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**DEPARTMENT
OF
CLINICAL INVESTIGATION**

**ANNUAL RESEARCH PROGRESS REPORT
Fiscal Year 1983**



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**MADIGAN ARMY MEDICAL CENTER
Tacoma, Washington 98431**

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ANNUAL PROGRESS REPORT

30 September 1983

DEPARTMENT OF CLINICAL INVESTIGATION

MADIGAN ARMY MEDICAL CENTER

TACOMA, WASHINGTON 98431

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REPORT DOCUMENTATION PAGE		READ INSTRUCTIONS BEFORE COMPLETING FORM
1. REPORT NUMBER MED-300	2. GOVT ACCESSION NO. AD-A141903	3. RECIPIENT'S CATALOG NUMBER
4. TITLE (and Subtitle) ANNUAL RESEARCH PROGRESS REPORT (U)		5. TYPE OF REPORT & PERIOD COVERED ANNUAL FY 83
		6. PERFORMING ORG. REPORT NUMBER
7. AUTHOR(s) BRUCE L. FARISS, M.D., COL, MC		8. CONTRACT OR GRANT NUMBER(s)
9. PERFORMING ORGANIZATION NAME AND ADDRESS Department of Clinical Investigation Madigan Army Medical Center Tacoma, Washington 98431		10. PROGRAM ELEMENT, PROJECT, TASK AREA & WORK UNIT NUMBERS
11. CONTROLLING OFFICE NAME AND ADDRESS Commander Madigan Army Medical Center Tacoma, Washington 98431		12. REPORT DATE 1 October 1983
		13. NUMBER OF PAGES 342
14. MONITORING AGENCY NAME & ADDRESS (if different from Controlling Office) U.S. Army Health Services Command Department of the Army ATTN: HSPA-I Fort Sam Houston, Texas 78234		15. SECURITY CLASS. (of this report) Unclassified
		15a. DECLASSIFICATION/DOWNGRADING SCHEDULE
16. DISTRIBUTION STATEMENT (of this Report) Approved for public release; distribution unlimited.		
17. DISTRIBUTION STATEMENT (of the abstract entered in Block 20, if different from Report) N/A		
18. SUPPLEMENTARY NOTES The findings in this report are not to be construed as an official Department of the Army position unless so designated by other authorized documents.		
19. KEY WORDS (Continue on reverse side if necessary and identify by block number) Unit summary; research protocols (objective, method, progress, status); publications; presentations.		
20. ABSTRACT (Continue on reverse side if necessary and identify by block number) Subject report identifies those individuals who are conducting investigative protocols at Madigan Army Medical Center. An abstract of each protocol giving abbreviated technical objectives, methods, and progress is presented.		

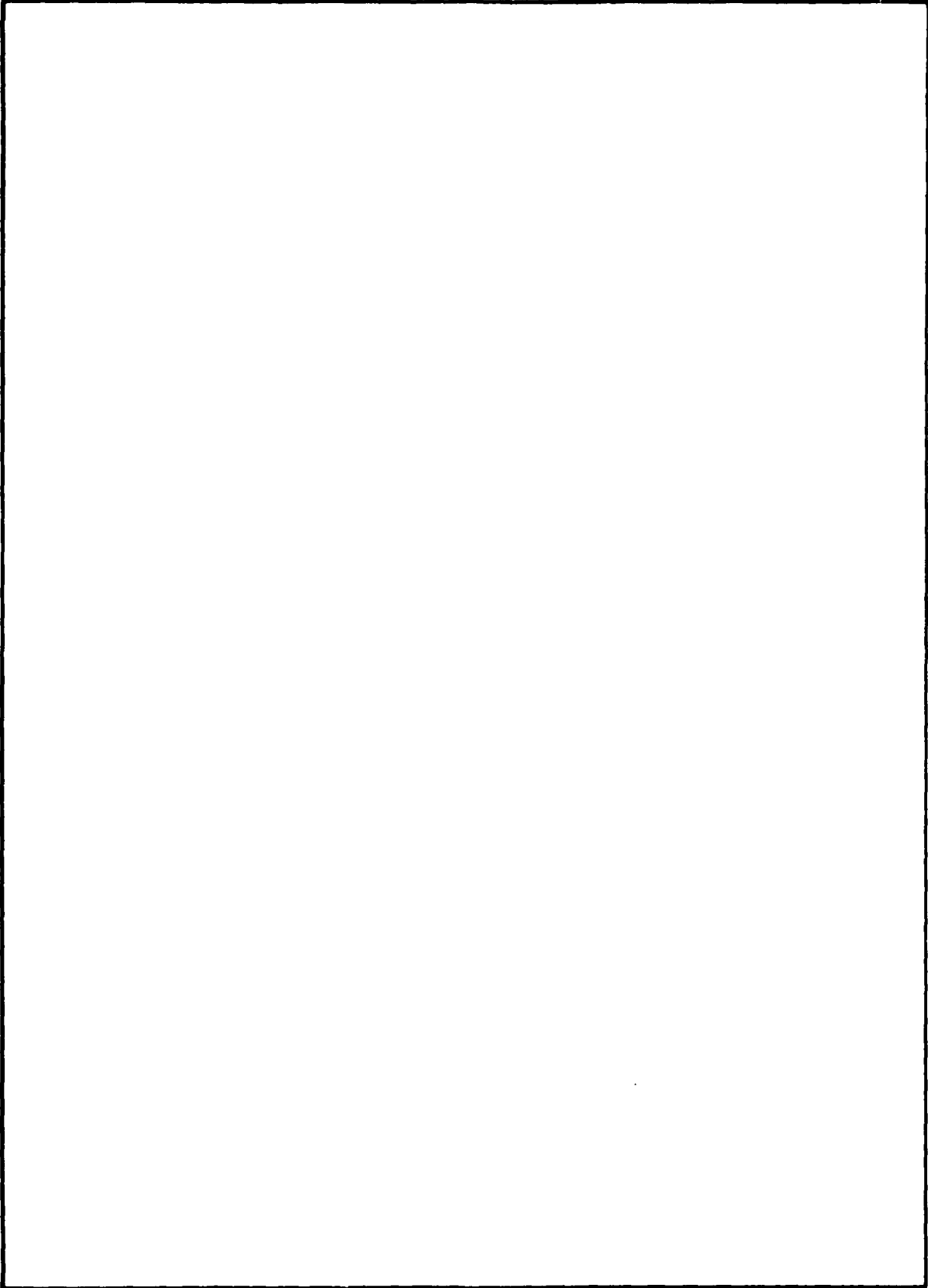
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ANNUAL RESEARCH PROGRESS REPORT

FISCAL YEAR 1983

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

In conducting the research described in this report, the investigators adhered to the "Guide for Laboratory Animal Facilities and Care" as promulgated by the Committee on the Guide for Laboratory Animal Resources, National Academy of Sciences-National Research Council, and the Guiding Principles in the Care and Use of Animals (Appendix I) approved by the Council of the American Physiological Society. The investigators follow the recommendations from the Declaration of Helsinki (Appendix II) in the performance of investigations involving human subjects.

ACKNOWLEDGEMENTS

I would like to take this opportunity to thank those investigators who replied to our requests promptly and, even though it is tempting, I will not castigate those investigators who were slow and at times delinquent in responding to our requests. I thank Nancy Whitten for the effort which is obvious in the compilation of this publication which is ever-increasing in size and Genie Hough for clerical assistance.



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FORWARD

The Department of Clinical Investigation was initiated in 1966 at Madigan Army Medical Center then known as Madigan General Hospital under the auspices of the Research and Development Command. At its inception, it was then known as R&D which has continued to be the name used by many of the people who use our services and facilities. Additional name changes were Medical Research Service, Clinical Investigative Service and finally with arrival at fruition the name of Department of Clinical Investigation. The Department of Clinical Investigation has had an increase from 1966 of five approved protocols to its current work load of 245 protocols. There has been an associated increase in the amount of administrative responsibilities, review activities and associated committee meetings to approve, review, and renew research endeavors. This brings to mind a story, "How It happened," by Isaac Asimov.¹

"In the beginning," he said, "exactly fifteen point two billion years ago, there was a big bang and the Universe--." "But are you going to tell the story of the Creation over a period of fifteen billion years?" "I have to," said my brother.... By now I had put down my stylus. "Do you know the price of papyrus?" (.... the inspiration didn't include such sordid matters as the price of papyrus). I said, "Suppose you describe one million years of events to each roll of papyrus. That means you'll have to fill fifteen thousand rolls. You'll have to talk long enough to fill them and you know that you begin to stammer after a while. I'll have to write enough to fill them and my fingers will fall off. And even if we can afford all that papyrus and you have the voice and I have the strength, who's going to copy it? We've got to have a guarantee of a hundred copies before we can publish.... My brother thought a while. He said, "You think I ought to cut it down?".... He said horrified, "You can't squeeze Creation into six days." I said, "This is all the papyrus I have. What do you think?...."

At times it is regrettable that there is no limitation to the amount of paper present to be used to pour out all the expected and required reporting that is necessary to support research endeavors.

One would wonder how an Institutional Review Board would have reviewed a protocol presented by Dr. Louis Pasteur who wished to inoculate a eight-year old boy who had just been bitten by a rabid dog with material that he had recently developed in his

laboratory.² Consider what would happen with a proposal of Dr. Walter Reed proposing that the members of his investigative group would attempt to infect themselves with yellow fever by using mosquitoes that had engorged on blood of individuals with yellow fever.³ What would have happened after one member of that group had died with yellow fever in view of today's political winds that blow for ever increasing controls and monitoring of research endeavors? Consider the case of Dr. Edward Jenner who inoculated James Philips, a healthy boy of eight-years of age, with the cow-pox virus and a short time later inoculated the boy with matter taken from the pustule of a smallpox patient.⁴ One could only marvel at the complexity of an informed consent in that situation. It becomes extremely important that the Department of Clinical Investigation make an effort not to stymie innovative research thought with all of the review process that is being imposed upon the research community. It is easy to curtail original thought and require that it fit a form or role model of research that has been comfortable for others. This attitude must be guarded against, at all times, by those individuals who have the responsibility to sponsor research. Research is similar to the performance of the artist who requires and needs a patron as the researcher needs a sponsor. The Department of Clinical Investigation has been nominated to be the sponsor for research endeavors within the hospital environment. This has been an ever increasing responsibility.

"The centipede was happy quite
until the toad in fun
said, "Pray, which leg goes after which?"
That worked her mind to such a pitch
She lay distracted in a ditch
Considering how to run."⁵

The Department of Clinical Investigation must be on guard not to ask inappropriate questions that will confuse investigators who present themselves to the Department with an innovative thought process. It would be inappropriate to ask too many questions that will confuse the issue and make it impossible to do the research. There must be space and opportunity for those individuals who have research thoughts to test them in a situation that is conducive to the analysis of the data. There must be a guard against the continuous mathematical, statistical testing with loss of sight as to whether it works or not.

"Making guesses at what might lie ahead, when the new facts have arrived, is the workaday business of science, but it is never the precise, sure-footed enterprise that it sometimes claims credit for being. Accurate prediction is the accepted measure of successful research."⁶

The Institutional Review Board and the Department of Clinical Investigation have the responsibility of supporting innovative research, not just to require a specific format that is comfortable to the reviewers.

The U.S. Army Medical Corps has a long tradition of clinical and basic researchers which should not be lost. Young investigators must be sought after, encouraged and permitted the opportunity in time and support to develop their thought processes in the laboratory and with their patients. It is the responsibility for each Clinical Department to encourage Research Endeavors. It is not just the responsibility for the Department of Clinical Investigation to support research, but research must continue to be one of the missions of each hospital in conjunction with patient care, education and logistical support.

Since this is to be my last annual report, I will introduce a few personal comments (like I haven't before). I have been associated with Clinical Investigation almost since its inception. Madigan General Hospital was either the first or second medical center to have an approved research division known now as the Department of Clinical Investigation. I began my stint with Clinical Investigation (Medical Research) in 1968 and have remained in that environment with the exception of three years when I was assigned to Europe. I have seen separation from the R&D Command to the Office of the Surgeon General and finally to Health Services Command. The number of publications, presentations and presented protocols which were carried to completion has increased over the years reflecting a dedicated, sincere group of investigators and staff. There has been a correspondent increase in the total budgetary needs for the research environment; however, the actual cost per protocol has not changed significantly since the beginning. The equipment for Clinical Investigation has gone from the beginnings of a floor model centrifuge, a junior spectrometer and a microscope to a well equipped laboratory with HPLCs, ultracentrifuges, spectrometers and other sophisticated equipment. There has continued to be an interest and support for research within the Medical Center which has been rewarding. There is an increasing need to encourage younger physicians to enter into the clinical investigative community in order to learn the administrative, logistical and technical skills of the research world. It will become more difficult in the future to have someone enter into the position of being responsible for a Department of Clinical Investigation without prior training and experience. It is no longer plausible to have an individual who has an interest in research to attempt to oversee a Department of Clinical Investigation without some training exposure prior to that responsibility. The Departments of Clinical Investigation need dedicated researchers with managerial skills if they are to continue to flourish. These skills are learned and earned by work and time. As the Service grew to fruition of being a Department, the increase in the administrative load has become oppressive with an exponential increase

in the number of Public Laws, Federal Registers, DOD and SGO directives, Army and HSC regulations not to mention the imposed site visits of the FDA, AALAC, IG, manpower, AAA, and desk audits. If only we had only six days worth of papyrus! Would the quality of research change? Unlikely. Most of the requirements placed on the research community are regulatory and not supportive.

I would like to end this with a portion of the last address given by Dr. Pasteur in 1892 at his 70th birthday when he was given a medal at a great meeting at the Sorbonne in Paris. Dr. Pasteur limped up the aisle leaning on the arm of the President of the French Republic and Pasteur's voice was so weak that his son had to give his presentation.

"... Do not let yourselves be tainted by deprecating and barren skepticism, do not let yourselves be discouraged by the sadness of certain hours which pass over nations. Live in the serene peace of laboratories and libraries. Say to yourselves first: What have I done for my instruction? and, as you gradually advance, What have I done for my country? until the time comes when you may have the immense happiness of thinking that you have contributed in some way to the progress and good of humanity:..."²

Bruce L. Fariss

BRUCE L. FARISS, M.D.
COL, MC
Chief, Department of Clinical Investigation

REFERENCES

1. Asimov, Isaac: How It Happened. In: The Winds of Change and Other Stories. Doubleday & Company, Inc., Garden City, New York, 1982.
2. de Kruif, Paul: And the Mad Dog. In: Microbe Hunters. Harcourt, Brace and Company, New York, 1926.
3. Norman, Colin: The Unsung Hero of Yellow Fever? Science 223:1370, 1984.
4. Bennett, Sir J. Risdon: Jenner and Pasteur. In: Little Masterpieces of Science. George Iles, Editor. Doubleday, Page & Company, New York, 1902.
5. Dustan, Harriet P.: Nutrition and Hypertension. Annals of Internal Medicine 98:660, 1983.
6. Thomas, Lewis: The Youngest Science. The Viking Press, New York, 1983.

UNIT SUMMARY FY 83

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>MANPOWER</u>	<u>RANK</u>	<u>MOS</u>
Chief, FARISS, Bruce L., M.D., COL, MC		O6	61C9A
C, Clin Studies Svc PLYMATE, Stephen R., M.D., COL, MC		O6	51C9B
C, Surg & Animal Care Svc LIEBENBERG, Stanley, D.V.M., MAJ, VC		O4	61C9B
C, Microbiology Svc HIGBEE, James W., Ph.D., MAJ, MSC		O4	68A9B
C, Biochemistry Svc LITTLE, James S., Ph.D., MAJ, MSC		O4	68C9C
C, Physiology Svc FRIEDL, Karl E., Ph.D, CPT, MSC		O3	68J9B
NCOIC MCDONALD, Karl O.		E5	91T2R
Med Lab Spec JONES, Richard E.		E7	92B4R
OR Tech SATTERFIELD, Thomas		E6	91D2R
Vet Animal Spec MORMILE, Andrea K.		E5	91T2R
Vet Animal Spec SCUTELLA, John		E3	91T1R
Vet Animal Spec VACANT		E3	91T1R

<u>DESCRIPTION</u>	<u>RANK</u>	<u>AGE</u>
Med Tech GARRISON, Mina J.	GS9	0644
Med Tech KETTLER, Thomas M.	GS9	0644
Med Tech MATEJ, Louis A.	GS9	0644
Edit Asst/Steno WHITTEN, Nancy J.	GS6	1047
Sec/Steno HOUGH, Eugenia R.	GS4	0312
Maintenance Worker MALLOUF, Jerry	WG7	4749

FUNDING

MEDCASE Equipment	\$137,400.00
Capital Equipment	13,693.00
Civilian Salaries	130,962.00
Consumable Supplies	93,999.00
Contractual Services	5536.00
Printing	55.00
TDY	5310.00
TOTAL	\$388,955.00

3. Progress

During FY 83 there were 245 active protocols that received administrative and/or technical support during the year. Of these, 171 are presently ongoing; 42 were completed; and 32 were terminated.

There were 52 publications, 10 papers are in press, and 23 papers have been submitted to journals for possible publication. There were 30 presentations at regional, national or international meetings resulting from these protocols.

Two theses from research protocols were presented and accepted as partial fulfillment of the requirements for advanced degrees.

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

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

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Chief, Pharmacy Service - COL Douglas Silvernale, MSC

Chief, Social Work Service - LTC Donald Greenhalgh, MSC

Chief, Clinical Studies Service, DCI - COL Stephen R. Plymate, MC

Chief, Biochemistry Service, DCI - MAJ James S. Little, MSC

Chief, Microbiology Service, DCI - MAJ James W. Higbee, MSC

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Surgery & Animal Care Service, DCI - MAJ Stanley Liebenberg, VC
Comptroller - LTC Gale B. Kulm, MSC

JAG Officer - MAJ James Kuklok, JA

Chief, EEO/EOO - Robert D. Peterson, DAC

Command Sergeant Major - CSM C. W. Mays

Representative, I Corps and Ft Lewis, designated by Commander, I Corps

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Recorder
Chief, Department of Clinical Investigation
COL Bruce L. Fariss, M.D., MC

Deputy, Veterinary Activities - COL William Van Zytveld, VC

Representative, Department of Nursing - MAJ Kathleen Mauro, ANC

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 1983:

Richard Meidell Intracranial Hemorrhage in Premature Infants: Correlation of Perinatal Factors with Timing and Evolution of the Hemorrhage. A Prospective Study.

Other nominees were:

Edward E. Dashow Significant Fetal Bradycardia During Antipartum Heartrate Testing

Michael E. Fincher The Effect of Daily L-Thyroxine Administration on Serum Copper, Serum Iron, and Body Weight in the Female Sprague-Dawley Rat

Gaspar Giorgi Exercise Prescription and Dietary Restriction for the Reduction of Weight and Cardiovascular Risk Factors

Frederick Harlass Correlation of Sex Hormone Binding Globulin and LH Pulse Frequency in Return Of Ovulation in the Obese Anovulatory Patient

James L. Wallingford Evaluation of Radiation Therapy in the Management of Endoscopically Visible Carcinomas of the Lung

PUBLICATIONS.....FY 83

DEPARTMENT OF CLINICAL INVESTIGATION

Publications:

Boatman, E.S., Ward, G., and Martin, C.J.: Morphometric Changes in Rabbit Lungs Before and After Pneumonectomy and Exposure to Ozone. J Appl Physiol: Respirat Environ Exercise Physiol 54(3): 778-784, 1983.

Hauer, E.C. and Little, J.S.: An Assay of RNA Synthesis in Hepatic Nuclei from Control and *Cryptosporidium parvum* Infected Rats. Proc Soc Exp Bio Med 172: 514-523, 1983.

Liebenberg, S.P.: Bone Marrow Depletion as a Coincidental Finding to Hypothermia in *Macaca mulatta*. J Med Primatology 11: 138-146, 1982

Liebenberg, S.P. and Jacob, W.H.: A Recent Survey of Income and Employment Data of Laboratory Animal Veterinarians. Lab Animal 12(6):17-28, 1983

Little, J.S.: Effect of *Cryptosporidium parvum* Infection on the Binding of Thyroxine to Plasma Membranes Isolated from Rat Liver. Fed Proc 42(3):324, 1983.

Little, J.S., Kishimoto, R.A., and Canonico, P.G.: Intracellular Fate of Phase I *Coccidia* Infection in Guinea Pig Peritoneal Macrophages. J Reticuloendothelial Soc 33: 331-41, 1983.

Martin, C.J., Boatman, E.S., and Ward, G.: Mechanical Properties of Alveolar Wall After Pneumonectomy and Ozone Exposure. J Appl Physiol: Respirat Environ Exercise Physiol 54(3):785-788, 1983.

Plymate, S.R.: Questions and Answers: Diagnosis of Polycystic Ovary Syndrome. JAMA 250: 671, 1983

Plymate, S.R., Fariss, B.L., and Smith, W.D.: Recovery of Fertility Following Vasovasotomy. Andrologia 15:279-81, 1983

Plymate, S.R., Leonard, J.M., Paulsen, C.A., Fariss, B.L., and Karpas, A.E.: Sex Hormone Binding Globulin Changes with Androgen Replacement. J Clin Endocrinol Metab 57: 645-48, 1983.

Plymate, S.R., Rains, V., Matej, L.A., and Fariss, B.L.: Influence of Physical and Environmental Stress on the Pituitary Testicular Axis. J Andrology 4(1): 26, 1983.

Plymate, S.R., Stanton, T.S., Fariss, B.L.: and Matej, L.A.: Abnormalities in Steroidogenesis Following Synthetic ACTH Infusion in Intertile Men. Fertill Steril 40(3): 415, 1983.

PUBLICATIONS - FY 83 (Dept Clin Invest - Cont)

Accepted for Publication:

Liebenberg, S.P. and Taylor, W.E.: Use of Carbon Dioxide Laser in Pharyngeal Surgery in the Dog. Accepted by VM/SAC, June 1983.

Little, J.S. The Effect of *Streptococcus pneumoniae* Infection on the Binding of Thyroxine to Purified Rat Liver Plasma Membranes. Accepted by Endocrinology, Sep 83.

Submitted for Publication:

Friedl, K.E. and Plymate, S.R.: Effects of Obesity on Reproduction in the Female. Submitted J Obesity Weight Reg, Sep 83.

Liebenberg, S.P.: Case Report on Dehydration Due to Automatic Watering System Failure. Submitted to Lab Animal, Oct 82.

Little, J.S.: Biochemical and Cytochemical Localization of Inosine 5'-Diphosphatase in Rat Liver Microsomal Fractions. Submitted to Biochem J, Apr 83.

Little, J.S.: Evidence for the Release of Phosphate by Inosine-5'-Diphosphatase on Both the Cisternal and Cytoplasmic Sides of the Microsomal Membrane. Submitted J Cell Biology, Nov 82.

Plymate, S.R., Stutz, F.E. and Fariss, B.L.: Relationship Between Sex Hormone Binding Globulin and Estrogen Receptors in Breast Cancer. Submitted to J Clin Oncology, May 83.

Plymate, S.R. and Ward, G.S.: The Effect of Lowered Prolactin on Hypothalamic Pituitary Testicular Function in the Male Rat. Submitted to J Endocrinology, May 83.

DENTAL ACTIVITY

Publications:

Axinn, S. and Brasher, W.J.: Frenectomy Plus Free Graft. J Prosthe Dent 50(1): 16-19, 1983.

Hartwell, G.R. and Cecic, P.A.: An Esthetic Restorative Technique for Use During the Stabilization Period After Vertical Root Extrusion. JADA 107(1): 59-60, 1983

Accepted for Publication:

Carroll, D, Stephan, M.J., and Hays, G.L.: Epidermolysis Bullosa --Review and Clinical Report. Accepted by J Amer Dental Assoc, Jul 83.

