for Stage I Grade 2 immature teratomas of the ovary following removal of all gross tumor.

Technical Approach: Previously untreated patients with histologically confirmed immature teratomas of the ovary, Stage I, Grade 2, that has been completely resected will be eligible. Following recovery from surgery, patients will receive vincristine in a single dose of $1.5 \text{ mg}/\text{m}^2$ IV every two weeks for 12 courses. Dactinomycin will be given $1.2 \text{ mg}/\text{m}^2$ IV every four weeks for 6 courses. Cyclophosphamide will be given $750 \text{ mg}/\text{m}^2$ IV every four weeks for six courses. If progression is noted during chemotherapy, patients will be transferred to an appropriate GOG protocol. After completion of therapy, patients will undergo a reassessment laparotomy. Those with progression of disease will be transferred to an appropriate GOG protocol. Those who have no evidence of disease will be followed on no further therapy. If recurrence develops, the patient will be entered on the appropriate GOG protocol.

Progress: No patients have been entered at MAMC.

The protocol was terminated by GOG in Feb 88.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 86/89 Status: On-going

Title: GOG 85: A Randomized Comparison of Hydroxyurea versus 5-FU Infusion and Bolus Cisplatin as an Adjunct to Radiation Therapy in Patients with Stages II-B, III, and IV-A Carcinoma of the Cervix and Negative Para-aortic Nodes

Start Date: 15 Aug 86 Est Completion Date: Indefinite

Department: OB/GYN Facility: MAMC

Principal Investigator: LTC Gordon O. Downey, MC

Associate Investigators: COL William Benson, MC

COL Roger B. Lee, MC

Key Words: carcinoma, cervix, chemotherapy, radiation

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: -0- Aug 88

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: No entries at MAMC.

Detail Summary Sheet

Date: 30 Sep 88	Protocol No.: 86/14	Status: On-going
Title: GOG 86/A: Master Protocol for Phase II Drug Studies in Treatment of Recurrent Carcinoma of the Endometrium		
Start Date: 18 Oct 85	Est Completion Date: Oct 87	
Department: OB/GYN	Facility: MAMC	
Principal Investigator: LTC Gordon O. Downey, MC		
Associate Investigators: COL William Benson, MC COL Roger B. Lee, MC		
Key Words: carcinoma, endometrium, recurrent, master protocol		
Accumulative MEDCASE	Est Accumulative	Periodic Review:
Cost: -0-	OMA Cost: -0-	Aug 88

Study Objective: To identify additional active agents, by studying single new drugs, in patients with advanced or recurrent endometrial carcinoma not previously exposed to chemotherapy. Sections relating to specific agents will be sequentially incorporated into this protocol as the use of each agent is approved by the Institutional Review Board.

Treatment of advanced or recurrent carcinoma of the endometrium has been studied only in a relatively small number of cases. To date, only hormonal therapy with progestins or tamoxifen and the cytotoxic drug adriamycin have been shown to be conclusively active. This study seeks to identify additional active agents by studying single new drugs in patients with advanced or recurrent endometrial carcinoma not previously exposed to chemotherapy. Approximately 30 evaluable patients will be accrued for each drug studied to allow for reasonable estimates of response rates.

Technical Approach: Specific treatment regimens will be given for each protocol as that section is submitted for approval. The principal parameters employed to evaluate the efficacy of each agent will be: the frequency and duration of objective response; the frequency and severity of observed adverse effects; survival time for all patients; and duration of progression-free interval for all patients. Anticipated annual accrual group-wide is approximately 40 patients (0-5 at MAMC). See section 2.0 of the master protocol for patient eligibility and exclusions. Consent forms will be provided for the use of each agent as the protocol for that agent is submitted for approval.

Progress: No entries at MAMC.

Continuing review will be performed for individual protocols.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 87/26 Status: Completed

Title: GCG 86D: A Phase II Trial of Methotrexate (NSC 740) in
Patients with Advanced or Recurrent Endometrial Carcinoma

Start Date: 21 Nov 86 Est Completion Date: Indefinite

Department: OB/GYN Facility: MAMC

Principal Investigator: COL Roger B. Lee, MC

Associate Investigator: COL William Benson, MC

Key Words: carcinoma, endometrial, methotrexate, phase II

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: -0- May 88

Study Objective: To identify additional active agents, by studying single new drugs, in patients with advanced or recurrent endometrial carcinoma not previously exposed to chemotherapy.

Technical Approach: Patients will receive methotrexate, 40 mg/m² IV, once weekly for a total of 12 weeks. After 12 weeks, patients with stable or responding disease will be continued on the same dosage every other week until there is documentation of disease progression or unacceptable side effects.

An adequate trial is defined as at least four weeks of therapy. Patients who die of progressive disease before this will be considered treatment failures and considered to have a progressive disease response. Patients who have toxicity before the four weeks and who are removed from the study will be considered evaluable for toxicity but not response.

Progress: No entries at MAMC. This protocol was closed to patient entry in February 1988.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 87/27 Status: On-going

Title: GOG 86E: A Phase II Trial of Vincristine (VCR) Given as a Weekly Intravenous Bolus in Advanced or Recurrent Endometrial Carcinoma

Start Date: 21 Nov 86 Est Completion Date: Indefinite

Department: OB/GYN Facility: MAMC

Principal Investigator: LTC Gordon O. Downey, MC

Associate Investigators: COL William Benson, MC
COL Roger B. Lee, MC

Key Words: carcinoma, endometrial, vincristine, phase II

Accumulative MEDCASE Est Accumulative Periodic Review:
Cost: -0- OMA Cost: -0- Sep 88

Study Objective: To identify additional active agents, by studying single new drugs, in patients with advanced or recurrent endometrial carcinoma not previously exposed to chemotherapy.

Technical Approach: Vincristine will be given as an IV bolus at a dose of 1.4 mg/m² (maximum dose 2.0 mg) weekly for four weeks. Patient response will be evaluated on the fifth week. Responders (complete or partial remission or stable disease) will be treated on the fifth week and then continued on treatment every two weeks until progression of disease or the development of unacceptable adverse effects.

An adequate trial is defined as at least four weeks of therapy. Patients who die of progressive disease before this will be considered treatment failures and considered to have a progressive disease response. Patients who have toxicity before the four weeks and who are removed from the study will be considered evaluable for toxicity but not response.

Progress: No entries at MAMC.

Detail Summary Sheet

Date: 30 Sep 88	Protocol No.: 87/101	Status: On-going
Title: GOG 86F: A Phase II Trial of Mitomycin-C (NSC #26980) in Patients with Advanced Endometrial Carcinoma		
Start Date: 21 Aug 87	Est Completion Date: Indefinite	
Department: OB/GYN	Facility: MAMC	
Principal Investigator: LTC Gordon O. Downey, MC		
Associate Investigators: COL William Benson, MC COL Roger E. Lee, MC		
Key Words: carcinoma, endometrial, advanced, mitomycin-C		
Accumulative MEDCASE	Est Accumulative	Periodic Review:
Cost: -0-	OMA Cost: -0-	Aug 88

Study Objective: To identify additional active agents, by studying single new drugs, in patients with advanced or recurrent endometrial carcinoma not previously exposed to chemotherapy.

Technical Approach: Patients will receive mitomycin-C, 20 mg/m² IV, every six weeks for two doses and then 10 mg/m² every six weeks thereafter, except for those patients at high risk for myelosuppression. No treatment course will be started until the white blood count is >100,000/mcl. Therapy will continue until there is documentation of disease progression or unacceptable adverse effects.

An adequate trial is defined as at least one drug course. Patients who receive at least one drug dose and follow-up adequate to permit assessment of response will be considered fully evaluable. Patients whose follow-up is inadequate to permit response assessment will be considered evaluable for toxicity only.

Progress: No entries at MAMC.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 86/24 Status: On-going

Title: GOG 87A: Master Protocol for Phase II Drug Studies in the
Treatment of Recurrent or Advanced Uterine Sarcomas

Start Date: 17 Jan 86 Est Completion Date: Indefinite

Department: OB/GYN Facility: MAMC

Principal Investigator: LTC Gordon O. Downey, MC

Associate Investigators: COL William Benson, MC
COL Roger B. Lee, MC

Key Words: sarcoma, uterine, recurrent, master protocol, drugs

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: -0- Sep 88

Study Objective: To identify new agents and combinations for treating this malignancy and to allow the best possible chance for a new cytotoxic agent to demonstrate activity. This study constitutes a Phase II design in a population of patients who have had no prior drug therapy.

Technical Approach: The study design will involve treating an average sample size of 30 evaluable patients per drug studied for each of the following cell type categories:

Mixed mesodermal tumor
Leiomyosarcoma
Other sarcomas

Patients will have had no prior drug therapy. Since this is a Phase II study, no randomization is involved. The principal parameters employed to evaluate the efficacy of each agent are:

The frequency and duration of objective response.
The frequency and severity of observed adverse effects.
Survival time for all patients.
Duration of progression-free interval for all patients.

In order to estimate the true response rate and be 90% certain - that the estimate is within $\pm 15\%$, 30 evaluable patients per histologic category will be needed (group wide). Reviews will be held at least twice yearly. Consequently, on at least two occasions, early termination can be considered if the results do not warrant conducting the study to completion. Although the exact number of patients accessioned cannot be forecasted at this time, the relatively slow accrual rates guarantee that inactive agents will be expeditiously recognized. The active phase of this study for each drug should be approximately:

Mixed mesodermal tumor - 1 to 1 1/4 years
Leiomyosarcoma - 3 years
Other sarcomas - 6 years

Progress: No entries at MAMC.

**Continuing review will be done on individual protocols.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 86/25 Status: Completed

Title: GOG 87B: A Phase II Trial of Ifosfamide (NSC #109724) and the Uroprotector, Mesna (NSC #25232), in the Treatment of Recurrent or Advanced Uterine Sarcomas

Start Date: 17 Jan 86 Est Completion Date: Indefinite

Department: OB/GYN Facility: MAMC

Principal Investigator: LTC Gordon O. Downey, MC

Associate Investigators: COL William Benson, MC

COL Roger B. Lee, MC

Key Words: sarcoma, uterine, recurrent, ifosfamide, mesna

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: -0- Sep 88

Study Objective: To identify new agents and combinations for treating this malignancy and to allow the best possible chance for a new cytotoxic agent to demonstrate activity. This study constitutes a Phase II design in a population of patients who have had no prior drug therapy. The agents to be studied in this protocol are ifosfamide and Mesna.

Technical Approach: Eligibility requirements are listed in the master protocol, 87B. Ifosfamide will be given in an initial dose of 1.8 g/M² daily for five days except those patients who have received prior pelvic radiation therapy. These patients will start at an initial dose of 1.5 g/M² daily for five days, once every four weeks. Mesna will be 20% of the ifosfamide dose, given three doses daily, at the completion of ifosfamide administration and four and eight hours after ifosfamide in order to reduce the urothelial toxicity of ifosfamide. Dosage will be modified according to adverse effects.

An adequate trial is defined as receiving one course of treatment and living four weeks for an additional tumor measurement. Toxicity, however, may be assessed as soon as the patient receives the drug. Each patient will remain on study and continue to receive the drug until the disease progresses or until adverse effects prevent further treatment.

Progress: No entries at MAMC.

Group-wide data indicate that ifosfamide/Mesna may be the most active single-agent therapy for advanced mixed mesodermal tumors of the uterus.

Detail Summary Sheet

Date: 30 Sep 88	Protocol No.: 87/102	Status: On-going
Title: GOG 87C: A Phase II Trial of Hydroxyurea, Dacarbazine (DTIC) and Etoposide (VP-16) in Patients with Advanced or Recurrent Uterine Sarcomas		
Start Date: 21 Aug 87	Est Completion Date: Indefinite	
Department: OB/GYN	Facility: MAMC	
Principal Investigator: LTC Gordon O. Downey, MC		
Associate Investigators: COL William Benson, MC COL Roger B. Lee, MC		
Key Words: sarcoma, uterine, recurrent, hydroxyurea, DTIC, VP-16		
Accumulative MEDCASE	Est Accumulative	Periodic Review:
Cost: -0-	OMA Cost: -0-	Aug 88

Study Objective: To identify new agents and combinations for treating this malignancy and to allow the best possible chance for a new cytotoxic agent to demonstrate activity. This study constitutes a Phase II design in a population of patients who have had no prior drug therapy. The agents to be studied in protocol are hydroxyurea, dacarbazine (DTIC), and etoposide (VP-16).

Technical Approach: The treatment regimen combines hydroxyurea, a chemotherapeutic agent with a known cell-cycle synchronizing effect with DTIC, an antimetabolite, and VP-16, a premitotic inhibitor.

On Day 1, Hydroxyurea, 500 mg capsules, will be given p.o. every 6 hours with no restrictions on diet or activity. On Day 2, VP-16, 100 mg/m², diluted in 250 cc NS will be infused over one hour beginning at exactly 24 hours after the start of hydroxyurea, followed by DTIC, 700 mg/m², diluted in 500 cc D₅W, infused over four hours. On Day 3, VP-16, 100 mg/m², diluted in 250 cc NS will be infused over one hour. On Day 4, VP-16, 100 mg/m², diluted in 250 cc NS will be infused over one hour. Pre-medication with antiemetic regimens will be given on Day 2. The treatment course will be administered every four weeks, if toxicity permits and will continue for 12 courses unless progression occurs.

An adequate trial is defined as receiving one course of treatment and living four weeks. If the patient suffers progressive disease before four weeks elapse, this indicates treatment failure. Patients will remain on study and continue to receive therapy for 12 months unless there is progression or adverse effects which prohibit further therapy. Patients who die of drug-related complications prior to having their disease re-evaluated will be considered inevaluable for response but evaluable for toxicity.

Progress: No entries at MAMC.

Detail Summary Sheet

Date: 30 Sep 88	Protocol No.: 87/103	Status: On-going
Title: GOG 87D: A Phase II Trial of VP-16 (NSC #141540) in Patients with Advanced Uterine Sarcoma		
Start Date: 21 Aug 87	Est Completion Date: Indefinite	
Department: OB/GYN	Facility: MAMC	
Principal Investigator: LTC Gordon O. Downey, MC		
Associate Investigators: COL William Benson, MC COL Roger B. Lee, MC		
Key Words: sarcoma, uterine, advanced, VP-16		
Accumulative MEDCASE	Est Accumulative	Periodic Review:
Cost: -0-	OMA Cost: -0-	Aug 88

Study Objective: To identify new agents and combinations for treating this malignancy; to allow the best possible chance for a new cytotoxic agent to demonstrate activity. This study constitutes a Phase II design in a population of patients who have had no prior drug therapy. The study design will involve treating an average sample size of 30 evaluable patients for mixed mesodermal tumor, leiomyosarcoma, and other sarcomas. This will allow agents found to be ineffective to be rapidly replaced by other agents.

Technical Approach: Patients will receive VP-16, 125 mg/m² IV, daily for three days every three weeks except for those patients at high risk for myelosuppression. No treatment course will be started until the white blood count is >3000/mcl and platelets are >100,000/mcl.

An adequate trial is defined as at least one course. Patients who receive at least one drug dose and follow-up adequate to permit assessment of response will be considered fully evaluable. Patients whose follow-up is inadequate to permit response assessment will be considered evaluable for toxicity only. The therapy will be continued until there is documentation of disease progression or unacceptable adverse effects.

Progress: No entries at MAMC.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 86/90 Status: On-going

Title: GOG 88: A Randomized Study of Radical Vulvectomy and
Bilateral Groin Dissection versus Radical Vulvectomy
and Bilateral Groin Radiation

Start Date: 15 Aug 86 Est Completion Date: Indefinite

Department: OB/GYN Facility: MAMC

Principal Investigator: LTC Gordon O. Downey, MC

Associate Investigators: COL William Benson, MC
COL Roger B. Lee, MC

Key Words: vulvectomy, radical, groin dissection, groin radiation

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: -0- Aug 88

Study Objective: To evaluate the comparative efficacy and morbidity of groin radiation therapy in lieu of groin dissection for selected patients with invasive squamous cell carcinoma of the vulva and to monitor patterns of recurrence and survival of patients treated with groin radiation therapy in lieu of groin dissection.

Technical Approach: Patients with invasive squamous cell carcinoma of the vulva who meet eligibility criteria as listed in the protocol will be randomized between radical vulvectomy and groin dissection and radical vulvectomy and groin radiation therapy. Complete clinical and radiographic evaluation will be performed prior to randomization. Needle aspiration cytology will be performed if there is concern over groin node status.

Progress: No entries at MAMC.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 87/13 Status: On-going

Title: GOG 90: Evaluation of Cisplatin, Etoposide, and Bleomycin (BEP) Induction Followed by Vincristine, Dactinomycin, and Cyclophosphamide (VAC) Consolidation in Advanced Ovarian Germ Cell Tumors

Start Date: 17 Oct 86 Est Completion Date: Indefinite

Department: OB/GYN Facility: MAMC

Principal Investigator: LTC Gordon O. Downey, MC

Associate Investigators: COL William Benson, MC

COL Roger B. Lee, MC

Key Words: tumors, ovarian, germ cell, BEP induction, VAC

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: -0- Aug 88

Study Objective: To evaluate the effect of induction chemotherapy with cisplatin plus etoposide plus bleomycin (BEP) followed by consolidation with vincristine plus dactinomycin plus cyclophosphamide (VAC) in previously untreated patients with advanced ovarian germ cell tumors.

Technical Approach: After adequate recovery from surgery (if done) previously untreated patients will be treated by three courses of BEP followed by three courses of VAC. Patients exhibiting disease progression on either phase will be taken off study. Patients who had previous VAC or similar regimens will be treated with four courses of BEP. After recovery from BEP therapy, reassessment laparotomy will be performed in patients with negative markers who are clinically free of disease. Progressing patients will be removed from the study. Patients with no evidence of disease at second look will be followed. Patients with persistent disease at second look will be removed from the study.

An adequate trial is defined as receiving two courses of the drug and living at least six weeks. Each patient will remain on study until adverse effects prohibit further therapy or until evidence of progression of disease.

Progress: No patients entered at MAMC.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 87/104 Status: On-going

Title: GOG 92: Treatment of Selected Patients with Stage 1B Carcinoma of the Cervix After Radical Hysterectomy and Pelvic Lymphadenectomy: Pelvic Radiation Therapy Versus No Further Therapy

Start Date: 21 Aug 87 Est Completion Date: Indefinite

Department: OB/GYN Facility: MAMC

Principal Investigator: LTC Gordon O. Downey, MC

Associate Investigators: COL William Benson, MC

COL Roger B. Lee, MC

Key Words: carcinoma, cervix, pelvic radiation vs no therapy

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: -0- Aug 88

Study Objective: To determine the value of adjunctive pelvic radiation in the treatment of Stage 1_B 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 1_B 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: One patient has been entered in the protocol (FY 88) at MAMC.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 87/48 Status: On-going

Title: GOG 94: A Phase II Study of the Treatment of Papillary Serous Carcinoma of the Endometrium Stages I and II and Maximally Debulked Advanced Endometrial Carcinoma with Total Abdominal Radiation Therapy

Start Date: 27 Feb 87 Est Completion Date: Indefinite

Department: OB/GYN Facility: MAMC

Principal Investigator: LTC Gordon O. Downey, MC

Associate Investigators: COL William Benson, MC

COL Roger B. Lee, MC

Key Words: carcinoma, endometrial, papillary serous, radiation

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: -0- Sep 88

Study Objective: To determine the survival and progression-free interval of patients with maximally debulked advanced endometrial carcinoma treated with abdominal radiation and to determine the progression-free interval and site of recurrence in patients with Stage I or II papillary serous carcinoma of the endometrium treated with abdominal radiation therapy with pelvic boost.

Technical Approach: Following surgery, the whole abdomen will be irradiated with opposed fields to a total dose of 3000 cGy in 20 fractions of 150 cGy each. If the treatment is not tolerated because of GI symptoms or leukopenia, the daily fraction will be decreased to 125 cGy per day. Whole abdominal radiation will require four to five weeks.

Following whole abdominal radiation, the pelvis will be boosted to a midplane dose of 980 cGy at 180 cGy per fraction for eleven treatments. The combined whole abdominal radiation and the total pelvic field radiation will require a total time of approximately six to seven weeks.

Patients will be followed quarterly for the first two years after completion of therapy and semi-annually for an additional three years.

Patients will continue on protocol until disease progression or adverse effects necessitates removal from the study. An adequate trial will consist of receipt of any protocol therapy.

Progress: Two patients were entered at MAMC in FY 88.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 87/28 Status: On-going

Title: GOG 95: Randomized Clinical Trial for the Treatment of Women with Selected Stage IC and II (A,B,C,) and Selected Stage IAi & IBi and IAii & IBii Ovarian Cancer, Phase III

Start Date: 21 Nov 86 Est Completion Date: Indefinite

Department: OB/GYN Facility: MAMC

Principal Investigator: LTC Gordon O. Downey, MC

Associate Investigators: COL William Benson, MC
COL Roger B. Lee, MC

Key Words: cancer, ovarian, chemotherapy, staged, cyclophosphamide, cisplatin, P32

Accumulative MEDCASE Est Accumulative Periodic Review:
Cost: -0- OMA Cost: -0- Sep 88

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. 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: No patients were entered in the study at MAMC in FY 88. Two patients were entered at MAMC in FY 87.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 87/40 Status: On-going

Title: GOG 97: Phase III Randomized Study of Cyclophosphamide (NSC #26271) and Cisplatin (NSC #119875) in Patients with Suboptimal Stage III and Stage IV Epithelial Ovarian Carcinoma Comparing Intensive and Non-intensive Schedules

Start Date: 16 Jan 87 Est Completion Date: Indefinite

Department: OB/GYN Facility: MAMC

Principal Investigator: LTC Gordon O. Downey, MC

Associate Investigators: COL William Benson, MC

COL Roger B. Lee, MC

Key Words: carcinoma, ovarian, epithelial, cyclophosphamide, cisplatin, intensive vs non-intensive

Accumulative MEDCASE Est Accumulative Periodic Review:
Cost: -0- OMA Cost: -0- Sep 88

Study Objective: To determine response rate, response duration and survival in suboptimal Stages III and IV ovarian carcinoma treated with Cytoxan and cisplatin administered by two different schedules, one intense and the other standard; to determine the relative toxicities of the two schedules; the therapeutic index of the two schedules; to evaluate if dose intensity is directly correlated with tumor response, response duration, and survival; to examine quality of life through the use of the FLIC questionnaire, and examine the ability of CA-125 levels to predict tumor response.

Technical Approach: Following optimal initial surgery, patients will be stratified according to whether or not measurable disease is present. They will then be randomized to cyclophosphamide, 1000 mg/m² and cisplatin 100 mg/m² every 21 days for four courses or to cyclophosphamide, 500 mg/m² and cisplatin 50 mg/m², every 21 days for eight courses. Patients with partial response, stable disease, or increasing disease will then go off study. Patients with no clinical evidence of disease will have second look surgery. Those with residual disease will go off study. Those with no evidence of disease will be followed every month for six months, then every three months for four years, and yearly thereafter. The FLIC quality of life evaluation will be completed by the patient when the consent form is signed, prior to each course of therapy, and six weeks after the last course of therapy or at the time of the second reassessment, whichever comes first. CA-125 levels will be recorded prior to admission, immediately after the initial course of therapy, after each course, on completion of therapy and at each follow-up for three years.

Adequate trial to evaluate response is defined as receiving one course of therapy and living three weeks for repeat lesion measurement. Adequate trial to evaluate toxicity is defined as receiving one course of therapy and receiving any follow-up information for observation of toxicity.

Progress: One patient was entered at MAMC in FY 87. No patients were entered in FY 88.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 87/91 Status: On-going

Title: GOG 99: A Phase III Randomized Study of Adjunctive Radiation Therapy in Intermediate Risk Endometrial Adenocarcinoma

Start Date: 19 Jun 87 Est Completion Date: Indefinite

Department: OB/GYN Facility: MAMC

Principal Investigator: LTC Gordon O. Downey, MC

Associate Investigators: COL William Benson, MC
COL Roger B. Lee, MC

Key Words: adenocarcinoma, endometrial, adjunctive radiation

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: -0- Sep 88

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: Two patients were entered at MAMC in FY 87. No new patients were entered at MAMC in FY 88.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 87/105 Status: On-going

Title: GOG 100: Monoclonal Antibody Against Free Beta HCG to Predict Development of Persistent Gestational Trophoblastic Disease (PGTD) in Patients with Hydatidiform Mole

Start Date: 21 Aug 87 Est Completion Date: Indefinite

Department: OB/GYN Facility: MAMC

Principal Investigator: LTC Gordon O. Downey, MC

Associate Investigators: COL William Benson, MC
COL Roger B. Lee, MC

Key Words: PGTD, hydatidiform mole, free beta HCG, monoclonal antibody

Accumulative MEDCASE Est Accumulative Periodic Review:
Cost: -0- OMA Cost: -0- Aug 88

Study Objective: To measure the serum concentration of free beta HCG and total beta HCG in patients with molar pregnancies in order to determine whether the ratio of free beta HCG to total beta HCG may be of value in predicting which molar pregnancies will undergo spontaneous remission and which will subsequently develop into persistent gestational trophoblastic disease.

Technical Approach: Patients with gross and microscopically verified diagnosis of hydatidiform mole, either classic (true) or partial (incomplete), obtained by evacuation of the uterus with uterine conservation will be eligible. Patients will have a pelvic ultrasound within two weeks of evacuation and the first serum will be drawn within 48 hours (prior to if at all possible) of evacuation for beta HCG and free beta HCG determinations. Following histologic confirmation of the hydatidiform mole (within one week of evacuation) the patient will be placed on study. Serum samples will be obtained weekly until a negative assay is attained or until a plateau or rise in titer is observed. All patients will remain on study for a minimum of twelve weeks after primary evacuation of the molar pregnancy. After spontaneous remission, patients will have beta HCG titers monthly for six months (free beta HCG assay is not necessary). After persistent disease, the patient will remain on study until remission. The principle parameters employed to investigate the prediction of which molar pregnancies will undergo spontaneous remission and which will subsequently develop into persistent trophoblastic disease are free beta HCG, total HCG concentration, ratio of free beta HCG to total HCG, and remission of disease as determined by weekly titers.

Progress: No patients have been entered at MAMC.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 87/106 Status: On-going

Title: GOG 101: A Phase II Evaluation of Pre-operative Chemo-radiation for Advanced Vulvar Cancer

Start Date: 21 Aug 87 Est Completion Date: Indefinite

Department: OB/GYN Facility: MAMC

Principal Investigator: LTC Gordon O. Downey, MC

Associate Investigators: COL William Benson, MC
COL Roger B. Lee, MC

Key Words: cancer, vulvar, chemoradiation, pre-operative

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: -0- Aug 88

Study Objective: To determine: the feasibility of using preoperative chemoradiotherapy to obviate the need for pelvic exenteration for patients with advanced vulvar cancer involving the proximal urethra, bladder, anal canal, or rectum; the feasibility of allowing a less extensive vulvar and vaginal resection in patients with a T3 primary tumor by using preoperative chemoradiotherapy; the survival rate for patients with Stage III or IV-A disease associated with this technique of therapy; the morbidity of a combined chemoradiosurgical approach to advanced vulvar cancer and to attempt to improve survival in patients with N3 groin nodes.

Technical Approach: Patients with primary, previously untreated, histologically confirmed invasive squamous or adenocarcinoma of the vulva clinically determined to be Stage III or IV will be treated with chemoradiation therapy according to the sub-stage.

Regimen I: Patients with T4 or unresectable T3 primary tumor and NO or N1 groin nodes will receive a split course of radiation therapy to the vulva by AP-PA fields. Twice daily fractions of 150 cGY will be given on days 1-4 and 1'-4'; once daily fractions of 180 cGY will be given on days 5, 8-12 and 5', 8'-12'. A 1 1/2 to 2 1/2 week split will be allowed between the two courses. Total midplane dose will be 4560 cGY.

During the twice daily radiation (days 1-4 and 1'-4'), patients will receive concurrent chemotherapy of 5-FU, 1000 mg/m² over 24 hours, allopurinol, 300 mg p.o., and cisplatin, 50 mg/m² IV, (days 1 and 1' only). Four to eight weeks following completion of chemoradiotherapy, patients considered to have resectable disease without the need for an exenterative procedure will undergo excision of the area previously replaced by primary tumor. An inguinal/femoral lymphadenectomy will also be performed.

Regimen II: The same as Regimen I with the addition of radiation to the inguinal/femoral and low pelvic lymph nodes. Total dose will be the same.

Progress: No patients have been entered at MAMC.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 88/60 Status: On-going

Title: GOG 102A: Master Protocol for Phase II Intraperitoneal Drug Studies in Treatment of Minimal Residual Ovarian Malignancies Documented at Second-Look Surgery

Start Date: 20 May 88 Est Completion Date: Indefinite

Department: OB/GYN Facility: MAMC

Principal Investigator: LTC Gordon O. Downey, MC

Associate Investigators: COL William Benson, MC
COL Roger B. Lee, MC

Key Words: chemotherapy, intraperitoneal, Cis-platin, 5-FU

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: -0- N/A

Study Objective: To determine the activity of various drugs or biologic response modifiers (BRM's) alone or in combination when used by the intraperitoneal route in patients who have persistent minimal residual disease epithelial ovarian malignancies after standard therapy and to evaluate further the toxicity (systemic and local) of drugs and BRM's or combinations used.

Technical Approach: Eligible patients: those with primary histologically documented epithelial carcinoma of the ovary; partial or incomplete responses to combination chemotherapy or minimal residual disease (≤ 1.0 cm maximum tumor diameter) at second-look surgery; a history of complete response followed by a recurrence with no nodule > 1 cm in diameter, GOG performance grade of 0, 1, or 2; at least three weeks from last treatment with chemotherapy or radiation, WBC ≥ 3000 , platelet count $> 100,000$, serum creatinine > 2.0 mg%, and bilirubin and SGOT \geq two times normal.

Ineligible patients: those with borderline tumors; leptomeningeal or cerebral metastases; current evidence of disease outside the peritoneal cavity; serious infection, septicemia, or pneumonia; major or extensive intra-abdominal adhesions or other factors - which would impair surgical placement of the intraperitoneal catheters; prior whole abdominal radiation therapy; or other specific criteria as detailed in the individual sections of the protocol.

Chemotherapy will start within 12 weeks of second-look surgery. The drug or drugs will be administered intraperitoneally through an implantable peritoneal dialysis catheter. The catheter will be placed at the time of second-look laparotomy or at a subsequent operation. Ovarian tumor tissue will be studied for sensitivity against various chemotherapeutic agents utilizing in vitro clonogenic assays. Patients who receive one or more courses of drug and live at least three weeks will be evaluable for response. Patients who receive one or more courses of drug are evaluable for adverse effects regardless of subsequent survival.

Progress: No patients entered in this master protocol at MAMC.

Detail Summary Sheet

Date: 30 Sep 88	Protocol No.: 88/61	Status: On-going
Title: GOG 102B: Intraperitoneal Administration of Cisplatin (NSC #119875) and 5-Fluorouracil (NSC #19893) in Residual Ovarian Carcinoma (Phase II)		
Start Date: 20 May 88	Est Completion Date: Indefinite	
Department: OB/GYN	Facility: MAMC	
Principal Investigator: LTC Gordon O. Downey, MC		
Associate Investigators: COL William Benson, MC COL Roger B. Lee, MC		
Key Words: chemotherapy, intraperitoneal, cisplatin, 5-FU		
Accumulative MEDCASE	Est Accumulative	Periodic Review:
Cost: -0-	OMA Cost: -0-	N/A

Study Objective: To determine the activity of the combination of cisplatin and 5-fluorouracil (5-FU) when used by the intraperitoneal route in patients who have persistent minimal residual disease epithelial ovarian malignancies after standard therapy and - to evaluate further the toxicity (systemic and local) of this combination of drugs.

Technical Approach: Eligible patients will be those who meet the criteria as set forth in the master protocol (102-A). Every - three weeks the subjects will receive a total dose of 100 mg of cisplatin and 2000 mg of 5-FU for a total of eight treatments (not per m²). Patients will be premedicated at the discretion of the physician and will be hydrated with D₅ - 1/2 NS with 20 mEq KCl at 500 cc/hr for two hours or at 250 cc/hr for four hours prior to treatment. Chemotherapy will continue through eight cycles unless disease progression is documented or unacceptable toxicity occurs. At the completion of eight cycles, patients will undergo surgical evaluation.

An adequate trial is defined as having received one cycle and the patient is alive three weeks thereafter. Patients receiving one dose of therapy and demonstrating progression in three weeks or less from study entry will be considered evaluable for response and toxicity.

Progress: No patients entered at MAMC.

Detail Summary Sheet

Date: 30 Sep 88	Protocol No.: 88/81	Status: On-going
Title: GOG 106: Evaluation of the Serum Marker, CA-125, in the Management of Carcinoma of the Endometrium		
Start Date: 16 Sep 88	Est Completion Date: Indefinite	
Department: OB/GYN	Facility: MAMC	
Principal Investigator: LTC Gordon O. Downey, MC		
Associate Investigators: None		
Key Words: serum marker, CA-125, carcinoma, endometrium		
Accumulative MEDCASE	Est Accumulative	Periodic Review:
Cost: -0-	OMA Cost: -0-	N/A

Study Objective: To evaluate the sensitivity of CA-125 for endometrial carcinoma; to correlate CA-125 levels with surgical-pathologic criteria (stage, grade, sites); to evaluate the efficacy of CA-125 in monitoring response to therapy (surgery, radiation, chemo, hormonal) in endometrial carcinoma; and to evaluate the efficacy of CA-125 in predicting survival and/or recurrence in endometrial cancer.

Technical Approach: Patients with endometrial carcinoma who are eligible for designated concurrently active GOG treatment protocols for endometrial cancer will be eligible. Specific protocols are selected to obtain a population of patients with tumor burdens and risks for recurrence appropriate to accomplish the study objectives. Serum for CA-125 will be collected according to a schema individually developed for each treatment protocol to be consistent with the regimen and anticipated findings. The collection schedules developed will follow the general schema below, modified as appropriate.

1. prior to surgery, if surgery is needed
2. prior to initiation of therapy
3. prior to each chemotherapy treatment
4. monthly during hormonal therapy
5. prior to initiation of postoperative radiation and at two week intervals during therapy
6. at the completion of therapy
7. at regular follow-up intervals, approximately every three months for the first year, every four months the second year, and every six months thereafter, on patients who are free of disease
8. in patients who progress, follow-up blood samples will not be required after progression is well documented and sera at those time points has been obtained

The duration of this study will be determined by the designated concurrently active GOG treatment protocols with five years of follow-up thereafter.

Progress: No patients entered at MAMC.

D E T A I L S H E E T S
F O R
P R O T O C O L S

NATIONAL CANCER INSTITUTE PROTOCOLS

Detail Summary Sheet

Date: 30 Sep 88	Protocol No.: 81/33	Status: On-going
Title: NCI #7602: All Stage I _C and II (A, B, C) and Selected Stage I _{Aii} and I _{Bii} Ovarian Cancer		
Start Date: 16 Jan 81	Est Completion Date: Jun 85	
Department: OB/GYN	Facility: MAMC	
Principal Investigator: LTC Gordon O. Downey, MC		
Associate Investigators: COL William Benson, MC COL Roger B. Lee, MC		
Key Words: cancer, ovarian, natural history		
Accumulative MEDCASE	Est Accumulative	Periodic Review:
Cost: -0-	OMA Cost: -0-	Sep 88

Study Objective: To define the natural history of patients treated with surgery plus either chemotherapy or radioisotope; to study the effect of various potential prognostic factors on the natural history of patients treated by each form of therapy; to determine the patterns of relapse for each form of therapy; to establish the value of various staging parameters on the stage of disease and its natural history.

Technical Approach: All patients with common epithelial ovarian cancer are eligible, if after definitive staging procedures the patient is zoned to be in Stages 2_A, 2_B, 2_C, 1_{Aii}, 1_{Bii}, or 1_{Ai} or 1_{Bi} with poorly differentiated tumors. Patients with prior therapy are ineligible. Patients will be stratified by histology, histological grade, and stage group for Regimen I. Regimen I will have staging laparotomy, total abdominal hysterectomy and bilateral salpingo-oophorectomy with no macroscopic residual disease found. Patients will then be randomized to receive melphalan or radioisotopes. Regimen II will be stratified by histology, histological grade, and extent of disease after surgery. Patients will have staging laparotomy, total abdominal hysterectomy, and bilateral salpingo-oophorectomy. If II_B, II_C, residual disease is found, will be randomized to pelvic radiotherapy plus melphalan alone. If after 18 months of therapy, the patient remains free of disease, chemotherapy will be discontinued. Second look will be done if the patient is free of disease after 18 months of chemotherapy.

Progress: No new entries in FY 88 at MAMC. The protocol was closed to new patient entry in September 1986. Two patients were entered in previous years and are still in follow-up.

D E T A I L S H E E T S
F O R
P R O T O C O L S

PUGET SOUND ONCOLOGY CONSORTIUM

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 87/71 Status: Completed

Title: PSOC 507: 5-FU, Cisplatin and VP-16 in the Treatment of Sub-optimal Stage III-IV Ovarian Cancer

Start Date: 17 Apr 87 Est Completion Date: Apr 90

Dept/Svc: Medicine/Hematology Facility: MAMC

Principal Investigator: LTC Howard Davidson, MC

Associate Investigators:

COL Irwin B. Dabe, MC

COL Roger B. Lee, MC

LTC Lauren K. Colman, MC

MAJ Thomas M. Baker, MC

MAJ David Dunning, MC

MAJ Ruben Sierra, MC

CPT David R. Bryson, MC

Key Words: cancer, ovarian, sub-optimal stages III-IV, 5-FU cisplatin, VP-16

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0-

OMA Cost: -0-

Sep 88

Study Objective: To determine the response rate and side effects in patients with ovarian cancer to a combination chemotherapy regimen of 5-FU, Cisplatin, and VP-16.

Technical Approach: Patients with a histologically confirmed diagnosis of ovarian cancer and disease that is either measurable by physical exam or CT scan or evaluable (CA-125 >100) will be eligible. Patients will be stratified based on measurable or evaluable disease and prior or no prior treatment.

5-FU by continuous infusion of 800 mg/m² per day will be given for four consecutive days (days 1-4).

Cisplatin, 100 mg/m² will be administered in 1000 ml D₅NS with 37.5 g mannitol IV over 1-2 hours on day 1. The starting dose for patients with serum creatinine 1.8-2.2 mg/dl will be 50 mg/m² on day 2. Those >65 or with extensive prior chemo or radiation therapy will start at 75 mg/m².

VP-16, 75 mg/m², will be administered in 250 ml D₅W over 1 hour on days 1-3. Patients >65 years or with extensive prior chemo or radiation therapy will start at 55 mg/m².

Drug alteration or removal from the study will be made for each course, based on the toxicity encountered.

Treatment will be repeated every 21 days. Patients with rapidly progressive disease after one cycle or progression after two cycles will be considered treatment failures and removed from the study.

An adequate trial is defined as at least one complete cycle of therapy showing some biologic activity (Grade 1 or greater toxicity) from drug(s) or two cycles with appropriate dose escalation if no toxicity is observed in the first cycle.