PUBLICATIONS - FY 83

DEPARTMENT OF EMERGENCY MEDICINE

Publications:

Benjamin, G.C.: Sickle Cell Trait and Sickle Cell Anemia - A Review. Mil Med 148(9): 701-06, 1983.

DeGarmo, B.H. and Dronen, S.: Pharmacology and Clinical Use of Neuromuscular Blocking Agents. Ann Emerg Med 12: 48-55, 1983.

Dronen, S.C.: Complications of TAC. Ann Emerg Med 12(5):333, 1983.

Accepted for Publication:

Maningas, P.A., DiJulio, M.A., and Dronen, S.C.: Diaphragmatic Rupture During G-Maneuvers in a T33 Jet Trainer. Accepted by Avia Space Environ Med, August 1983.

Submitted for publication:

Benjamin, G.C.: Emergency Transvenous Cardiac Pacing. IN Clinical Procedures in Emergency Medicine, W.B. Saunders. Submitted, Oct 82.

Benjamin, G.C. and Tintinalli, J.: Lung Abscess, Aspiration Pneumonia and Bacterial Pneumonia. IN Emergency Medicine - A Comprehensive Study Guide, McGraw Hill. Submitted Jun 83.

Frumkin, K.: The Pneumatic Anti-Shock Garment (PASG). In J.R. Roberts and J.R. Hedges (eds) Clinical Procedures in Emergency Medicine. Submitted, Nov 82

Frumkin, K.: Tube Thoracostomy. In J.R. Roberts and J.R. Hedges (eds) Clinical Procedures in Emergency Medicine. Submitted, Nov 82.

Maningas, P.A. and Friedl, K.E.: Transcutaneous Oxygen Monitoring of Emergency Department Patients. (Letter to the Editor) Submitted to Amer J Emer Med, Sept 83.

Rockey, P., Wood, R.W., Wolcott, B.W., Slay, L.: Reducing Costs in the Care of Patients with Back Pain: A Prospective Study of a Clinical Algorithm. Submitted, May 83.

PUBLICATIONS - FY 83

DEPARTMENT OF FAMILY PRACTICE

Submitted for Publication:

Sullivan, R.A. and Fitzgerald, R.: Problem Drinking in Women.
Submitted to Female Patient, Jun 83.

DEPARTMENT OF MEDICINE

Publications:

Colman, L.K. and Baker, T.M.: Lactic Acidosis Associated with Extensive Oat Cell Carcinoma of the Lung - Not Necessarily a Poor Prognostic Sign: Case Report. Mil Med 148: 440, 1983.

Covelli, H.D., Beekman, J.F., and Weled, B.J.: CPAP, not the Treatment of Choice for Atelectasis - Reply. Chest 83(3): 587, 1983.

Covelli, H.D., Knodel, A. and Heppner, B.: The Changing Characteristics of Theophylline-Induced Seizures. Chest 84(3):332, 1983.

Covelli, H.D., Nesson, V.J., and Tuttle, W.K., III: Oxygen Derived Variabels in Acute Respiratory Failure. Crit Care Med 1(8): 646-649, 1983.

Georgitis, W.J., Treece, G.L., and Hofeldt, F.D.: Gonadotropin-Releasing Hormone Provokes Prolactin Release in Hypergonadotropic Hypogonadal Women - A Response not Altered by Dexamethasone. Clin Endocrinol 19(3):319-24, 1983.

Gibbons, R.B.: Mushroom Poisoning. Comp Therapy 8:33-39, 1982.

Hough, D.R.: Anemia Associated with Primary Hyperparathyroidism. Mil Med 148:686-88, 1983.

Hough, D.R., Chan, A., and Davidson, H.: Von Recklinghausen's Disease Associated with Gastrointestinal Carcinoid Tumors. Cancer 51:2206-08, 1983.

Jones, R.E.: Nutrient and Hormonal Adaptations to Starvation. Present Concepts in Internal Medicine, Nutritional Support Symposium 14(1): 23-41, Summer 83.

O'Meara, T.F. and Jackson, M.: A Unique Variant of Dubin-Johnson Syndrome. Gastroenterology 84(5): 1388, 1983.

PUBLICATIONS - FY 83 (Dept Medicine - Cont)

Sullivan, M.J., Hough, D.R., and Agodoa, L.C.Y.: Peripheral Arterial Thrombosis Associated with the Nephrotic Syndrome: A Review of the Clinical Spectrum. South J Med 76:1011-1016, 1983

Terebelo, H.R., Taylor, H.G., Brown, A., Martin, N., Stutz, F.H., Blom, J., and Geier, L.: Late Relapse of Testicular Cancer. J Clin Oncol 1(9):566-571, 1983.

Accepted for publication:

Harris, J.M.: Coronary Angiography and Its Complications. The Search for Risk Factors. Accepted by Arch Int Med, Aug 83.

Hofeldt, F.D., Kidd, G.S., Bornemann, M., McDermott, M.T., Treece, G.L., Clark, J., Sims, J., and Ghaed, N.: Practical Application of Fine Needle Thyroid Aspiration Biopsy in Clinical Medicine. Accepted by Mil Med.

Treece, G.L., Georgitis, W.J., and Hofeldt, F.D.: Resolution of Recurrent Thyroid Cysts with Tetracycline Instillation. Accepted by Arch Int Med, May 83.

DEPARTMENT OF NURSING

Accepted for Publication:

Reeder, J.M.: Using the AORN Basic Competencies: A Qualitative Study of Intraoperative Nursing Activities. Accepted by AORN Journal, Jun 83.

Reeder, J.M. and Clutter, L.M.: Staff Development - An Evolving Role in Army OR Nursing. Accepted by Today's OR Nurse, Aug 83.

DEPARTMENT OF OB/GYN

Accepted for publication:

Harlass, F.J., Plymate, S.R., Fariss, B.L., and Belts, R.P.: Correlation of Sex Hormone Binding Globulin and LH Pulse Frequency in Return of Ovulation in the Obese Anovulatory Patient. To be published by the International Medical News Group as a news report.

Submitted for Publication:

Harlass, F.E., Plymate, S.R., Belts, R.P.: Weight Loss Corrects Gonadotropin and Sex Steroid Abnormalities of Polycystic Ovarian Disease. Submitted to J Clin Endocrinol, Jan 83.

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DETAIL SHEETS
FOR
PROTOCOLS

DEPARTMENT OF CLINICAL INVESTIGATION

TITLE: The Effects of Chronic Hyperglycemia on Pregnancies and Fetuses in Sheep During Gestation

PRINCIPAL INVESTIGATOR: COL Bruce L. Fariss, MC

PROFESSIONAL ASSISTANTS: LTC Paul B. Jennings, VC
LTC George S. Ward, VC

WORK UNIT NO: 74/06

TECHNICAL OBJECTIVE

The objectives of this project are to determine the effects of hyperglycemia upon pregnancies as manifested by frequency of abortions and hydramnios and possible developmental abnormalities of the fetuses.

METHOD

The study will be composed of three groups of pregnant ewes with as close proximity of the date of conception as possible. All groups will be given food and water ad libitum. Group I: This will be the control group of six animals with no treatment. Group II: Seven animals which have undergone subtotal pancreatectomy. The diabetes mellitus produced surgically will be managed by the injection of intermediate acting insulin such as NPH. Blood sugars will be monitored frequently as indicated clinically. Group III: Seven animals which have indwelling catheters for infusion of hypertonic sugar solutions with a lambda infusion system. The systems are portable, weighing less than 3 pounds and can be strapped to the backs of the animals without difficulty. Blood sugars will be monitored at frequent intervals with an attempt to keep blood sugars between 200 and 300 mg/100 ml of blood at all times.

The course of the pregnancies will be observed for each group of animals. Blood sugars for each group will be determined at frequent intervals during the gestation. At delivery the neonate will be examined pathologically for evidence of pulmonary, liver, pancreatic, kidney, and possible developmental abnormalities.

PROGRESS

(82 10 - 83 09) Six sheep had total pancreatectomies. Prior to pancreatectomy, the sheep were studied with sodium butyrate, I.V. arginine, I.V. tolbutamide, somatostatin, and glucagon. Somatostatin blocks the release of insulin when glucose or sodium butyrate is injected. None of the administered agents caused a rise in insulin levels after pancreatectomy.

PRESENTATION: Fariss, B.L., Hane, S., Rodd, G., Jacob, W.H., and Plymate, S.R.: Pancreatectomized Sheep Do Not Develop Overt Diabetes Mellitus. Presented to Society of Uniformed Endocrinologists Annual Meeting, San Antonio, Texas, 7-8 June 1983.

STATUS: (O)

TITLE: Adrenal Hyperplasia in Pacific Salmon

PRINCIPAL INVESTIGATOR: COL Bruce L. Fariss, MC

PROFESSIONAL ASSISTANT: COL Stephen Plymate, MC

WORK UNIT NO: 80/01

TECHNICAL OBJECTIVE

To determine if the administration of a salt-retaining hormone, desoxycorticosterone, will prevent adrenal gland hyperplasia in the Pacific salmon and to determine if the Pacific salmon can spawn and survive.

METHOD

It is proposed that a total of 20 Pacific salmon be captured while in salt water. These fish are to be sexually mature and will be retained in holding pens. Half of the fish will be treated with desoxycorticosterone in oil, intramuscularly. Blood samples will be obtained from the fish for the measurement of plasma hydroxycorticosteroid, desoxycorticosterone, and aldosterone. Following the administration of the desoxycorticosterone, all of the fish (treated and controls) will be placed in a holding tank until spawning occurs. Following spawning, the fish will be returned to the holding pen in the salt water for follow-up observations of survival.

PROGRESS

(82 10 - 83 09) ACTH stimulation tests and insulin tolerance tests have been performed in silver, sockeye, and chum salmon. The changes in steroid levels appeared to be seasonal and not related to the degree of maturation.

PRESENTATION: Fariss, B.L., Mallouf, J., Ward, G.S., Liebenberg, S.P., and Plymate, S.R.: Evaluation of Pituitary-Adrenal Axis in the Pacific Coast Silver Salmon (*Oncorhynchus kisutch*) Society of Military Endocrinologists, 15 Jun 82, San Francisco, CA.

STATUS: (0)

TITLE: Serum Glucose Levels in Restrained vs Non-Restrained Rabbits

PRINCIPAL INVESTIGATOR: COL Bruce L. Fariss, MC

PROFESSIONAL ASSISTANTS: LTC George S. Ward, VC
SSG James Hayes, USA

WORK UNIT NO: 81/14

TECHNICAL OBJECTIVE

To compare serum glucose levels in rabbits at hourly intervals under normal bleeding (stressful) conditions with serum glucose levels in blood obtained by cage bleeding (non-stressful) conditions.

METHOD

Ten New Zealand white rabbits will be anesthetized and a catheter placed in an external jugular vein. Two days later the rabbits will be placed in restraint boxes, the ears irritated to dilate blood vessels, and 4 consecutive hourly blood samples taken. A period of two weeks rest will be given during which the rabbits are handled daily to reduce fear of handling. The rabbits will then be anesthetized and a catheter placed in the contralateral external jugular. Two days later 4 consecutive hourly blood samples will be drawn while the rabbits remain in their cages unrestrained. The samples will be analyzed for levels of glucose, cortisol, and norepinephrine. The differences between the restrained and non-restrained values will be compared by the paired t-test method of statistical analysis.

PROGRESS

(82 10 - 83 09) Serum glucose levels show a progressive rise in restrained rabbits. Epinephrine and total catecholamines are not statistically correlated to the rise in glucose. There is no change in plasma cortisol. In conclusion, rabbits show a rise in glucose when restrained; the exact mechanism is unknown.

STATUS: (C)

PRESENTATION: Ward, G.S., Fariss, B.L., Liebenberg, S.P., and Hayes, J.: Elevation of Blood Sugar Associated with Stress of Handling in the Rabbit. HSC Annual Clinical Investigation Conference, San Antonio, TX, Sep 81.

TITLE: A Comparison of the Effect of Glucose vs Sodium Butyrate on the Levels of Insulin and Glucagon in Normal and Pancreatectomized Sheep

PRINCIPAL INVESTIGATOR: COL Bruce L. Fariss, MC

PROFESSIONAL ASSISTANTS: MAJ Stanley P. Liebenberg, VC
CPT Duane J. Jeffers, MC

WORK UNIT NO: 82/18

TECHNICAL OBJECTIVE

To delineate additional mechanisms of insulin and glucagon release in sheep, with specific attention directed at the role of the pancreas in the secretion of these two hormones.

METHOD

Six adult female sheep will be fasted for 24 hours and then given 25 gm IV glucose. Blood samples will be drawn every 10 minutes for 90 minutes and glucose, insulin, and glucagon levels will be measured in these samples. Two weeks later, the animals will again be fasted for 24 hours and then receive 0.2 mmole/kg body weight of a solution of sodium butyrate adjusted to pH of 7.4. Again blood samples will be obtained every 10 minutes for 90 minutes as above. Approximately 3 weeks or as soon as technically possible after the first administration of sodium butyrate, all sheep will undergo complete pancreatectomy. Glucose and sodium butyrate in the same amounts used previously will be administered and the same measurements of glucose, insulin and glucagon will be performed.

PROGRESS

(82 10 - 83 09) Six sheep underwent total pancreatectomy. Comparison of insulin and glucagon levels were made in these sheep when stimulated with glucose and sodium butyrate before and after pancreatectomy. There was no response to insulin with the administration of sodium butyrate, indicating completeness of pancreatectomy. Sodium butyrate causes a greater rise in insulin than in glucose.

STATUS: (C)

TITLE: The Effects of Alloxan and Streptozotocin in Pancreatectomized Sheep

PRINCIPAL INVESTIGATOR: J. E. Grande, D. Evans, MC

PROFESSIONAL ASSISTANTS: LTC Preston Carter, MC
MAJ Michael Elnether, MC
MAJ Robert Lickson, MC
MAJ Stanley Liebenberg, VC

WORK UNIT NO: 82-09

TECHNICAL OBJECTIVE

To further elucidate the mechanisms of hyperglycemia following the administration of alloxan or streptozotocin.

METHOD

Twelve (12) adult ewes given food and water *ad libitum* will be subjected to total pancreatectomy utilizing a modification of the method described by Jaretz, et al. Prior to administration of the alloxan or streptozotocin, serum butyrate in a dose of 1.25 mM/kg pH 7.0 will be administered intravenously to substantiate the completeness of the pancreatectomy. Basal and then 10 minute-interval for 90 minutes blood samples will be drawn for glucose, glucagon, and insulin determinations. Glucagon will be determined, using an RIA method and the antibody of Uniger. The insulin will be determined utilizing an RIA method. Glucose will be determined by an alkaline ferricyanide method utilizing a Beckman instrument. One week following pancreatectomy, six of the pancreatectomized sheep will be given 65 mg/kg body weight of alloxan as a bolus, intravenously. The other six pancreatectomized sheep will be given streptozotocin freshly dissolved in 0.01 M citrate buffer, pH 4.3, 100 mg/kg body weight. Daily blood samples for glucose will be drawn in both groups. Statistical analysis will be performed by the appropriate Student's t test. The primary analysis, though, will be whether there is the development of diabetes mellitus, following the addition of alloxan or streptozotocin in the pancreatectomized sheep.

PROGRESS

(82-10 - 83-09) Pancreatectomized sheep do not develop diabetes mellitus. Blood sugars remain within the limits of normal following pancreatectomy. Administration of alloxan or streptozotocin will cause the development of diabetes mellitus in the pancreatectomized sheep. From this study it can be concluded that both of these agents cause a significant change in cellular carbohydrate metabolism. It has been assumed but not proven that these agents cause diabetes mellitus by the effects on the B cells. This study disproves that conclusion.

STATUS: (C)

TITLE: Evaluation of the Hypothalamic-Pituitary-Adrenal (HPA) Axis in Psychiatric Patients Who Do Not Suppress Serum Cortisol After overnight Dexamethasone.

PRINCIPAL INVESTIGATOR: COL Bruce L. Fariss, MC

PROFESSIONAL ASSISTANTS: LTC Stephen R. Plymate, MC
Thomas H. Lampe, M.D.
Steven C. Risse, M.D.

WORK UNIT NO: 83-86

TECHNICAL OBJECTIVE

To determine whether psychiatric patients who do not suppress serum cortisol after the overnight dexamethasone suppression test will suppress cortisol production after the more extensive dexamethasone suppression test developed for the diagnosis of Cushing's disease.

METHOD

Patient Selection: Fifteen psychiatric in-patients at American Lake VA Medical Center who have been found to be nonsuppressors from a dexamethasone suppression test.

Patient Exclusion: A diagnosis or past history of pituitary or adrenal disease or if they, in the opinion of the investigators, have medical conditions or receive medications that have been reported to give a "false" nonsuppression to dexamethasone.

Procedures: Baseline 0800 cortisols will be obtained on all subjects prior to beginning the study.

Days 1 and 2: 0.5 mg of dexamethasone by mouth every six hours with blood samples for serum cortisol collected at 1600 on Day 2.

Days 3 and 4: 2 mg of dexamethasone by mouth every 6 hours with blood samples for serum cortisol drawn at 1600 on Day 4.

Whenever possible 24 hour urines for creatinine, total volume and hydroxycorticosteroids will be obtained the day before and each day of the dexamethasone testing. Within one week of completion of the above testing, an overnight dexamethasone suppression test will be readministered to ascertain the constancy of response to this test. A diagnostic interview for purposes of diagnosis by DSM-III criteria and a BPRS will be performed on each subject.

PROGRESS

(83 09 - 83 09) Patients are being collected for entry into this study by the psychiatric staff at American Lake VA Medical Center.

STATUS: (0)

TITLE: The Effect of 2- α -Hydroxy-4-Pregnen-3-one Treatment on Spermatogenesis and Gonadotrophins in Rats.

PRINCIPAL INVESTIGATOR: CPT Karl E. Friedl, MSC

PROFESSIONAL ASSISTANTS: COL Bruce L. Fariss, MC
COL Stephen R. Plymate, MC
LTC James L. Kelley, MC
Mina Garrison, DAC, B.S., M.T.

WORK UNIT NO: 83/64

TECHNICAL OBJECTIVE

To examine the possibility of a physiological role for the steroid metabolite 2- α -hydroxy-4-pregnen-3-one in the hypothalamic-pituitary-testes axis. The effect on gonadotrophins will be studied in castrated animals and the effect on spermatogenesis through both direct actions on the testes and indirect actions through any effects on gonadotrophins will be observed.

METHOD

Thirty-two young adult male rats (250 gms) will be anesthetized with ketamine and castrated on the day prior to the start of treatments. These animals will be randomly distributed into four treatment groups. In a second experiment, thirty-two intact rats from the same shipment will also be randomized into four treatment groups. In both experiments, the groups will be injected daily for 30 days with 1 mg progesterone, 1 mg 2- α -OHP, 5 mg 2- α -OHP, or sesame oil. The steroids will be dissolved in sesame oil and animals will receive 0.2 ml volumes I.M.

After 30 days of treatment the rats will be quillotined and trunk blood will be collected into heparinized containers, centrifuged and plasma aliquots for the hormone assay will be made and stored at -80°C.

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 at -80°C until assay of intratesticular T, E₂, and androgen binding protein (ABP). For all animals, the ventral prostate and seminal vesicles will be ligated, removed and weighed. Epididymides will also be weighed (from intact animals) and the right epididymis will be frozen at -80°C for later assay of T, E₂, and ABP. Adrenals will be collected and weighed from all animals and preserved for possible later histological study.

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

Testes will be sectioned at 4 μ and the slides will be stained with PAS and hematoxylin. The slides will then be studied in the following quantitative manner. Twenty round tubules representing 7th stage cellular associations will be used per animal. Inner and outer tubule diameters will be measured. 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 the Sertoli cells will be noted. Leydig cell tissue volumes may be morphometrically measured if preliminary findings are indicative of differences. Means of all counts and tubule diameters will be compared between the four groups by t test.

Steroids and gonadotrophins will be measured for all eight groups by radioimmunoassay and these values will also be 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

(83 05 - 83 09) Sixty-four (64) rats have been studied. Hormonal data indicate that 20- α -OHP acts on both the hypothalamic/pituitary and the testis mechanisms. The actions result in a substantial activation of the seminiferous tubule component of the testes as demonstrated by significant increases in androgen binding protein concentrations. A quantitative assessment of spermatogenesis is currently underway from the completed histological preparations. Completion of this study will require approximately 95 hours of microscope work.

STATUS: (0)

TITLE: Evaluation of the Cyclic Nature of Human Semen Content

PRINCIPAL INVESTIGATOR: MAJ WILLIAM H. JONES, MSC

PROFESSIONAL ASSISTANTS: MAJ MICHAEL L. SMITH, MSC
Robert Molarelli, M.D., LTC, MC, (Ret)

WORK UNIT NO: 78734

TECHNICAL OBJECTIVE

To determine semen quality by measuring sperm count, sperm motility, sperm morphology, and various constituents of seminal fluid. These findings will then be analyzed for cyclic patterns.

METHOD

Test Subjects: Twenty to thirty healthy volunteers will be selected based on physical examination and medical history. Individuals will be excluded from the project for any of the following reasons: evidence of active venereal disease; a history of testicular varicocele; currently using the sauna on a regular basis; currently taking any medication; any adverse finding during the physical examination. Volunteers will abstain from the use of alcohol and other drugs throughout the semen collection phase of the project. Volunteers will abstain from sexual intercourse for a period beginning 48 hours before collection of the first semen sample and extending throughout the sample collection period.

Semen Collection and Analysis: Semen samples will be collected daily for a period of 20-25 days. Samples will be collected during a specified 30-minute period each day. The semen, obtained through masturbation, will be ejaculated directly into plastic containers which are free of trace metals. The samples will be allowed to liquefy for one hour at room temperature (24°C). The liquefied samples will be measured for volume and color, and then will be divided into two portions. One portion will be assayed immediately for viscosity, sperm count, sperm motility, and sperm morphology. The other portion of the samples will be centrifuged and the sperm-free seminal fluid will be retained for assay of seminal fluid constituents to include prostaglandins, gonadotropins, trace metals, and carbohydrates.

PROGRESS

(82 09 - 83 09) No further patients were entered during FY 83. In previous years, twelve healthy young men obtained daily semen specimens for 20 days. There were wide variations in sperm density, semen volume, and total count in each subject. Percentage

Evaluation of the Cyclic Nature of Human Semen Content - Jacob

of oval forms was the most stable semen factor. Significant positive correlations were found between sperm density and total counts in ten subjects. However, when all specimens from all subjects were combined, there were significant positive correlations between sperm density and total count, total count and semen volume, and total count and percentage of oval forms. There was a significant negative correlation between sperm density and the semen volume. No cyclic or regular, pattern could be detected in any of the subjects.

One manuscript has been submitted for publication and one other manuscript is now in preparation.

PRESENTATION: Jacob, W.H., Smith, M.L., Plymate, S.R., and Cricco, C.F.: Daily Variations in Human Semen Quality. Pacific Coast Fertility Society, October 1979.

STATUS: (C)

TITLE: Correlation of the Effects of Semen Sperm Count and Prostaglandin Content on Fertility in Human Males

PRINCIPAL INVESTIGATOR: MAJ WILLIS H. JACOB, MSC

PROFESSIONAL ASSISTANTS: MAJ Michael L. Smith, MAC
Robert Modarelli, M.D., LTC, MC (ret)
Jeffrey S. Rakoff, M.D.

WORK UNIT NO: 73 45

TECHNICAL OBJECTIVE

To compare the semen quality of men of known fertility to that of men who are apparently infertile. The parameters of semen quality will be sperm count, sperm motility, sperm morphology, sperm viability, seminal prostaglandins, seminal fructose, seminal zinc, seminal gonadotropins, and gonadal steroids. Seminal prostaglandin content will be compared with each of these parameters.