Progress: No patient entered on this study in FY 88. The one patient entered in FY 87 is deceased. The study is closed to patient entry.

Detail Summary Sheet

Date: 30 Sep 88	Protocol No.: 87/79	Status: On-going
Title: PSOC 615: Intraperitoneal Consolidation Therapy Following Second-Look Operation in Ovarian Cancer		
Start Date: 15 May 87	Est Completion Date: Indefinite	
Department: OB/GYN	Facility: MAMC	
Principal Investigator: LTC Gordon O. Downey, MC		
Associate Investigators: COL William Benson, MC COL Roger B. Lee, MC		
Key Words: cancer, ovarian, P-32, cis-platinum, 5-FU, surgery		
Accumulative MEDCASE	Est Accumulative	Periodic Review:
Cost: -0-	OMA Cost: -0-	Sep 88

Study Objective: To examine the effect of intraperitoneal therapy on disease free survival in patients with no disease or minimal residual disease following second-look surgery and to document the complication rate associated with the use of intraperitoneal chronic phosphate or chemotherapy in patients previously treated with systemic chemotherapy.

Technical Approach: Following standard induction chemotherapy, patients with Stage IIb, IIc, or III epithelial carcinoma of the ovary will have second-look laparotomy in the standard fashion. The second look procedure will include resection of any remaining female genital organs. If the patient has no evidence of gross persistent disease greater than 1.0 cm at the time of second look, a Tenckhoff catheter will be inserted.

If the pathologic findings from the second look procedure show no evidence of persistent tumor, the patient will receive 15 millicuries of intraperitoneal P-32 in 1000-1500 ml of normal saline, with appropriate rotation of position to assure proper distribution of the P-32.

If the patient has positive disease within the peritoneal cavity, she will receive chemotherapy with cisplatin (100 mg/m^2) and 5-FU (1000 mg/m^2) through the Tenckhoff catheter every three weeks for a maximum of four doses unless there are unacceptable side effects.

Progress: No patients entered at MAMC in FY 88. One patient was entered in FY 87 at MAMC and is in the follow-up phase of the study.

DETAIL SHEETS
FOR
PROTOCOLS

SOUTHWEST ONCOLOGY GROUP PROTOCOLS

Detail Summary Sheet

Date: 30 Sep 88	Protocol No.: 78/42	Status: On-going
Title: SWOG 7804: Adjuvant Chemotherapy with 5-Fluorouracil, Adriamycin, and Mitomycin-C (FAM) vs Surgery Alone for Patients with Locally Advanced Gastric Adenocarcinoma		
Start Date: 16 Jun 78	Est Completion Date: Jun 80	
Dept/Svc: Medicine/Oncology	Facility: MAMC	
Principal Investigator: LTC Howard Davidson, MC		
Associate Investigators: COL Friedrich Stutz, MC		
LTC H. Irving Pierce, MC		
Suresh B. Katakhar, M.D., DAC		
Key Words: adenocarcinoma, gastric, adjuvant FAM vs surgery		
Accumulative MEDCASE	Est Accumulative	Periodic Review:
Cost: -0-	OMA Cost: -0-	Sep 88

Study Objective: To determine the efficacy of adjuvant chemotherapy with FAM on the disease-free interval and survival of patients with TNM stage-groups I_B, I_C, II and III gastric adenocarcinoma compared to potentially curative surgery alone.

Technical Approach: Patient Eligibility: patients must have TNM stage-group I_B, I_C, II, or III gastric adenocarcinoma and no microscopic or gross residual postoperatively; no prior chemotherapy or radiotherapy; no medical contraindications to chemotherapy with FAM; serum bilirubin <2.0 mg/100 ml; SGOT and SGPT <3 times the upper limit of normal values; creatinine clearance >75 cc/min; BUN ≤25 mg%; serum creatinine ≤1.5 mg%; WBC >4,000; platelets >100,000. Treatment: After surgery, patients will be randomized to either: Treatment 1 (no further therapy) or Treatment 2: FAM - 5-FU, 600 mg/M² IV days 1 & 8, 29 & 36; adriamycin, 30 mg/M² IV days 1 & 29; mitomycin-C, 10 mg/M² IV day 1.

A total of 6 courses, one every 8 weeks, will be administered. After 12 months, the active therapy phase is completed. The patient will be followed at six month intervals for five years if remission continues.

Progress: No entries in FY 88 at MAMC. One entry in FY 84 at MAMC on the observation arm.

Group-wide: 180 patients were evaluated. Seven patients on the observation arm had major deviations because they received treatment and two patients on the FAM arm refused treatment; 29 patients were taken off FAM due to toxicity or refusal of further FAM treatment because of side effects. Of the 80 patients evaluated for toxicity, there was one fatal cardiac toxicity. The Grade 3 "Cardiac other" toxicities were pericardial effusion (1), elevated PIP/LVET (1), an ejection fraction of .47 (1 patient) and clinically mild coronary heart failure (1). Two patients experience Grade 4 thrombocytopenia while 33 patients had severe, but not worse, toxicities. The miscellaneous toxicities were moderate pulmonary fibrosis and moderate microangiopathic-hemolytic anemia.

Detail Summary Sheet

Date: 30 Sep 88	Protocol No.: 78/47	Status: On-going
Title: SWOG 7808, Combination Modality Treatment for Stages III and IV Hodgkin's Disease, MOPP #6		
Start Date: 11 Aug 78	Est Completion Date: Jan 88	
Dept/Svc: Medicine/Oncology	Facility: MAMC	
Principal Investigator: LTC Howard Davidson, MC		
Associate Investigators: COL Friedrich Stutz, MC		
LTC James E. Congdon, MC		
LTC H. Irving Pierce, MC		
Suresh B. Katakhar, M.D., DAC		
Key Words: Hodgkin's disease, stages III and IV, MOPP #6		
Accumulative MEDCASE	Est Accumulative	Periodic Review:
Cost: -0-	OMA Cost: -0-	Sep 88

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: No new patients entered at MAMC in FY 88. Seven patients were entered in previous years, who are still being followed. The study is closed to patient entry.

Detail Summary Sheet

Date: 30 Sep 88	Protocol No.: 79/96	Status: Ongoing
Title: SWOG 7827: Combined Modality Therapy for Breast Carcinoma, Phase III		
Start Date: 21 Sep 79	Est Completion Date: Sep 81	
Dept/Svc: Medicine/Oncology	Facility: MAMC	
Principal Investigator: LTC Howard Davidson, MC		
Associate Investigators: COL Irwin B. Dabe, MC LTC James E. Congdon, MC		
Key Words: carcinoma, breast, combined modality therapy		
Accumulative MEDCASE	Est Accumulative	Periodic Review:
Cost: -0-	OMA Cost: -0-	Sep 88

Study Objective: To compare the disease-free interval and recurrence rates in: (1) estrogen receptor positive (ER+) premenopausal patients with Stage II disease using combination chemotherapy alone vs combination chemotherapy and oophorectomy; (2) ER+ postmenopausal patients with Stage II disease using combination chemotherapy plus tamoxifen vs tamoxifen alone vs combination chemotherapy alone; (3) estrogen receptor negative (ER-) patients with Stage II disease using one vs two years of combination chemotherapy; to compare the effect of adjuvant therapy in Stage II breast cancer using partial mastectomy and radiation vs modified radical or radical mastectomy; to compare the effect of the various adjunctive therapy programs upon survival patterns; and to correlate the estrogen receptor status with disease-free interval and survival.

Technical Approach: Patients with a histologically proven diagnosis of breast cancer (Stage II or Stage III) with one or more pathologically involved axillary nodes will receive one of the following treatments: (CMFVP = cyclophosphamide, methotrexate, 5-FU, vincristine, and prednisone):

- (1) CMFVP for 1 yr - pre or postmenopausal ER- patients.
- (2) CMFVP for 2 yr - pre or postmenopausal ER- patients.
- (3) CMFVP for 1 yr - premenopausal ER+ patients.
- (4) Oophorectomy + CMFVP - premenopausal ER+ patients.
- (5) Tamoxifen alone for 1 yr - postmenopausal ER+ patients.
- (6) CMFVP for 1 yr - postmenopausal ER+ patients.
- (7) Tamoxifen + CMFVP for 1 yr - postmenopausal ER+ patients.

Patients undergoing segmental mastectomy (lumpectomy) will receive 6 wks of radiation therapy in addition to the treatment they are randomized to receive.

Progress: Three patients entered at MAMC in FY 88. Twenty-six patients were entered in previous years for a total of 29 entries.

The consent form was amended in FY 88 to include the proper description for radiation therapy side effects and to add the possibility of abnormal blood clotting related to tamoxifen.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 86/06 Status: Completed

Title: SWOG 8208: Trial Chlorozotocin and 5-FU in Metastatic Islet Cell Carcinoma, Phase II

Start Date: 15 Oct 85 Est Completion Date: Sep 87

Dept/Svc: Medicine/Oncology Facility: MAMC

Principal Investigator: MAJ Thomas M. Baker, MC

Associate Investigators:

COL Irwin B. Dabe, MC MAJ David Dunning, MC

LTC Howard Davidson, MC MAJ Michael D. Stone, MC

MAJ Lauren K. Colman, MC CPT David R. Bryson, MC

Key Words: carcinoma, islet cell, metastatic, chlorozotocin, 5-FU

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: -0- N/A

Study Objective: To study the response of functioning and non-functioning islet cell carcinoma to Chlorozotocin (CTZ) and 5-fluorouracil (5-FU) and to determine the toxicity of CTZ and 5-FU when given in combination.

Technical Approach: Patients with prior chemotherapy will be ineligible, but those with prior radiation therapy are eligible. Patients will receive CTZ and 5-FU at intervals of 6 weeks.

Induction therapy will consist of the following for a period of 4 courses: Good risk - CTZ, 175 mg/M² IV day 1 and 5-FU, 800 mg/M² IV, 24 hour infusion, days 1-4. Poor risk - CTZ, 75 mg/M² IV - day 1 and 5-FU, 600 mg/M² IV 24 hour infusion, days 1-4.

Maintenance therapy will consist of: Good risk - CTZ, 100 mg/M² IV day 1 and 5-FU, 600 mg/M² bolus IV days 1 and 8, every six weeks. Poor risk - CTZ, 50 mg/M² IV day 1 and 5-FU, 400 mg/M² bolus IV days 1 and 8, every 6 weeks.

An adequate trial is one course of therapy in the presence of progressive disease. Therapy with CTZ and 5-FU will be continued in the presence of stable disease or a response until increasing disease is documented. Therapy with CTZ and 5-FU will be continued or a maximum of 18 months in the presence of a complete response.

Progress: No entries at MAMC. The study is closed to patient entry.

Detail Summary Sheet

Date: 30 Sep 88	Protocol No.: 84/18	Status: On-going
Title: SWOG 8216/38: Comparison of BCG Immunotherapy and Adriamycin for Superficial Bladder Cancer, Phase III		
Start Date: 18 Nov 83	Est Completion Date: Sep 85	
Dept/Svc: Medicine/Oncology	Facility: MAMC	
Principal Investigator: LTC Howard Davidson, MC		
Associate Investigators: MAJ Thomas M. Baker, MC		
COL William D. Belville, MC	MAJ Alfred H. Chan, MC	
COL Irwin B. Dabe, MC	MAJ Timothy J. O'Rourke, MC	
COL Friedrich H. Stutz, MC	MAJ Michael D. Stone, MC	
Key Words: cancer, bladder, BCG immunotherapy, adriamycin		
Accumulative MEDCASE	Est Accumulative	Periodic Review:
Cost: -0-	OMA Cost: -0-	Sep 88

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: In FY 88, the protocol was no longer open to new patients, but only for patients crossing over from one arm to the other. Three patients were entered at MAMC during FY 84.

Group-wide, 230 patients were evaluated for toxicity. The severity of the toxicities is roughly equal for the two treatments. For patients in whom carcinoma *in situ* was present, there is strong evidence that BCG is superior to ADR with respect to response and progression-free survival. There is also strong evidence BCG is superior to ADR with respect to relapse-free survival for patients in whom carcinoma *in situ* was absent.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 84/19 Status: On-going

Title: SWOG 8221: Treatment of Advanced Bladder Cancer with Preoperative Irradiation and Radical Cystectomy Versus Radical Cystectomy Alone, Phase III

Start Date: 18 Nov 83 Est Completion Date: Oct 85

Dept/Svc: Medicine/Oncology Facility: MAMC

Principal Investigator: LTC Howard Davidson, MC

Associate Investigators:

COL William Belville, MC	MAJ Thomas M. Baker, MC
COL Irwin B. Dabe, MC	MAJ Alfred H. Chan, MC
COL Donald Kull, MC	MAJ Timothy J. O'Rourke, MC
COL Friedrich H. Stutz, MC	MAJ Michael D. Stone, MC

Key Words: cancer, bladder, irradiation, cystectomy

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: -0- Sep 88

Study Objective: To compare survival and pelvic recurrence rates in patients with transitional cell bladder cancer treated with radical surgery alone versus patients treated with preoperative irradiation with 2,000 rads followed by cystectomy.

Technical Approach: Patients eligible to be entered, must have histologically proven transitional cell carcinoma of the urinary bladder, and must have one of the following characteristics:

1. Evidence of muscle invasion.
2. Rapidly recurring superficial high-grade tumors and/or diffuse carcinoma in situ not amenable to trans-urethral resection and/or intravesical chemotherapy.

Patients will be randomized to receive either surgery with radical cystectomy or radiation therapy plus radical cystectomy. Patients will be seen in follow-up every three months following the cystectomy. Patients with either local or distant recurrence will be removed from the study. Five-year survival rates and two-year recurrence rates will be the major objectives of this study.

Progress: No entries in FY 88. One patient was entered during FY 84 and was randomized to cystectomy alone and tolerated the procedure well. Patient was lost to follow-up in FY 86.

This protocol was temporarily closed by SWOG because of slow accrual, the availability of a higher priority competing study (SWOG 8710), and sufficient data for answering the primary question may be available. An effort to complete data collection for this study is underway. The study will then be analyzed.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 83/61 Status: On-going

Title: SWOG 8229/30: Combined Modality Therapy for Multiple Myeloma, VMCP-VBAP for Remission Induction Therapy: VMCP + Levamisole vs Sequential Half-Body Radiotherapy + Vincristine-Prednisone for Patients Who Fail to Achieve Remission Status with Chemotherapy Alone, Phase III

Start Date: 15 Apr 83 Est Completion Date: Mar 85

Dept/Svc: Medicine/Oncology Facility: MAMC

Principal Investigator: LTC Howard Davidson, MC

Associate Investigators:

COL Irwin B. Dabe, MC MAJ Thomas M. Baker, MC

COL Friedrich H. Stutz, MC MAJ Alfred H. Chan, MC

LTC James E. Congdon, MC MAJ Timothy J. O'Rourke, MC

Key Words: multiple myeloma, chemotherapy, radiotherapy

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: -0- Sep 88

Study Objective: To compare the effectiveness of two intermittent pulse schedules of VMCP (vincristine, melphalan, cyclophosphamide, and prednisone) and VBAP (vincristine, BCNU, adriamycin and prednisone) for induction of remission in previously untreated patients with multiple myeloma. Results will also be compared with other combination regimens in previous SWOG studies. In patients proven to achieve remission, to compare the value of 12 months of chemo-immunotherapy maintenance (VMCP + levamisole) vs a consolidation program consisting of sequential half-body radiotherapy plus vincristine and prednisone followed by unmaintained remission. In patients who only achieve improvement, to determine whether sequential half-body radiotherapy plus vincristine and prednisone will increase the remission rate. To determine whether sequential half-body radiotherapy plus vincristine and prednisone can serve as an effective form of induction therapy for patients who fail to respond to chemotherapy or suffer early relapse.

Technical Approach: Patients with previously untreated multiple myeloma will be stratified as to tumor mass status and then randomized to induction therapy on VMCP alternated every three wks with VBAP for a minimum of 6 months to a maximum of one yr or to VMCP for 3 cycles followed by 3 cycles of VBAP, repeated every 3 wks, for a minimum of 6 months to a maximum of one year. Upon completion of induction, patients with documented 75% regression with chemotherapy alone will be randomized to receive VMCP + levamisole, repeated every three wks or to sequential half-body radiotherapy and concomitant vincristine and prednisone. Partial responders or nonresponders following induction therapy will receive sequential half-body radiotherapy, vincristine, and prednisone for six weeks.

Progress: No new patients entered at MAMC in FY 88; 5 patients were entered in previous years. The study is closed to patient registration, but the data collection has not been completed.

Detail Summary Sheet

<u>Date: 30 Sep 88</u>	<u>Protocol No.: 83/56</u>	<u>Status: On-going</u>
<u>Title: SWOG 8294: Evaluation of Adjuvant Therapy and Biological Parameters in Node Negative Operable Female Breast Cancer (ECOG, EST-1180), Intergroup Study</u>		
<u>Start Date: 18 May 83</u>	<u>Est Completion Date: Feb 85</u>	
<u>Dept/Svc: Medicine/Oncology</u>	<u>Facility: MAMC</u>	
<u>Principal Investigator: LTC Howard Davidson, MC</u>		
<u>Associate Investigators:</u>		
COL Irwin B. Dabe, MC	MAJ Thomas M. Baker, MC	
COL Friedrich H. Stutz, MC	MAJ Alfred H. Chan, MC	
LTC James E. Congdon, MC	MAJ Timothy J. O'Rourke, MC	
<u>Key Words: cancer, breast, operable, node negative, chemotherapy</u>		
<u>Accumulative MEDCASE</u>	<u>Est Accumulative</u>	<u>Periodic Review:</u>
<u>Cost: -0-</u>	<u>OMA Cost: -0-</u>	<u>Sep 88</u>

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 cms 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: No patients were entered in FY 88. Eleven patients have been entered at MAMC in previous years. The protocol was closed to patient entry in May 88, but data collection has not been completed.

Preliminary group-wide data indicate that this has proven to be a positive study; the CMFP arm has shown superior disease free survival.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 85/08 Status: On-going

Title: SWOG 8300: Treatment of Limited Non-Small Cell Lung Cancer: Radiation versus Radiation Plus Chemotherapy (FOMi/CAP), Phase III

Start Date: 16 Nov 84 Est Completion Date: Oct 86

Dept/Svc: Medicine/Hematology Facility: MAMC

Principal Investigator: LTC Howard Davidson, MC

Associate Investigators:

COL Irwin B. Dabe, MC

MAJ Timothy O'Rourke, MC

COL Friedrich H. Stutz, MC

MAJ Michael Stone, MC

MAJ Thomas M. Baker, MC

CPT David Bryson, MC

Key Words: Toxicity, patterns, prophylaxis

Accumulative MEDCASE

Est Accumulative

Periodic Review:

Cost: -0-

OMA Cost: -0-

Sep 88

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

Technical Approach: Patients will be randomized to four treatment arms: (1) radiation alone to the chest; (2) radiation therapy to the chest and prophylactic radiation to the brain; (3) chemotherapy with FOMi/CAP followed by radiation therapy to the chest (those patients showing some response will receive two additional cycles of chemotherapy after completion of radiation therapy); (4) same treatment as in #3 with the addition of concomitant prophylactic brain irradiation to 3750 rads.

Progress: One patient was entered in FY 88 for a total of three entries at MAMC. Two of the patients have expired of the disease and one patient is still in follow-up at MAMC. The study was closed to patient entry in March 1988.

Group-wide data show that none of the regimens has been highly toxic. A significant difference has been shown among the four arms and a difference in favor of the two arms not receiving prophylactic cranial irradiation. Final analysis of the data is in progress.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 87/87 Status: On-going

Title: SWOG 8309: Autologous Marrow Transplantation for the Treatment of Non-Hodgkin's Lymphoma, Phase II-Pilot

Start Date: 19 Jun 87 Est Completion Date: May 90

Dept/Svc: Medicine/Hematology Facility: MAMC

Principal Investigator: LTC Howard Davidson, MC

Associate Investigators:

COL Irwin B. Dabe, MC MAJ David Dunning, MC

LTC Lauren K. Colman, MC MAJ Ruben Sierra, MC

MAJ Thomas M. Baker, MC CPT David R. Bryson, MC

Key Words: non-Hodgkin's lymphoma, marrow transplantation, autologus

Accumulative MEDCASE	Est Accumulative	Periodic Review:
Cost: -0-	OMA Cost: -0-	Sep 88

Study Objective: To determine the therapeutic potential of high-dose cyclophosphamide and total body irradiation followed by autologous marrow transplantation in patients with an otherwise poor prognosis for cure in the following disease categories: lymphoblastic lymphoma, Burkitt's lymphoma, or diffuse undifferentiated lymphoma presenting with central nervous system (CNS) involvement or in relapse after initial therapy; diffuse histiocytic lymphoma presenting with CNS/and or marrow involvement or in relapse after initial therapy; and favorable histology lymphomas with recurrent disease after initial therapy.

Technical Approach: Patients as stated in the study objective will be eligible. Bone marrow will be collected and stored until the proper time for implantation as determined by disease category and availability of a transplant bed. Patients will receive a preparative regimen of chemo/radiation therapy consisting of cyclophosphamide (60 mg/kg/day) on two successive days, followed by a day of rest and then fractionated total body irradiation (200 rad/day) for six days, followed on the last day of irradiation by the infusion of the bone marrow. After transplant, patients will receive methotrexate, 12 mg/m² intrathecally, on days 32, 46, 60, 74, 88, and 102. Platelets will be transfused to prevent bleeding and an attempt will be made to keep the circulating platelet level >20,000/ μ l at all times. Infection prophylaxis will be determined by the physician and can include any reasonable form, including laminar air flow isolation, prophylactic granulocytes, or prophylactic antibiotics. Patients with stable disease or a partial or complete remission will be followed until definite evidence of disease progression, at which time they will be taken off study.

Progress: No patients have been entered at MAMC.

Detail Summary Sheet

Date: 30 Sep 88	Protocol No.: 84/72	Status: On-going
Title: SWOG 8312, Megestrol Acetate and Aminoglutethimide/ Hydrocortisone in Sequence or in Combination as Second- Line Endocrine Therapy of Estrogen Receptor Positive Metastatic Breast Cancer, Phase III		
Start Date: 17 Aug 84	Est Completion Date: Jun 86	
Dept/Svc: Medicine/Oncology	Facility: MAMC	
Principal Investigator: LTC Howard Davidson, MC		
Associate Investigators:	MAJ Thomas M. Baker, MC	
COL Irwin B. Dabe, MC	MAJ Timothy J. O'Rourke, MC	
COL Friedrich H. Stutz, MC	MAJ Michael D. Stone, MC	
Key Words: cancer, breast, ER+, metastatic, chemotherapy		
Accumulative MEDCASE	Est Accumulative	Periodic Review:
Cost: -0-	OMA Cost: -0-	Sep 88

Study Objective: To determine if combination hormonal therapy with aminoglutethimide and hydrocortisone + megestrol acetate, agents thought to have different mechanisms of action, offers an improved response rate with prolonged response duration and increased survival over the sequential use of each agent in ER+ patients who have progressed after responding to primary hormonal treatment with tamoxifen; to assess the relative toxicities of megestrol acetate and medical adrenalectomy, and the value of progesterone receptors in predicting subsequent responses to a variety of hormonal therapies.

Technical Approach: Patients who have had an adequate trial of tamoxifen and have achieved at least a partial response or maintained stable disease for six months with documented disease progression and clear-cut bone scan evidence of cortical bone metastases will be randomized to: Arm I - megestrol acetate, 40 mg p.o., q.i.d., given alone until there is documented evidence of disease progression; Arm II - aminoglutethimide, 250 mg p.o., b.i.d., for 2 weeks, then 250 mg p.o., q.i.d., plus hydrocortisone, 20 mg p.o. upon rising, 20 mg p.o. at 1700 hrs, and 60 mg p.o. at bedtime, daily for 2 weeks, then reduced to 10 mg given on the same schedule; or Arm III - megestrol acetate as in Arm I plus aminoglutethimide as in Arm II plus hydrocortisone as in Arm II. An adequate trial of each arm will consist of at least eight weeks of daily therapy in the absence of documented evidence of disease progression. Patients in Arms I and II with documented progressive disease after an adequate trial will be crossed over to the other treatment arm. The only exception to crossover will be patients who develop life threatening brain, liver, or pulmonary metastases who require systemic chemotherapy. Patients randomized to Arm III will go off study at the time of disease progression.

Progress: No patients were entered at MAMC in FY 88. One patient entered at MAMC in FY 86 has died of the disease.

Group-wide, toxicity has been moderate on megestrol acetate. Severe or life threatening toxicities were reported in 23% of the patients on the aminoglutethimide arms of the study.

Detail Summary Sheet

Date: 30 Sep 88	Protocol No.: 84/59	Status: On-going
Title: SWOG 8313: Multiple Drug Adjuvant Chemotherapy for Patients with ER Negative Stage II Carcinoma of Breast, Phase III		
Start Date: 18 May 84	Est Completion Date: May 86	
Dept/Svc: Medicine/Oncology	Facility: MAMC	
Principal Investigator: LTC Howard Davidson, MC		
Associate Investigators: MAJ Thomas Baker, MC		
COL Irwin B. Dabe, MC	MAJ Timothy J. O'Rourke, MC	
COL Friedrich H. Stutz, MC	MAJ Michael D. Stone, MC	
Key Words: carcinoma, breast, ER-, adjuvant, multiple drug		
Accumulative MEDCASE	Est Accumulative	Periodic Review:
Cost: -0-	OMA Cost: -0-	Sep 88

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 postmastectomy 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: No patients were entered in FY 88. Three have been entered in previous years. Two of these patients have died of progressive breast cancer.

Group-wide: The percentage of patients experiencing severe or worse toxicities have been similar for the two arms.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 88/02 Status: Completed

Title: SWOG 8321: Evaluation of Carboplatin versus Cisplatinum + Infusion 5-Fluorouracil + Allopurinol in the Treatment of Metastatic or Recurrent Squamous Carcinoma of the Uterine Cervix, Phase II

Start Date: 16 Oct 87 Est Completion Date: Sep 90

Dept/Svc: Medicine/Hematology Facility: MAMC

Principal Investigator: MAJ Thomas M. Baker, MC

Associate Investigators:

COL Irwin B. Dabe, MC

COL Roger B. Lee, MC

LTC Lauren K. Colman, MC

LTC Howard Davidson, MC

MAJ David M. Dunning, MC

MAJ Ruben D. Sierra, MC

CPT Denis P. Bouvier, MC

Key Words: carcinoma, uterine cervix, metastatic, recurrent, carboplatin, cisplatinum, 5-FU, allopurinol

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: -0- N/A

Study Objective: To carry out a randomized Phase II trial of two treatment regimens, carboplatin and cisplatinum plus continuous infusion 5-fluorouracil (5-FU) plus allopurinol in patients with metastatic or recurrent squamous carcinoma of the uterine cervix, who have failed treatment protocols of higher priority, and to determine and compare the nature and degrees of toxicity of each of these treatment regimens.

Technical Approach: Patients with histologically proven metastatic or recurrent squamous carcinoma of the uterine cervix and no prior systemic chemotherapy will be eligible. They will be randomized to one of the following treatment arms:

Arm I patients will receive carboplatin, 400 mg/M², IV day 1, every 28 days, as tolerated, until progression.

Arm II patients will receive cisplatinum, 100 mg/M², IV, day 1, plus 5-FU, 1 gm/M², IV continuous infusion days 1-4. Patients on this arm will be further randomized to receive allopurinol, 900 mg po daily, either on odd numbered or even numbered courses. Allopurinol will be started five days prior to the first day of chemotherapy and continued until the conclusion of the four-day 5-FU infusion. Courses will be repeated every 28 days (entry is closed to Arm II of this study due to sufficient accrual).

The initial dose of 5-FU will be reduced to 750 mg/M² for patients >65 years of age and those who have had prior radiotherapy exceeding 10% of the bone marrow space. An adequate trial will be the completion of two courses of therapy with no evidence of response or one course of therapy if followed by progression.

Progress: No patients were entered at MAMC. The protocol was closed to patient entry in May 1988.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 88/16 Status: On-going

Title: SWOG 8325: Combination Chemotherapy with O,P'-DDD and
Cis-Platinum in Metastatic Adrenal Carcinoma, Phase II

Start Date: 11 Dec 87 Est Completion Date: Oct 90

Dept/Svc: Medicine/Hematology Facility: MAMC

Principal Investigator: LTC Howard Davidson, MC

Associate Investigators:

COL Irwin B. Dabe, MC

COL Gary L. Treece, MC

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MAJ Ruben D. Sierra, MC

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Key Words: carcinoma, adrenal, metastatic, O,P'-DDD, cis-platinum

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0-

OMA Cost: \$365.00

N/A

Study Objective: To study the responsiveness of adrenocortical carcinoma to combination chemotherapy consisting of cis-platinum and Mitotane (O,P'-DDD); to study the prognostic features of patients with metastatic and/or resectable adrenal carcinoma receiving chemotherapy; and to document the toxicity of chemotherapy in this group of patients.

Technical Approach: Patients with metastatic or residual adrenocortical carcinoma in whom further surgical removal of disease is not possible will be eligible. Prior radiotherapy or chemotherapy other than cis-platinum is allowed. Patients will be divided into good and poor risk categories with poor risk defined as the presence of one or more of the following criteria: (1) age ≥ 65 years, (2) poor tolerance to prior chemotherapy, and (3) extensive prior radiation therapy to over 30% of the bone marrow bearing areas.

Regimens: Good risk patients: cis-platinum, 100 mg/M² IV, repeated every three weeks, if recovery from toxicities occurs) plus O,P'-DDD, 1000 mg PO, three times a day. Poor risk patients: cis-platinum, 75 mg/M² IV, repeated every three weeks (if recovery from toxicities occurs, plus O,P'-DDD, 1000 mg PO, four times a day, continuously. In the absence of a complete response, chemotherapy will be continued until progressive disease or unacceptable toxicity occurs. If complete response occurs, chemotherapy will be continued for 18 months or until progressive disease occurs.

An adequate trial will be defined as one course of chemotherapy with both drugs followed by three weeks of observation.

Progress: Two patients were entered at MAMC in FY 88. One patients developed persistent nausea, anorexia, and alteration of taste. As a result, cisplatin was stopped and the Mitotane dose was halved.

Group-wide: There have been no fatal toxicities in the 28 patients evaluated for toxicity.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 88/32 Status: On-going

Title: SWOG 8326/27: Evaluation of Combination Chemotherapy Using High Dose Ara-C in Adult Acute Leukemia and Chronic Granulocytic Leukemia in Blastic Crisis, Phase III

Start Date: 19 Feb 88 Est Completion Date: Feb 91

Dept/Svc: Medicine/Hematology Facility: MAMC

Principal Investigator: LTC Howard Davidson, MC

Associate Investigators:

COL Irwin B. Dabe, MC

MAJ David M. Dunning, MC

LTC Lauren K. Colman, MC

MAJ Ruben D. Sierra, MC

MAJ Thomas M. Baker, MC

CPT Denis P. Bouvier, MC

Key Words: leukemia, chemotherapy, induction, consolidation

Accumulative MEDCASE

Est Accumulative

Periodic Review:

Cost: -0-

OMA Cost: -0-

N/A

Study Objective: To compare the effectiveness of three different drug combinations, using high dose Ara-C or high dose Ara-C in combination with m-AMSA or mitoxantrone for remission induction in relapsed adult leukemias including both acute non-lymphocytic leukemia, chronic granulocytic during accelerated or blastic phase, and untreated secondary acute leukemias, and to monitor the side effects of the above combination chemotherapy schedules.

Technical Approach: Patients will be randomized to ARM I: Ara-C, 3 gm/M², IV infusion every 12 hrs for 6 days; ARM II: Ara-C as in Arm I plus m-AMSA, 100 mg/M²/day on days 7, 8, and 9; or ARM III: Ara-C as in Arm I plus mitoxantrone, 10 mg/M²/day on days 7, 8, and 9. Bone marrow aspiration and biopsy will be performed on day 14, following induction therapy, with subsequent aspirations and biopsies performed every 7-10 days to determine when marrow recovery has occurred to start the next course of therapy. Patients with complete response will receive consolidation therapy. Consolidation therapy will consist of Arm I: Ara-C, 3 gm/M², IV infusion every 12 hrs for 3 days; ARM II: Ara-C as in Arm I plus m-AMSA, 100 mg/M²/day on day 1; and ARM III: Ara-C as in Arm I plus mitoxantrone, 10 mg/M²/day on day 1. Three courses of consolidation therapy will be given, administered every 28 days. A bone marrow aspiration and biopsy will be done prior to each consolidation course. No further treatment will be given after consolidation therapy. Pyridoxine will be given for 10 days during induction and 5 days during consolidation for control of neurotoxicity. Patients whose bone marrow remains A₃ at day 14, those who relapse after the attainment of a complete or partial remission, and those who develop potentially fatal nonmyelosuppressive toxicity will be taken off study.

Progress: Two patients were entered at MAMC in FY 88 with no unexpected reactions.

Group-wide: Arm II was closed at the end of 1987 because of unacceptable toxicity and also the corresponding consolidation ARM V.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 87/88 Status: Completed

Title: SWOG 8406: Evaluation of Esorubicin (4'Deoxydoxorubicin NSC-267269) in Malignant Lymphoma, Phase II

Start Date: 19 Jun 87 Est Completion Date: Jun 1990

Dept/Svc: Medicine/Hematology Facility: MAMC

Principal Investigator: LTC Howard Davidson, MC

Associate Investigators:

COL Irwin B. Dabe, MC MAJ David Dunning, MC

LTC Lauren K. Colman, MC MAJ Ruben Sierra, MC

MAJ Thomas M. Baker, MC CPT David R. Bryson, MC

Key Words: lymphoma, malignant, esorubicin

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: -0- N/A

Study Objective: To determine the response rate and response duration of malignant lymphoma treated with Esorubicin (4'deoxydoxorubicin) and to define the qualitative and quantitative toxicities of Esorubicin administered in a Phase II study.

Technical Approach: Patients with a pathologically verified histologic diagnosis of malignant lymphoma refractory to prior chemo or radiation therapy will be eligible. Good risk patients with no prior nitrosourea or mitomycin-C therapy, good tolerance to other prior chemotherapy, and no prior extensive pelvic or mediastinal irradiation will receive Esorubicin at an initial dose of 30 mg/m², every 21 days. Poor risk patients with prior nitrosourea or mitomycin-C therapy, severe myelosuppression from other previous chemotherapy or prior extensive pelvic or mediastinal irradiation will receive Esorubicin, initial dose of 25 mg/m², every 21 days. Esorubicin will be given by rapid IV infusion. Dose adjustments will be made on the basis of myelosuppression. Esorubicin will be discontinued in the event of clinically detectable evidence of congestive heart failure or in the event of a decrease in the ejection fraction as measured by MUGA scan of $\geq 10\%$ or below the lower limits of normal. A MUGA scan will be done after a total cumulative dose of 150 mg/m². If the ejection fraction is above the lower limits of normal, a MUGA scan will be required at a cumulative dose of 250 mg/m² and then before every other cycle. An adequate trial is defined as at least two courses of Esorubicin.

Progress: No patients have been entered at MAMC. This study was closed to patient entry in March 1988.

Group-wide: Preliminary analysis indicates that Esorubicin is clearly active in non-Hodgkin's and Hodgkin's lymphoma. The early results in Hodgkin's disease are encouraging. Toxicity seems to be limited to myelosuppression (approximately 25% of patients with life-threatening complications). Side effects have not been severe. Although the response rate is substantially higher for good risk patients than for low risk patients, similar degrees of serious toxicity were seen in both groups.

Detail Summary Sheet

Date: 30 Sep 88	Protocol No.: 85/43	Status: On-going
Title: SWOG 8409: Evaluation of Fludarabine Phosphate in Refractory Multiple Myeloma, Phase II		
Start Date: 15 Mar 85	Estimated Completion Date: Feb 87	
Dept/Svc: Medicine/Oncology	Facility: MAMC	
Principal Investigator: LTC Howard Davidson, MC		
Associate Investigators:		
COL Irwin B. Dabe, MC	MAJ Timothy O'Rourke, MC	
COL F.H. Stutz, MC	MAJ Michael D. Stone, MC	
MAJ Thomas M. Baker, MC	CPT David Bryson, MC	
Key Words: fludarabine phosphate, refractory, multiple myeloma		
Accumulative MEDCASE	Est Accumulative	Periodic Review:
Cost: -0-	OMA Cost: -0-	Sep 88

Study Objective: To determine the response rate and response duration to fludarabine phosphate in patients with refractory multiple myeloma when treated on a daily times five, every three week schedule and to define the qualitative and quantitative toxicities of fludarabine phosphate administered in a Phase II setting.

Technical Approach: Patients with multiple myeloma who are no longer responsive to standard chemotherapy will be treated with fludarabine phosphate, 15 mg/M²,* IV daily times five, repeated every 3 weeks. Poor risk patients will receive 12 mg/M². Patients with progression of disease after two courses of therapy will be taken off study. Patients with a complete remission will receive three additional courses beyond the point of achieving a complete remission and followed with no further treatment. Patients who obtain a partial remission will be treated until disease progression or until a total of 12 courses has been given. Patients with stable disease after two courses can receive an additional three courses at the discretion of the treating physician.

Progress: No entries at MAMC.

Group-wide: This study was temporarily closed on 1 Apr 88 for evaluation of the patients on the highest dose group, 18 mg/M²; 17 patients were entered at that dose of whom two were ineligible due to large volume prior radiotherapy. One patient is still too early for toxicity evaluation and two are too early for response evaluation. There was one case of life-threatening thrombocytopenia at 12 mg/M², but none at the higher doses. There have been no responses at any of the doses, though one patient on 18 mg/M² did show clinical improvement. A final analysis will be done when the remaining two patient are off treatment.

Detail Summary Sheet

Date: 30 Sep 88	Protocol No.: 85/44	Status: Completed
Title: SWOG 8411: Evaluation of DTIC in Metastatic Carcinoid, Phase II		
Start Date: 15 Mar 85	Estimated Completion Date: Feb 87	
Dept/Svc: Medicine/Oncology	Facility: MAMC	
Principal Investigator: MAJ Thomas J. Baker, MC		
Associate Investigators:		
COL Irwin B. Dabe, MC	MAJ Timothy O'Rourke, MC	
COL F.H. Stutz, MC	MAJ Michael D. Stone, MC	
LTC Howard Davidson, MC	CPT David Bryson, MC	
Key Words: IV, every 28 days, non-amenable to surgery		
Accumulative MEDCASE	Est Accumulative	Periodic Review:
Cost: -0-	OMA Cost: -0-	N/A

Study Objective: To determine the effectiveness of dimethyl triazeno imidazole carboxamide (DTIC) in the treatment of metastatic carcinoid and to determine the survival of patients with metastatic carcinoid receiving DTIC.

Technical Approach: Patients with metastatic carcinoid not amenable to surgery who have had no prior chemotherapy or have had no radiotherapy within six weeks will be eligible. Patients will receive DTIC, 850 mg/M² IV, every 28 days. Poor risk will receive 650 mg/M². An adequate trial will be defined as two cycles of therapy with evidence of increasing disease. Patients with stable disease or in PR or CR will continue on therapy until increasing disease or relapse occurs.