METHOD

Semen specimens will be collected from 20-25 volunteers of known fertility and from 20-25 volunteers with apparent infertility. Following a urological evaluation, each volunteer will be asked to provide three semen specimens. Each volunteer will provide a semen specimen following a 48-hour period of abstinence from sexual activity. Subsequent samples, obtained at the end of a 48-hour abstinence period, will be given at one-week intervals for a two-week period. Each volunteer will ejaculate directly into a plastic container which is free of trace metals. The specimens will be analyzed for volume, color, sperm count, sperm motility, sperm morphology, prostaglandins F, prostaglandins F, and various other seminal fluid components such as fructose, zinc, gonadotropins, and gonadal steroids.

PROGRESS

(73 06 - 83 09) Fifteen subjects, all expectant fathers, were entered in this study. No infertile men were entered. Data from the expectant fathers were used in the publication listed below. No further studies were done due to the departure of the principal investigator and the co-investigators.

PUBLICATION: Fariss, B.L., Fenner, D.K., Plymate, S.R., Brannen, G.E., Jacob, W.H., and Thomason, A.M.: Seminal Characteristics in the Presence of a Varicocele Compared to Expectant Fathers and Pre-Vasectomy Individuals. Fertil Steril 35:325-27, 1981.

STATUS: (C)

TITLE: Effect of Naloxone on Hypovolemic Hypotension in the Pig-Tailed Monkey

PRINCIPAL INVESTIGATOR: MAJ Willis H. Jacob, MSC

PROFESSIONAL ASSISTANTS: LTC George S. Ward, VC
MAJ Stanley P. Liebenberg, VC
MAJ John B. McClain, MC
CPT Harry L. Walker, VC

WORK UNIT NO: 81/58

TECHNICAL OBJECTIVE

To determine if naloxone, an opiate antagonist with no agonist activity, will reverse endotoxin induced hypotension and hypovolemic hypotension in other species as has been demonstrated in the rat model. The effectiveness of this agent in the dose ranges where it has been used in humans with no ill effects will also be studied.

METHOD

Six monkeys will be given 20 mg of ketamine hydrochloride and then administered halothane via a mask. When a surgical plane of anesthesia is reached, intracaths will be inserted in the femoral artery and vein and systolic, diastolic, and mean blood pressures and electrocardiogram will be recorded simultaneously. Halothane anesthesia will be stopped, and when the blood pressure reaches a stable maximum, hypovolemia will be induced by withdrawing blood into heparinized syringes over at least a 20 minute period until a mean of approximately 35-40 mm Hg is reached. This mean will be maintained for a minimum of 20 minutes and then the test solution, either 2 mg/kg naloxone prepared in 1 cc of sterile water or 2 cc saline alone, will be administered. The amount of volume administered will be predrawn to negate volume effect. The blood pressure will be followed for one hour or until stability is reached. If drastic blood pressure decreases occur or death seems imminent, blood readministration will be immediate. After blood pressure measurements have been completed, the blood will be readministered and the catheters removed. Each monkey will serve as its own saline control in a random manner with the trials being at least 30 days apart. Blood pressure data will be analyzed for significance with the Student's t test to compare values post-saline treatment with values post-naloxone administration.

PROGRESS

(81 03 - 83 09) Six female monkeys and six male monkeys were studied. There was no change in blood pressure in any of the females or five of the six males. However, a noticeable change occurred in one of the males, who had a noticeable decrease in systolic, diastolic, and mean pressures. The general impression was that naloxone had no effect on hypovolemic hypotension in the pig tailed monkey. A paper is being written for publication.

STATUS: (C)

TITLE: Effect of *Streptococcus pneumoniae* Infection on the Binding of Insulin to Plasma Membranes Isolated from Rat Liver

PRINCIPAL INVESTIGATOR: MAJ James S. Little, MSC

PROFESSIONAL ASSISTANTS: LTC James Anderson, MC
CPT Jerald Merrill, MSC

WORK UNIT NO: 82/24

TECHNICAL OBJECTIVE

To determine if *Streptococcus pneumoniae* infection affects the binding of insulin to hepatic plasma membranes and to determine if observed results can be correlated with hepatic alterations known to occur during this infection.

METHOD

Male albino rats (150-250 gm) of the Sprague-Dawley strain will be maintained on stock lab chow and tap water, 12° $^{\circ}$ and acclimatized to a 12-hr day/night cycle for at least 12 days prior to experimentation in order to eliminate circadian variations. Rats will be inoculated subcutaneously with 3×10^5 to 6×10^5 heat-killed or virulent *S. pneumoniae* serotype I, A5 strain organisms. At 40 hr post inoculation, plasma membranes will be prepared from both groups of rats. These membranes, which have been shown to be essentially devoid of other cellular contaminants, will be washed by suspension and recentrifugation to remove absorbed cytoplasmic proteins. Preliminary experiments conducted at BAMC will be designed to determine optimum plasma membrane protein concentration, time, pH, and temperature for the binding of labeled insulin to isolated plasma membranes. In a total incubation volume of 450 microliters, buffer, plasma membranes, cold standards, and labeled hormone will be incubated at the predetermined temperature, pH, and time. Non-specific binding is determined by parallel incubation with excess cold hormone. Scatchard analysis will be used to assess affinity and binding capacity of 125 I insulin to plasma membranes isolated from 10 control and 10 infected animals. Group mean values will be compared by the unpaired Student's t test and differences will be considered significant at $P < 0.05$.

PROGRESS

(82 10 - 83 09) Hepatic plasma membranes were isolated from control and *Streptococcus pneumoniae*-infected rats in order to determine the effect of *S. pneumoniae* infection on the binding capacity and

Effect of Streptococcus pneumoniae Infection on the Binding of
Insulin to Plasma Membranes Isolated from Rat Liver - Little

affinity of hepatic plasma membranes for insulin. Infection did not affect the purity or the yield of isolated membranes. A significant increase in serum insulin was observed during infection. Scatchard analysis of membrane binding, determined under optimal conditions, confirmed the presence of insulin receptors on plasma membranes isolated from the liver of control and infected rats. Preliminary results suggest that infection did not significantly affect the binding capacity or affinity of the membrane receptor for insulin. These results suggest that the increased serum insulin observed during infection does not "down regulate" its receptor on the liver. In addition, the observed metabolic effects observed during infection, such as increased RNA, protein, and lipid synthesis appear not to be mediated by altered hepatic insulin receptors.

STATUS: (0)

TITLE: The Effect of *S. pneumoniae* Infection on the Binding of Thyroxine (T_4) to Purified Rat Liver Plasma Membranes

PRINCIPAL INVESTIGATOR: MAJ James S. Little, MSC

PROFESSIONAL ASSISTANT: MAJ Stanley P. Liebenberg, VC

WORK UNIT NO: 82/65

TECHNICAL OBJECTIVES

To determine if there are specific receptors for T_4 on hepatic plasma membranes; if these receptors are affected by *S. pneumoniae* infection; and if receptor changes can be correlated with alterations known to occur in hepatic metabolism during infection.

METHOD

Male Sprague-Dawley rats (200-250 g) will be maintained on stock Purina lab chow and tap water *ad libitum*. All rats will be acclimated to a 12-hour day-night cycle for 14 days before experimentation to standardize circadian variations. Rats will be inoculated with varying doses (3×10^4 - 3×10^5 ; 6×10^5 - 1×10^6 ; and 6×10^6) of heat-killed (control) or virulent (infected) colony-forming units of *S. pneumoniae* serotype I, A-5 strain. After inoculation, all rats will be fasted but allowed access to water and euthanized 40 hours after inoculation, a time corresponding to the midpoint of the night cycle. Fasting of controls will be necessary because infected rats are anorectic. Hepatic plasma membranes will be isolated and the purity assessed. For initial studies to determine optimum time, temperature, protein concentration, and pH, plasma membranes from control or infected animals will be pooled. Once the binding assay has been optimized with respect to time, temperature, plasma membrane protein concentration, and pH, plasma membranes will be prepared from individual control and infected animals. Each control or infected group will contain at least 6 animals. Three groups of infected animals will be studied with each group receiving an increasingly larger dose of *S. pneumoniae*. Receptor assays will be performed in a total volume of 0.2 ml contained in 10x75 mm borosilicate glass test tubes. The assay will contain ^{125}I T_4 (50,000 to 100,000 counts per minute), from 0 to 10^{-5} M cold T_4 , and plasma membranes at the determined concentration. All components will be diluted in buffer (T_4 Buffer) containing 0.25 M sucrose, 20 mM Tris-Cl, 1 mM $MgCl_2$, 2 mM EDTA, 50 mM NaCl, 1 mM dithiothreitol, and 5% (v/v) glycerol. Assays will be performed in triplicate at the optimal temperature and time. Assays will be stopped by the addition of 1.0 ml of ice cold T_4 buffer and centrifugation at 2200 g for 15 minutes. Following centrifugation, the supernatant will be aspirated and the plasma membrane pellets washed by the addition of 1.0 ml of ice cold T_4 buffer. The

The Effect of *Streptococcus pneumoniae* Infection on the Binding of Thyroxine (T₄) to Purified Rat Liver Plasma Membranes - Little

membranes will again be pelleted as described above, the supernatants aspirated, and the membranes counted. Non-specific binding will be determined by parallel incubation with excess cold hormone (10⁻⁵ M). Scatchard analysis will be used to assess the affinity and maximum binding capacity of the receptor for T₄. Counting efficiency will be determined by the channel ratio method.

PROGRESS

(82 10 - 83 09) Hepatic plasma membranes were isolated from control and *Streptococcus pneumoniae* infected rats in order to determine the effect of *S. pneumoniae* infection on the binding capacity and affinity of hepatic plasma membranes for thyroxine (T₄). Infection did not affect the purity or the yield of isolated membranes. A significant decrease in both total and free serum (T₄) was observed during infection. Scatchard analysis of membrane binding, determined under optimal conditions, confirmed the presence of high affinity, low capacity sites, as well as low affinity sites for T₄ on membranes isolated from both control and infected rats. T₄ maximum binding capacity (MBC) of the high affinity sites decreased significantly as the infection became more severe. However, the affinity of these receptors did not change. Neither MBC nor affinity of the low affinity sites was altered by infection. The observed decrease in MBC of the high affinity binding sites for T₄ on hepatic plasma membranes cannot account for the decrease in serum T₄ or the hepatic metabolic alterations also known to occur during *S. pneumoniae* infection.

PUBLICATION: Little, J.S. The Effect of *Streptococcus pneumoniae* Infection on the Binding of Thyroxine to Purified Rat Liver Plasma Membranes. *Endocrinology*, in press.

PRESENTATIONS: Little, J.S.: Effect of *Streptococcus pneumoniae* Infection on the Binding of Thyroxine to Plasma Membranes Isolated from Rat Liver. Presented: The Society of Armed Forces, Medical Laboratory Scientists, San Antonio, Texas, 19-23 March 1983. *Fed Proc* 12: 27, 1983.

IBID: The Federation of the American Society for Experimental Biology, Chicago, Ill., 10-15 April 1983, *Fed Proc* 42:324, 1983.

STATUS: (O)

TITLE: Mechanism of HCG in Spermatogenesis During Testosterone Suppression

PRINCIPAL INVESTIGATOR: COL Stephen R. Plymate, MC

PROFESSIONAL ASSISTANTS: COL Bruce Fariss, MC
LTC George Ward, VC
Mina Garrison, MT

WORK UNIT NO: 80/70

TECHNICAL OBJECTIVE

To determine if, during testosterone suppression, spermatogenesis which is reinitiated by HCG is due only to a rise in testicular testosterone or if HCG also stimulates androgen binding protein production.

METHOD

Three groups of male rats >90 days old (20 rats/group) will be studied. Initially, each animal will have serum drawn for LH, prolactin, FSH, and testosterone, and a unilateral orchiectomy will be done on each animal with the testicular contents assayed for androgen binding protein, testosterone, estradiol, and dihydrotestosterone plus histology. For six weeks, Group I (control group) will be injected with sesame oil alone. Groups 2 and 3 will be injected with testosterone propionate and sesame oil at a dose of 150 µgm/100 gm body weight. Then, for six more weeks both groups will continue to receive the testosterone propionate and Group 3 will also receive the HCG at a dose of 6 U/100 gm body weight daily. Group I will continue to receive the sesame oil alone. At the end of this six week period, each animal will again have serum drawn for prolactin, FSH, LH, and testosterone, and the animal will then be sacrificed with the other testicle removed and assayed for androgen binding protein, testosterone, estradiol, and dihydrotestosterone as well as histology.

PROGRESS

(82 10 - 83 09) During FY 83, the investigators confirmed the findings that long-term treatment (56 days of HCG and testosterone) significantly lowers intratesticular testosterone. This decrease in testosterone is associated with a significant increase in intratesticular estradiol and a progressive loss of LH/HCG plasma membrane receptors. A paper has been submitted to the Journal of Reproductive Biology.

PRESENTATIONS: Mechanisms of Prolactin Regulation of Testicular Function; Endocrine Society Meeting, 17 Jun 81. Abstract #56, p 96.

Effect of Chronic Administration of Testosterone and Human Chorionic Gonadotropin on Testicular Function. Pacific Coast Fertility Society, Palm Springs, CA, 16 Oct 81; abstract #48.

STATUS: ()

TITLE: Testosterone and HCG Effects on Testicular Steroidogenesis

PRINCIPAL INVESTIGATOR: COL Stephen R. Plymate, MC

PROFESSIONAL ASSISTANTS: COL Bruce L. Fariss, MC
MAJ Stanley Liebenberg, VC
MAJ Allan Avbel, MC
SSG James Hayes
Louis Matej, B.S.

WORK UNIT NO: 81/92

TECHNICAL OBJECTIVE

To determine the mechanism of inhibition of intratesticular testosterone production by HCG and testosterone.

METHOD

Six groups of adult male Wistar rats >250 gm will have baseline serum drawn for LH, FSH, and testosterone. All animals will be kept on a 14 hour light, 10 hour dark cycle. Group A will receive sesame oil twice weekly for 12 weeks. Group B will receive 150 µgm/100 gm BW testosterone enanthate twice weekly for 12 weeks. Group C will receive 150 µgm/100 gm BW testosterone enanthate twice weekly for six weeks and the same regimen plus 18 U HCG QD for an additional six weeks. Group D will receive 300 µgm/100 gm BW testosterone enanthate for six weeks and the same regimen plus 18 U HCG QD for an additional six weeks. Group E will receive 150 µgm testosterone enanthate/100 gm BW plus 18 U HCG twice weekly for six weeks, and the same regimen plus the addition of Teslac 5 µgm daily for six more weeks. Group F will receive 150 µgm testosterone enanthate/100 gm BW twice weekly for six weeks and then 18 U HCG daily plus 10 mg Teslac twice a day for six weeks. After the 12 weeks, blood will again be drawn, the animals sacrificed, the testes, and epididymis removed, weighed, and frozen. Intratesticular DHT, E₂, and ABP will be measured in the testicle and androgen binding protein measured in the epididymis. Histology will be performed to include mean seminiferous tubule diameters.

PROGRESS

(82 10 - 83 09) The technical portion of this protocol has been completed, and a paper is in preparation. This study demonstrated that administration of testosterone and HCG had a greater effect on suppression of testicular testosterone levels than administration of testosterone alone. Testosterone alone lowered intratesticular testosterone by LH suppression and increased intratesticular E₂.

Testosterone and HCG Effects on Testicular Steroidogenesis -
Plymate

The combined effect of HCG and testosterone appeared to be by further increases in intratesticular E₂ as well as greater suppression of serum LH.

PRESENTATION: Influence of Long Term Testosterone (T) and Human Chorionic Gonadotropin (HCG) Administration on Intratesticular Testosterone. 3rd Annual Military Endocrinologists Meeting, San Francisco, CA, 15 June 1982.

STATUS: (O)

TITLE: The Effect of Opiate on the Release of Gonadotropins
in the Female Rhesus Monkey

PRINCIPAL INVESTIGATOR: COL Stephen R. Plymate, MC

PROFESSIONAL ASSISTANT: MAJ Stanley P. Liebenberg, MC

WORK UNIT NO: 81-93

TECHNICAL OBJECTIVE

To further study the effects of endorphins on the hypothalamic-pituitary gonadal axis of the female Rhesus monkey. Opiate compounds have been shown to release LH from the glands of humans. It is well known that the morphine-addicted human can become hypogonadotropic.

METHOD

Six female Rhesus monkey monkeys will be addicted to morphine. When they become amenorrheic with maintenance of their weight by appropriate food supplement and have not lost significant body weight, gonadotropins will be drawn every 10 min for 1 hr and 20 minutes. Next, a bolus of naloxone will be given and samples drawn for 120 minutes. The animals will be continued on morphine and 2 weeks later given a bolus of LH releasing hormone with samples for gonadotropins drawn every 10 min for 120 minutes. The animals will then be withdrawn from the morphine and again a bolus of naloxone will be administered during the luteal phase of the menstrual cycle with serum samples drawn every 10 min for 120 min before and after administration of naloxone. Samples will be assayed for progesterone to determine the point of time in the menstrual cycle. Menstrual cycle timing will be determined by watching sex skin swelling. LH will be measured by Leydig cell bioassay. Data will be analyzed by appropriate T test and linear regression.

PROGRESS

(82 10 - 83 09) This study demonstrated a significant suppression of LH by chronic morphine sulphate addiction unrelated to weight loss and this suppression was also seen with acute morphine sulphate administration when a sensitive bioassay for LH was used. This suppression is reversed by Naloxone. A paper to be submitted for publication is in preparation.

The Effect of opiates on the Release of Gonadotropins in the
Primate - Plymate

PRESENTATIONS: Bimodal Effects of opiates in LH secretion in the
Primate. HSC Annual Clinical Investigation
Conference, Sep 81, San Antonio, TX.

Morphine Sulfate Addiction Suppresses Gonadotropin
Secretion in the Female Primate. *Abstracts of the*
64th Annual Meeting, The Endocrine Society, San
Francisco, CA, 16 June 1982. Abstract #579,
Abstracts of the 64th Annual Meeting of The
Endocrine Society, June 1982.

IBID, 3rd Annual Meeting, Military Endocrinologists
Society, San Francisco, CA, 15 June 82.

STATUS: (C)

TITLE: Differentiation of Luteinizing hormones From Different
Animal Species Utilizing the HPLC

PRINCIPAL INVESTIGATOR: COL Stephen R. Plymate, MC

PROFESSIONAL ASSISTANTS: COL Bruce I. Fariss, MC
MAJ Willis H. Jacob, MSC

WORK UNIT NO: 82/23

TECHNICAL OBJECTIVE

To determine if high pressure liquid chromatography can be a means by which the pituitary gonadotrophins can be separated and quantitated between species.

METHOD

Various nanogram amounts of LH ranging from 1-50 ng/ml will be assayed by the HPLC using the protein 125 column. Human, primate, ovine, rat, and rabbit LH will be assayed. Human LH which has been labelled by chloramine-T or lactoperoxidase will also be used. The same concentrations of LH will then be added to the mouse Leydig's cell bioassay system. The results between these two techniques will be compared as well as the points at which the various LH's are detected on the HPLC. The statistical analysis will be performed by linear regression and T tests.

PROGRESS

(32 10 - 33 09) In the previous year, 125 I-DHT linked to SHBG, using P-125 columns in tandem, has been separated. Using a high salt gradient, SHBG has successfully been isolated.

STATUS: TO

TITLE: Effect of HCG and T on Regulation of Leydig Cell Function

PRINCIPAL INVESTIGATOR: COL Stephen R. Plymate, MC

PROFESSIONAL ASSISTANTS: COL Bruce L. Fariss, MC
MAJ James S. Little, MSC
John White, Ph.D.
Mina Garrison, M.T.
Louis Matej, M.T.

WORK UNIT NO: 82-67

TECHNICAL OBJECTIVE

To expand further the studies which the investigators have reported showing the relationship between LH and testosterone (T) in regulating testosterone production. The current study is designed to determine the time course of events following HCG administration to testosterone suppressed animals by determining changes in intratesticular testosterone and LH receptors at specified intervals following HCG administration.

METHOD

Male Wister rats >90 days and weighing 200-250 gms will be given testosterone enanthate 150 μ gm/100 gm body weight IM biweekly for six weeks and control animals will be injected with sesame oil. This will be time zero time. Eight control and eight treatment animals will be sacrificed at this point. Then HCG 18 IU each day will be started on all animals treated with T and control animals will be injected daily with saline. Eight control and eight treatment animals will be sacrificed at 3, 7, 14, 28, and 56 days after zero time and trunk blood collected. Testes and epididymae will be removed, trimmed of fat, weighed, and frozen at -70°C until assayed. Serum will be separated and frozen until assayed. Serum will be analyzed for T and LH. Testes will be analyzed for T, E_2 , ABP, and HCG receptors. Testes from six control and six treatment animals sacrificed at 7, 28, and 56 days will be prepared for electron-microscopy. Electron-microscopy and stereological analysis of the smooth endoplasmic reticulum in the Leydig cells will be performed. Serum T and LH will be performed by RIA. The testes, while still frozen, will be cut in half. One half along with the epididymis, will be thawed and homogenized in a phosphosaline buffer pH 7.4 with 6 ml used per gm of tissue. This homogenate will then be assayed for T, E_2 , and ABP and results expressed per ng of protein. The other half of the testes will then be assayed for HCG/LH receptors. Comparison between groups will be made using the non-paired Student's T test or a non-parametric test such as the Mann Whitney test.

Effect of HCG and LH on secretory and Leydig cell function - 14 plate

Group 1

(82 10 - 83 09) During this phase of the present test-sterone study, a sequential increase in test-sterone was noted during the first seven days of stimulation. However, after that point in time up to 56 days, there was a gradual decrease in test-sterone. The testicular and epididymal extracts have not yet been examined.

STATUS: (0)

TITLE: Evaluation of Metabolic Effects of Micronized Oral
Estradiol and Progesterone Combinations

PRINCIPAL INVESTIGATOR: COL Stephen R. Plymate, MC

PROFESSIONAL ASSISTANTS: Donald E. Moore, M.D., Univ of Washington
Robert H. Knopp, M.D., Univ of Washington
Louis Matej, M.T., DAC

WORK UNIT NO: 83/11

TECHNICAL OBJECTIVE

To test basic biochemical parameters of toxicity in women ingesting combinations of estradiol/norgestrel as an oral contraceptive. Acceptability, relative potency, and ovulation suppressive ability will be tested.

METHOD

Two studies are planned. In the first study, after one control non-treatment cycle, four groups of twelve women will daily ingest various combinations of norgestrel plus estradiol, for 21 days out of a 28 day cycle. D-1-norgestrel (300 µg) or levonorgestrel (150 µg) and 0.5, 1, 2, and 4 µg of micronized estradiol will be tested. A control group of 12 women will ingest 300 µg of d,1-norgestrel or 150 µg of levonorgestrel plus 30 µg of ethinyl estradiol. Serum levels of progesterone will be obtained weekly in order to detect any ovulation that might occur. Any abnormal bleeding, nausea, headaches and other symptoms will be recorded. Pharmacodynamic responses will be studied by measuring serum levels of estrone and estradiol. Relative estrogen potencies will be compared by measuring serum levels of sex steroid binding protein (SBP-BC). Biochemical measures of liver and renal function, the coagulation, lipid, cholesterol, and endocrine systems will also be studied. Each subject's non-treatment cycle biochemical levels will act as a control value. Data will be analyzed using the paired t test or the Wilcoxon matched-pairs signed-ranks test.

In the second study, the combination from the first study that is associated with no evidence of ovulation, good menstrual cycle control, tolerable side effects, little or no change in the biochemical parameters, and little or no elevation of SBP-BC will be given to 60 women for six cycles, preceded by one control non-treatment cycle and followed by two control non-treatment cycles. The same control medication as above will be used in a group of 24 women. The same biochemical tests will be performed. If toxicity indices are low, the medication is well tolerated, and ovulation is completely inhibited, further clinical trials using lower combinations of norgestrel and estradiol will be proposed.