Progress: No entries at MAMC.

The study was closed to patient entry 15 Feb 88 due to sufficient accrual of evaluable patients.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 86/53 Status: On-going

Title: SWOG 8412: Carboplatin/Cyclophosphamide versus
Cisplatin/Cyclophosphamide in Patients with Measurable
and Non-Measurable (Sub-Optimal) Disease Stages III and
IV Ovarian Cancer, Phase III

Start Date: 21 Mar 86 Est Completion Date: Mar 88

Dept/Svc: Medicine/Hematology Facility: MAMC

Principal Investigator: LTC Howard Davidson, MC

Associate Investigators:

COL Irwin B. Dabe, MC

MAJ David Dunning, MC

LTC Lauren K. Colman, MC

MAJ Michael D. Stone, MC

MAJ Thomas M. Baker, MC

CPT David R. Bryson, MC

Key Words: ovarian cancer, stages III and IV, chemotherapy

Accumulative MEDCASE

Est Accumulative

Periodic Review:

Cost: -0-

OMA Cost: -0-

Sep 88

Study Objective: To determine the efficacy (as determined by percentage of pathologically proven complete response) of carboplatin plus cyclophosphamide as compared to cisplatin plus cyclophosphamide in suboptimally resected Stages III and IV ovarian carcinoma; to evaluate the comparative toxicities of the two drug regimens; and to prospectively evaluate the power of human tumor clonogenic assay to predict objective clinical response to combination chemotherapy with cyclophosphamide plus one of two platinum compounds.

Technical Approach: Patients will be stratified by Stage II vs Stage IV disease, measurable versus nonmeasurable, suboptimal disease, and institution and randomized to one of the following:
Arm I: cisplatin, 100 mg/M² IV in 1/2-1 liter NS, 1 mg/min, following prehydration with at least 1 liter NS over 1 hr, Day 1, plus cytoxan, 600 mg/M² IV, Day 1; or Arm II: carboplatin, 300 mg/M², IV, Day 1 plus cytoxan, 600 mg/M² IV, Day 1. Courses will be repeated every four weeks as tolerated. All patients will receive at least two courses of therapy (an adequate trial) before being removed from the study due to progression. Six courses of therapy will constitute the remission induction phase of the protocol, after which they will be re-evaluated. All patients in clinical or complete remission will undergo second-look exploratory laparotomy to document complete remission. Patients found to be free of disease at time of surgical reevaluation will have all chemotherapy discontinued, but will remain on study and be followed. Patients with residual tumor detected at re-evaluation will go off study.

Progress: No patients entered in FY 88 at MAMC. One patient was entered in FY 86 with no unexpected reactions.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 88/15 Status: Completed

Title: SWOG 8415: Evaluation of Tamoxifen in Unresectable and Refractory Meningiomas, Phase II

Start Date: 11 Dec 87 Est Completion Date: Oct 90

Dept/Svc: Medicine/Hematology Facility: MAMC

Principal Investigator: LTC Howard Davidson, MC

Associate Investigators:

COL Irwin B. Dabe, MC

MAJ David M. Dunning, MC

COL Michael Potter, MC

MAJ Ruben D. Sierra, MC

LTC Lauren K. Colman, MC

CPT Denis P. Bouvier, MC

MAJ Thomas M. Baker, MC

Robert Goodkin, M.D.

Key Words: meningiomas, unresectable, refractory, tamoxifen

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0-

OMA Cost: \$185.00

N/A

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

Technical Approach: Patients must have a biopsy-proven diagnosis of benign meningiomas and measurable disease by CT scan or NMR scan.

All patients will receive tamoxifen, 40 mg/M² PO, given twice a day for four days, and thereafter 10 mg/M² PO twice a day. Tamoxifen will be continued until there is documented progression of disease or unacceptable toxicity.

Tamoxifen will not be discontinued due to thrombocytopenia as it is usually a transient phenomenon.

An adequate trial will consist of four to six months on tamoxifen therapy.

Progress: No patients entered at MAMC. The study was closed to patient entry on 1 Jul 88 as it had accrued enough evaluable patients for statistical analysis.

Detail Summary Sheet

Date: 30 Sep 88	Protocol No.: 86/07	Status: On-going
Title: SWOG 8417/19: Evaluation of Two Consolidation Regimens in the Treatment of Adult Acute Lymphoblastic Leukemia, Ph II		
Start Date: 18 Oct 85	Est Completion Date: Sep 87	
Dept/Svc: Medicine/Oncology	Facility: MAMC	
Principal Investigator: COL Irwin B. Dabe, MC		
Associate Investigators: MAJ Thomas M. Baker, MC		
LTC Lauren K. Colman, MC	MAJ Michael D. Stone, MC	
LTC Howard Davidson, MC	CPT David R. Bryson, MC	
Key Words: leukemia, lymphoblastic, consolidation regimens		
Accumulative MEDCASE	Est Accumulative	Periodic Review:
Cost: -0-	OMA Cost: -0-	Sep 88

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/L-asparaginase 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 to complete therapy). On or about day 30, patients will have an Ommaya reservoir placed in the frontotemporal area of the skull. After completion of therapy there will be a 14 day rest period. Following completion of induction therapy, patients will have a bone marrow performed. Those patients failing to achieve an A₁ marrow status will be taken 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 given IV daily x 5 on days 1, 36, and 71; Ara-C (IV) and 6-thioguanine (PO) every 12 hr for 12 doses on days 15, 50, and 85; methotrexate (IT, days 15, 17, 57, and 59); vincristine (IV) and prednisone (PO) days 50 and 57; L-asparaginase (IV beginning day 99 and given 3 times weekly for a total of 6 doses), and cyclophosphamide (IV day 110 following last dose of L-asparaginase. Arm II: daunomycin (IV days 1-3), Ara-C (IV continuous infusion days 1-5), 6-thioguanine (PO every 12 hr days 1-5), followed by a 21-28 day rest period. Methotrexate (IV every 10 days from 28-98, L-asparaginase (IM 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. This cycle will be repeated every 21 wk for 36 mth or until relapse. An adequate trial will be the completion of remission induction therapy.

Progress: No patients were entered at MAMC in FY 88. Four patients were entered in FY 86. Three have expired from their disease. No adverse effects reported.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 87/33 Status: On-going

Title: SWOG 8501 (INT-0051): Intraperitoneal Cis-Platinum/
Intravenous Cyclophosphamide vs Intravenous Cis-Platinum/
Intravenous Cyclophosphamide in Patients with Non-
Measurable (Optimal) Disease Stage III Ovarian Cancer,
Phase III Intergroup

Start Date: 16 Jan 87 Est Completion Date: Dec 89

Dept/Svc: Medicine/Hematology Facility: MAMC

Principal Investigator: LTC Howard Davidson, MC

Associate Investigators:

LTC Irwin B. Dabe, MC MAJ David Dunning, MC

MAJ Thomas M. Baker, MC MAJ Ruben Sierra, MC

MAJ Lauren K. Colman, MC CPT David R. Bryson, MC

Key Words: cancer, ovarian, cis-platinum, cyclophosphamide,
intraperitoneal, intravenous

Accumulative MEDCASE	Est Accumulative	Periodic Review:
Cost: -0-	OMA Cost: -0-	Sep 88

Study Objective: To perform a Phase III randomized trial of intermediate dose intraperitoneal cis-platinum plus intravenous cyclophosphamide versus intermediate dose intravenous cis-platinum and cyclophosphamide for optimal Stage III ovarian cancer; to evaluate the comparative toxicities of the two regimens; and to determine, in the setting of a prospective randomized trial, if the human tumor clonogenic assay with a wide range of drug concentration testing can accurately predict pathologic complete response to two-drug combination therapy in the setting of systemic and intraperitoneal drug administration.

Technical Approach: Only patients with epithelial neoplasms will be eligible. Patients will be stratified by residual disease (<0.5 cm vs residual disease >0.5 cm but ≤ 2 cm individual tumor masses) and performance (status 0-1 versus 2). They will be randomized to Arm I or Arm II. Arm I: IV cisplatin, 100 mg/m^2 plus IV cyclophosphamide, 600 mg/m^2 every 28 days for six courses. Arm II: IP cisplatin, 100 mg/m^2 plus IV cyclophosphamide, 600 mg/m^2 , every 28 days for six courses. Patients with partial or no response will go off study. Those with clinical complete response will undergo second look laparotomy. Those with residual tumor at second look laparotomy will be taken off study and entered in an appropriate protocol. Those with pathologic complete response will be followed by observation only until evidence of progression of disease appears. All patients who receive any amount of chemotherapy will be evaluable for toxicity. Patients who receive at least two courses of therapy will be evaluable for response and survival.

Progress: No entries at MAMC in FY 88. One patient was entered in FY 87.

Group-wide: Abdominal cramping and pain are reported predominantly for patients on the IP arm. More patients with leukopenia and granulocytopenia have been observed on the IV arm.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 87/107 Status: On-going

Title: SWOG 8507: Maintenance versus No Maintenance BCG Immunotherapy of Superficial Bladder Cancer, Phase III

Start Date: 21 Aug 87 Est Completion Date: Aug 90

Dept/Svc: Medicine/Hematology Facility: MAMC

Principal Investigator: LTC Howard Davidson, MC

Associate Investigators:

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COL Irwin B. Dabe, MC	MAJ David M. Dunning, MC
COL Victor Kiesling, MC	MAJ Ruben D. Sierra, MC
LTC Lauren K. Colman, MC	CPT Denis P. Bouvier, MC

Key Words: cancer, bladder, BCG immunotherapy

Accumulative MEDCASE	Est Accumulative	Periodic Review:
Cost: -0-	OMA Cost: -0-	Sep 88

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: Ten patients were entered at MAMC in FY 88 for a total of 11 subjects. One patient was taken off study due to severe urticarial reactions to BCG; another had severe hematuria attributed to BCG and was taken off study.

Group-wide: 223 patients had preliminary toxicity evaluations for induction therapy. Two patients were coded as having treatment related deaths. Of the remaining patients, 5% had degree 3 toxicities dominated by dysuria, frequency, and hematuria; 58% of those evaluated had no reported toxicities.

Detail Summary Sheet

Date: 30 Sep 88	Protocol No.: 86/27	Status: Completed
Title: SWOG 8509: Evaluation of Menogaril (NSC-269148) in Adenocarcinoma of the Prostate, Phase II		
Start Date: 17 Jan 86	Est Completion Date: Dec 87	
Dept/Svc: Medicine/Hematology	Facility: MAMC	
Principal Investigator: LTC Howard Davidson, MC		
Associate Investigators:		
COL Irwin B. Dabe, MC	MAJ David Dunning, MC	
LTC Lauren K. Colman, MC	MAJ Michael D. Stone, MC	
MAJ Thomas M. Baker, MC	CPT David R. Bryson, MC	
Key Words: adenocarcinoma, prostate, menogaril		
Accumulative MEDCASE	Est Accumulative	Periodic Review:
Cost: -0-	OMA Cost: -0-	Sep 88

Study Objective: To assess the antitumor activity of menogaril in patients with advanced adenocarcinoma of the prostate and to define the qualitative and quantitative toxicities of menogaril administered in a Phase II study.

Technical Approach: Patients may not have received prior chemotherapy. Prior hormonal or immunotherapy is permitted. All patients must have a pretreatment total absolute granulocyte count $\geq 2000/\mu\text{l}$ and platelet $\geq 100,000/\mu\text{l}$. Menogaril, 200 mg/M², will be administered IV in 500 ml of 5% Dextrose in water over one hour on day 1. Courses of menogaril will be repeated every 28 days. An adequate trial will consist of two doses requiring a total duration of observation of 8 weeks. Patients will be taken off study with 25% increase in the size of measured lesion, the appearance of new lesions, unacceptable stable disease after one or more courses of therapy, unacceptable toxicity, or patient's refusal to continue treatment.

Progress: One patient was entered at MAMC in FY 88. This patient had drug-induced phlebitis. The patient expired in Jun 88 from the disease.

Group-wide: The study was closed to entry on 1 Mar 88. Of the 76 patients evaluated for toxicity, there was one treatment-related death from leukopenia and sepsis. The Grade 4 toxicities were leukopenia (5), thrombocytopenia and leukopenia (1), granulocytopenia and thrombocytopenia (1), thrombocytopenia (1), and renal failure with elevated creatinine (1). The miscellaneous toxicities were Grade 2 extravasation and Grade 1 thrombophlebitis.

Detail Summary Sheet

Date: 30 Sep 88	Protocol No.: 87/09	Status: On-going
Title: SWOG 8510: Intra-Arterial Cis-Platinum and Radiation Therapy in Primary Brain Tumors; A Phase II Randomized Study Comparing Sequential and Combined Treatments		
Start Date: 17 Oct 86	Est Completion Date: Oct 89	
Dept/Svc: Medicine/Hematology	Facility: MAMC	
Principal Investigator: LTC Howard Davidson, MC		
Associate Investigators:		
COL Irwin B. Dabe, MC	MAJ David Dunning, MC	
MAJ Thomas M. Baker, MC	MAJ Ruben Sierra, MC	
MAJ Lauren K. Colman, MC	CPT David R. Bryson, MC	
Key Words: tumor, brain, cis-platinum, intra-arterial, radiation		
Accumulative MEDCASE	Est Accumulative	Periodic Review:
Cost: -0-	OMA Cost: -0-	Sep 88

Study Objective: To assess the toxicity and response to therapy of intra-arterial cis-platinum administered in two schedules, sequential and concomitant, with radiation therapy in the treatment of patients with primary malignant gliomas and to determine the time to progression and overall survival in these patients.

Technical Approach: Patients must have a histologically confirmed diagnosis of primary malignant glioma (Kernohan's astrocytoma, Grade 3 or 4, or WHO classification glioblastoma and glioblastoma multiforme with no prior chemo or radiotherapy. Chemotherapy will be initiated 7-28 days after surgery. Patients will be randomized to: Arm I - Sequential chemotherapy and radiation therapy. Cis-platinum, 150 mg (adjusted for size and creatinine clearance) intra-arterial administration, Day 1. Three weeks later, the dose will be repeated followed by a three week rest. The entire intra-cranial contents will then receive 4500 cGy at 180 cGy per fraction, five fractions per week, followed by a boost of 180 cGy daily fractions for six fractions (per week). Total dose will be 5580 cGy. Arm II: Concomitant chemotherapy and radiation therapy. Cis-platinum will be given on Day 1 as in Arm I. Radiation therapy will be initiated within 24-48 hours after the first dose of intra-arterial chemotherapy. The total dose is 5580 cGy as outlined for Arm I. The second dose of intra-arterial cisplatinum will be given three weeks following the first chemotherapy dose (concomitant with radiation therapy). Following the completion of two cycles of cis-platinum and the prescribed radiation therapy, patients will receive no further therapy and will be followed.

Progress: No patients have been entered at MAMC.

Group-wide: There were no fatal toxicities noted in 16 evaluated patients; nine patients had Grade 3 and one had Grade 4 toxicities. Other toxicities included mild pharyngitis, moderate malaise and personality changes, severe optic neuropathy, and life-threatening thrombosis.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 86/71 Status: On-going

Title: SWOG 8514: Randomized Comparison of Cis-Platin + 5 Fluorouracil versus CBDCA + 5-Fluorouracil versus Methotrexate in Advanced Squamous Cell Carcinoma of the Head and Neck, Phase III

Start Date: 20 Jun 86 Est Completion Date: Jun 1989

Dept/Svc: Medicine/Hematology Facility: MAMC

Principal Investigator: LTC Howard Davidson, MC

Associate Investigators:

COL Irwin B. Dabe, MC

MAJ David Dunning, MC

LTC Lauren K. Colman, MC

MAJ Michael D. Stone, MC

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Key Words: carcinoma, squamous cell, head & neck, chemotherapy

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: -0- Sep 88

Study Objective: To determine and compare the response rate (complete and partial), duration of response, and survival time of patients treated with two combination chemotherapy regimens: (Arm I) cis-platin + 5-FU, (Arm II) CBDCA - 5-FU, with Arm III (single agent methotrexate).

Technical Approach: Patients who have received prior chemotherapy for recurrent disease or who have concomitant second primary cancer are not eligible. Patients who have received induction chemotherapy only are eligible. Patients may have received prior radiotherapy (not within past 6 months).

Arm I: (every 21 days)
cis-platinum, 100 mg/M², IV, pre and post-treatment hydration
5-FU 1000 mg/M² continuous IV infusion x 4 days

Arm II: (every 21 days)
CBDCA 300 mg/M², IV, no hydration required
5-FU 1000 mg/M² continuous IV infusion x 4 days

Arm III: methotrexate 40 mg/M², IV bolus every week.

In patients achieving disease regression, the duration of disease regression will be measured from the start of chemotherapy to the first sign of progression or relapse. Patients will be removed from the study if there is progression of disease after at least four weeks of treatment, if there is unacceptable toxicity, or if the patient does not want to continue treatment.

Progress: One patient was entered at MAMC in FY 88 and one in FY 87, with no unusual toxicities reported. Both patients have died from their disease.

The consent form was revised at MAMC in FY 88 to add potential hepatotoxicity and interstitial interstitial pneumonitis to the risks associated with CBDCA.

Detail Summary Sheet

Date: 30 Sep 88	Protocol No.: 88/53	Status: On-going
Title: SWOG 8515: Evaluation of Menogaril (NSC 269148) in Non-Hodgkin's Lymphoma, Phase II		
Start Date: 20 May 88	Est Completion Date: Apr 91	
Dept/Svc: Medicine/Hematology	Facility: MAMC	
Principal Investigator: LTC Howard Davidson, MC		
Associate Investigators:		
COL Irwin B. Dabe, MC	MAJ David M. Dunning, MC	
LTC Lauren K. Colman, MC	MAJ Ruben D. Sierra, MC	
MAJ Thomas M. Baker, MC	CPT Denis P. Bouvier, MC	
Key Words: lymphoma, non-Hodgkin's, histology, menogaril		
Accumulative MEDCASE	Est Accumulative	Periodic Review:
Cost: -0-	OMA Cost: -0-	N/A

Study Objective: To estimate the response rate and response duration for favorable and unfavorable histology Non-Hodgkin's lymphoma (NHL) treated with menogaril and to define the qualitative and quantitative toxicities of menogaril administered in a Phase II study.

Technical Approach: Patients will be stratified at initial registration by histology (favorable versus unfavorable).

Menogaril 160 mg/M² will be administered over 1 hour in 500 ml of 50% dextrose in water once every 28 days, provided the patient has a total absolute granulocyte count $\geq 2000 \mu\text{l}$ and a platelet count $\geq 100,000/\mu\text{l}$.

Treatment with menogaril will continue until disease progression. Patients with documented progression of disease or unacceptable toxicity will be removed from the study. All patients will be followed until death.

Doses will be modified in subsequent courses based on nadir counts. Patients experiencing granulocytopenia $< 1000/\mu\text{l}$ or thrombocytopenia $< 50,000/\mu\text{l}$, following two dosage reductions will be taken off protocol treatment unless they have achieved a partial response, in which case one further dose reduction will be attempted.

Menogaril will be discontinued in the event of clinically detectable evidence of congestive heart failure. Patients who have received prior Adriamycin will undergo a follow-up MUGA scan prior to every third course of menogaril. The drug will be discontinued if the ejection fraction drops by more than 15% from baseline.

Progress: One patient was entered in this study in FY 88. Drug-induced phlebitis was reported in this patient.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 86/80 Status: On-going

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

Start Date: 15 Aug 86 Est Completion Date: Jul 89

Dept/Svc: Medicine/Hematology Facility: MAMC

Principal Investigator: LTC Howard Davidson, MC

Associate Investigators:

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MAJ Thomas M. Baker, MC

CPT David R. Bryson, MC

Key Words: non-Hodgkin's, CHOP, m-BACOD, ProMACE-CytaBOM, MACOP-B

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: -0- Sep 88

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 leukovorin 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 leukovorin 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 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: No entries at MAMC. Group-wide: Two fatal toxicities were reported on the m-BACOD arm. Life threatening toxicities were: CHOP - 16%, m-BACOD - 45%, ProMACE-CytaBOM - 24%, and MACOP-B - 26%.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 87/96 Status: On-going

Title: SWOG 8519: Phase II Evaluation of Methyl-Glyoxal
Bis-Guanylhydrazone (MGBG) in Patients with Advanced
Bladder Cancer

Start Date: 17 Jul 87 Est Completion Date: July 1990

Dept/Svc: Medicine/Hematology Facility: MAMC

Principal Investigator: LTC Howard Davidson, MC

Associate Investigators:

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MAJ Thomas M. Baker, MC CPT Denis Bouvier, MC

Key Words: cancer, bladder, advanced, MGBG

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: -0- Sep 88

Study Objective: To determine response rate and remission duration with weekly intravenous therapy using MGBG in patients with metastatic carcinoma who have failed on higher priority protocols and to define the qualitative and quantitative toxicity of this regimen.

Technical Approach: Patients must have a histologically confirmed diagnosis of metastatic transitional cell carcinoma of the urothelium. Only patients with one prior systemic chemotherapy or immunotherapy regimen are eligible. Patients with up to two prior intravesicle regimens are acceptable. Patients with prior radiotherapy are eligible if the disease has progressed and measurable sites of disease exist outside of the previous radiation field.

An initial dose of MGBG, 600 mg/m², will be given as an IV infusion over 90 minutes. Treatment will be repeated every week until disease progression.

Progress: No entries at MAMC.

Group-wide: Of 17 patients evaluated for toxicity, all but one had toxicity of some grade. One patient had Grade 4 anorexia and Grade 4 weight loss. The patient subsequently died. Other toxicities were: Grades 1, 2, and 3 fatigue or weakness (4); Grade 3 hypoglycemia (1); Grade 2 weight loss together with Grade 1 facial flushing (1), and uncontrolled shaking (1).

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 88/03 Status: On-going

Title: SWOG 8520: Cis-Diamminedichloroplatinum (II), Methotrexate and Bleomycin in the Treatment of Advanced Epidermoid Carcinoma of the Penis, Phase II

Start Date: 16 Oct 87 Est Completion Date: Sep 90

Dept/Svc: Medicine/Hematology Facility: MAMC

Principal Investigator: LTC Howard Davidson, MC

Associate Investigators:

COL Irwin B. Dabe, MC MAJ David M. Dunning, MC

LTC Lauren M. Colman, MC MAJ Ruben D. Sierra, MC

MAJ Thomas M. Baker, MC CPT Denis P. Bouvier, MC

Key Words: penis, carcinoma, epidermoid, cis-diamminedichloroplatinum (II), methotrexate, bleomycin

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: -0- Sep 88

Study Objective: To determine the response rate in patients with advanced epidermoid carcinoma of the penis treated with cis-platinum, methotrexate, and bleomycin and to evaluate the toxicity of this three-drug combination in this patient population.

Technical Approach: Cis-platinum, 75 mg/M², will be administered by IV infusion at 1 mg/min in normal saline (1 mg/cc) on day 1. Prior to, during, and after treatment with cis-platinum, the patient will be vigorously hydrated, intravenously and orally. Lasix, 40 mg IV bolus, will be given prior to cis-platinum. Patients will also receive methotrexate, 25 mg/M², IV bolus on days 1 and 8 and bleomycin, 10 units/M², IV bolus on days 1 and 8. Courses will be repeated every 21 days provided absolute granulocyte count is $\geq 1500/\mu\text{l}$ and platelet count is $\geq 100,000/\mu\text{l}$.

Dosage modifications will be made for all three drugs following the initial and all subsequent cycles of chemotherapy, using standard Southwest Oncology Group chemotherapy toxicity criteria for any of the following toxicities: hematopoietic, renal, pulmonary, and neurotoxicity. Chemotherapy with bleomycin will be discontinued when a total cumulative dose of 200 units/M² has been reached.

Two cycles of chemotherapy will constitute an adequate trial. Patients with stable or responding disease will continue on treatment beyond two cycles until evidence of disease progression or unacceptable toxicity. Patients who have achieved a complete remission will discontinue all chemotherapy after six cycles. Patients who achieve a complete response will receive 6 courses of treatment.

Progress: No patients entered at MAMC.

Group-wide: The toxicities experienced by the one patient evaluated were moderate mucositis and nausea/vomiting and mild neuropathy.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 87/44 Status: On-going

Title: SWOG 8530: Efficacy of Prednisone in Refractory and Relapsing Multiple Myeloma and Measurement of Glucocorticoid Receptors, Phase II

Start Date: 27 Feb 87 Est Completion Date: Feb 90

Dept/Svc: Medicine/Hematology Facility: MAMC

Principal Investigator: LTC Howard Davidson, MC

Associate Investigators:

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MAJ Ruben Sierra, MC

MAJ Thomas M. Baker, MC

CPT David R. Bryson, MC

Key Words: myeloma, refractory, glucocorticoid receptors

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: -0- Sep 88

Study Objective: To estimate the response rate and duration with high dose prednisone in patients with refractory myeloma and to measure glucocorticoid receptors in multiple myeloma.

Technical Approach: Patients must have had prior chemotherapy or hormonal therapy for myeloma with progression of disease. Fasting blood glucose must be ≤ 160 mg% and stool guaiac must be negative.

Therapy: Prednisone, 100 mg po, every other day for two weeks followed by 50 mg po every other day for ten weeks.

Each patient will receive three months of therapy to be considered evaluable for response. If no response is observed after three months of therapy, the patient will be removed from the study.

Therapy may be continued after three months of treatment with 50 mg PO every other day, providing the toxicities remain acceptable and the patient remains responsive to therapy.

Progress: One patient was entered at MAMC (FY 83). This patient had no response and is now deceased.

Group-wide: Eighty three (83) patients have been accrued. There have been two instances of life-threatening thrombocytopenia, though one may be unrelated to treatment. The life-threatening infection was septicemia. Other toxicities were hyperglycemia, muscle weakness, malaise, blurred vision, weakness, weight gain, muscle cramps, bruising, and insomnia.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 87/10 Status: On-going

Title: SWOG 8562: High-Dose Cisplatin in Hypertonic Saline for the Treatment of Metastatic or Recurrent Malignant Melanoma, Phase II-Pilot

Start Date: 17 Oct 86 Est Completion Date: Oct 89

Dept/Svc: Medicine/Hematology Facility: MAMC

Principal Investigator: LTC Howard Davidson, MC

Associate Investigators:

COL Irwin B. Dabe, MC

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MAJ Thomas M. Baker, MC

CPT David R. Bryson, MC

Key Words: melanoma, cisplatin, high-dose, hypertonic saline

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: -0- Sep 88

Study Objectives: To estimate the response rate and duration of response to high-dose cisplatin in hypertonic saline in recurrent and/or metastatic melanoma; to assess qualitative and quantitative toxicities of this treatment program; and to measure time to progression of disease and survival of patients.

Technical Approach: Subjects must have biopsy-proven metastatic melanoma with measurable disease and no prior chemotherapy. Patients will be hospitalized the night before the start of chemotherapy. An infusion of normal saline at 250 cc/hr with potassium chloride, 20 meq/L, will be started 12 hours prior to each dose of cisplatin and continued for 12 hours after each dose. The maintenance hydration will be continued until the patient is taking po fluids well. Furosemide, 20 mg, will be given intravenously 20-30 minutes before each dose of cisplatin. Daily serum electrolytes, calcium, magnesium, BUN, and creatinine will be checked.

Therapy: Cisplatin, 100 mg/m², days 1 and 8. The cisplatin will be reconstituted in 250 ml of 3% saline and infused over 30 mins. Courses will be repeated at 4-week intervals until dose-limiting toxicity is reached or there is progression of disease.

Progress: No entries at MAMC.

Group-wide: The study was temporarily closed to patient entry on 15 Dec 87 to evaluate response and toxicity. Only one patient has had Grade 4 toxicities (leukopenia, thrombocytopenia, and granulocytopenia). Other toxicities include edema, mood swings, dry hands, questionable gastric candida, upper back pain, abdominal pain, weakness, shaking, jerking, numbness in fingertips, and an undefined toxicity.

Two of the patients evaluated for response had partial responses lasting two months and three months. The overall response rate was therefore 15%. There have been 10 deaths and the median survival is 5.1 months.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 87/108 Status: Completed

Title: SWOG 8571: Induction Chemotherapy with High-Dose Cyclophosphamide for Poor Prognosis, Disseminated Breast Cancer with Radiation Therapy in Complete Responders, Phase II Pilot

Start Date: 21 Aug 87 Est Completion Date: Aug 90

Dept/Svc: Medicine/Hematology Facility: MAMC

Principal Investigator: LTC Howard Davidson, MC

Associate Investigators:

COL Irwin B. Dabe, MC

MAJ David M. Dunning, MC

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MAJ Ruben D. Sierra, MC

MAJ Thomas M. Baker, MC

CPT Denis P. Bouvier, MC

Key Words: breast cancer, cyclophosphamide, radiation therapy

Accumulative MEDCASE

Est Accumulative

Periodic Review:

Cost: -0-

OMA Cost: -0-

N/A

Study Objective: To define toxicity and response rate to a brief, intensive program of combination chemotherapy (FUVA); to determine feasibility, toxicity, and effect on response quality of high-dose cyclophosphamide consolidation; and to assess response duration and survival resulting from this approach.

Technical Approach: Patients with recurrent or disseminated breast cancer with estrogen receptor cytosol protein ≤ 4 or primary tumors which were estrogen receptor positive but failed to respond to hormonal therapy will be eligible. Patients will have had no previous chemotherapy for disseminated or recurrent breast cancer other than prior adjuvant chemotherapy provided the interval between its discontinuation and recurrence or dissemination is ≥ 6 months. Patients will have had no prior exposure to doxorubicin.

Induction chemotherapy (FUVA) will start on day 1 and will consist of 5-FU by continuous infusion, $1000 \text{ mg/m}^2/\text{day}$, for three days; Adriamycin, 25 mg/m^2 , by rapid infusion on days 1 and 3; and vinblastine, 2 mg/m^2 , by rapid IV infusion on days 1 and 3. Treatment will be repeated every 21 days for four cycles. Intensification chemotherapy will start four weeks after cycle #4 of FUVA and will consist of cyclophosphamide, 60 mg/kg/day , on two successive days. Patients with complete response will have whole brain irradiation plus four cycles of FUVA (as in induction) starting eight weeks after cyclophosphamide intensification therapy. Radiation treatment will be delivered through parallel opposed lateral ports to deliver a midplane, central axis dose of 3600 cGy at 180 cGy/day , 20 total fractions, five days per week. Partial responders will be given FUVA (as in induction) for four cycles starting eight weeks after intensification.

Progress: No entries at MAMC.

Toxicity has been severe, particularly on high dose Cytosan, as expected. Eleven of 13 patients evaluated group-wide have been reported to have grade four hematologic toxicity.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 86/72 Status: On-going
Title: SWOG 8573: Treatment of Limited Small Cell Lung Cancer with Concurrent Chemotherapy, Radiotherapy, and Intensification with High Dose Cyclophosphamide, Phase II Pilot
Start Date: 20 Jun 86 Est Completion Date: Jun 89
Dept/Svc: Medicine/Hematology Facility: MAMC
Principal Investigator: LTC Howard Davidson, MC
Associate Investigators: MAJ Thomas M. Baker, MC
COL Irwin B. Dabe, MC MAJ David Dunning, MC
LTC Lauren K. Colman, MC CPT David R. Bryson, MC
Key Words: cancer, small cell lung, chemotherapy, radiotherapy
Accumulative MEDCASE Est Accumulative Periodic Review:
Cost: -0- OMA Cost: -0- Mar 88

Study Objective: To estimate the response rate and survival of patients with limited small cell lung cancer when treated with concurrent chemo-radiotherapy followed by chemotherapy and late intensification with high dose cyclophosphamide and to assess the toxicity of this treatment program.

Technical Approach: Patients treated previously with chemo or radiotherapy are ineligible, except if radiation was given for localized, controlled skin cancer. Only patients with limited disease will be eligible. Patients will be taken off study for non-response or increasing disease after induction therapy, increasing disease at any time, inability to tolerate the lowest prescribed dose of chemotherapy, or to deliver the radiotherapy within the allowable time.

Induction (days 1-36): VP-16, 60 mg/M², days 1-5, 22-26
CDDP, 50 mg/M², days 1,8,22, & 29
Chest XRT - 4500 rads (180/day) days 1-36

Consolidation (days 64-92): VP-16, 60 mg/M², days 64-66 & 85-87
CDDP, 50 mg/M², days 64 & 85
Adriamycin, 50 mg/M², days 64 & 85
Vincristine, 2 mg, days 64,71,85, and 92

Late intensification (days 113-141): cyclophosphamide 50 mg/kg, days 113-115
Brain XRT, 3000 rads, 200/day, days 120-141

Progress: One patient entered at MAMC in FY 88 for a total of four entries at MAMC. The patient entered in FY 88 had treatment related neutropenic fever, sepsis, transient renal insufficiency, radiation pneumonitis, and peripheral neuropathy; however, the patient is currently doing well.

Group-wide: This study was closed to patient entry 1 May 88; 56 patients were entered; 30 patients have been evaluated for toxicity and 28 for response. Myelosuppression was the main life-threatening toxicity to date. There were two treatment-related deaths due to granulocytopenia (one also had infection). Preliminary response results are encouraging with 17 complete responses and 8 partial responses, but the regimen is highly toxic.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 85/73 Status: On-going

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 Study, EST 2382)

Start Date: 28 Jun 85 Est Completion Date: May 87

Dept/Svc: Medicine/Oncology Facility: MAMC

Principal Investigator: LTC Howard Davidson, MC

Associate Investigators:

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MAJ Thomas M. Baker, MC

COL William H. Gernon, MC

MAJ Timothy J. O'Rourke, MC

COL F.H. Stutz, MC

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LTC Don Blakeslee, MC

CPT David R. Bryson, MC

Key Words: carcinoma, head and neck, squamous, chemotherapy, radiotherapy, surgery

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0-

OMA Cost: -0-

Sep 88

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 cis-platinum 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: One patient was entered at MAMC in FY 88 for a total of three patients entered at MAMC. Lhermitte's syndrome occurred in one patient after radiation treatment.

Group-wide: Of 248 patients evaluable for toxicity, no treatment-related deaths were reported. As expected, the chemotherapy and radiation arm had a higher incidence of patients with Grade ≥ 3 toxicities; 40% vs 15% on the radiation only arm. Most Grade 4 toxicities were myelosuppression occurring during chemotherapy. A recurring problem with the study has been the high percentage of patients assigned to the chemotherapy arm who never start chemotherapy. As of this report, 25% of those reviewed with respect to the amount of drug administered were classified as having an unacceptable treatment variation. Either none of the assigned chemotherapy was given or less than one complete course was given for reasons other than toxicity, death, or progression.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 85/64 Status: On-going

Title: SWOG 8591: NCI Intergroup #0035, An Evaluation of Levamisole Alone or Levamisole plus 5-Fluorouracil as Surgical Adjuvant Treatment for Resectable Adenocarcinoma of the Colon, Phase III - Intergroup

Start Date: 24 May 85 Estimated Completion Date: Apr 87

Dept/Svc: Medicine/Oncology Facility: MAMC

Principal Investigator: LTC Howard Davidson, MC

Associate Investigators: MAJ Timothy O'Rourke, MC
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COL F.H. Stutz, MC MAJ Jens A. Strand, MC
MAJ Thomas Baker, MC CPT David Bryson, MC

Key Words: adenocarcinoma, colon, surgical, levamisole, 5-FU

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: -0- Sep 88

Study Objective: To assess the effectiveness of levamisole alone and levamisole plus 5-FU as surgical adjuvant regimens for resectable colon cancer; to compare each regimen to untreated controls to determine whether it yields improved survival and if it yields improved time to recurrence, with evaluations conducted independently in patients with Dukes stage B and Dukes stage C lesions.

Technical Approach: Patients with adenocarcinoma arising in the colon who have had a potentially curative section will be eligible. The patients with modified Dukes B₂ (serosal penetration) or B₃ (invasion of adjacent organs by direct extension) will be randomized to either follow-up without adjuvant therapy or adjuvant therapy with levamisole plus 5-FU. Patients with modified Dukes Stage C (involvement of regional lymph nodes) will be randomized to follow-up without adjuvant therapy, adjuvant therapy with levamisole alone, or adjuvant therapy with levamisole plus 5-FU.

Progress: No patients entered at MAMC in FY 88. Seven patients were entered in previous years with no unexpected toxicities.

Group-wide: This study was closed to patient entry 1 Oct 87. Of 755 patients evaluated for toxicity during the first course of chemotherapy, there were no Grade 4 or 5 toxicities on the Levamisole alone arm. One patient on levamisole + 5-FU died due to leukopenia and 16 Duke's B and Duke's C patients on this regimen had Grade 4 toxicities during the first cycle, including leukopenia (11), granulocytopenia (4); stomatitis (2); thrombocytopenia (1) or combinations thereof. One patient died of anemia after completion of the first cycle of Levamisole + 5-FU. For all cycles of treatment there were a large number of miscellaneous Grade 1, 2, or 3 toxicities. The investigators will continue to gather data on patient survival and disease free survival for analysis at a later date.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 87/117 Status: Completed

Title: SWOG 8592: Evaluation of Low-Dose Ara-C versus Supportive Therapy Alone in the Treatment of Myelodysplastic Syndromes, Phase III. (ECOG EST 4483)

Start Date: 18 Sep 87 Est Completion Date: Apr 90

Dept/Svc: Medicine/Hematology Facility: MAMC

Principal Investigator: LTC Howard Davidson, MC

Associate Investigators:

COL Irwin B. Dabe, MC

MAJ David Dunning, MC

LTC Lauren K. Colman, MC

MAJ Ruben Sierra, MC

MAJ Thomas M. Baker, MC

CPT David R. Bryson, MC

Key Words: myelodysplastic syndromes, Ara-C, supportive therapy

Accumulative MEDCASE

Est Accumulative

Periodic Review:

Cost: -0-

OMA Cost: -0-

N/A

Study Objective: To compare the benefit of low-dose Ara-C therapy vs supportive care in patients with myelodysplastic syndromes. The endpoints will be transfusion requirements, incidence of bleeding and infectious complications, time to progression and leukemia transformation, frequency of leukemic transformation and survival from diagnosis. Also, to determine the frequency, extent, and duration of response to this regimen in these patients, to assess the toxicity of a 21 day course of low-dose Ara-C, and to correlate patient response with presenting clinical characteristics and marrow cytogenetic and morphological features.

Technical Approach: Stratification factors include morphologic type and prior chemotherapy for other malignancies or autoimmune-disease excluding prednisone, oxymetholone, and pyridoxine. Patients will be randomized to one of two treatment arms: (I) Supportive therapy only with red cell and platelet transfusions for symptoms or to maintain hematocrits $\geq 25\%$. Patients with progressive disease of at least 2 months duration will be switched to the low-dose Ara-C arm of the study. (II) Therapy with low-dose ara-C, 10 mg/m², subcutaneously every 12 hours for 21 days after which patients with a complete or partial response will receive no further therapy and will be followed monthly with a blood count, and a bone marrow aspirate and a biopsy one month after therapy and then every three months during the first year. During subsequent years, a bone marrow aspirate and biopsy will be obtained every six months. Patients with stable disease or documented progression after eight weeks of therapy will be considered treatment failures and will be followed as in the supportive therapy arm. Patients who respond to Ara-C with at least a four-week documented complete or partial response and then relapse will be retreated with a 21 day course of Ara-C at the time of relapse or progression. Low dose Ara-C may be repeated as long as the patient continues to demonstrate a response.