Evaluation of Metabolic Effects of Micronized Oral Estradiol and Progesterone Combinations - Plymate

PROGRESS

(82 10 - 83 09) Twelve women who had normal menstrual and fertility histories with ovulation documented by a rise in basal body temperature had daily blood samples drawn during a menstrual cycle. In ten subjects a significant increase in mean SHBG was noted in the luteal phase and immediately following the preovulatory increase in E₂ (P<0.001). In two of the subjects, the rise in SHBG was not significant. In these subjects, there was a significant rise in E₂ prior to the LH surge, but no increase in luteal phase E₂ compared to early follicular levels.

	Follicular Phase	Pre- Ovulation	Luteal Phase	
SHBG-All Subjects ng DHT bound/ml (SEM)	15.7 0.60	19.4 0.7	20.8 1.55	P<0.001
SHBG-s Luteal *	21.1 1.5	21.4 1.7	23.7 1.9	N.S.
		P<0.001		
	P<0.001			
E ₂ pg/ml-All Subjects	69 3.5	170 12.3	149 12	
E ₂ pg/ml s SHBG *	37.4 2.6	63.5 7.9	32.7 2.1	
	P<0.01			
		N.S.		

Associated with a failure of a rise in luteal phase E₂ was a significantly lower level of LH by both bio and RIA during the mid-cycle LH surge compared to subjects with a rise in SHBG postovulation (546 125 ng/ml vs 895 50 ng/ml; P<0.02). There was no difference in FSH between the groups. This study demonstrates that SHBG changes during the menstrual cycle corresponding with E₂ changes. SHBG is a sensitive marker of estrogen status in women.

PRESENTATIONS: Plymate, S.R., Moore, D.E., Matej, L.A., and Fariss, B.L.: Sex Hormone Binding Globulin Increases During the Menstrual Cycle. Presented to Society of Uniformed Endocrinologists Annual Meeting, San Antonio, Texas, 7-8 June 1983.

Plymate, S.P., Moore, D.E., Matej, L.A., Bremner, W.J., and Fariss, B.L.: Sex Hormone Binding Globulin Increases During the Menstrual Cycle. Presented to the 65th Annual Meeting, the Endocrine Society, San Antonio, Texas, 8-10 June 1983.

STATUS: (0)

TITLE: Effect of Weight Loss on Changes in Sex Hormones in the Obese Anovulatory Polycystic Female

PRINCIPAL INVESTIGATOR: COL Stephen R. Plymate, MC

PROFESSIONAL ASSISTANTS: COL Bruce L. Fariss, MC
LTC Richard P. Belts, MC
CPT Frederick E. Harlass, MC

WORK UNIT NO: 83/57

TECHNICAL OBJECTIVE

To determine if weight loss can cause a return to normal of the gonadotropin and sex steroid changes in the obese woman with polycystic ovarian syndrome.

METHOD

PATIENT SELECTION: Ten obese women who are at least 80% greater than ideal body weight, who have not had a menstrual period for three months, and who have not taken sex or steroid hormones prior to entering into this study. Patients with elevated prolactin or FSH will be excluded.

Routine baseline blood samples will be drawn for LH, FSH, prolactin, testosterone, sex hormone binding globulin, and estradiol, and three cc's every 10 minutes for four to six hours with an in-dwelling catheter to determine LH pulse amplitude and frequency. The women will then be placed on a weight reduction diet and followed until they go off the diet, are within 20% of their ideal body weight, or have a return of two normal menstrual cycles. Following two cyclic menses with ovulation as documented by luteal phase progesterone measurements, blood will again be drawn for LH, FSH, prolactin, testosterone, SHBG and E₂ along with blood sampling for pulse amplitude and frequency. Sampling will be done during the early follicular phase of their menstrual cycle. Statistical analysis will be done by paired Student's t test, simple linear regression analysis, and ANOV where applicable.

PROGRESS

(83 03 - 83 09) Six infertile anovulatory women with a body mass index (W/H^2) ≥ 30 were placed on a weight reduction diet and followed weekly until cyclic ovulation returned. The return of ovulation was documented by serum progesterone measurement. The mean percent decrease in weight was 10.8 \pm 3.2. LH pulse frequency and amplitude were both significantly decreased after

Effect of Weight Loss on Changes in Sex Hormones in the Obese Anovulatory Polycystic Female - Plymate

weight loss (P<.05). Mean blood hormone measurements before and after weight loss are seen in the following table:

	SHBG ng DHT Bound/ml	T ng/ml	LH ng/ml	FSH ng/ml	α -Lipotropin
Before Weight Loss	1.59 0.76(SEM)	0.89 0.08	34 4.6	3.9 0.9	0.64 ± 0.03
After Weight Loss	2.02 0.73	0.67 0.09	21 0.7	5.1 0.6	0.68 ± 0.04
P	.01	.01	<.01	<.05	<.01

There was no significant change in estradiol. This study demonstrated that weight loss with return of ovulation is associated with a return to normal of both gonadotropins and sex steroids.

Presented at the 1983 Annual Meeting of the Society of Endocrinologists and Metabolic Physicians, San Antonio, Texas, 1983.

Address correspondence to: Dr. R. P. Holt, Department of Obstetrics and Gynecology, University of Texas Medical Branch, P.O. Box 30000, Galveston, Texas 77550. Presenting Author. Address reprint requests to Dr. R. P. Holt, Department of Obstetrics and Gynecology, University of Texas Medical Branch, P.O. Box 30000, Galveston, Texas 77550.

Holt, R.P., Plymate, S.H., Ertter, J.L., and
Holt, R.P.: Weight Loss Corrects Gonadotropin and
Sex Steroid Abnormalities of Polycystic Ovarian
Disease. Presented to Society of Endocrinologists
and Gynecologists Annual Meeting, San Antonio, Texas,
2-3 June 1983

Holt, R.P., Plymate, S.H., Ertter, J.L., and
Holt, R.P.: Weight Loss Corrects Gonadotropin and
Sex Steroid Abnormalities of Polycystic Ovarian
Disease. Presented to Society of Endocrinologists
and Gynecologists Annual Meeting, San Antonio, Texas,
2-3 June 1983

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

PRINCIPAL INVESTIGATOR: COL Stephen R. Plymate, MC

PROFESSIONAL ASSISTANTS: COL Bruce L. Fariss, MC
LTC Gary L. Treece, MC
MAJ Stanley P. Liebenberg, VC
CPT Karl E. Friedl, MSC
Mina J. Garrison, DAC, M.T.
Louis A. Matej, DAC, M.T.

WORK UNIT NO: 83/83

TECHNICAL OBJECTIVE

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

METHOD

Six female beagles, not in estrus, will have three baseline serums drawn for T₄, T₃ uptake, T₃ RIA, TeBG, testosterone, androstenedione, and estradiol weekly for a three week baseline period. The animals will be weighed weekly and then allowed unlimited access to food with decreased exercise. Weekly blood samples will again be drawn until the animals have gained 30% of their starting body weight. At that point in time the animal's food intake will be determined and the weight maintained at the 30% level. The animals will then be given two subcutaneous injections (two days apart) of estradiol valerate (40 mg). One and two weeks after the last injection, the previously mentioned blood samples will again be drawn. Next, the animals will be given tamoxifen, an antiestrogen, at a dose of 10 mg twice a day intramuscularly and TeBG levels again drawn one week and two weeks after tamoxifen administration. The animals will then be allowed one month's rest while maintaining their weight at 30% above their ideal body weight. Baseline studies as mentioned above will then be obtained weekly for two weeks. Then the animals will be given 1 mg of levothyroxine intramuscularly weekly for two weeks, and blood studies will be repeated at the time of the second injection and for three weeks after the administration of levothyroxine. A similar group of six normal weight female beagles, age-matched and not in estrus, will be studied with similar blood drawings and administration of medications; however, the animals will be maintained at their ideal body weight.

PROGRESS

(83 09 - 83 09) Animals and materials are being collected. The protocol will commence in November 1983.

STATUS: (0)

TITLE: Evaluation of Efficacy of Varicocele Repair

PRINCIPAL INVESTIGATOR: COL Stephen R. Plymate, MC

PROFESSIONAL ASSISTANTS: MAJ Brian Miles, MC
C. A. Paulsen, M.D.
Richard E. Burger, M.D.

WORK UNIT NO: 83/84

TECHNICAL OBJECTIVE

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

METHOD

Four groups (75 men each) will be studied: (1) infertile men who are going to have their varicoceles repaired, (2) infertile men without varicoceles; (3) fertile men who have varicoceles, 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 eight to ten semen analyses performed, two sperm penetration assays performed at least four weeks apart, and two LH/RH stimulation tests performed using 200 mg of LH/RH. Blood samples will be drawn every 15 minutes for two hours after the injection of the LH/RH. Following repair of the varicocele, the men will have a seminal fluid analysis performed every two to four weeks, sperm penetration assay performed at six months and twelve months after the varicocele ligation, and LH/RH again performed at six and twelve months after the varicocele ligation.

PROGRESS

(83 09 - 83 09) Fifty-nine subjects have been enrolled and begun the testing.

STATUS: (0)

TITLE: Role of Depression in Modulation of Hypothalamic-Pituitary-Gonadal-Axis

PRINCIPAL INVESTIGATOR: COL Stephen R. Plymate, MC

PROFESSIONAL ASSISTANTS: COL Bruce L. Fariss, MC
Thomas Lampe, MD, American Lake VA Hospital
Steve R. Risse, MD, American Lake VA Hospital

WORK UNIT NO: 83/85

TECHNICAL OBJECTIVE

To evaluate the hypothalamic gonadal function in a biochemically defined depressive state in order to further define the role of neurotransmitters in both the depression and the control of the hypothalamic-pituitary-gonadal (HPG) axis.

METHOD

Subjects: Ten women and ten men admitted for depression who have nonsuppressible DST as defined by a cortisol level greater than 5 $\mu\text{g/dl}$ after 1 mg dexamethasone given at 2300 hours and plasma cortisol measured at 0800, 1600, and 2300 hours the following day. Following the DST at 0800 hours, a 200 mg bolus of LH/RRH will be given IV. Blood samples will be drawn at -15, 0, 15, 30, 45 and 60 minutes for LH, FSH, and prolactin. This will be followed by a 100 μg bolus of TRH with blood samples drawn at 60, 75, 90, 105 and 120 minutes for prolactin, TSH and growth hormone. When the DST returns to normal the studies will be repeated on all patients. Any patients on phenothiazines will be excluded from the study. In addition the -15 and zero time samples will have β -lipotropin, ACTH, β -endorphin, testosterone, estradiol, and sex hormone binding globulin measured. The female patients will have a menstrual history noted. If they are cycling, the time of the blood drawing in relationship to their cycle will be calculated and confirmed by measurement of serum progesterone.

PROGRESS

(83 09 - 83 09) This protocol is to begin in November 1983.

STATUS: (0)

DETAIL SHEETS
FOR
PROTOCOLS

9TH INFANTRY DIVISION

TITLE: Ranger Medic Procedures Training

PRINCIPAL INVESTIGATOR: CPT Robert E. Kane, MC

PROFESSIONAL ASSISTANT: MAJ Stanley P. Liebenberg, VC

WORK UNIT NO: 83/34

TECHNICAL OBJECTIVE

To provide training to acquire the necessary manipulative skills in performing emergency life-saving measures in support of wartime field operations.

METHOD

The Medical Platoon of the 2/75th Infantry (Ranger) consists of two MC officers and approximately 20 additional enlisted personnel (MOS 91B). Each of these 20 personnel will be trained on a quarterly basis. Classes will be conducted monthly utilizing the two MC officers as preceptors, training 6-7 Ranger medics at each session.

Two mongrel dogs will be used for each training class with the exception of debridement exercises which will each use four sheep as animal models. All animals will initially be anesthetized with sodium pentobarbital with anesthesia maintained by halothane throughout the duration of each class. Wounds for debridement will be caused by a Captive Bolt Pistol. Upon completion of the exercise, all animals will be euthanized by lethal injection of sodium pentobarbital without allowing the animal to regain consciousness. The carcasses will be disposed of by incineration. Procedures to be performed on dogs consist of:

Periphreral venous cutdown (femoral/jugular)	Pericardiocentesis
Tube thoracotomy (chest tube insertion)	Peritoneal lavage
Resuscitative techniques	Suturing techniques
Reversal of hypovolemic shock	Cricothyroidotomy

PROGRESS

(83 01 - 83 09) Training sessions have been conducted as planned. Some of the medics involved in this training were involved in the fighting in Grenada and point out that information gained in this training improved their performance both from a hands-on and a confidence perspective. All persons involved feel that this program needs to be continued on a monthly basis to maintain skill levels and to train in-coming medics.

STATUS: (0)

DETAIL SHEETS
FOR
PROTOCOLS

DEPARTMENT OF EMERGENCY MEDICINE

TITLE: Emergency Room Procedure Training

PRINCIPAL INVESTIGATOR: MAJ Steven C. Drönen, MC

PROFESSIONAL ASSISTANTS: LTC Samuel T. Coleridge, MC
MAJ Stanley P. Liebenberg, VC

WORK UNIT NO: 82/25

TECHNICAL OBJECTIVE

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

METHOD

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 catheterization
2. Peritoneal lavage
3. Tube thorostomy
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. Sengstaken-Blakemore tube placement
8. Auto transfusion from hemothorax
9. Twist drill decompression
10. Skull Trephination

PROGRESS

(82 09 - 83 09) Incoming Emergency Medicine Residents were trained as a part of their orientation program.

STATUS: (0)

TITLE: The Use of Naloxone in the Management of Hemorrhagic Shock

PRINCIPAL INVESTIGATOR: MAJ Steven C. Dronen, MC

PROFESSIONAL ASSISTANTS: CPT Richard Foutch, MC
CPT Karl Friedl, MSC
CPT Peter Maningas, MC

WORK UNIT NO: 83/82

TECHNICAL OBJECTIVE

To evaluate the effect of the opiate antagonist naloxone on various cardiovascular and biochemical parameters in the setting of hemorrhagic shock.

METHOD

Twelve (12) dogs will be divided into three groups. Group I dogs (six) will receive naloxone, a 2 mg/kg bolus followed by 2 mg/kg/hr as an injection prior to phlebotomy. They will then be bled and reinfused according to the protocol described below. Group II dogs (three) will be bled and reinfused according to the protocol. Group III dogs (three) will not be bled or reinfused but will undergo all other steps in the protocol as described below, receiving naloxone in the same fashion as Group I.

Each dog will be given water but no food 18-24 hours prior to experimentation. The dogs will be anesthetized 30 minutes prior to phlebotomy with 30 mg/kg of IV pentobarbital. Additional anesthesia will be in 2 mg/kg increments to maintain the desired level of sedation. The dogs will be placed in the left lateral decubitus position and tracheally intubated with a cuffed tube. A Swan-Ganz catheter will be placed via cutdown on the right external jugular vein. The left femoral artery will be cannulated with PE 205 tubing. Vascular pressures (blood pressure, central venous pressure, and pulmonary capillary wedge pressure) will be measured by quartz transducers and recorded on a multichannel oscillograph. Blood pressure measurements will be interrupted only for blood sampling and phlebotomy. Central venous pressure measurements will be continuous. After two-point calibration, P_{tCO_2} and P_{aCO_2} electrodes will be placed on the abdomen of the dog. The electrode temperatures will be 44° and 45°, respectively.

Baseline arterial, venous, and mixed venous blood samples will be drawn prior to hemorrhage for determination of control pH, pO_2 , pCO_2 , MVO_2 , Hgb , and serum lactate. Cardiac output will be determined by the standard thermodilution technique. Simultaneous recording of P_{tCO_2} and P_{aCO_2} will be done at each sampling period.

The Use of Naloxone in the Management of Hemorrhagic Shock -
Dronen

Serum lactate levels will be measured photometrically by the modified Marbach and Weil method. The volume of blood samples will remain constant and will be included in the total amount of blood to be withdrawn. Forty percent (40%) of the calculated blood volume (approximately 35 cc/kg) will be aspirated by syringe from the femoral artery catheter over a 30 minute period with 1/5 of the total volume being withdrawn during the first 5 1/2 minutes of each six minute period. Syringes will be changed and sequential arterial, venous, and mixed venous blood samples will be taken during the last 30 seconds of each six minute period. After the total amount of blood is withdrawn, the dog will under a 60 minute period of stabilization with four sampling periods 15 minutes apart. The dog will be reinfused at the same rate and with the same volume of blood withdrawn, minus the amount taken for blood samples. At the end of reinfusion, the dog will undergo a one hour period of stabilization and observation. Repeat blood samples will be taken every 15 minutes during that time. At the end of the hour, all catheters will be removed, cutdown sites sutured, and the dog extubated after achieving the appropriate level of consciousness.

PROGRESS

(83-09 - 83-09) Animals and materials are being assembled.

STATUS: (0)

TITLE: hemodynamic Responses to Application and Removal of Nitroglycerin Ointment in Normal Subjects

PRINCIPAL INVESTIGATOR: MAJ Kenneth Frankin, MC

PROFESSIONAL ASSISTANTS: CPT Ted A. McMurry, MC

WORK UNIT NO: 82/17

TECHNICAL OBJECTIVE

To determine the temporal characteristics of the action of topically applied nitroglycerin on pulse and blood pressure volunteers. The onset of action, time required for maximal hemodynamic response, and the time for return to baseline values after the ointment has been removed will be measured.

METHOD

Sixteen (16) healthy male volunteer subjects with a normal blood pressure and pulse without orthostatic changes during the baseline phase of the experiment will be used. An automated Critikon blood pressure cuff and an automatic dental chair in the fully erect position will be used. Initially, orthostatic vital signs will be taken. Patients will then have pulse and blood pressure taken after being supine for two minutes and again after two minutes of standing. Those with a decrease in systolic blood pressure of 20, a decrease in diastolic blood pressure of 10, or a rise in pulse of >20 beats /minute will be excused from the study. Non-orthostatic patients will then sit erect in the chair and pulse and blood pressure will be recorded automatically by the device every two minutes for 14 minutes (baseline). Two inches (30 grams) of 2% nitroglycerin ointment will then be applied to a 33 cm² area at the left costal margin in the midclavicular line. Blood pressure and pulse will be recorded every two minutes by the machine and also by a physician. Symptomatic hypotension will be treated by Trendelenberg position and other standard means. After 40 minutes of continuous monitoring, one half of the patients (randomly assigned) will have the nitroglycerin paste completely wiped off with a clean terrycloth towel. Monitoring of these patients will continue for another 60 minutes. The control subjects will have the paste left on and will be monitored for the same period of time.

PROGRESS

(82 09 - 83 09) A total of seven subjects has been entered in the study. Reproducible effects on baseline pulse and blood pressure were not obtained with the nitroglycerin doses specified in the protocol. Further work with subjects either standing or given increased nitroglycerin doses also yielded poorly reproducible results. Further work is planned.

STATUS: (0)

TITLE: The Utility of Base Deficit as a Parameter in the Evaluation of Hemorrhagic Shock

PRINCIPAL INVESTIGATOR: CPT Peter A. Maningas, MC

PROFESSIONAL ASSISTANTS: COL Bruce L. Fariss, MC
MAJ Steven C. Dronen, MC
MAJ Stanley P. Liebenberg, VC

WORK UNIT NO: 83/58

TECHNICAL OBJECTIVE

To evaluate the usefulness of the calculated base deficit as a parameter for the diagnosis, management, and prognosis of hemorrhagic shock.

METHOD

Ten dogs (within a specific weight range) will be given water but no food 18-24 hr prior to experimentation. The dogs will be anesthetized 30 minutes prior to starting bleeding and maintained with IV administration of pentobarbital, 30 mg/kg of body weight, restrained in the supine position, and tracheally intubated with a cuffless tube to maintain the airway. Cannulation of the external jugular vein with a Swan Ganz catheter and cannulation of the common carotid artery with a standard size angiocath will be done via a neck cutdown. Vascular pressures will be measured by quartz transducers and recorded on a multichannel oscillograph. The Swan Ganz catheter will allow constant monitoring of the central venous pressure and intermittent monitoring of the pulmonary capillary wedge pressure. Mixed venous blood gases may be obtained via the distal port of the Swan Ganz catheter. Next, the femoral artery and vein will be cannulized via a femoral cutdown. Blood samples will be withdrawn from the ligated vessels.

Baseline arterial, venous, and mixed venous blood samples will be drawn prior to hemorrhage for determination of control pH, pCO₂, base deficit, MVO₂, and serum lactate. Base deficit is calculated simultaneously using a formula based on the Siggard-Andersen Nomogram. Serum lactate levels will be measured photometrically by the modified Marbach and Weil method. The volume of blood samples will remain constant and will be included in the total amount of blood to be withdrawn. The amount of blood to be withdrawn will be 50% of the calculated blood volume (approximately 44 cc/kg). This volume will be aspirated by syringe from the femoral artery catheter over a 30 min period with 1/5 of the total volume being withdrawn during the first 5 1/2 min of each 6 min period. Syringes will be changed and sequential arterial,

The Utility of Base Deficit as a Parameter in the Evaluation of Hemorrhagic Shock - Maningas

venous, and mixed venous blood samples will be taken during the last 30 sec of each six min period. After the total amount of blood is withdrawn, the dog will undergo immediate reinfusion at the same rate and with the same volume of blood withdrawn, minus the amount taken for blood gases and serum lactate levels. Sequential arterial, venous, and mixed venous blood samples will again be taken during the last 30 sec of each 6 min period for determination of pH, pCO_2 , base deficit, MVO_2 , and serum lactate levels. At the end of reinfusion, the dog will undergo a one hr period of stabilization and observation. Repeat blood samples will be taken every 15 min during that time. At the end of the hour, all catheters will be removed, cutdown sites sutured, and the dog extubated after achieving an appropriate level of consciousness.

PROGRESS

(83 04 - 83 09) Nine dogs were bled 40% of their calculated intravascular volume over thirty minutes (35 cc/kg). There were five sampling periods (H1-H5) at six minute intervals corresponding to an 8% reduction in intravascular volume during each period. A fall in PVO_2 and PCWP, which occurred after the initial withdrawal period, preceded a significant change in all other parameters. This was followed by a reduction in CVP and an increase in serum lactate after H2. P_{tCO_2} fell after H3 and base deficit increased after H4. Four dogs maintained mean arterial pressures greater than 70 mm Hg after hemorrhage. Six dogs had abnormally elevated base deficits during the control period despite normal lactate levels. Two dogs had normal lactate levels after hemorrhage. There was a poor correlation between CVP and PCWP, and only a fair correlation between base deficit and serum lactate. We conclude that of the parameters measured, PVO_2 and PCWP are the most sensitive indicators of intravascular volume changes during graded hemorrhage in the animal model. We recommend further investigation on the clinical utility of these parameters in the Emergency Department management of the traumatized patient at risk for significant hemorrhage.

A manuscript is in preparation.

STATUS: (C)

TITLE: Effect of Fluosol DA on Massive Theophylline Intoxication
in Rats

PRINCIPAL INVESTIGATOR: CPT Peter A. Maningas, MC

PROFESSIONAL ASSISTANTS: MAJ Steven C. Dronen, MC
MAJ Stanley P. Liebenberg, VC
CPT Karl E. Friedl, MSC

WORK UNIT NO: 83/71

TECHNICAL OBJECTIVE

To evaluate the effectiveness of partial exchange transfusion with Fluosol DA in reducing serum theophylline concentrations and mortality after massive intoxication in rats.