Progress: No entries at MAMC. This study was closed to patient entry 1 Jul 88 because accrual goals had been achieved.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 87/22 Status: On-going

Title: SWOG 8594: A Phase III Trial of Cis-Platin Alone or in Combination with Doxorubicin, Vinblastine, and Methotrexate in Advanced Bladder Cancer (SEG/NCI #GU-305)

Start Date: 21 Nov 86 Est Completion Date: Oct 89

Dept/Svc: Medicine/Hematology Facility: MAMC

Principal Investigator: LTC Howard Davidson, MC

Associate Investigators:

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MAJ Thomas Baker, MC

MAJ Ruben Sierra, MC

MAJ Lauren K. Colman, MC

CPT David R. Bryson, MC

Key Words: cancer, bladder, cis-platin, doxorubicin, vinblastine, methotrexate, alone, combination

Accumulative MEDCASE Est Accumulative Periodic Review:
Cost: -0- OMA Cost: -0- Sep 88

Study Objective: To determine if cisplatin in combination with doxorubicin, vinblastine, and methotrexate is more effective than cisplatin alone in the treatment of patients with advanced bladder cancer in terms of objective response rate, response duration, and survival.

Technical Approach: Patients must have histologically proven advanced bladder carcinoma not curable by surgery or radiation therapy. Patients will be stratified by performance status and history of prior radiation therapy. Patients will be randomized to Regimen A or Regimen B with cycles repeated every 28 days.

Regimen A: cisplatin, 70, g/m² IV by 70 minute infusion

Regimen B: methotrexate, 30 mg/m² IV - days 1, 15, and 22
vinblastine, 3 mg/m² IV - days 2, 15, and 22
adriamycin, 30 mg/m² IV - day 2
cisplatin, 70 mg/m² IV by 70 minute infusion, day 2

Patients will be hydrated with D₅ 1/2 NS IV at 150 ml/hour for 10-15 hours before and 24 hours after cisplatin treatment. Patients will receive therapy until evidence of progression or for a maximum of six cycles. Patients with evidence of disease progression on cis-platin alone may be crossed over to Regimen B at the discretion of the investigator.

Progress: No entries at MAMC.

Group-wide: Accrual to this study has been rapid. There were 23 responses reported of the 104 analyzed cases (6 complete and 17 partial). One lethal toxicity (MVAC) and 16 life-threatening toxicities (MVAC/15 and cisplatin/1) were reported from the 104 cases analyzed with respect to induction therapy. Most of these reactions have been hematologic in nature. One patient treated with MVAC on crossover experienced life-threatening leukopenia and thrombocytopenia.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 87/72 Status: Completed

Title: SWOG 8597: Randomized Phase III Intergroup Study of
Supradiaphragmatic Irradiation in Stage II-A Seminoma
(RTOG 8514/Intergroup 0055)

Start Date: 17 Apr 87 Est Completion Date: Apr 1990

Dept/Svc: Medicine/Hematology Facility: MAMC

Principal Investigator: LTC Howard Davidson, MC

Associate Investigators:

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CPT David R. Bryson, MC

Key Words: seminoma, stage II-A, supradiaphragmatic irradiation

Accumulative MEDCASE

Est Accumulative

Periodic Review:

Cost: -0-

OMA Cost: -0-

N/A

Study Objective: To compare the recurrence rates and the patterns of recurrence in Stage II A seminomas treated with either infradiaphragmatic irradiation only or infradiaphragmatic irradiation followed by supradiaphragmatic irradiation; to assess the tolerance to salvage chemotherapy and the salvage rate in relapsing patients; and to examine the effect of the treatment on gonadal function.

Technical Approach: Patients with Stage II-A seminoma (<5 cm nodal disease), no prior malignancies other than skin cancer, no prior radio or chemotherapy, and no evidence of disease spread beyond the abdomen will be randomized to: (1) infradiaphragmatic irradiation with 25.00 Gy (1.50-1.80 Gy/day) plus boost to gross tumor to 35.00 Gy; or (2) infradiaphragmatic irradiation with 25.00 Gy (1.50-1.80 Gy/day) plus supradiaphragmatic irradiation with 25.00 Gy (1.75-2.00 Gy/day). Treatment will be given four or five times a week. Allowing for treatment related reactions or other factors that could interrupt treatment, the overall duration of the radiotherapy course should not exceed 45 days for patients on arm 1 and 65 days for patients on arm 2. Patients who relapse will receive chemotherapy determined by the physician for salvage. Data regarding tolerance to salvage chemotherapy will be collected systematically on all relapsing patients.

Progress: No entries at MAMC.

Group-wide: This study was closed to patient entry in Feb 88 due to sufficient patient accrual.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 87/109 Status: On-going

Title: SWOG 8598 (RTOG-85-01): Prospective Trial for Localized Cancer of the Esophagus: Comparing Radiation as a Single Modality to the Combination of Radiation Therapy and Chemotherapy, Phase III, Intergroup

Start Date: 21 Aug 87 Est Completion Date: Aug 90

Dept/Svc: Medicine/Hematology Facility: MAMC

Principal Investigator: COL Irwin B. Dabe, MC

Associate Investigators:

LTC Lauren K. Colman, MC MAJ David M. Dunning, MC

LTC Howard Davidson, MC MAJ Ruben D. Sierra, MC

MAJ Thomas M. Baker, MC CPT Denis P. Bouvier, MC

Key Words: cancer, esophagus, radiation therapy versus radiation plus chemotherapy

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: -0- Sep 88

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

Technical Approach: Patients with squamous cell or adenocarcinoma of the thoracic esophagus, no evidence of disseminated cancer, negative bone scan, and WBC $\geq 4,000/\text{mm}^3$, platelets $\geq 100,000/\text{mm}^3$, creatinine $\leq 1.5 \text{ mg\%}$, BUN $\leq 22 \text{ mg\%}$, and/or creatinine clearance $\geq 60 \text{ cc/min}$ are eligible. Patients will be stratified according to weight loss, lesion size, and histology. Patients will be randomized to arms I or II.

(I) Cisplatinum, 75 mg/m^2 the first day of weeks 1, 5, 8, and 11, 5-FU, 1000 mg/m^2 96-hr continuous fusion, weeks 1, 5, 8 and 11; Radiotherapy, 2 Gy five days a week for three weeks followed by boost of 2 Gy five days a week for five weeks

(II) 2 Gy for five days a week for five weeks followed by a boost of 2 Gy five days a week for 1.4 weeks

If 12 weeks after therapy is completed, tumor remains in the esophagus or there is recurrence, the patient has failed therapy but continues to be followed for survival. Patients with no evidence of tumor upon esophagoscopy and esophagram will be considered response to therapy and followed until relapse or death.

Progress: One patient was entered at MAMC in FY 88. No patients were entered in previous years.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 87/45 Status: On-going

Title: SWOG 8600: A Randomized Investigation of High-Dose Versus Standard Dose Cytosine Arabinoside with Daunorubicin in Patients with Acute Non-Lymphocytic Leukemia

Start Date: 27 Feb 87 Est Completion Date: Feb 90

Dept/Svc: Medicine/Hematology Facility: MAMC

Principal Investigator: COL Irwin B. Dabe, MC

Associate Investigators:

LTC Lauren K. Colman, MC MAJ David Dunning, MC

LTC Howard Davidson, MC MAJ Ruben Sierra, MC

MAJ Thomas M. Baker, MC CPT David R. Bryson, MC

Key Words: leukemia, non-lymphocytic, cytosine arabinoside, high dose vs standard dose with daunorubicin

Accumulative MEDCASE Est Accumulative Periodic Review:
Cost: -0- OMA Cost: -0- Sep 88

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: Four patients have been entered at MAMC, all in FY 88. One patient experience adult respiratory distress syndrome (ultimately fatal) on high dose Ara-C, which is a recorded effect of the drug.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 87/34 Status: On-going

Title: SWOG 8605: Cyclophosphamide, Ara-C Infusion and Vincristine for Relapsed or Refractory Extensive Small Cell Lung Cancer: A Phase II Study of the Southwest Oncology Group, Phase II Pilot

Start Date: 16 Jan 87 Est Completion Date: Dec 89

Dept/Svc: Medicine/Hematology Facility: MAMC

Principal Investigator: LTC Howard Davidson, MC

Associate Investigators:

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MAJ Thomas M. Baker, MC CPT David R. Bryson, MC

Key Words: small cell lung cancer, chemotherapy, CAV

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: -0- Sep 88

Study Objective: To determine the maximum tolerated dose of cyclophosphamide, cytosine arabinoside (Ara-C) and vincristine in a specific treatment schedule for patients with relapsing or refractory extensive small cell lung cancer, to obtain a qualitative and quantitative assessment of toxicity at each dose level, and to estimate the efficacy of the combination at the maximal tolerated dose.

Technical Approach: Induction chemotherapy: Cycle 1, cyclophosphamide, 500 mg/M, IV over 1 hour, Day 1, plus vincristine 2 mg, day 14, plus Ara-C, 250 mg/M/hour, every 12 hours continuous infusion (total dose 3 gm/M), beginning 3 hours after completion of cyclophosphamide infusion. If no Grade IV toxicity is observed, the dose of cyclophosphamide will be escalated for each course by 250 mg/M to a maximum of 1,000 mg/M. Therefore, cycle 2 (day 22) will have cyclophosphamide increased to 750 mg/M, Cycle 3 (day 43) increased to 1000 mg/M and other drugs the same as Cycle 1. Cycle 4 (day 64) will be the same as Cycle 3. Prophylactic whole brain irradiation (3,000 cGy in 15 fractions, 200 cGy/fraction) will be given three weeks after Cycle 4 (day 85) to patients with a complete or partial remission. Patients presenting with brain metastasis will receive therapeutic brain irradiation beginning on day 1 of protocol treatment. For patients presenting with a solitary brain metastasis the dose will be 30 Gy in 10 fractions for two weeks. Irradiation will be adjusted for bulky or poorly responsive lesions and will be boosted by 3 Gy for multiple metastases. Late intensification: Day 169 repeat one cycle of induction chemotherapy at the previous maximum acceptable dose and Day 337 the same as day 169.

Progress: One patient was entered at MAMC in FY 87. This patient suffered marked leukopenia but recovered.

Group-wide: 60 eligible patients have been entered. The major toxicity noted was myelosuppression; two patients with life-threatening myelosuppression died of sepsis. There were one partial response and 6 stable diseases in the first 47 patients evaluated.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 87/110 Status: On-going

Title: SWOG 8616: Intergroup Phase III Randomized Study of Doxorubicin and Decarbazine with or without Ifosfamide and Mesna in Advanced Soft Tissue and Bone Sarcoma (INT-#0072)

Start Date: 21 Aug 87 Est Completion Date: Aug 90

Dept/Svc: Medicine/Hematology Facility: MAMC

Principal Investigator: LTC Howard Davidson, MC

Associate Investigators:

COL Irwin B. Dabe, MC MAJ David M. Dunning, MC

LTC Lauren K. Colman, MC MAJ Ruben D. Sierra, MC

MAJ Thomas M. Baker, MC CPT Denis P. Bouvier, MC

Key Words: sarcoma, soft tissue, bone, doxorubicin, decarbazine
ifosfamide, mesna

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: -0- Sep 88

Study Objective: To determine if the addition of ifosfamide to doxorubicin and dacarbazine significantly changes the response rate, survival, and toxicity.

Technical Approach: Patients with histologically documented metastatic or unresectable sarcoma will be eligible. Metastatic osteogenic (OGS), Ewing's (ES), and rhabdomyosarcoma (RMS) will be assigned to Arm II (doxorubicin/DTIC plus ifosfamide) and will be analyzed separately. Kaposi's sarcoma and mesothelioma will be excluded. Patients will have had no prior chemotherapy for sarcomas and no prior doxorubicin. Patients will be stratified by stage, grade, and radiotherapy history. Patients will be randomized to receive either doxorubicin/DTIC or doxorubicin/DTIC + ifosfamide. Doxorubicin, 15 mg/m², will be given by continuous infusion, Days 1-4. DTIC, 250 mg/m², will be given by continuous infusion, Days 1-4. Ifosfamide, 2500 mg/m², will be given by continuous infusion, Days 1-3. Mesna will be infused continuously Days 1-4 to counteract urotoxicity. Each regimen will be given every 21 days. OGS, ES, and RMS patients will be removed from study and crossed to a standard regimen after four cycles if response is documented. Complete responders will continue combination chemotherapy for six cycles after documentation of response. Partial response and stable disease patients will continue treatment at the highest tolerable dose for a least two cycles after the maximum response or until disease progression. Patients with rapid disease progression will be removed from the study. Otherwise, there will be a minimum of two cycles of chemotherapy before removal.

Progress: One patient was entered at MAMC in FY 87 and one in FY 88. Both patients had marked leukopenia with some new openic fever.

Group-wide: Of the 144 patients randomized, four on ADR/DTIC/IFF had fatal infections and 16 others had life-threatening hematologic toxicity, compared to five patients with life-threatening toxicity on ADR/DTIC.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 87/60 Status: On-going

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

Start Date: 20 Mar 87 Est Completion Date: Sep 90

Dept/Svc: Medicine/Hematology Facility: MAMC

Principal Investigator: LTC Howard Davidson, MC

Associate Investigators:

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LTC Lauren K. Colman, MC

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MAJ Thomas M. Baker, MC

CPT David R. Bryson, MC

Key Words: myeloma, multiple, VMCP, VBAP, VAD, VMCP, VBAPP, alpha-2b interferon, dexamethasone

Accumulative MEDCASE Est Accumulative Periodic Review:
Cost: -0- OMA Cost: -0- N/A

Study Objective: To compare the effectiveness in achieving remission of the three regimens; to determine if interferon alpha-2b prolongs remission duration and survival compared to no maintenance therapy for patients achieving remission; to determine if dexamethasone plus interferon alpha-2b will enable patients achieving only improvement with the chemotherapy induction to achieve remission, and to study various proposed prognostic factors in multiple myeloma.

Technical Approach: Agents to be used are Adriamycin (A), BCNU (B), cyclophosphamide (C), dexamethasone (D), melphalan, (M), prednisone (P), vincristine (V), and alpha-2b interferon. Patients previously untreated with chemotherapy with the diagnosis of multiple myeloma are eligible. Patients will be stratified as to tumor mass, prior radiation therapy, and risk category. Patients will be randomized to induction therapy as follows: Arm I - VMCP alternating with VBAP every 3 weeks; Arm II - VAD every 3 weeks; or Arm III - VMCP alternating with VBAPP every 3 weeks. Induction therapy on arms I and III will be given for a minimum of 9 cycles and a maximum of 18 cycles. Arm II (VAD) induction therapy will be given for a minimum of 6 cycles and a maximum of 9 cycles. Arms I and III will require a minimum of 9 cycles of induction therapy and Arm II a minimum of 6 cycles before beginning maintenance therapy. Supplemental treatment with transfusions, dialysis, and radiation therapy may be given at the discretion of the investigator. At the appropriate time, responding patients will be randomized for maintenance to alpha-b interferon or no maintenance. Evaluable patients failing to achieve 75% tumor regression will be ineligible for remission maintenance but will be registered on a non-randomized trial of dexamethasone plus alpha 2b interferon to determine if this therapy can convert the patient to a remission status.

Progress: No entries at MAMC. The consent form was revised in Oct 87 to add a statement regarding treatment and response.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 88/33 Status: On-going

Title: SWOG 8626: Phase II Study of Recombinant DNA Gamma Interferon in Advanced Cancer of the Pancreas

Start Date: 19 Feb 88 Est Completion Date: Feb 91

Department/Service: Medicine/Oncology Facility: MAMC

Principal Investigator: LTC Howard Davidson, MC

Associate Investigators: MAJ David Dunning, MC

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MAJ Thomas M. Baker, MC Cpt Denis Bouvier, MC

Key Words: pancreas, cancer, recombinant DNA gamma interferon

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: -0- N/A

Study Objective: To determine the clinical response rate of recombinant gamma interferon in pancreatic adenocarcinoma and to define the qualitative and quantitative toxicities of recombinant gamma interferon in a Phase II study.

Technical Approach: Patients must have pathologically verified measurable pancreatic adenocarcinoma, performance status of 0-2, adequate bone marrow, renal, and cardiac function. Patients without tumor involvement of the liver must have normal hepatocellular enzymes. Patients with tumor involvement of the liver must have a bilirubin less than two times the upper limit of normal and have SGOT/SGPT and alkaline phosphatase values less than five times the upper limit of normal. Patients may have had prior surgery and prior radiotherapy provided that no more than 25% of the bone marrow was irradiated, two weeks have elapsed since the last dose, and they have recovered from any toxicity. They may be receiving concomitant radiotherapy, provided that <10% of the bone marrow is irradiated and the irradiated lesion is not being followed for determination of response. They may not have had prior cytotoxic chemotherapy or biologic response modifiers. Patients must not have had a previous malignancy other than nonmelanomatous skin cancer or *in situ* cervical cancer. Patients will be stratified by prior radiotherapy and institution. Patients will be randomized to receive r-GIFN on either Arm I (IV bolus x 5 every other x 2) or Arm II (continuous infusion x 5). Patients on Arm I will receive a starting dose of 4.0×10^6 IU/M². Patients on Arm II will receive a starting dose of 0.25×10^6 IU/M². Courses of r-GIFN will be repeated at four week intervals as tolerated. Treatment with r-GIFN will continue until progression of disease.

Progress: No entries at MAMC.

Group-wide: Because of limited drug supply, the bolus arm was permanently closed to accrual on 15 Jan 88. The continuous infusion arm is temporarily closed for evaluation of response and toxicity. Of the 6 patients evaluated for toxicity on the bolus arm, two experienced Grade 4 toxicities (fever and flu-like symptoms with Grade 3 hypotension).

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 87/47 Status: On-going

Title: SWOG 8691: A Randomized Comparison of Deoxycoformycin
versus Alpha-Interferon in Previously Untreated Patients
With Hairy Cell Leukemia

Start Date: 27 Feb 87 Est Completion Date: Feb 90

Dept/Svc: Medicine/Hematology Facility: MAMC

Principal Investigator: LTC Howard Davidson, MC

Associate Investigators:

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Key Words: hairy cell leukemia, deoxycoformycin, alpha interferon

Accumulative MEDCASE

Est Accumulativ

Periodic Review:

Cost: -0-

OMA Cost: -0-

Sep 88

Study Objective: To compare deoxycoformycin (dCF) versus alpha-interferon (α -IFN) in terms of relative efficacy in hairy cell leukemia patients who have not had splenectomy and to evaluate toxicities of both.

Technical Approach: Patients will be stratified according to performance status and randomized to either Arm I or Arm II.

Arm I: α -IFN, 3×10^6 IU, subcutaneously, 3 times a wk for 6 mon. Complete or partial remissions will continue treatment for 6 more months. Non-responders will be crossed over to dCF. After the second 6 months of treatment, if either a complete or partial remission has been achieved, therapy will be discontinued and the patient will be observed on a monthly basis to document duration of response.