METHOD

Five groups (10 rats each) of male Sprague-Dawley rats weighing between 200-250 gms will be kept in an oxygen chamber filled with 100% O₂. Three of the groups will receive partial exchange transfusion with Fluosol DA after intoxication with intravenous aminophylline and then transfused to a final hematocrit of 4%, 7%, and 10%, respectively. The last two groups will serve as controls for both the exchange procedure and for the theophylline intoxication. One group will undergo exchange without theophylline infusion and the other group will undergo theophylline infusion without exchange. Each animal will be anesthetized with 30.0 mg/kg IV sodium thiopental. All animals will have both the carotid artery and the tail vein cannulated. Fifty milligrams (250 mg/10 cc) aminophylline will be injected into the tail vein of each animal over 2 minutes, with a 15 minute stabilization period after injection. Those animals undergoing exchange transfusion will be bled through the carotid artery at a rate of 5 ml/kg/min. Infusion of Fluosol DA will occur through the tail vein at the same rate. Final hematocrits of 10%, 7%, and 4% will be obtained after approximately 15, 20, and 25 times the number of repetitions, respectively. Each of the Fluosol DA treated groups will also undergo supplemental infusion equal to 1.5 ml/100 gm body weight at one hour post-transfusion. Blood samples will be withdrawn from all groups every 5 minutes for measurement of hematocrit, fluorocrit, (in the transfused group) and serum theophylline. Serum theophylline will be measured by HPLC. After transfusion, or the equivalent time period for the control group, catheters will be removed. The transfused groups will remain in 100% O₂ for the first 24 hours. Thereafter, they will be placed in 70% O₂, 30% N₂ until the hematocrit returns to at least 20%, whereupon they will be returned to room air. All animals will be returned to routine pre-experimental care.

TITLE: *Effect of Acute Myocardial Infarction on the Metabolism of*
Rats - Myocardial

PROGRESS:

(83 08 - 83 09) Preparation of special equipment necessary for this study has been completed: three oxygen tanks have been constructed in which rats can be weaned to room air after fluosol infusion and double lumen catheters have been prepared. Theophylline standards have been run on the HPLC, and this method of analysis will be suitable. Theophylline doses have been tested on several rats. The experiment has not proceeded further because the investigator has been unable to obtain a reciprocal infusion/withdrawal pump from manufacturers or local sources and the purchase of this item was omitted from the Capital Expense Fund listing.

STATUS: (0)

TITLE: The Utility of Transcutaneous PO_2 and PCO_2 as Parameters in the Evaluation of Hemorrhage and Impending Shock

PRINCIPAL INVESTIGATOR: CPT Peter A. Maningas, MC

PROFESSIONAL ASSISTANTS: MAJ Steven C. Dronen, MC
MAJ Stanley P. Liebenberg, VC
CPT Karl E. Friedl, MSC

WORK UNIT NO: 83/78

TECHNICAL OBJECTIVE

To evaluate the usefulness of transcutaneous PO_2 and PCO_2 monitoring for the early diagnosis and management of hemorrhage and impending shock.

METHOD

Eight to ten dogs will be given water but no food 18-24 hr prior to experimentation. The dogs will be anesthetized 30 minutes prior to starting bleeding and maintained with IV administration of pentobarbital, 30 mg/kg of body weight, placed in the left lateral decubitus position, and tracheally intubated with a cuffed tube to maintain the airway. Cannulation of the external jugular vein with a Swan Ganz catheter and cannulation of the left femoral artery with PE205 will be done. Vascular pressures will be measured by quartz transducers and recorded on a multichannel oscillograph. The Swan Ganz catheter will allow constant monitoring of the central venous pressure and intermittent monitoring of the pulmonary capillary wedge pressure. Mixed venous blood gases will be obtained via the distal port of the Swan Ganz catheter.

Baseline arterial, venous, and mixed venous blood samples will be drawn prior to hemorrhage for determination of control pH, pCO_2 , base deficit, MVO_2 , Hgb, and serum lactate. Cardiac output will be determined by standard thermodilution technique. Simultaneous recording of P_{tCO_2} and P_{vCO_2} will be done at each sampling period. Base deficit will be calculated simultaneously using a formula based on the Siggard Andersen Nomogram. Serum lactate levels will be measured photometrically by the modified Marbach and Weil method. The volume of blood samples will remain constant and will be included in the total amount of blood withdrawn. The amount of blood to be withdrawn will be 40% of the calculated blood volume (approximately 35 cc/kg). This volume will be aspirated by syringe from the femoral artery catheter over a 30 min period with 1/5 of the total volume being withdrawn during the first 5 1/2 min of each 6 min period. Syringes will be changed and sequential arterial, venous, and mixed venous blood samples will be taken during the last 30 sec of each six min

The Utility of Transcutaneous PO_2 and PCO_2 as Parameters in
the Evaluation of Hemorrhage and Impending Shock - Maningas

period. After the total amount of blood is withdrawn, the dog will undergo a 30 min period of stabilization with two sampling periods 15 minutes apart. After the stabilization period, the dog will be reinfused at the same rate and with the same volume of blood withdrawn, minus the amount taken for blood gases and serum lactate levels. Sampling and recording will again be done during the last 30 sec of each 6 min period. At the end of reinfusion, the dog will undergo a one hr period of stabilization and observation. Repeat blood samples will be taken every 15 min during that time. At the end of the hour, all catheters will be removed, cutdown sites sutured, and the dog extubated after achieving an appropriate level of consciousness.

PROGRESS

(83 09 - 83 09) Animals and materials are being assembled.

STATUS: (0)

TITLE: Clinical Application of Transcutaneous Oxygen Monitoring
in Emergency Department Patients

PRINCIPAL INVESTIGATOR: CPT Peter A. Maningas, MC

PROFESSIONAL ASSISTANTS: MAJ Steven C. Brown, MC
CPT Carl E. Friedl, MC

WORK UNIT NO: 83/79

TECHNICAL OBJECTIVE

To evaluate the clinical usefulness of transcutaneous oxygen monitoring for the early recognition and management of hemorrhage and impending shock in emergency department patients.

METHOD

Acutely traumatized patients triaged to the major resuscitation area based on a high potential for major injury will be utilized. Patients with a prior history of cardiovascular or respiratory disease will be excluded from the study. Each patient will be evaluated and resuscitated appropriately per ATLS guidelines. A $P_{tc}O_2$ electrode will be placed on the right deltoid after all standard prehospital resuscitative measures are completed. Each patient will undergo insertion of a CVP line for intermittent monitoring of central venous pressure. Fifteen minutes after electrode placement, an arterial blood gas will be obtained for measurement of PaO_2 , pH, base deficit, and serum lactate. $P_{tc}O_2$ will be continuously monitored. Blood pressure will be monitored each minute with a self-inflating cuff. CVP, pulse, and respirations will be recorded at each sampling period or as the patient's condition dictates. Additional sampling periods will occur at 15 minute intervals until transfer of the patient from the Emergency Department. Each patient will be followed for recognition of final outcome.

Serum lactate levels will be measured photometrically by the modified Weil and Marbach method. Base deficit will be calculated using a formula based on the Siggaard Andersen Nomogram.

A minimum of 20 patients will be studied. $P_{tc}O_2$ values will be compared by Student's t test to standard cardiorespiratory and biochemical parameters for the evaluation of hemorrhagic shock.

PROGRESS

(83 09 - 83 09) No work has been done to this date.

STATUS: (0)

TITLE: A System for Identifying Depression: Impacts and Costs

PRINCIPAL INVESTIGATOR: COL Barry W. Wolcott, MC

PROFESSIONAL ASSISTANTS: Robert W. Wood, M.D., Univ Washington
Staff, Department of Emergency Medicine

WORK UNIT NO: 83-07

TECHNICAL OBJECTIVES

To adapt to the Madigan setting a previously developed triage tool which will use only a few questions to help providers detect potential cases of depression; to implement the rule as part of a computerized triage/screening system for all walk-in patients at Madigan; and to assess the impact of the rule on: (1) process of care given by providers; (2) patient outcomes, including health status, satisfaction with care, and subsequent utilization; (3) utilization of health care services by family members, and (4) costs of care.

METHOD

This study will be done in conjunction with the University of Washington. A triage tool using only a few question to help providers detect potential cases of depression for further treatment has been developed at the University of Washington. Due to the preliminary nature of the study, this tool has not been examined for generalizability, performance, impacts, or costs of its use. The tool will be tested at Madigan, with minor modifications, in the Acute Minor Illness Clinic, utilizing patients that agree to participate and sign a volunteer agreement. In the second phase, after revisions based on computerized analysis of the first phase, the depression tool will be implemented at MAMC as part of a computerized triage system used for all walk-in patients. In the third phase, a randomized study in which half of the health care providers will be told the patient's probability of depression and half will not will be implemented to allow a determination of the impact of the tool on providers (do they prescribe more psychotropic drugs or make more referrals to behavioral/social services); patient outcomes (utilization, days lost from work, depression, health status, satisfaction with care); family care utilization (does improved recognition of depression in one patient change the health care utilization of other family members as well); and costs including provider care costs, drugs, and test utilization, as opposed to the costs of the triage system.

PROGRESS

(32-14 - 83-00) This protocol was not implemented due to the failure of the University of Washington to obtain a grant from the NIMH.

STATUS: (1)

DETAIL SHEETS
FOR
PROTOCOLS

DEPARTMENT OF FAMILY PRACTICE

TITLE: Diamine Oxidase Levels and Asthma in Pregnancy

PRINCIPAL INVESTIGATOR: CPT Julie Dacey, MC

PROFESSIONAL ASSISTANTS: MAJ James S. Little, MSC
MAJ Rebecca Sullivan, MC
CPT Diane J. Madlon-Kay, MC

WORK UNIT NO: 81/73

TECHNICAL OBJECTIVE

To determine if a correlation exists between serum diamine oxidase levels and disease activity in pregnant asthmatic women.

METHOD

Approximately 25 new obstetric patients who have had an asthma attack within the previous three years and a control group of 12 newly pregnant non-asthmatic women will have a detailed history taken. In particular, any history of allergy, hayfever, or smoking will be noted, and in asthmatics the frequency and severity of attacks and their treatment. In addition to the routine initial laboratory tests, the patients will have determinations of their diamine oxidase levels and spirometry measurements of FVC AND FEV. At every clinic visit, the asthmatic patients will be examined for wheezing and questioned in particular about their respiratory symptoms and medications. Every four weeks and at six weeks postpartum both the control and asthmatic patients will have spirometry and diamine oxidase determinations. The asthmatic patients' clinical conditions during pregnancy will be classified as worse, unchanged, or improved by evaluating the change in respiratory symptoms, severity of wheezing on physical exam, medication changes required, and spirometry. A chi-square analysis will be done to determine if any correlation exists between the diamine oxidase levels and the asthmatic patients' clinical conditions.

PROGRESS

(82 10 - 83 09) Five additional asthmatic patients were enrolled in FY 83. Data collection is now complete. Initial evaluation of the data did not identify a statistical difference between diamine oxidase levels in controls and asthmatic patients. However, there may be a difference between asthmatics who generally did well and those who did poorly during pregnancy. Further testing is planned using frozen serum to determine diamine oxidase levels in pregnant and nonpregnant asthmatic patients.

STATUS: (0)

TITLE: A Comparison of Nystatin and 1% Hydrocortisone Cream to Nystatin Alone in the Treatment of Diaper Rashes

PRINCIPAL INVESTIGATOR: CPT Matthew J. Gaspar, MC

PROFESSIONAL ASSISTANTS: MAJ James W. Higbee, MSC
CPT Cheryl Wofford, ANC

WORK UNIT NO: 83-87

TECHNICAL OBJECTIVE

To test the hypothesis that the use of Nystatin cream and 1% Hydrocortisone cream significantly increases the rate of healing of simple diaper rashes when compared to Nystatin cream alone, 1% Hydrocortisone cream alone, or a placebo.

METHOD

Approximately 200 untreated infants of both sexes from one to 24 months of age will be evaluated as to the presence of a typical irritant type diaper dermatitis or candidiasis. Infants with seborrheic, atopic, impetiginous, or bacterial type lesions will be excluded from the study. All infants will be graded initially as to the type of rash isolated, the amount of erythema, and the location of rash. The rash will be cultured by gently scrubbing the margins of the rash with a swab moistened in transport media. The swab will be plated on Sabouraud agar for yeast and fungal growth and on McConkeys' and blood agar for gram negative and gram positive growth respectively. A questionnaire will then be completed. Mothers will then be issued in a blind, randomized fashion: water-based cream; Nystatin cream; 1% Hydrocortisone cream, or Nystatin cream with 1% Hydrocortisone cream. Mothers will be instructed to apply the cream evenly to the affected area four times daily. No other medications will be permitted during the study period. A reassessment will be made as to the effect of treatment 10 to 14 days later and the lesions or site of the lesions recultured. An instruction sheet concerning general skin care and diapering techniques will be explained and the parents will be given a follow-up appointment in 7 to 10 days. At the conclusion of the study, the patient code will be broken and statistical analysis performed using the Mann-Whitney test for non-parametric data.

PROGRESS

(83 09 - 83 09) The coding of the medication and placebo has begun. No patients entered.

STATUS: (0)

TITLE: Exercise Prescription and Dietary Restriction for the Reduction of Weight and Cardiovascular Risk Factors.

PRINCIPAL INVESTIGATOR: CPT Gaspar Giorgi, MC

PROFESSIONAL ASSISTANT: MAJ Diana M. Barefoot, SP

WORK UNIT NO: 82/61

TECHNICAL OBJECTIVE

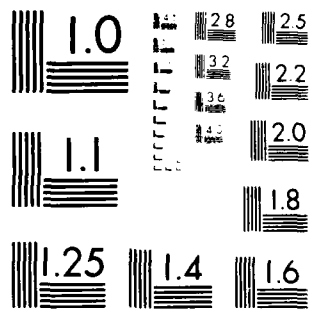
To establish through the aegis of the Family Practice Clinic a program of exercise therapy coupled with dietary restriction for the reduction of weight and other cardiovascular risk factors.

METHOD

Thirty (30) obese patients will be enrolled. Obesity will be defined according to the Metropolitan Life Insurance Tables. Patients 20-60 years of age are eligible; patients >35 will be screened by treadmill to determine functional capacity and the presence of latent cardiovascular disease; patients with established cardiovascular disease after a myocardial infarction or coronary bypass will not be allowed into the program; screening history and physical and labs pertinent for cardiovascular risk factors will be obtained before and after the program; routine chest x-ray and spirometry will be obtained in patients with a history of pulmonary disease. Laboratory screen will include CBC, SMA-20, HDL-cholesterol, triglycerides, and urinalysis. This will be an individual, rather than a group, exercise program and will consist of swimming or running. Patients will be admitted into the program bi-monthly. Exercise prescriptions utilizing a training heart rate zone for 20 minutes, 3 times a week, coupled with diet therapy appropriate for age and weight will be given at that time. Follow-up will be at 1 week and 2 weeks, and then monthly. Weight, compliance, and various cardiovascular performance and risk factors will be checked at each follow-up with further dietary and risk factor counselling at that time. Data from the program analyzing its success will be taken in 12 months.

PROCESS

(82 09 - 83 09) Over a period of 4-6 months, 17 participants lost an average of 6.5% of their initial weight. All participants lost weight except for one. Compliance was a large factor in weight loss; if a participant would loose weight. The need for more frequent sessions was important to many participants in regular sessions. Preliminary results show that if compliance is maintained, duty troops placed in such a program would be expected to lose weight and meet the objectives of the Army weight program.



MICROCOPY RESOLUTION TEST CHART
NATIONAL BUREAU OF STANDARDS-1963-A

Exercise Prescription and Dietary Restriction for the Reduction
of Weight and Cardiovascular Risk Factors - Giorgi

PRESENTATION: Giorgi, G, Barefoot, D, and DeWinne, C: Exercise
Prescription and Dietary Restriction for the
Reduction of Weight and Cardiovascular Risk Factors.
Presented to 10th Anniversary Family
Practice Alumni Conference, 28 Jan 83, MAMC.

STATUS: (C)

TITLE: Metronidazole Therapy for Nonspecific Vaginitis: 3 vs 7 Days

PRINCIPAL INVESTIGATOR: CPT Mark B. Mengel, MC

PROFESSIONAL ASSISTANTS: MAJ Shannon Harrison, MC
MAJ James Higbee, MSC
CPT William Watson, MC

WORK UNIT NO: 82/66

TECHNICAL OBEJCTIVES

To determine the effectiveness of 3 days of metronidazole therapy (500 mg po bid) vs 7 days (500 mg po bid) in the treatment of nonspecific vaginitis (NSV) and to determine if treatment of the male sexual partner of a woman with NSV reduces the rate of recurrence of that disease in previously cured women.

METHOD

Women 18-50 years of age who complain of abnormal vaginal discharge or vulvar itching, are non-pregnant, non-menopausal, have not used oral antibiotics or vaginal medications in the previous month, do not have clinical evidence of a mucopurulent cervical discharge or genital herpes, but do have negative wet-mounts for *Trichomonas vaginalis* and negative KOH prep for *Candida albicans* will be admitted to the study if their vaginal discharge fulfills two of the following four criteria: grey, homogenous discharge that adheres to the vaginal wall; pH >4.5; positive "clue cells" on wet mount or gram stain; or release of a "fishy" amine odor on addition of 10% KOH. Cultures will be taken from the vaginal vault for *G. vaginalis*, *T. vaginalis*, *C. albicans* and *N. gonorrhoea*. Women with positive cultures for the latter 3 organisms or negative cultures for *G. vaginalis* will be excluded from the study at the first follow-up visit. Epidemiologic data will include age, race, number of sex partners, marital status, contraceptive use, number of pregnancies, and rank. All women will then be given a 3-day supply of metronidazole and a 3 day supply of placebo or metronidazole for their sexual partner. Women will be asked to abstain from sexual intercourse during the 1-week treatment period.

Thirty asymptomatic women will be used as controls and asked to have a clinical assessment done, cultures taken, and to provide epidemiologic data.

The first follow-up visit will be conducted at 3 days. A clinical assessment and cultures will again be taken. Patients will then be randomized to receive 4 additional days of metronidazole or 4 days of placebo. Sexual partners of the 7-day treatment group will be randomized to receive 4 days of placebo or 4 days of metronidazole. Because of the randomization process the sexual partners of the 7-day treatment group will be divided into those that receive placebo, those that receive a 3-4 day course, and those that receive a 7-day course.

Metronidazole Therapy for Nonspecific Vaginitis: 3 vs 7 Days -
Mengel

A follow-up visit at one week after the start of therapy will be conducted to judge cure. A full clinical assessment and cultures will be taken. Cure will be judged by culture results and lack of symptoms. Cultures will not be taken from the male sexual partner as evidence of eradication of the organism from the male can be judged by the rate of recurrence in the female. Follow-up visits will occur at 3 and 6 weeks post start of therapy. A full clinical assessment and cultures will be taken at these visits as well. Recurrences will be treated with a 7-day course of metronidazole for both patient and partner.

Appropriate statistical techniques will then be used to analyze the data. A minimum of 60 women in each treatment group will be used in order to assure statistical significance.

PROGRESS

(82 10 - 83 09) No patients were entered in the protocol.

STATUS: (T)

TITLE: Post-Partum Weight Loss in Lactating and Non-Lactating Females

PRINCIPAL INVESTIGATOR: CPT Richard Turner, MC

PROFESSIONAL ASSISTANTS: MAJ Philip Marinelli, MC
CPT Cathy Canny, AMSC
CPT Kevin Kiley, MC
Catherine Yokan, M.D., DAC

WORK UNIT NO: 82/44

TECHNICAL OBJECTIVE

To examine the short term post-partum weight reduction in lactating and non-lactating females, specifically to see if the caloric expenditure of the mother for the infant is clinically effective in allowing lactating women to return to pre-pregnancy weight sooner, in greater numbers, or with less dietary restriction than non-lactating women.

METHOD

The weights of patients will be taken after a positive urine HCG, at time of admission for delivery, at discharge from hospital, and at 2 weeks, six weeks, 2 months, and 6 months. A questionnaire to obtain demographic data and determine the reasons for breast versus bottle feeding will be filled out on the post-partum ward. An ideal body weight will be estimated and compared with height and weight curves to check its validity. A dietary and activity questionnaire will be filled out at six months to obtain an estimate of caloric intake and activity levels, and the mother will be asked if she is still breast feeding and if she has stopped the reason why. The data will be analyzed to determine if a statistically significant difference in post-partum weight loss exists between breast and bottle feeders and to determine if any other correlations exist between post-partum weight loss and the maternal age, education, and socio-economic status. The normal expected rate of weight loss following parturition will be documented.

PROGRESS

(82 09 - 83 09) Two hundred and seven women completed this study, which shows that breast feeding is markedly more popular in women with more education, higher incomes, and whose friends and relatives breast feed, with the expected benefit for the infant being the most powerful motivation. Maternal employment had only a mild effect on the decision to breast feed. Black mothers generally preferred to bottle feed for reasons not clearly delineated. Lactation appeared to cause no increase in postpartum weight loss at 2 or 6 weeks, with the caloric loss to the infant equalized by increased intake.

PRESENTATION: Turner, RB, Kiley, K, and Marinelli, P: Factors Influencing the Decision to Breast or Bottle Feed and the Effect of Lactation on Postpartum Weight Loss. Presented to 10th Anniversary Family Practice Alumni Conference, 28 Jan 83, MAMC.

STATUS: (C)

DETAIL SHEETS
FOR
PROTOCOLS

DEPARTMENT OF MEDICINE

TITLE: Cis-Platinum, 5-FU Chemotherapy of Advanced Head and Neck Squamous Cell Carcinoma (Stage III and Stage IV)

PRINCIPAL INVESTIGATOR: MAJ Thomas M. Baker, MC

PROFESSIONAL ASSISTANTS: COL Donald Kull, MC
COL Frederick H. Stutz, MC
LTC Dennis M. Lanier, MC

WORK UNIT NO: 81/106

TECHNICAL OBJECTIVES

To determine response rates of patients with previously untreated Stage III and IV squamous cell CA of head and neck as well as response rates of similar patients who have had prior treatment and have local or systemic recurrence; to determine survival of previously untreated patients receiving preoperative or preradiotherapy chemotherapy and compare this survival to that of previously treated similar patients at MAMC or from the literature; to determine type and severity of adverse effects of the chemotherapy.

METHOD

Patients who meet the criteria as listed in the protocol will receive cis-platinum, 80 mg/M², given with hydration and manitol diuresis, followed by 5-FU, 1000 mg/M² by IV infusion, for 4 consecutive days. A second course is repeated in 3 weeks. After 2 courses, patients that have not had prior treatment should then be re-evaluated by radiotherapy and surgery for further therapy. In patients who have recurrent or metastatic disease, treatment is given every 3-4 weeks for as long as the tumor is controlled and the patient tolerates the side effects reasonably well.

PROGRESS

(82 09 - 83 09) Seventeen (17) patients (4 with no prior treatment and 13 with extensive prior surgery and/or RT and/or chemotherapy) were treated with Cis-Platinum (100 mg/M²) followed by a 96 hour infusion of 5-FU (1000 mg/M²/d). Two of four patients with no prior treatment responded and 3 of 7 evaluable patients who had extensive prior treatment responded. When results of this study were compared to other studies using similar chemotherapy regimens, the conclusions were: very high response rates can be obtained in patients with no previous treatment; patients who achieve complete response to induction chemotherapy have prolonged survival over those who have less than a complete response; response rates in patients with recurrent and/or metastatic head and neck cancer were comparative to single agent chemotherapy rates; survival benefit using chemotherapy as either induction therapy or as salvage therapy remains to be proven. A paper has been submitted for presentation at the 4th Annual Current Concepts in Hematology/Medical Oncology Meeting to be held in February 1984.

STATUS: (O)

TITLE: Prophylactic Alternate Day Corticosteroid Therapy
Following Irradiation for Lung Carcinoma

PRINCIPAL INVESTIGATOR: COL J. Waylon Black, MC

PROFESSIONAL ASSISTANTS: COL Donald Kull, MC
LTC Jerome F. Beekman, MC

WORK UNIT NO: 81/91

TECHNICAL OBJECTIVE

To evaluate the effectiveness of alternate day corticosteroids in preventing radiation pneumonitis and pulmonary fibrosis with their associated loss in lung function due to chest irradiation for lung carcinoma.

METHOD

Patients receiving chemotherapy will be excluded from the study. Forty to fifty patients selected for irradiation therapy will be assigned in a double blind random fashion by the pharmacy to receive either 60 mg of prednisone qod or a placebo qod for one year. The placebo will contain all except the active ingredient of the prednisone tablet. PFT's, CXR, and clinical exam will be performed prior to treatment at 3, 6, and 12 months. This evaluation will add only an additional PFT to what is now routine followup. The data will be analyzed using the objective and subjective evaluation of patients after the placebo code is broken.

PROGRESS

(82 09 - 83 09) This protocol was terminated due to a lack of time after the principal investigator was assigned to another position at MAMC. No patients were entered on the study.

STATUS: (T)

TITLE: Vinblastine - Continuous 5-Day Infusion in Refractory
Advanced Solid Tumors

PRINCIPAL INVESTIGATOR: MAJ Alfred H. Chan, MC

PROFESSIONAL ASSISTANTS: COL Friedrich H. Stutz, MC
LTC James E. Congdon, MC
LTC Irwin B. Dabe, MC
MAJ Thomas M. Baker, MC
MAJ Lauren K. Colman, MC
MAJ Howard Davidson, MC

WORK UNIT NO: 82/10

TECHNICAL OBJECTIVE

To determine the response rate and remission duration using Velban as a continuous IV infusion in patients with advanced solid tumors refractory to all effective forms of conventional treatment; and to define further the qualitative and quantitative toxicity of the continuous infusion of Velban.

METHOD

Since the response rate of these tumors at this stage to any particular agent or combination of agents has been dismal in the past, it would be meaningful, if a response rate of >15% can be established, to add this method to the existing regimens for the treatment of refractory solid tumors such as breast cancer, non-seminomatous testicular germ-cell cancer, small cell undifferentiated cancer of the lung, renal cell cancer, ovarian cancer, and lymphomas. This will be a single-armed study. The results will be compared with historical data whenever available. All patients registered on this study will be considered evaluable and be analyzed. Patients will be stratified according to tumor cell types. In the case of breast cancer, further substratification into ER+/- and pre- vs post-menopausal status will be carried out. Vinblastine will be given as a continuous infusion over five days every three weeks, provided there has been recovery from hematologic toxicity.

PROGRESS

(82 09 - 83 09) A total of sixteen (4 entered in FY 83) patients were infused with vinblastine at 1.5 mg/M²/24 hrs for 5 days. Four patients received one cycle, seven received 2 cycles, two had 3 cycles, and one received 16 cycles. One patient has had nine cycles to date, another has completed two courses, and both are still on study. One patient with widely metastatic breast cancer had stable disease for some 12 months. Another patient with

Vinblastine - Continuous 5-Day Infusion in Refractory Advanced
Solid Tumors - Chan

ovarian cancer and prior IV bolus vinblastine achieved a partial response. No fatal or life-threatening complications were seen; myelosuppression was usually mild; nausea and vomiting were rare; and neurotoxicity was not seen. The number of patients was too small for conclusive analysis. Though generally well tolerated, the treatment was not particularly effective in this group of patients as reported elsewhere. However, stable disease or even partial response was occasionally attained. The cost and inconvenience were substantial.

A paper has been submitted for presentation at the 4th Annual Current Concepts in Hematology and Oncology Meeting to be held in February 1984.

STATUS: (O)

TITLE: Conjunctival Biopsy in the Diagnosis of Sarcoidosis

PRINCIPAL INVESTIGATOR: LTC Henry D. Covelli, MC

PROFESSIONAL ASSISTANTS: COL Stanley Sollie, MC
COL Stanley Allison, MC
LTC Jerome Beekman, MC
MAJ Bruce Bellin, MC
MAJ Leslie P. Fox, MC
MAJ Barry Weled, MC
CPT Myron Whitehead, MC

WORK UNIT NO: 79/85

TECHNICAL OBJECTIVE

To evaluate the usefulness of conjunctival biopsy as a primary means of diagnosing sarcoidosis.

METHOD

Patients with a tentative diagnosis of sarcoidosis based on accepted clinical, radiologic, and biochemical criteria will have baseline evaluations to include chest x-ray, PPD and energy battery, angiotension converting enzyme level, erythrocyte sedimentation rate, arterial blood gases, and pulmonary function tests to assess disease activity. These patients will undergo slit lamp examination. Patients with conjunctival follicles will have those follicles biopsied and those with normal appearing conjunctiva will have random biopsies. Tissue will be examined histologically for noncaseating epithelioid granulomata with hematoxylin and eosin stain. If granulomata are observed, the specimen will be examined utilizing polarized light microscopy and stained and examined for acid fast bacilli and fungi. If no granulomata are observed, no further examination will be done. Patients will then be evaluated with transbronchial lung biopsy. If the diagnosis is not established by this method, further invasive diagnostic procedures will not be done unless deemed necessary for the management of the patient. Data on the field from transbronchial biopsy will be compared to that from conjunctival biopsy. In addition, disease activity as manifest by serum ACE level will be correlated with biopsy positivity.

PROGRESS

(82 09 - 83 09) Forty patients have been entered - ten during FY 83 - with no adverse effects. Data are now being analyzed.

STATUS: (0)

TITLE: Evaluation of High Dose vs Low Dose Corticosteroid in the Treatment of Acute Bronchospasm

PRINCIPAL INVESTIGATOR: LTC Henry D. Covelli, MC

PROFESSIONAL ASSISTANTS: COL J. Waylon Black, MC
COL Bruce L. Fariss, MC
LTC Gary Treece, MC
MAJ Arthur R. Knodel, MC
CPT James Wallingford, MC

WORK UNIT NO: 82/64

TECHNICAL OBJECTIVES

To evaluate the optimal dose of corticosteroids used in the treatment of acute exacerbations of bronchospasm and to assess the difference in the duration of adrenal suppression between low and high dose corticosteroid therapy.

METHOD

Approximately 50 patients hospitalized for an acute exacerbation of bronchospasm from either chronic obstructive lung disease or asthma will be evaluated in a double blind randomized trial. Treatment will consist of the usual therapeutic measures of IV aminophylline and orally inhaled bronchodilators. Then one of four corticosteroid regimens will be used. Regimen 1: 125 mg of IV methylprednisolone (MP) q 6 hrs x 3 days with a weaning oral prednisone dose of 60 mg x 3 days, 40 mg x 3 days, and 20 mg x 3 days. Regimen 2: 125 mg of IV MP q 6 hrs x 3 days with a weaning dose of oral prednisone of 30 mg x 3 days, 20 mg x 3 days, and 10 mg x 3 days. Regimen 3: 125 mg MP q day x 3 days, then a weaning dose of oral prednisone of 60 mg x 3 days, 40 mg x 3 days, and 20 mg x 3 days. Regimen IV: 125 mg MP q day x 3 days, then a weaning dose of oral prednisone of 30 mg x 3 days, 20 mg x 3 days, and 10 mg x 3 days. A placebo of IV glucose will be given q 6 hrs to patients receiving regimens 3 and 4. Routine studies such as eosinophil counts and peak expiratory flow rates (spirometry) will be performed during this time. After discharge, patients will be evaluated with a cortrosyn stimulation test one or two weeks after discontinuing a weaning dose of oral prednisone. If the cortrosyn stimulation test is abnormal, a repeat study will be performed weekly until it normal.

PROGRESS

(82 09 - 83 09) Twenty-five patients have been entered - all during FY 83. The blinded code will not be broken until fifty patients have been entered.

STATUS: (0)

TITLE: Evaluation of Androgen Levels in Patients with Chronic
Obstructive Pulmonary Disease and Sleep Apnea

PRINCIPAL INVESTIGATOR: LTC Henry D. Covelli, MC

PROFESSIONAL ASSISTANTS: COL Bruce L. Fariss, MC
COL Stephen R. Plymate, MC
MAJ Arthur R. Knodel, MC
MAJ Robert W. Taylor, MC
Marueeen Nuccio, M.D., Amer Lake V.A. Hosp
Leonard Sarff, RRT, DAC

WORK UNIT NO: 83/77

TECHNICAL OBJECTIVE

To compare patients with obstructive lung disease without sleep apnea to patients with carbon dioxide retention but no evidence of sleep apnea and to patients with a diagnosis of sleep-apnea. Also to evaluate the side effects of exogenous testosterone in patients receiving this agent for urological problems.

METHOD

This study will evaluate three different groups of male patients in the following categories:

Group I: Fifteen male patients with obstructive lung disease without CO₂ retention. Hormonal levels will be evaluated by measurement of total serum testosterone, free serum testosterone, estradiol, 17-OH progesterone, and progesterone. Sleep apnea studies will be performed at the VA Medical Center.

Group II: Fifteen male patients with obstructive lung disease with CO₂ retention. Hormone level analysis and sleep apnea studies as in Group I.

Group III: Fifteen male patients who have a diagnosis of sleep-apnea and have previously had sleep studies will be evaluated with serum hormonal analysis.

Data will be analyzed using analysis of variance.

PROGRESS

(83 09 - 83 09) This is a new study and has not been started to date.

STATUS: (0)

TITLE: 5-Azacytadine in Acute Leukemia

PRINCIPAL INVESTIGATOR: LTC Irwin Dabe, MC

PROFESSIONAL ASSISTANTS: COL Friedrich Stutz, MC
MAJ Lauren Colman, MC

WORK UNIT NO: 80/19

TECHNICAL OBJECTIVE

To examine the efficacy of 5-Azacytadine in patients with acute leukemia refractory to conventional therapy.

METHOD

5-Azacytadine will be given in a dose of 300 mg/M²/day for 5 days in three or four divided doses each day. Courses will be repeated every three weeks unless there is earlier evidence of recovery from myelotoxicity. If bone marrow cellularity is less than 20% at three weeks from the last course, chemotherapy will be withheld until marrow cellularity exceeds 20%. Dosages for the next course will then be reduced by one third. If there is no improvement in the bone marrow after the initial course, the drug dosage for the second course will be increased by one third.

PROGRESS

(82 09 - 83 09) Two patients were treated on this study in FY 80 with very little response to the drugs, followed by death from uncontrolled leukemia. No patients were entered during FY 81 or FY 82. One patient was entered during FY 83 and developed a temperature spike to 105° after the first dose. Her temperature remained normal for the next two doses, but the patient developed cellulitis of the lower right leg which resolved upon discontinuation of the drug. The patient was restarted on 5-azacytadine, but PB blasts reappeared by day 20 confirmed by bone marrow aspirate. No further 5-azacytadine was given and the patient later expired.

STATUS: (0)

TITLE: The Effects of Thyroid Hormone on Sex Steroid Binding Globulin

PRINCIPAL INVESTIGATOR: MAJ Michael E. Fincher, MC

PROFESSIONAL ASSISTANTS: COL Bruce Fariss, MC
LTC Stephen Plymate, MC
LTC Gary Treece, MC
MAJ Allan Avbel, MC
MAJ Robert Jackson, MC

WORK UNIT NO: 82/06

TECHNICAL OBJECTIVE

To determine the effects of thyroid hormone on sex-steroid binding globulin (SSBG).

METHOD

Male and female patients (approximately 20 total) will have plasma estradiol, testosterone, and SSBG levels drawn as well as LH and LSH when first presenting with hyperthyroidism before any treatment except propranolol. Following treatment, SSBG levels will be drawn every two weeks until the patient becomes euthyroid or until he becomes hypothyroid. In addition to the SSBG parameters, TSH, T₄, T₃ uptake and T₃ by RIA will be drawn at each visit. The results will be analyzed by linear regression analysis.

PROGRESS

(82 09 - 83 09) Six patients were entered in the study, none during FY 83. No conclusions could be drawn from the data accumulated.

STATUS: (T)

TITLE: The Effects of Hyperthyroidism on Serum Zinc, Iron, and
Copper Values in the Sprague-Dawley Rat

PRINCIPAL INVESTIGATOR: MAJ Michael Fincher, MC

PROFESSIONAL ASSISTANTS: COL Bruce Fariss, MC
COL Stephen Plymate, MC
LTC Gary Treece, MC
MAJ James Little, MSC

WORK UNIT NO: 83/27

TECHNICAL OBJECTIVE

To determine the effect of thyroxine on serum copper, zinc, iron, ferritin, and ceruloplasmin in Sprague-Dawley rats and to correlate these findings with reported observations in human patients with thyrotoxicosis.

METHOD

Thirty (30) male Sprague-Dawley rats, approximately 8 weeks of age, weighing between 200 and 250 gm will be allowed access to food and water. Control and experimental rats will be injected intraperitoneally daily with either 1.0 ml saline (control) or 30 µgm L-thyroxine (T₄) in saline (experimental). Each group will consist of fifteen rats and on days 0, 14, 28, and 56 both control and experimental groups will be anesthetized with halothane and bled by cardiac puncture. Serum copper, zinc, and iron will be measured by atomic absorption. Serum total T₄, free T₄, ceruloplasmin, and ferritin will be measured by radio-immunoassay. Results of control and experimental groups will be compared by the unpaired Student's t Test.

PROGRESS

(82 11 - 83 09) Serum T₄, T₃, copper, and iron were measured in ten male and ten female rats in both the control and the experimental groups. Female rats were shown to have lower basal serum T₄ concentrations than male rats. This may, in part, be due to enhanced metabolism and/or excretion of thyroxine in the female rats. In the levothyroxine injected rats, the serum T₄ value became elevated in the male but not the female (again, possibly due to enhanced metabolism or clearance of T₄ in the female). Serum copper fell in the rats as T₄ rose in the serum. Serum iron values were inconsistent and reflected no definite pattern in the control versus the experimental animals. Methodology is still being worked out to determine serum zinc values by atomic absorption in these animals.

PRESENTATION: Fincher, ME, Little, JS, Plymate, SR and Fariss, BL: Effect of Hyperthyroidism in the Rat on Body Weight, Serum Copper, and Serum Iron. Presented to Society of Uniformed Endocrinologists Meeting, San Antonio, TX, 7-8 June 1983.

STATUS: (O)

TITLE: Therapy of the Costochondralgia Syndrome - A Randomized
Controlled Therapeutic Study

PRINCIPAL INVESTIGATOR: MAJ James D. Fitz, MC

PROFESSIONAL ASSISTANTS: LTC Michael J. Weaver, MC
CPT Donald R. Skillman, MC

WORK UNIT NO: 83/38

TECHNICAL OBJECTIVE

To evaluate the efficacy, when treating anterior chest wall pain of an oral analgesic; an injection of anesthetic/steroid suspension; a combination of oral analgesic and the anesthetic/steroid injection; and a placebo.

METHOD

Inclusion criteria will be anterior chest wall pain which is replicated by palpation or pressure upon costochondral junctions. Exclusion criteria will be allergy or other reaction to local anesthetics, steroids, or aspirin or underlying cardiopulmonary or esophageal conditions which in the opinion of the evaluating physician account for the pain syndrome.

Approximately 100 patients will be randomized into five treatment groups. Group A will receive an injection of a combination of local anesthetic (Marcaine HCl®) plus steroid (Aristospan®) in addition to oral Ecotrin. Group B will receive an injection of the anesthetic plus steroid in addition to an oral placebo. Group C will receive Ecotrin. Group D will receive an injection of normal saline in addition to an oral placebo. Group E will receive an oral placebo only. Patients will be given a diary in which to record daily assessment of pain and will return the diary on the 14th day following injection. An objective evaluation of tenderness will be performed by the use of "Dolorometer" prior to injection, 30 minutes following injection, and then on days 1, 2, 3, 7, and 14. Patients in each group will be given an oral non-anti-inflammatory analgesic for PRN use.

PROGRESS

(83 01 - 83 09) Fourteen patients were entered into the study and randomized to one of three groups (Ecotrin, placebo, Ecotrin plus injection of anesthetic plus steroid). Preliminary evaluation of the results to date indicate that not enough patients have been entered to achieve clinical or statistical significance. More patients will be enrolled.

STATUS: (0)

TITLE: Prospective Evaluation of Clinical, X-Ray, Histologic, Scintigraphic and Microbiologic Characteristics of Diabetic Feet

PRINCIPAL INVESTIGATOR: COT John Gnann, MC

PROFESSIONAL ASSISTANT: LTC Thomas Parr, MC
MAJ Shannon Harrison, MC

WORK UNIT NO: 83/51

TECHNICAL OBJECTIVE

To correlate specific x-ray, scintigraphic, clinical and microbiologic characteristics with each other and with the histology of the diseased diabetic foot so clinicians may better manage their patients.

METHOD

This will be a blinded, multicenter study with 30 patients entered study-wide.

Eligibility: Any diabetic patient whose physician for any reason has decided with the patient that amputation of the foot is indicated except for urgency of surgery which would preclude diagnostic studies and pregnancy. It is not necessary for a patient to have probable infection to be entered into the study as they will be a natural control group.

The following diagnostic procedures will be performed: radiograph of the foot to be amputated in the dorsal and lateral views; bone scan of the part to be amputated; two intra-operative trephine biopsies of any radiolucent areas or areas of elevated periosteum (one will be fixed for histology and one will be cultured for anaerobes and aerobes); neurologic examination of the foot to include vibration, proprioception reflexes to pinprick and light touch; (e) manual palpation of the D. pedis and P. tibial pulses; and aerobic and anaerobic cultures of drainage from sinuses. Doppler determination is important but not required.

Data Analysis: The histology will be compared to radiographs and scans and the results of the trephine biopsy. The sensitivity and specificity of the trephine and the radiologic studies will be determined relative to the histology. The clinical worksheets will be evaluated to see if there are any clinical characteristics which are peculiar to bone infections.

PROGRESS

(83 03 - 83 09) The study has been inactive due to the departure of MAJ Harrison who was the original principal investigator. No patients have been enrolled in the study. The study will be activated in the near future with Dr. Gnann as the principal investigator.

STATUS: (0)

TITLE: Metronidazole Pharmacokinetics and Metabolism in Liver Disease, Aging, and Drug-Drug Interactions

PRINCIPAL INVESTIGATOR: MAJ Shannon Harrison, MC

PROFESSIONAL ASSISTANTS: CPT David W. Towle, MSC
Lawrence L. Pelletier, Jr., M.D.,
American Lake VA Medical Center
Robert Vestal, M.D.,
Boise VA Medical Center

WORK UNIT NO: 82/33

TECHNICAL OBJECTIVE

To compare the levels of metronidazole and its two major metabolites to see if metabolites accumulate in liver patients with liver disease; to attempt to define the contribution of active metabolites to the therapeutic outcome in patients with serious anaerobic infections; and to develop guidelines for metronidazole dosage in patients with liver disease.

METHOD

This protocol will be done in conjunction with the American Lake VA Medical Center, Tacoma, WA, and the Boise VA Medical Center. Twenty patients with liver disease and ten controls with proven or suspected anaerobic infection requiring in-hospital antimicrobial therapy will be enrolled. Metronidazole will be administered IV and serum levels of metronidazole and its two major metabolites will be determined. Serum levels will be correlated to the minimum inhibitory concentration of metronidazole and the two metabolites, results of serial cultures, and clinical outcome. Dosage will be adjusted to maintain therapeutic serum levels and any reduction in dosage correlated with the type and severity of liver disease. In subsequent studies, the investigators will determine whether metronidazole metabolism is altered in patients over 70 years and in individuals receiving phenytoin or cimetidine.

PROGRESS

(82 09 - 83 07) No patients were entered on this protocol due to the departure of the principal investigator and the departure of the co-investigator from the American Lake VA Hospital.

STATUS: (T)

TITLE: Double-Blinded Prospective Placebo Controlled Trial of Doxycycline in Treatment of Leptospirosis

PRINCIPAL INVESTIGATOR: MAJ Shannon Harrison, MC

PROFESSIONAL ASSTS: MAJ James W. Higbee, MSC

WORK UNIT NO: 83/06

METHOD

To determine whether doxycycline, 200 mg/day by mouth, will modify the course of leptospirosis.

TECHNICAL OBJECTIVE

This is a multicenter, double-blind, placebo-controlled efficacy trial against naturally-acquired disease. Patients will be treated with doxycycline or a placebo. Temperatures and blood cultures for leptospirosis will be followed for differences in responses. Leptospirosis will be defined as a positive blood or urine culture for *Leptospira* or a four-fold rise in antibody to a specific leptospiral serovar by the microagglutination technique.

PROGRESS

(82 10 - 83 07) Sixteen (16) patients were admissible by culture or serology. One half were treated with placebo and the other half were treated with doxycycline. When the data were compiled with data from 14 patients from Fort Bragg, NC, and results computed, there was a mean difference of 2.5 febrile days with treatment. A paper will be completed from this protocol by Dr. Harrison and Dr. Bruce McClain at WRAIR.

STATUS: (C)

TITLE: Comparison of Ticarcillin/Tobramycin vs Mezlocillin/
Tobramycin in the Empiric Treatment of Acutely
Decompensating Intensive Care Unit Patients

PRINCIPAL INVESTIGATOR: MAJ Shannon M. Harrison, MC

PROFESSIONAL ASSISTANTS: COL Joel W. Black, MC
LTC James Congdon, MC
MAJ James W. Higbee, MC
CPT Michael W. Spangler, MC

WORK UNIT NO: 83/29

TECHNICAL OBJECTIVE

To assess the control of infection and appropriateness of empiric antibiotic coverage in the acutely decompensating postoperative or medical intensive care unit patients; to assess the effect on electrolytes with special attention to hypokalemia in the use of these broad spectrum penicillins; and to assess platelet function and quantity when these broad spectrum penicillins are used.

METHOD

Entry Criteria (30 subjects): acute decompensation as defined by a temperature $>100.6^{\circ}\text{F}$, two values, white count increased >2000 , decrease of systemic vascular resistance or in peripheral arterial pressure, or clinical suspicion of impending bacterial shock and a situation which would usually call for a broad spectrum penicillin plus an aminoglycoside for empiric coverage.

Treatment: 3 gm Ticarcillin or mezlocillin IV q4h plus 2 mg/kg Tobramycin IV loading dose, to be adjusted by creatinine clearance. Randomized by pharmacy with table of random numbers. Treat for 72 hrs or until clinical situation changes. No antipyretics. If culture is negative, D/C medications at 72 hours or when clinical judgment deems appropriate. If cultures are positive and organisms are not sensitive, off study and replacement with other agents.

Laboratory: Bleeding time (Simplate) if platlets $<100,000$ at 48 hrs, 7 days, and end of treatment. SMAC on beginning protocol, at 48 hr, 7 days, and the end of treatment. Platelet count on admission, at 48 hrs, 6 days, and end of treatment. Tobramycin levels, peak and trough, second and fifth, and every 3 days. MIC's on positive cultures to Ticar, CARB, aminoglycosides, Mezlocillin, and probably third generation Cephalosporins. Cultures of blood x 3; sputum with gram stain; urine with gram stain; throat and local site.

PROGRESS

(82 11 - 83 09) One patient was treated. He survived and did well. Some bacteria were resistant to mezlocillin.

This protocol was terminated due to the departure of the principal investigator.

STATUS: (T)

TITLE: Cefotaxime in the Treatment of Rabbit Syphilomas

PRINCIPAL INVESTIGATOR: MAJ Shannon M. Harrison, MC

PROFESSIONAL ASSISTANT: MAJ James W. Higbee, MSC
CPT Paul F. McKenney, MC

WORK UNIT NO: 83/51

TECHNICAL OBJECTIVE

To determine treponemicidal doses and the efficacy of single-dose cefotaxime in the treatment of early syphilis, using a rabbit testicular syphiloma model.

METHOD

Phase I: Estimate mg/kg dose (dose X) of cefotaxime expected to provide treponemicidal serum levels in rabbits and set up bioassay for levels using microtiter method. Construct dose-serum level curve for rabbits using peak serum levels obtained after IM injection of dose X, 0.1X and 10X.