Arm II: dCF, IV, every 2 weeks for 6 months. Performance status 0, 1, or 2 patients will receive 4 mg/m^2 and status 3 patients will receive 2 mg/m^2 and escalated as permitted by toxicity. If a complete remission is achieved, 2 additional doses of dCF will be given, treatment will then be stopped and the patient observed at monthly intervals. If a complete or partial remission has not been achieved by 6 months, the patient will be crossed over to the α -IFN arm. If a partial remission is achieved, dCF will be continued. When a complete remission is documented, 2 additional doses of dCF will be given and then treatment will be stopped. At 12 months on either therapy, if the best response is a partial remission, therapy will be discontinued and the patient will be observed at monthly intervals.

Progress: No entries at MAMC. Group-wide of 160 patients entered, no treatment-related deaths have occurred. Grade 4 granulocytopenia and leukopenia were reported in one patient on the alpha-interferon arm. Four patients on the deoxycoformycin arm had Grade 4 leukopenia and granulocytopenia and one of those also had a Grade 4 pseudomonas pneumonia.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 87/111 Status: On-going

Title: SWOG 8694: (CALGB-8582), A Comparison of Pentostatin (NSC-377523) in Splenectomized Patients with Active Hairy Cell Leukemia

Start Date: 21 Aug 87 Est Completion Date: Aug 90

Dept/Svc: Medicine/Hematology Facility: MAMC

Principal Investigator: COL Irwin B. Dabe, MC

Associate Investigators:

LTC Lauren K. Colman, MC

MAJ David M. Dunning, MC

LTC Howard Davidson, MC

MAJ Ruben D. Sierra, MC

MAJ Thomas M. Baker, MC

CPT Denis P. Bouvier, MC

Key Words: leukemia, hairy cell, splenectomized, pentostatin

Accumulative MEDCASE

Est Accumulative

Periodic Review:

Cost: -0-

OMA Cost: -0-

Sep 88

Study Objective: To compare the frequency of response between pentostatin and alpha-interferon treatment in patients with hairy cell leukemia who following splenectomy manifest active or progressive disease; to compare time to response, response duration, and toxicity of these two treatments; and to determine if pentostatin salvages nonresponders to alpha-interferon treatment and if alpha-interferon salvages nonresponders to pentostatin treatment.

Technical Approach: Patients will have had splenectomy at least 3 months prior to treatment, with no prior treatment with pentostatin or interferon. Patients will be randomized to either interferon or pentostatin.

Interferon (2×10^6 IU/m²) will be given by injection (s.c.) 3 times a week. Patients will be assessed at 3 months but will continue interferon treatment. Patients will be assessed at 6 months and those with complete (CR) or partial remission (PR) or stable disease (SD) will continue treatment for 6 months more. Non-responders will be crossed over to pentostatin. Patients will be assessed at 12 months, and those with CR, PR, or SD will be followed with no further therapy. If progression occurs, patients will be retreated with interferon.

Pentostatin, 4 mg/m², will be given IV on days 1 and 15, and repeated every 4 weeks with dosage adjusted for performance status. Patients will be assessed at 3 months and the pentostatin will be reduced to once every 4 weeks. At the 6 month assessment, patients with CR, PR, or SD will continue treatment for 6 more months. Nonresponders will be crossed over to interferon. Patients will be assessed at 12 months and those with CR, PR, or SD will be followed with no further therapy. If progression occurs, patients will be retreated with pentostatin.

Progress: No entries at MAMC.

Detail Summary Sheet

Date: 30 Sep 88	Protocol No.: 88/64	Status: On-going
Title: SWOG 8715: Evaluation of Amonafide in Advanced Sarcomas, Phase II		
Start Date: 15 Jul 88	Est Completion Date: Jun 91	
Dept/Svc: Medicine/Hematology	Facility: MAMC	
Principal Investigator: LTC Howard Davidson, MC		
Associate Investigators: COL Irwin B. Dabe, MC CPT Denis P. Bouvier, MC		
Key Words: sarcoma, advanced, amonafide, response, toxicity		
Accumulative MEDCASE	Est Accumulative	Periodic Review:
Cost: -0-	OMA Cost: -0-	N/A

Study Objective: To evaluate the response rate of advanced sarcomas treated with amonafide and to assess the qualitative and quantitative toxicities of amonafide in a Phase II study.

Technical Approach: To be eligible, patients must have pathologically verified soft tissue sarcoma, at least one bidimensionally measurable site of disease, Karnofsky performance status of 2 or better, and an expected survival of at least eight weeks. Patients must not be pregnant. Mesothelioma, Kaposi's sarcoma, and osteogenic sarcoma will be ineligible for the study.

Patients will be treated with amonafide, 300 mg/M² IV on days 1-5, repeated every 21 days. Disease assessment will be every six weeks. Patients who require radiation therapy for new lesions or lesions increasing in size will be considered to have progressive disease and taken off study. Patients will continue treatment with amonafide until tumor progression; unacceptable toxicity, a delay in treatment of ≥ 3 weeks, or at the patients request for withdrawal. All patients will be followed until death.

Progress: No patients entered at MAMC. This study was temporarily closed to patient entry 15 Sep 88 while it is determined if the number of patients entered is sufficient for analysis.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 88/75 Status: On-going

Title: SWOG 8723: Evaluation of Amonafide in Disseminated Malignant Melanoma, Phase II

Start Date: 16 Sep 88 Est Completion Date: Sep 91

Dept/Svc: Medicine/Hematology Facility: MAMC

Principal Investigator: LTC Howard Davidson, MC

Associate Investigators:

LTC Irwin B. Dabe, MC

MAJ Mark Kozakowski, MC

MAJ Everardo Cobos, MC

CPT Denis Bouvier, MC

Key Words: melanoma, amonafide, response rate, toxicities

Accumulative MEDCASE

Est Accumulative

Periodic Review

Cost: -0-

OMA Cost: -0-

N/A

Study Objective: To evaluate the response rate of disseminated malignant melanoma treated with amonafide and to assess the qualitative and quantitative toxicities of amonafide administered in a Phase II study.

Technical Approach: An initial dose of amonafide, 300 mg/M² will be administered by IV infusion over one hour daily for five days and repeated every 21 days. One course of therapy consists of one daily x 5 administration of amonafide. Measurable disease will be assessed at least every other course (every six weeks). Patients will continue treatment with amonafide until they fulfill one of the following criteria for removal from protocol treatment: (1) tumor progression at any time while on study; (2) unacceptable toxicity requiring discontinuation of chemotherapy; (3) patient withdrawal at his/her request; or (4) delay of treatment of \geq three weeks.

Patients with no prior chemotherapy, stage IV disease, and pathologically verified malignant melanoma are eligible. Patients must have objectively measurable disease and a life expectancy of at least eight weeks. Pregnant patients are not eligible.

Progress: No patients entered at MAMC.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 88/69 Status: On-going

Title: SWOG 8734: A Phase II Trial of Low Dose Pala and High Dose 5-FU as a Short Term Infusion in the Treatment of Adenocarcinoma of the Stomach

Start Date: 19 Aug 88 Est Completion Date: Jun 91

Dept/Svc: Medicine/Hematology Facility: MAMC

Principal Investigator: LTC Howard Davidson, MC

Associate Investigators:
COL Irwin B. Dabe, MC
CPT Denis P. Bouvier, MC

Key Words: adenocarcinoma, stomach, low dose Pala, high dose 5-FU

Accumulative MEDCASE Est Accumulative Periodic Review:
Cost: -0- OMA Cost: -0- N/A

Study Objective: To evaluate response to a new regimen consisting of a 24-hour infusion of high dose (effector) 5-FU and low dose (modulator) PALA in patients with advanced adenocarcinoma of the stomach and to assess the qualitative and quantitative toxicities of the regimen.

Technical Approach: To be eligible, patients must have a verified diagnosis of advanced gastric adenocarcinoma, objectively measurable lesions (excluding CNS metastases), central venous access placement prior to starting therapy, a Karnofsky performance status of 2 or better, and an expected survival of at least eight weeks. Patients must not have received prior chemotherapy and must not be pregnant.

An initial dose of PALA, 250 mg/M² IV over 15 minutes will be followed 24 hours later by 5-FU, 2,600 mg/M² IV over 24 hours. The PALA will remain constant. 5-FU will be monitored and dosage modifications made if necessary. One course of therapy will consist of eight weeks of administration of PALA and 5-FU, following which response evaluation will be made. Measurable disease will be assessed at least every course (every eight weeks). Patients failing to achieve a complete or partial remission or stable disease after one course of therapy will be removed from the study. Patients will remain on treatment until tumor progression at any time while on study; unacceptable toxicity requiring discontinuation of chemotherapy; or withdrawal by the patient at his/her request. All patients will be followed until death.

Progress: No entries at MAMC. The study is temporarily closed to patient entry as it has achieved accrual goals. If the number of patients entered is adequate for statistical analysis, the study will be permanently closed to entry.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 88/65 Status: On-going

Title: SWOG 8736: Treatment of Localized Non-Hodgkin's Lymphoma: Comparison of Chemotherapy (CHOP) to Chemotherapy Plus Radiation therapy

Start Date: 15 Jul 88 Est Completion Date: Jun 91

Dept/Svc: Medicine/Hematology Facility: MAMC

Principal Investigator: LTC Howard Davidson, MC

Associate Investigators: COL Irwin B. Dabe, MC

CPT Denis P. Bouvier, MC

Key Words: non-Hodgkin's lymphoma, chemotherapy (CHOP), radiation

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: -0- N/A

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 I_e vs nonbulky II or II_e); (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: No patients entered at MAMC.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 88/76 Status: On-going

Title: SWOG 8738: Treatment of Extensive Non-Small Cell Lung Cancer: Standard Dose Cisplatin versus High-Dose Cisplatin in Hypertonic Saline Alone versus High-Dose Cisplatin/Mitomycin-C, Phase III

Start Date: 16 Sep 88 Est Completion Date: Sep 91

Dept/Svc: Medicine/Hematology Facility: MAMC

Principal Investigator: LTC Howard Davidson, MC

Associate Investigators:

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MAJ Mark Kozakowski, MC CPT Denis Bouvier, MC

Key Words: non-small cell lung cancer, cisplatin, mitomycin-C

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: -0- N/A

Study Objective: To compare standard dose cisplatin chemotherapy to high dose cisplatin in hypertonic saline alone to high dose cisplatin/mitomycin-C in a randomized study with stratification for known important prognostic factors with regard to response rate, response duration, and survival duration; and to compare the relative toxicities of these three chemotherapy regimens in patients with extensive non-small cell lung cancer.

Technical Approach: Patients will be randomized to one of the following:

- ARM I: standard dose cisplatin (50 mg/M^2 , IV) every four weeks for a maximum of eight cycles,
ARM II: high dose cisplatin alone (100 mg/M^2 , IV) every four weeks for a maximum of four cycles,
ARM III: high dose cisplatin (100 mg/M^2 IV) plus mitomycin-C (8 mg/M^2 IV) given every four weeks for a maximum of four cycles.

All patients will have an initial assessment of response after two cycles and then reassessment after four cycles of therapy. Patients on Arm I who respond to treatment may receive continued therapy to a maximum of eight cycles. Upon progression of disease, unacceptable toxicity, or patient request, patients will be taken off treatment. All patients will be followed until death.

Progress: No patients entered at MAMC.

Detail Summary Sheet

Date: 30 Sep 88	Protocol No.: 88/21	Status: On-going
Title: SWOG 8792 (EST 2886, INT 0079): Phase III Study of Alfa-n1 (Wellferon) as Adjuvant Treatment for Resectable Renal Cell Carcinoma		
Start Date: 15 Jan 88	Est Completion Date: Dec 90	
Dept/Svc: Medicine/Hematology	Facility: MAMC	
Principal Investigator: LTC Howard Davidson, MC		
Associate Investigators:	MAJ David M. Dunning, MC	
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MAJ Thomas M. Baker, MC	CPT Denis P. Bouvier, MC	
Key Words: carcinoma, renal cell, Alfa-n1		
Accumulative MEDCASE	Est Accumulative	Periodic Review:
Cost: -0-	OMA Cost: -0-	N/A

Study Objective: To assess in a controlled fashion the effectiveness of interferon alfa-n1 (Wellferon) as a surgical adjuvant in patient with renal cell carcinoma. Study endpoints will be patient survival and time to recurrence.

Technical Approach: Patients must have histologic proof of adenocarcinoma of the kidney where complete resection of the primary tumor has been performed with neither gross nor microscopic evidence of residual disease. The primary kidney cancer must show at least one of the following indicators of poor prognosis: tumor invading perinephric fat; invasion of renal vein or vena cava; regional lymph node metastases, or contiguous metastases resected. Surgical margins must be free of tumor and radical nephrectomy and lymphadenectomy must have been performed. Performance status must be 0 or 1. Patients with prior or concurrent radiotherapy, chemotherapy, or systemic corticosteroid therapy are ineligible. Patients with impaired hepatic function, impaired renal function, angina or active congestive heart failure, and seizure disorders are ineligible. Pregnant or lactating females are also ineligible. Patients will be randomized to Wellferon or observation following definitive surgery. Adjuvant treatment will be started no later than 30 days after resection of the primary and regional nodes. Patients will be stratified according to modified TNM classification for renal tumors, tumor invasion of neighboring structures, and tumor involving regional nodes. Patients randomized to observation only will be followed at 3, 6, 9, 12, 18, and 24 months and every 6 months thereafter. Patients randomized to observation only will be taken off study on recurrence. Patients on the treatment arm will receive Wellferon as an intramuscular injection daily x 5 days every 3 weeks for a total of 12 cycles (nine months) unless recurrence of renal cell carcinoma is documented or intolerable toxicity occurs. These patients will be followed at 12, 18, and 24 months after entry and at six month intervals thereafter.

Progress: No patients entered at MAMC. Grade 3 toxicities reported in 14 patients group-wide were flu-like symptoms including fever and fatigue.

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 88/66 Status: On-going

Title: SWOG 8796: Combination Chemotherapy for Advanced Hodgkin's Disease, Phase III Intergroup (INT 0074)

Start Date: 15 Jul 88 Est Completion Date: Jun 91

Dept/Svc: Medicine/Hematology Facility: MAMC

Principal Investigator: LTC Howard Davidson, MC

Associate Investigators: COL Irwin B. Dabe, MC

CPT Denis P. Bouvier, MC

Key Words: Hodgkin's, advanced, chemotherapy, MOPP, ABVD

Accumulative MEDCASE Est Accumulative Periodic Review:

Cost: -0- OMA Cost: -0- N/A

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: No patients entered at MAMC.

D E T A I L S H E E T S
F O R
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UNIVERSITY OF WASHINGTON NEURO-ONCOLOGY GROUP

Detail Summary Sheet

Date: 30 Sep 88 Protocol No.: 88/73 Status: On-going

Title: UWNG 86/01: Phase II Study of External Brain Irradiation and Hydroxyurea Followed by Procarbazine, CCNU, and Vincristine (PCV) for the Treatment of Primary Malignant Brain Tumors

Start Date: 19 Aug 88 Est Completion Date: Jul 91

Dept/Svc: Medicine/Hematology Facility: MAMC

Principal Investigator: LTC Howard Davidson, MC

Associate Investigators:

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Robert Goodkin, M.D., DAC

Key Words: brain, tumors, external irradiation, chemotherapy

Accumulative MEDCASE

Est Accumulative

Periodic Review:

Cost: -0-

OMA Cost: -0-

N/A

Study Objective: To evaluate radiation therapy plus hydroxyurea and PCV in terms of the following parameters: time to progression from start of therapy, response rates and stabilization rate, survival time from start of therapy, and quality of life and activity level (Karnofsky).

Technical Approach: Patients must have a primary intracranial malignant glioma. Most patients will have had some form of surgery. Treatment will begin within four weeks of the operation at which the current diagnosis was made or within four weeks of clinical diagnosis. No prior cytotoxic, chemotherapy, or radiation therapy will be permitted. Local field radiotherapy will be employed. Only one course of radiotherapy will be given. The total dose to the tumor will be 5940 cGy delivered in a period of 6-7 weeks. The tumor volume will include at least the enhanced portion of tumor based on CT scan and a 2-3 cm margin of normal tissue in all directions. Every other day during radiotherapy, beginning day 1, patients will receive hydroxyurea, 300 mg/M² every six hours. PCV treatment will begin within two weeks after radiotherapy. CCNU, 110 mg/M² po, will be given on day one of each course. Procarbazine, 60 mg/M² po will be given days 8-14. Vincristine, 1.4 mg/M², will be given IV push on days 8 and 29. Patients will be evaluated and courses given at six to eight week intervals in the absence of irreversible toxicity. Patients will remain on protocol until the completion of two full courses of PCV. If tumor progression is documented after the second course, the patient will be taken off protocol. If tumor progression is not demonstrated, PCV will be given for one year or a minimum of 6 courses (not to exceed 8 courses) and then stopped. All patients will be followed for survival. Patients who expire from tumor progression early in the course of therapy will be evaluable for analysis if one full course of PCV was administered.

Progress: No patients entered at MAMC.

Detail Summary Sheet

<u>Date:</u> 30 Sep 89	<u>Protocol No.:</u> 88/17	<u>Status:</u> On-going
<u>Title:</u> UWNG 87-01: Phase II Study of TPDCFH for Recurrent Malignant Brain Tumor		
<u>Start Date:</u> 11 Dec 87	<u>Est Completion Date:</u> Sep 90	
<u>Dept/Svc:</u> Medicine/Oncology	<u>Facility:</u> MAMC	
<u>Principal Investigator:</u> LTC Howard Davidson		
<u>Associate Investigators:</u>		
COL Irwin B. Dabe, MC	MAJ Joseph H. Piatt, MC	
COL Michael Potter, MC	MAJ Ruben Sierra, MC	
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MAJ David Dunning, MC	Frederic Helmer, M.D.	
<u>Key Words:</u> brain tumor, 6-thioguanine, procarbazine, dibromodulcitol, CCNU, 5-FU, hydroxyurea		
<u>Accumulative MEDCASE</u>	<u>Est Accumulative</u>	<u>Periodic Review:</u>
<u>Cost:</u> -0-	<u>OMA Cost:</u> \$100.00	N/A

Study Objective: To determine whether TPDCFH chemotherapy for recurrent malignant glioma will increase time to progression and survival rate and to document the toxicity attendant on combined treatment.

Technical Approach: Patients will be eligible for this study if: they have received primary surgical treatment, radiotherapy, or adjuvant chemotherapy but no radiotherapy or chemotherapy for 8 weeks prior to entry; the tumor is a histopathologically confirmed recurrence of a malignant supratentorial glioma; liver and renal function are not seriously impaired (liver enzymes and serum creatinine within 1.5 x normal for laboratory; Karnofsky performance status is $\geq 60\%$. Recurrence will be signaled by worsening neurologic symptoms and signs measured by a neurologic examination. Enlargement of tumor volume as measured in contrast and noncontrast CT scans will serve as an additional criterion of recurrence. All patients will receive the following schedule:

0-66 hr: 6-thioguanine, 30 mg/sq.m., q. 6 hr p.o. x 12 doses
 60-78 hrs: procarbazine, 50 mg/sq.m., q. 6 hr p.o. x 4 doses
 60 hrs: dibromodulcitol, 400 mg/sq.m., p.o.

72 hrs: CCNU, 100 mg/sq.m., p.o.

Days 14 & 15: 5-FU, 1 g/sq.m. continuous infusion over 48 hrs

Day 15, hydroxyurea, 1 g/sq.m. p.o., 4 hours before the 5-FU infusion ends and at 4 hr intervals for a total of 3 doses

The cycle will be restarted on day 37-48, depending on toxicity level. In general WBC and platelets should increase to WBC $>4000/\text{cu mm}$ and platelets $>125,000/\text{cu mm}$. Exceptions may be made to restart when WBC $>3600/\text{cu mm}$ for patients with chronically depressed bone marrow.

Progress: No patients entered at MAMC.

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