Phase II: Ascertain that all (30) rabbits have negative RPR test. Harvest treponemes from stored testicular extract into basal reducing media and confirm treponemal activity by darkfield exam. Inject half the rabbits intratesticularly with $10^6 - 10^7$ treponemes. Confirm development of orchitis (expected within 10-14 days) by exam and seroconversion of RPR. Treat syphilitic rabbits with either single-dose cefotaxime IM (doses X, 0.1X, and 10X) or with controls of high-dose penicillin G or 0.9% NaCl. Determine peak serum levels of antibiotic in treated rabbits. Sacrifice treated rabbits after 14 days, harvest testes and extract remaining surviving spirochetes. Inject supernatant containing spirochetes into uninfected group of rabbits to determine infectivity (by rechecking for orchitis and seroconversion of RPR after 14 days).

PROGRESS

(83 01 - 83 07) Five adult New Zealand white rabbits RPR negative for *Treponema pallidum* were injected intratesticularly with infective doses. None of the rabbits developed syphilomas and were RPR and FTA negative. The negative results were probably caused by an accidental temperature inactivation or attenuation of the organism which resulted in a low infectivity rate.

The protocol was terminated due to the departure of the principal investigator.

STATUS: (T)

TITLE: Intracoronary Thrombolysis with Streptokinase in the Hyperacute Phase of Myocardial Infarction (Western Washington Randomized Trial)

PRINCIPAL INVESTIGATOR: COL John C. Hill, MC

PROFESSIONAL ASSISTANTS: COL W. Theodore Steudel, MC
LTC Roger F. Chamusco, MC
LTC John W. Kirk, MC

WORK UNIT NO: 81/114

TECHNICAL OBJECTIVE

To determine the efficacy of intracoronary thrombolysis in the therapy of acute transmural myocardial infarction.

METHOD

This will be a randomized community-wide therapeutic trial. To qualify, patients must be <75 years of age and in reasonably good health and functional state prior to the acute event. Patients found, on arteriography and ventriculography, to have thrombosis of the coronary artery supplying the ischemic region of myocardium will enter the randomized trial. Control patients will be maintained on IV heparin and then coumadin for the remainder of their hospitalization. Patients randomized to Streptokinase will receive 4,000 units/min into the thrombosed vessel for a period of up to 60 min. Arteriography of the thrombosed vessel will be done every 15 min or when clot lysis is suspected. Following thrombolysis or after 60 min of Streptokinase infusion, the patient will undergo repeat left ventriculography and then monitored on IV heparin for four days and on coumadin until hospital discharge. Treatment and control groups will undergo identical evaluation including serial enzymes and electrocardiograms and early (12-48 hr) and follow-up isotope ventriculograms (12-16 days). Follow-up tomographic thallium imaging for the quantification of infarct size will be at 25-35 days following study.

PROGRESS

(81 99 - 83 02) This study has been completed with the randomization of 250 subjects. The FDA has approved intracoronary administration of streptokinase in acute MI. The initial experience would suggest salvage of myocardium by this therapy in those patients treated within the first five hours.

PRESENTATION: Army Association of Cardiology, May 1982.

STATUS: (C)

TITLE: Effects of Somatostatin on Plasma Insulin and Glucagon
in Sheep

PRINCIPAL INVESTIGATOR: MAJ Robert Jackson, MC

PROFESSIONAL ASSISTANT: COL Bruce L. Fariss, MC

WORK UNIT NO: 82/62

TECHNICAL OBJECTIVE

To examine the effects of somatostatin on insulin and glucagon release from the sheep pancreas.

METHOD

Six adult female sheep, after a 24-hr fast, will be immobilized and an intravenous catheter inserted into the jugular vein for the introduction of test substances. Another catheter will be inserted into the contralateral jugular vein for withdrawal of blood samples. Each sheep will receive an infusion of a solution of sodium butyrate 1.25 mM/kg of body weight adjusted to a pH of 7.4. Blood samples will be drawn every 10 min for the next 90 min and analyzed for insulin, glucagon and glucose. Two weeks later the sheep will receive an infusion of somatostatin 0.8 mcg/kg/min and blood specimens drawn every 10 min for insulin, glucagon, and glucose. While the somatostatin is infusing, the sheep will be given sodium butyrate 0.2 nmole/kg body weight and blood samples again drawn every 10 min for 90 min and sent for glucagon, insulin, and glucose. Plasma glucose will be measured by the glucose oxidase method.

PROGRESS

(82 09 - 83 09) Sodium butyrate causes the release of insulin and glucagon to very high levels in sheep. Somatostatin will block the release of both insulin and glucagon. Sodium butyrate will not break through the blockage of somatostatin. Total pancreatectomy shows comparable levels of insulin as seen in those animals given somatostatin.

STATUS: (C)

TITLE: Regulation and Kinetics of Fatty Acid Activation in Liver
and Skeletal Muscle

PRINCIPAL INVESTIGATOR: MAJ Robert E. Jones, MC

PROFESSIONAL ASSISTANTS: COL Bruce L. Fariss, MC
COL Stephen R. Plymate, MC
LTC Gary L. Treece, MC
MAJ James S. Little, MSC

WORK UNIT NO: 83/09

TECHNICAL OBJECTIVE

To explore the cellular and hormonal mechanisms which control the rate of mitochondrial fatty acid activation.

METHOD

Thirty (30) male rats (6-8 in each phase) will be the source of enzyme used in these experiments. After sacrifice by decapitation, mitochondria will be prepared from the quadriceps femoris muscle group and liver using differential centrifugation or a gradient. Ligase activity will be measured using a modification of the radiochemical millipore filter assay proposed by Polokoff and Bell. Approximately 0.08 μ Ci of (3H)-coenzyme A will be used per assay. The initial phase of the study will consist of re-establishing the basic assay and kinetic parameters of the enzyme from each tissue and preparative methodology. The second phase will involve examining the effects of various known intracellular mediators (calcium, cAMP) and cytoplasmic fractions on enzymatic rate. The third phase will analyze the action of insulin and glucagon on ligase activity by preincubating these hormones with crude tissue homogenates or other cellular components and mitochondria. The majority of attention will be paid to effects on palmitic acid kinetics by holding all other reactants and cofactors at saturating concentrations while varying palmitate levels. Each experiment will be run in a paired fashion with tissue from each animal serving as its own control. Enzymatic rates will be normalized to nanomoles palmitoyl CoA formed/minute/mg protein. Maximal velocity will be experimentally determined and Michaelis constants will be calculated using Cleland's hyperbolic best-fit formulation. Statistical analysis will be performed using a paired t test or analysis of variance.

PROGRESS

(82 10 - 83 09) Both liver and muscle tissue have been obtained from control rats (n=14), thyrotoxic rats (n=12), aged rats (n=8), and fasted rats (n=12). These tissue samples are being held at -70°C awaiting measurement of ligase activity.

STATUS: (0)

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

PRINCIPAL INVESTIGATOR: MAJ Robert E. Jones, MC

PROFESSIONAL ASSISTANTS: COL Bruce L. Fariss, MC
COL Stephen R. Plymate, MC

WORK UNIT NO: 83/81

TECHNICAL OBJECTIVE

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

METHOD

Normal human semen samples will be used to establish a ligase assay. Ligase activity will be measured using a sensitive radio-ligand/millipore filter procedure that utilizes (3H)-coenzyme A as the radioactive trace. Approximately 0.2 microcuries 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 200 million per 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 sulphydryl reagents, albumin, and detergents will be studied to assist in estimation of latency.

PROGRESS

(83 09 - 83 09) Ligase activity has been identified in intact spermatozoa and can be readily solubilized with 1.0% Triton X100. However, enzymatic activity is not present in seminal plasma. This reaction is dependent upon time, temperature, and added protein and requires ATP, Mg⁺⁺, palmitic acid, and coenzyme A. The Km (approximate) has been determined for ATP and coenzyme A (1.4 mM and 4 μ M respectively). Technical difficulties have precluded an accurate estimation of the Km for palmitic acid.

STATUS: (0)

TITLE: Theophylline Induced Seizure: Increased Susceptibility
with Prior Episode

PRINCIPAL INVESTIGATOR: MAJ Arthur R. Knodel, MC

PROFESSIONAL ASSISTANTS: LTC Jerome F. Beekman, MC
LTC Henry D. Covelli, MC
LTC Giorgio Turella, MC
MAJ Stanely P. Liebenberg, VC
MAJ James S. Little, MSC

WORK UNIT NO: 81/96

TECHNICAL OBJECTIVE

To evaluate whether the seizure threshold for theophylline is altered by a prior theophylline induced seizure.

METHOD

Ten beagle dogs will have continuous EEG monitoring. An arterial line will be used to draw serum theophylline levels while a venous line will serve for the infusion. A baseline EEG will be obtained and the animal will then be given a theophylline bolus, a linear decreasing concentration of theophylline, and a continuous infusion of theophylline. This will result in an immediately achieved steady state level of serum theophylline. Five, fifteen, and thirty min after the bolus, serum theophylline determinations will be made to assure a steady state level. Every one-half hour the dosage of theophylline will be increased to achieve a 10 mg/mm increment of theophylline. This will be continued until an EEG documented seizure occurs. One week later the study will be repeated on the same dogs to determine if their threshold has been altered by the prior theophylline induced seizure.

PROGRESS

(82 09 - 83 09) Initially, beagle dogs were the experimental animals used in this study. Utilizing curare, the first dog died approximately 15 minutes after he was paralyzed and placed on mechanical ventilation. During the study on the second dog, in which pavalon was used, the animal experienced cardiopulmonary instability, but was fortunately resuscitated. At this time, it was elected to change the experimental animal from a paralyzed dog to an awake sheep which would be suspended in a sling, which required an implantable electrode in the brain to obtain an EEG. The protocol was terminated due to the inability of obtaining the implantable electrode.

STATUS: (T)

TITLE: Face Mask CPAP for Prevention of Post-Op Atelectasis

PRINCIPAL INVESTIGATOR: MAJ Arthur R. Knodel, MC

PROFESSIONAL ASSISTANTS: COL Waylon J. Black, MC
LTC Henry D. Covelli, MC
LTC Michael Moon, MC
CPT Richard Dearman, MC
CPT William Weaver, MC
Donald Wintrey, DAC

WORK UNIT NO: 82/72

TECHNICAL OBJECTIVE

To evaluate the usefulness of continuous positive airway pressure (CPAP) delivered by a face mask as a prophylactic measure in the prevention of post-operative pulmonary atelectasis.

METHOD

One hundred patients undergoing elective abdominal or thoracic surgery will be studied: Patients with acute pulmonary diseases, including ARDS, CHF, and pneumonia, diagnosed immediately post-operatively, will be excluded. No intubated patient will be included in the study. The patients will be randomly assigned to one of three groups: (1) control group - conservative therapy of cough deep breath; no device; (2) incentive spirometry (3) CPAP by mask at a level of 10. All patients will get pre-operative instructions on the modality of the post-operative therapy they will receive. Pre-operative evaluation will include pulmonary function test, arterial blood gas, and chest x-ray. Four hours post-operatively all of these studies will be repeated. The patient will then be given a treatment followed in 15-30 minutes by repeat pulmonary function test and arterial blood gas. During waking hours the patient will receive the treatment for 15 minutes every four hours. Pulmonary function test, arterial blood gas, and chest x-ray will be done at 24, 48, and 72 hours. At that time the study will be completed.

PROGRESS

(82 09 - 83 09) Thirty four subjects have been entered. Data will not be analyzed until 16 patients have been entered in each group.

STATUS: (0)

TITLE: Theophylline Induced Seizure: Increased Susceptibility
with Prior Episode

PRINCIPAL INVESTIGATOR: MAJ Arthur R. Knodel, MC

PROFESSIONAL ASSISTANTS: LTC Jerome F. Beekman, MC
LTC Henry D. Covelli, MC
LTC Georgio Turella, MC
MAJ Stanely P. Liebenberg, VC
MAJ James S. Little, MSC

WORK UNIT NO: 81/96

TECHNICAL OBJECTIVE

To evaluate whether the seizure threshold for theophylline is altered by a prior theophylline induced seizure.

METHOD

Ten beagle dogs will have continuous EEG monitoring. An arterial line will be used to draw serum theophylline levels while a venous line will serve for the infusion. A baseline EEG will be obtained and the animal will then be given a theophylline bolus, a linear decreasing concentration of theophylline, and a continuous infusion of theophylline. This will result in an immediately achieved steady state level of serum theophylline. Five, fifteen, and thirty min after the bolus, serum theophylline determinations will be made to assure a steady state level. Every one-half hour the dosage of theophylline will be increased to achieve a 10 mg/mm increment of theophylline. This will be continued until an EEG documented seizure occurs. One week later the study will be repeated on the same dogs to determine if their threshold has been altered by the prior theophylline induced seizure.

PROGRESS

(82 09 - 83 09) Initially, beagle dogs were the experimental animals used in this study. Utilizing curare, the first dog died approximately 15 minutes after he was paralyzed and placed on mechanical ventilation. During the study on the second dog, in which pavalon was used, the animal experienced cardiopulmonary instability, but was fortunately resuscitated. At this time, it was elected to change the experimental animal from a paralyzed dog to an awake sheep which would be suspended in a sling, which required an implantable electrode in the brain to obtain an EEG. The protocol was terminated due to the inability of obtaining the implantable electrode.

STATUS: (T)

TITLE: Effect of Cigarette Smoking on Plasma Carboxyhemoglobin
and on the Diffusion Capacity of Carbon Monoxide

PRINCIPAL INVESTIGATOR: CPT Perry R. Lloyd, MC

PROFESSIONAL ASSISTANTS: Leonard Sarff, DAC

WORK NO: 83/66

TECHNICAL OBJECTIVE

To evaluate the effect of cigarette smoking on the diffusing capacity of carbon monoxide (D_{CO}) and on the carboxyhemoglobin (COHb) levels in cigarette smokers.

METHOD

Twenty to thirty consenting cigarette smokers (outpatient alert men and women >18 years of age) will be asked not to smoke after midnight before the day of testing. Routine PFT, D_{CO} , PO_2 , COHb, Hb, height, and weight will be obtained in the morning before testing. Subjects will then chain smoke high carbon monoxide-producing cigarettes as noted in the Federal Trade Commission's March 1983 report. This will be done in a room ventilated by a wall fan. The number of cigarettes smoked by each subject will not be controlled, but the number of cigarettes smoked by each subject will be noted and results will be correlated according to the number of cigarettes smoked. Repeat D_{CO} , PO_2 , and COHb will be performed and a hemoglobin will be obtained by a hemogram. An arterial puncture of the radial artery will be performed both before and after the smoking period with collection of 3-5 cc of blood each time.

PROGRESS

(83 07 - 83 09) Patients are being enrolled and testing will begin in the near future.

STATUS: (0)

TITLE: Arrhythmias with Bronchodilators

PRINCIPAL INVESTIGATOR: CPT Perry R. Lloyd, MC

PROFESSIONAL ASSISTANTS: COL John C. Hill, MC
Anselmo Rodriguez

WORK UNIT NO: 83/76

TECHNICAL OBJECTIVE

To evaluate the cardiac rhythm effects of bronchodilators in chronic obstructive pulmonary disease patients.

METHOD

Twenty (20) non-steroid dependent chronic obstructive pulmonary disease outpatients with an $FEV_1/FVC \leq 55\%$ substantiated by two sequential PFT's, who maintain theophylline levels at 10-20 $\mu\text{gm/ml}$ at six to eight hours after their morning dose, and who use aerosolized metaproterenol or albuterol, will carry two-channel Holter monitors on three occasions for 24 hr: once with no beta-2 agonist, once with albuterol, and once with metaproterenol. They will be asked to record times and amounts of drugs, caffeine, and alcohol used and to use no new drug therapies such as steroids or antibiotics for two weeks prior to the initial Holter monitoring and until after completion of all three monitorings. Prior to entry patients will have a cardiopulmonary exam and an EEG. An electronic electrographic scanner will be used to record rhythm abnormalities by the time of day in the standard format for interpretation. The ECG interpreter will be blinded as to the inhaler used. Two weeks prior to the initial testing while on a stable regimen, the patients will have theophylline levels determined. Potassium levels and an ear oximetry will be done prior to the first Holter monitoring: a level of 3.5-5.0 $\text{K}^+ \text{mEq/dl}$ and an ear oximetry indicating saturation of $\geq 90\%$ will be required. Peak flow rates will be measured before and after the Holter monitoring.

Patients using beta-blocker therapy or any anti-arrhythmic medications or oral steroids up to two weeks prior to and through the testing, erythromycin and any of its congeners, or any other antibiotics for airways disease will be excluded, as will patients with histories of congestive heart failure, myocardial ischemia, myocardial infarction, or ECG's suggesting ischemia or infarction.

PROGRESS

(83 09 - 83 09) New protocol; no patients entered to date.

STATUS: (0)

TITLE: Liver Function Tests in the Normal Postpartum Female

PRINCIPAL INVESTIGATOR: CPT Paul F. McKenney, MC

PROFESSIONAL ASSISTANTS: MAJ V. Duane Bohman, MC
MAJ Arthur S. Maslow, MC
MAJ Thomas F. O'Meara, MC
CPT Stephen H. Koopmeiners, MC

WORK UNIT NO: 83/32

TECHNICAL OBJECTIVE

To determine when liver function tests return to normal levels after uncomplicated pregnancy and delivery.

METHOD

One hundred third trimester patients with uncomplicated courses will be interviewed on age, parity, alcohol intake, and medications, including contraceptives. Information on lactation will be included after delivery. Patients with a history of hepatobiliary disease, renal disease, or diabetes will be excluded. Blood samples will be obtained at 36-40 weeks, labor, one week postpartum, two weeks postpartum if prior liver function tests were abnormal, and at 6 weeks postpartum if prior liver function tests were abnormal. Bilirubin, LDH, SGOT, GGT, alkaline phosphatase, serum protein, and albumin will be tested on a routine SMAC.

PROGRESS

(83 01 - 83 09) No patients have been entered. Both Dr. McKinney and Dr. Maslow have been reassigned. Dr. Amy Tsuchida has agreed to assume responsibility for this protocol. Dr. Arthur Schipul from OB will assist on this protocol to replace Dr. Maslow. Dr. Tsuchida will begin to enter patients when she returns from TDY.

STATUS: (O)

TITLE: The Role of Topical Anesthesia in Upper Gastrointestinal Endoscopy

PRINCIPAL INVESTIGATOR: MAJ Thomas F. O'Meara, MC

PROFESSIONAL ASSISTANTS: MAJ Duane Bohman, MC
MAJ Willis Jacob, MSC

WORK UNIT NO: 83/36

TECHNICAL OBJECTIVE

To determine whether topical anesthetic spray eases the performance of upper endoscopy.

METHOD

Eighty consecutive patients undergoing elective upper endoscopy will be entered in the study with the following exceptions: allergy to cetecaine, diazepam, or meperidine; significant underlying cardiopulmonary or liver disease; and pregnancy.

Patients will be premedicated with IV diazepam/meperidine, with slurred speech, nystagmus, and drowsiness used as endpoints. The physician will leave the room and the patient's posterior pharynx will be sprayed by the assisting technician, utilizing a radmonization sequence. The procedure will then be performed and will be evaluated by both physician and patient. The patient will assess throat soreness (following procedure and 24 hours later), ease of passage of the scope, and overall ease of procedure. The agent will be sprayed in the room where the patient is so that the physician will be unable to tell by the odor from the patient which patient receives the agent and which receives the placebo.

PROGRESS

(83 01 - 83 09) Seventy-five subjects were studied. The study groups did not differ with respect to age, sex, nor average diazepam/meperidine dosage. No difference was noted in the level of sedation, physician/patient assessment of scope passage or physician/patient assessment of procedure's ease. No difference could be detected as to the presence of sore throat immediately following and 24 hours after endoscopy. When patients are adequately sedated with diazepam/meperidine, the addition of a topical anesthetic spray probably does not add to the ease of the procedure or patient comfort. Its use may be avoided in such patients to prevent the risks of aspiration or anaphylaxis.

PRESENTATION: O'Meara, TF, Bohman, VD, and Jacob, WS: The Role of Topical Anesthesia in Upper Gastrointestinal Endoscopy. William Beaumont Army Medical Center GI Symposium, El Paso, TX, March 1983.

STATUS: (C)

TITLE: High Dose Intravenous Gammaglobulin for Chronic Idiopathic Thrombocytopenic Purpura

PRINCIPAL INVESTIGATOR: MAJ Timothy J. O'Rourke, MC

PROFESSIONAL ASSISTANTS: COL Friedrich H. Stutz, MC
LTC James Congdon, MC
LTC Irwin B. Dabe, MC
MAJ Thomas M. Baker, MC
MAJ Alfred H. Chan, MC
MAJ Howard Davidson, MC

WORK NO: 83/62

TECHNICAL OBJECTIVES

To evaluate the efficacy of human immunoglobulin in treatment of chronic idiopathic thrombocytopenic purpura (ITP) that has not responded to conventional therapy and to observe changes in the serum proteins pertinent to the immune system during therapy.

METHOD

This is to be a multicenter study among the Army MEDDACs. It is anticipated that 5-6 patients will be needed to begin a valid study. At MAMC, 1-2 patients per year are expected. All patients with ITP documented by a compatible bone marrow picture and absence of secondary etiologies will be eligible. This will be restricted to patients who have failed conventional therapy, have severe thrombocytopenia and/or have spontaneous hemorrhage. Patients who are otherwise being treated but have life-threatening hemorrhage or who must undergo surgery may be included at the discretion of the study coordinator.

Patients will be treated with 0.4 mg/kg/day I.V. gammaglobulin as an infusion on each of five successive days. Should a response occur, weekly or biweekly maintenance will be continued. If the response is prolonged, the frequency will be lengthened and ultimately stopped.

PROGRESS

(83 05 - 83 09) One patient was entered who did not respond with a significant increase in platelet count and expired within two weeks of the completion of treatment from an intracranial hemorrhage.

STATUS: (0)

TITLE: An Evaluation of Local Anesthetic Skin Testing and Progressive Challenge in Patients with a History of an Adverse Reaction to Local Anesthetics

PRINCIPAL INVESTIGATOR: LTC John M. Piersol, MC

PROFESSIONAL ASSISTANTS: COL H.S. Nelson, MC
LTC Richard Weber, MC
Bonnie Baswell, M.D.
Richard deShazo, M.D.
Richard Summers, M.D.

WORK UNIT NO: 82/21

TECHNICAL OBJECTIVE

To confirm the safety and usefulness of local skin testing and progressive challenge in a large number of patients with histories of previous suspected adverse reactions to local anesthetics.

METHOD

After a history is taken, skin tests will be performed as described in the protocol and the 20 minute results recorded. If the history suggests a severe prior reaction, skin tests and progressive dose testing (PDT) may not be performed at the discretion of the attending physician. If PDT is indicated, a LA that does not cross-react with the LA implicated in the prior reaction will be used for PDT. If the prior LA is unknown, a Group II LA will be chosen. If the history suggests a delayed LA reaction, the patient will be evaluated at 24 hours after initial evaluation. The patient will be questioned for any delayed symptoms and examined for delayed physical findings at this time. An attempt will be made to obtain follow-up on the subsequent clinical history in each patient regarding the LA use and the presence or absence of a reaction. Serum (5cc) will be obtained from all patients with positive skin tests or with reaction to PDT or subsequent LA administration and frozen for subsequent analysis, including RAST or P-K testing.

PROGRESS

(82 10 - 82 12) Thirteen patients have been studied at MAMC in previous years. Testing was negative on all patients and the literature reports no positives; therefore, the investigators determined that further testing on this protocol would not be worthwhile.

STATUS: (C)

TITLE: The Role of Phosphate in the Anemia of Chronic Renal Failure.

PRINCIPAL INVESTIGATOR: COL Poong S. Shim, MC

PROFESSIONAL ASSISTANTS: COL Stephen R. Plymate, MC
MAJ Edward Lelonek, MC
CPT Wayne R. Heaton, MC
CPT Douglas R. Hough, MC

WORK UNIT NO: 82/60

TECHNICAL OBJECTIVE

To study the role of serum phosphate levels in the anemia of chronic renal failure patients on maintenance hemodialysis. It has been proposed that parathyroid hormone is a uremic toxin. The contribution of secondary hyperparathyroidism to the anemia of hemodialysis patients will be studied. The elevated serum phosphate levels and parathyroid hormone levels of secondary hyperparathyroidism are expected to be reduced with low phosphate diet, oral phosphate binders, and Rocaltrol. The response of the anemia to the treatment of the secondary hyperparathyroidism will be evaluated.

METHOD

Subjects undergoing hemodialysis and patients with chronic renal failure and evidence of secondary hyperparathyroidism will be studied. Patients with chronic constipation or documented non-compliance will be excluded. Pre-study bloodwork for each patient will include SMA-20, CBC, serum iron/TIBC, serum ferritin, folate, B-12, and PTH level. Radiographs of the hands for evidence of secondary hyperparathyroidism will be done. All patients will receive written and verbal instructions describing the study and the need for compliance with a low phosphate diet, oral phosphate binders, and Rocaltrol, a potent metabolite of vitamin D given to manage the hypocalcemia and reduce the elevated parathyroid hormone levels. Serum phosphate and calcium levels will be monitored monthly during the study; the calcium phosphate product will be maintained at <70. Alucaps or aluminum hydroxide will be given to control serum phosphate levels. Patients will be examined every two weeks for adverse side effects. The study duration will be for a minimum of six months. At the end of the study, all the pre-study bloodwork will be repeated. Radiographs will be repeated only for patients with pre-study evidence of bone cysts or subperiosteal resorption. Each patient will serve as his own control with pre-study values compared with study values using the Student's t Test. Also each individual will be compared with the group.

PROGRESS

(82 09 - 83 09) Due to the departure of staff personnel, no further progress has been made on this protocol and no patients have been entered. With the recent assignment of MAJ Lelonek, it is anticipated that work will begin on this protocol within the next few months.

STATUS: (0)

TITLE: Comparison of Ticarcillin/Tobramycin vs Mezlocillin/
Tobramycin in the Empiric Treatment of Febrile
Granulocytopenic Patients

PRINCIPAL INVESTIGATOR: CPT Michael W. Spangler, MC

PROFESSIONAL ASSISTANTS: LTC James Congdon, MC
MAJ Shannon Harrison, MC
MAJ James Higbee, MC

WORK UNIT NO: 83/28

TECHNICAL OBJECTIVES

To assess the effect on electrolytes, with special attention to hypokalemia; assess platelet function and quantity; and assess control of infection and appropriateness of empiric antibiotic coverage.

METHOD

This will be a randomized, double blind study of adult, febrile, granulocytopenic patients. The study will accrue patients until 30 documented infectious episodes are included.

Entry criteria: neutropenia, defined as <1000 segs plus bands; fever, $>100.6^{\circ}\text{F}$ 39°C , two values, two hours apart; not on antibiotics for one week prior to study; creatinine clearance >50 ml/min or ≤ 1.0 mg%; and if history of Pen allergy will skin test.

Treatment: 3 mg Mezlin IV q 4 hr plus 2 mg/kg Tobramycin IV loading dose, dose to be adjusted by Tobramycin levels, or 3 gm Ticar IV q 4 hr plus 2 mg/kg Tobramycin IV loading dose, dose to be adjusted by Tobramycin levels. Treat at least 3 days for evaluation, treat at least 10 days if infection is documented. No antipyretics. If cultures negative, discontinue medications when granulocytes $>1,000$. If cultures positive but not sensitive, off protocol and treat according to disk sensitivity. If patient has a drug reaction or is febrile longer than 7 days, off protocol.

PROGRESS

(82 11 - 83 09) Four patients have been entered.

STATUS: (0)

TITLE: The Incidence of Unsuspected Partial 21-Hydroxylase
Deficiency in Infertile Men with Idiopathic Oligospermia

PRINCIPAL INVESTIGATOR: CPT Thomas B. Stanton, MC

PROFESSIONAL ASSISTANTS: COL Bruce L. Fariss, MC
COL Stephen R. Plymate, MC
LTC William Belville, MC

WORK UNIT NO: 83/15

TECHNICAL OBJECTIVE

To determine whether previously undiagnosed partial 21-hydroxylase deficiency is a significant cause of reversible infertility in oligospermic men.

METHOD

Fifty consecutive men demonstrating oligospermia or azoospermia with normal serum FSH and seminal fructose on two consecutive semen analyses will have thorough fertility work-ups and complete physical exams. Subjects with well-documented orchitis, cryptorchidism, excessive drug or alcohol abuse, or systemic illnesses which may result in infertility will be excluded. Varicocele alone will not be grounds for exclusion. Ten age-matched men with normal semen analyses and evidence of fertility by paternity will be the controls. Diagnostic evaluation will include baseline serum testosterone, FSH, LH, prolactin, and a 24-hour urinary pregnanetriol determination. All subjects will undergo an AM cortrosyn stimulation test with measurement of plasma cortisol and 17-hydroxyprogesterone (17-OHP) prior to and 30 and 45 minutes after administration of cortrosyn 25 mg IV push. Subjects with elevated baseline urinary pregnanetriols and plasma 17-OHP levels or abnormally elevated 17-OHP responses to ACTH stimulation will undergo HLA typing. Family pedigrees will be constructed on subjects with 21-hydroxylase deficiency. Families will be studied clinically, biochemically, and with HLA typing, if possible. Patients with partial 21-hydroxylase deficiencies will be treated with glucocorticosteroids. Treatment will be monitored monthly by serum gonadotropin levels, serial semen analyses, and paternity histories.

PROGRESS

(11 82 - 83 09) Eight normal men and 25 men with idiopathic infertility were studied. The mean baseline 17-OHP level was higher in the infertile men, with five having levels greater than three standard deviations from the men of the normal men. The stimulated value of 17-OHP for infertile men was higher than in fertile men, and similarly the increase in 17-OHP after stimulation was greater in the infertile men. Serum T was lower in the infertile men and DHEA-S, 11-desoxycortisol, and cortisol were not different between the two groups. This demonstrates a defect in steroidogenesis in a subgroup of infertile men following cosyntropin stimulation. A paper has been accepted for presentation at the Pacific Coast Fertility Society in October 1983.

STATUS: (C)

TITLE: High Dose Oral Provera for ER+ and ER Unknown Metastatic Breast Cancer in Post-menopausal Women

PRINCIPAL INVESTIGATOR: COL Friedrich H. Stutz, MC

PROFESSIONAL ASSISTANTS: MAJ Lauren K. Colman, MC
CPT Thomas M. Baker, MC

WORK UNIT NO: 81/101

TECHNICAL OBJECTIVE

To determine whether or not Provera administered orally in a dose of 800 mg per day can cause regression of recurrent breast cancer occurring in the post-menopausal woman.

METHOD

Patients with histologically proven breast cancer who are at least one year post-menopausal with extensive breast cancer are eligible for this protocol. Patients with estrogen receptor positive tumor are eligible as well as those where the estrogen receptor status is unknown. Patients must have measurable disease and will have a careful preoperative evaluation and follow-up. Treatment will consist of 800 mg of oral Provera per day taken in divided doses. Treatment will continue for as long as the tumor remains stable or regresses. Unacceptable toxicity or patient refusal of treatment will be reasons for removal from the study.

PROGRESS

(82 09 - 83 09) No suitable patients have been found to enter on this protocol; thus, it has been terminated.

STATUS: (T)

TITLE: Syntex Laboratories #21-6276: Multicenter, Double-Blind, Randomized, Parallel Comparison of Two Different Dosage Regimens of Naproxen Sodium in Patients with Bone Pain Due to Metastatic Cancer

PRINCIPAL INVESTIGATOR: COL Friedrich H. Stutz, MC

PROFESSIONAL ASSISTANTS: LTC James E. Congdon, MC
LTC Irwin B. Dabe, MC
MAJ Thomas M. Baker, MC
MAJ Alfred H. Chan, MC
MAJ Howard Davidson, MC
MAJ Timothy J. O'Rourke, MC

WORK UNIT NO: 83/42

TECHNICAL OBJECTIVE

To compare the relative efficacy and safety of a higher total daily dose of naproxen sodium (1650 mg per day for three days) to a lower total daily dose (1100 mg on day 1, followed by 825 mg on days 2 and 3) in patients with moderate to severe, persistent, bone pain due to metastatic cancer.

METHOD

This will be a multicenter, double-blind, randomized, parallel comparison study of 3 days duration using in-patients or suitable outpatients who will be randomly assigned to receive naproxen sodium, 1650 mg/day, for 3 days or naproxen sodium, 1100 mg on day 1 followed by 825 mg on days 2 and 3. Patients will be asked to evaluate pain severity using an analogue scale (0-99) every two hours beginning 0600 and ending at 2200 each day.

PROGRESS

(83 02 - 83 09) Two patients were entered at MAMC. In both patients, pain was not adequately controlled. There are too few patients study-wide to draw any conclusions at this time.

STATUS: (0)

TITLE: The Effect of Nephrosis on Treated Hypothyroidism

PRINCIPAL INVESTIGATOR: LTC Gary L. Treece, MC

PROFESSIONAL ASSISTANTS: COL Bruce L. Fariss, MC
COL Stanton Brown, MC
COL Stephen R. Plymate, MC
MAJ Lawrence Agodoa, MC
MAJ Louis N. Pangaro, MC
MAJ David Turnbull, MSC

WORK UNIT NO: 81/56

TECHNICAL 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?

METHOD

SUBJECTS: normals; normal treated with L-thyroxine for one month; subjects with hyperthyroidism; with hypothyroidism, primary untreated; with hypothyroidism treated for one month with L-thyroxine; with the nephrotic syndrome; subjects with the nephrotic syndrome treated for one month with L-thyroxine. All subjects will have a 24-hr urine for volume, creatinine, total protein, urine protein, electrophoresis, T₄, and T₃ completed. After an overnight fast, blood will be drawn for SMAC-20, T₄, T₃ resin, T₃ by RIA, TSH, TBG (an extra tube will be drawn for free T₄, reverse T₃, and TBG). A fasting TRH test will then 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 T₄ for the treated groups. Excluded will be: 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 age >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

(82 09 - 83 09) Five subjects have been entered (3 during FY 83). The urinary T₄ and T₃ assays have yet to be fully developed. The methodology has been selected, however, utilizing alkalization of the urine sample to dissociate the thyronine bound to urine proteins with subsequent separation and concentration of the thyronines using Sephadex columns. Buffer containing TBG (from sera of pregnant patients) will be used to elute T₄ from the Sephadex resulting in a competitive protein binding assay for either T₄ or T₃. Three patients with the nephrotic syndrome and two patients with primary hypothyroidism have been studied. There is insufficient data to allow any conclusions.

STATUS: (0)

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

PRINCIPAL INVESTIGATOR: LTC Gary L. Treece, MC

PROFESSIONAL ASSISTANTS: COL Bruce Fariss, MC
MAJ Robert Jackson, MC

WORK UNIT NO: 82/05

TECHNICAL 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.

METHOD

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 three parts. During all three parts, the dose of any mineralocorticoid will not be altered. Patients having been on previous maintenance dose of glucocorticoid for at least three days and free of acute illness will be asked to collect two consecutive 24^o 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 seven 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 amounts of the other drug in the maintenance dosage for seven 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. Also, 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

(82 09 - 83 09) No subjects were studied during FY 83 as no patients with primary adrenal insufficiency were available. The blood and urine samples from the two previously studied patients are in frozen storage to be analyzed later as part of a larger group of samples that hopefully will be acquired during the next year in order to have a sufficient number of patients to allow for statistical analysis of the data.

STATUS: (0)

TITLE: The Effect of Rapid, Short Term Blood Glucose Control on Leukocyte Function in Diabetic Patients

PRINCIPAL INVESTIGATOR: LTC Gary L. Treece, MC

PROFESSIONAL ASSISTANTS: COL Bruce L. Fariss, MC
COL Stephen R. Plymate, MC
MAJ Michael Fincher, MC
MAJ James Higbee, MSC
MAJ Robert E. Jones, MC

WORK UNIT NO: 83/37

TECHNICAL OBJECTIVE

To study the effect on leukocyte function testing *in vitro* of rapid and sustained normalization of blood glucose levels in poorly controlled diabetic patients. Blood glucose control is to be accomplished using the Biostator - GCIIS (Glucose Controlled Insulin Infusion System).

METHOD

Six Type I and six Type II adult, non-pregnant, non-infected, poorly controlled diabetic patients will be the subjects for this study. They will not be taking antibiotics, glucocorticoids or other drugs known to affect hormonal or cellular immunity or leukocyte or bacterial activity. Any diabetic drug therapy will be discontinued during the period of Biostator Control.

After admission to the hospital, each patient will be connected to the Biostator, initially in Monitor Only mode, and blood for baseline fasting blood glucose, insulin, SMA-20, CBC, blood culture, triglycerides, Hg A₁C, and leukocyte function will be drawn. The Biostator will then be programmed to lower the blood glucose to 100 mg % and maintain the blood glucose at 100 mg % for 24-72 hours with the patient ingesting a weight maintaining diet divided into sevenths (2/7, 2/7, 2/7, 1/7). Blood for leukocyte function will be drawn at 2, 4, and 6 hours after normalization of blood sugar and every 6 hours thereafter. Should it be determined that leukocytic function can be altered with less than 6 hours of blood glucose normalization, the Biostator will be programmed to raise the blood glucose to 200 mg % 12 hours prior to termination of the study period. After 6 hours of a sustained blood glucose of 200 mg %, blood for leukocytic function will again be drawn. Then the blood glucose will be raised to 300 mg % for an additional 6 hours followed by repeat leukocytic function testing. Biostator control of the patient's blood glucose will then be terminated and the patient placed back on prior treatment regimen.

The Effect of Rapid, Short Term Blood Glucose Control on Leukocyte Function in Diabetic Patients - Treece

PROGRESS

(83 01 - 83 09) The majority of effort expended on this protocol has gone toward the development of the bactericidal leukocyte function test assay. The methodology has been developed and blood from a number of control and diabetic subjects has been analyzed utilizing the assay. The results are not yet consistent enough to allow reporting of results. The effort now is to strictly standardize the assay to allow sufficient inter- and intra-assay reproducibility of results. The Biostator has been acquired and personnel have been trained in its usage. The current plan is to first study the leukocyte function test assay and then begin studying patients before and after normalization of the blood glucose profile. It is hoped that the first patient might be studied by the end of the first quarter of FY 84. Supplies have been acquired to allow the study of approximately 10 patients.

STATUS: (0)

TITLE: Evaluation of Radiation Therapy in the Management of
Endoscopically Visible Tumors of the Lung

PRINCIPAL INVESTIGATOR: CPT James Wallingford, MC

PROFESSIONAL ASSISTANTS: LTC Jerome Beekman, MC
LTC Henry D. Covelli, MC
LTC Donald Kull, MC
MAJ Barry Weled, MC

WORK UNIT NO: 79/77

TECHNICAL OBJECTIVE

To evaluate in a prospective manner the utility of using radiation therapy to decrease tumor size in obstructing carcinomas of the lung.

METHOD

A minimum of 15 patients with carcinoma of the lung will be evaluated in the usual manner. If the patient is a non-operable candidate with endoscopically visible lesions, he will receive radiation therapy and/or chemotherapy in the usual manner with reassessment of pulmonary functions, arterial blood gases, and fiberoptic bronchoscopy approximately one month after radiation and again approximately six months after radiation. The parameters used to evaluate progression or regression of disease will be changing roentgenographic effect (collapse, atelectasis) in the area of involvement, alteration of pulmonary function and arterial blood gases, and changing luminal size of obstructing lesions as noted by fiberoptic bronchoscopy. Repeat biopsy results from prior areas of involvement will also be used to assess therapeutic results.

PROGRESS

(82 09 - 83 09) Twenty-nine patients (ten entered during FY 83) were entered on this protocol with no adverse effects. It was found that radiotherapy significantly reduced bronchoscopically visible obstructing carcinoma in a majority of patients. Dyspnea was relieved or stabilized regardless of objective response of the tumor. Chest x-ray appears adequate to follow the patient clinically with pulmonary function tests adding little helpful information. Improvement in flows and volume can only be anticipated in patients with mainstem obstruction. Post obstructive pneumonias were not prevented by palliative radiotherapy.

STATUS: (0)

DETAIL SHEETS
FOR
PROTOCOLS

DEPARTMENT OF NURSING

TITLE: Social Support and Symptomatology: A Study of First Time Expectant Parents

PRINCIPAL INVESTIGATOR: MAJ Jan Graham, ANC

PROFESSIONAL ASSISTANT: Marie Annette Brown, M.N.

WORK UNIT NO: 82/47

TECHNICAL OBJECTIVE

To describe the dimensions of social support perceived by expectant mothers and fathers; to compare the similarities and differences between expectant mothers and fathers in their experience of the dimensions of support; to explore the relationship between social support and symptomatology in expectant parents; to explore the effect of marital quality on the relationship between social support and symptomatology.

METHOD

The data will be collected using a questionnaire designed by the investigator which takes about 45 minutes to complete. The sample will include 125 couples (at least 250 individuals) who are living together and expecting their first child. The questionnaires will be coded and will not include names. The expectant parents will be asked to fill out the questionnaire and the consent form separately with no consultation or discussion between themselves. Subject numbers will be assigned and questionnaires will be numbered.

PROGRESS

(82 10 - 83 09) Questionnaires were completed by 313 couples. Findings indicate that age, education, socio-economic status, employment status, history of previous chronic illness, presence of pregnancy complications, marital problems, and stress are associated with expectant parents' health. Satisfaction with support from partners and social networks was related to lower levels of symptomatology and higher well-being. A number of associations between husbands and wives in both symptomatology and support suggested that expectant families operate as a system. The cultural stereotype of support-giving expectant father and supportreceiving pregnant woman was not reflected in this sample. Instead support behavior tended to be widely reciprocal. Using the support importance tool included in this study, health care providers could more specifically inform expectant parents and their significant others of what actions they might take to provide appropriate support. A thesis based on this study was submitted and accepted by the School of Nursing, University of Washington, as partial fulfillment of the requirements for a doctorate degree for Ms. Brown.

STATUS: (C)

TITLE: Hemoglobin Saturation During Spinal Anesthesia

PRINCIPAL INVESTIGATOR: CPT William A. Richling, ANC

PROFESSIONAL ASSISTANTS: LTC Leo A. Le Bel, ANC
LTC Michael R. Moon, MC
MAJ Donald Christensen, ANC
CPT Martha Downs, ANC
CPT James Spivey, ANC

WORK UNIT NO: 82/43

TECHNICAL OBJECTIVE

To determine whether subarachnoid block anesthesia significantly alters oxygen saturation of hemoglobin.

METHOD

Approximately 30 subjects undergoing elective surgery, subarachnoid block anesthesia, ASA classification I or II, whose surgical position will be supine will be studied. The subjects will receive no premedication. Oxygen-hemoglobin saturation will be measured by oximetry before administration of subarachnoid block anesthesia and thirty minutes after the administration of the subarachnoid block anesthesia. Data will be examined to determine if there is a significant change in oxygen-hemoglobin saturation resulting from the subarachnoid block anesthesia.

PROGRESS

(82 09 - 83 09) Eleven (11) subjects were studied during Fy 82. Oxygen-hemoglobin saturation was painlessly measured by ear oximetry before administration of subarachnoid block anesthesia and thirty minutes after administration of the subarachnoid block. Analysis of data revealed no statistical difference between pre- and post-subarachnoid block anesthesia measurements. On the basis of this study, oxygen need not be utilized for unmedicated ASA I or II adults between the ages of 19-45 years who undergo uncomplicated subarachnoid block anesthesia. Under these circumstances, hypoxemia does not appear to be a problem.

Thesis to fulfill requirements for the Academy of Health Sciences, Anesthesiology for ANC Officers Course, accepted:

Christensen DG, Downs, MC, Richling, WA, and Spivey, JA:
Hemoglobin Saturation During Spinal Anesthesia

STATUS: (C)

TITLE: Intravenous Administration of Lidocaine to Decrease
Cardiovascular Pressor Responses Following Laryngoscopy
and Endotracheal Intubation

PRINCIPAL INVESTIGATOR: CPT Michael Walsh

PROFESSIONAL ASSISTANTS: LTC Leo A. Le Bel, ANC
MAJ Steven Amster, MC
CPT Deborah Castellan, ANC
CPT David Forsythe, ANC
CPT Robert Norgan, ANC
CPT Lee Porisch, ANC

WORK UNIT NO: 83/50

TECHNICAL OBJECTIVE

To quantify the efficacy of intravenously administered lidocaine hydrochloride in obtunding cardiovascular pressor responses to laryngoscopy and intubation during general anesthesia using standard rate pressure product and an investigator devised index (Modified Rate Pressure Product, MRPP) based on heart rate, mean arterial blood pressure, and rate/pressure product.

METHOD

Healthy adult patients undergoing elective surgery requiring general anesthesia with laryngoscopy/endotracheal intubation will be selected for each of two study groups. One group will serve as a control population. All patients will receive a standard premedication. All measurements will be taken with a non-invasive Dinamapp recorder. Induction of anesthesia will be standardized. Patients will be randomized to either the study or control group on the basis of the last digit of their social security number. Study and control group sizes will be calculated prior to the start of the study.

Induction sequence: Preoxygenation with 100% oxygen for 3-5 minutes Administration of a defasciculating dose of non-depolarizing muscle relaxant; test dose of sodium thiopental; vital signs checked and respirations supported with mask and manual ventilation throughout induction sequence; sleep dose of sodium thiopental; upon loss of lid reflex administration of succinylcholine

Study sequence: Post induction baseline measurements obtained; study group receives lidocaine HCl intravenously in a dose of 1.5 mg/Kg followed at 1 minute by laryngoscopy and intubation within 30 seconds; control group will receive normal saline solution instead of lidocaine; incremental heart rate and mean arterial blood pressure recordings will be obtained every minute

Intravenous Administration of Lidocaine to Decrease
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for five minutes for both groups. Once the five minute measurement is obtained, the study procedure is complete. Anesthesia will then be continued in a normal manner.

Each measurement made for the study consists of pre-induction, post-induction and post laryngoscopy recordings of systolic, diastolic, and mean arterial blood pressures and heart rate. Rate pressure products and Modified Rate Pressure Products will be calculated for each patient measurement. The pre-induction measurements will not be utilized in the analysis. They will be used as a check for the post-induction measurements which will serve as a baseline. Post laryngoscopy measurements will be combined for each patient and a mean value obtained. This will be compared to the baseline (post-induction) measurement for statistical significance ($p < 0.05$) using a Student's t-test.

PROGRESS

(83 03 - 83 09) A subject size of 40 had originally been calculated. Due to limitations in time and acceptable surgical candidates, equipment shortages, defective equipment, and general anesthesia restraints, the final study population consisted of 20 adult subjects. The major clinical limitation of this study was the inability to maintain an adequate level of anesthesia during the three minute data collection period. Other limitations consisted of the small sample size and the frequent inaccessability of the blood pressure monitor. Using the Student's t test, the data with an absolute t value of 1.73 or greater ($p < 0.05$) showed no statistical difference between the treatment group and the control group. It is recommended that this study be repeated utilizing a larger population and a more effective premedicant in order to address the problem of inadequate anesthesia.

Thesis to fulfill a requirement of the U.S. Army Academy of Health Sciences/State University of New York at Buffalo, Anesthesiology for Army Nurse Corps Officers Course, accepted:

Castellan, DM, Norgan, R, Walsh, MV, Forsythe, DA, and Porisch, LA: Intravenous Administration of Lidocaine to Decrease Cardiovascular Pressor Response Following Laryngoscopy and Endotracheal Intubation.

STATUS: (C)

DETAIL SHEETS
FOR
PROTOCOLS

DEPARTMENT OF OB/GYN

TITLE: Mezlocillin Therapy for Empiric Treatment of Serious
Gynecological Infections

PRINCIPAL INVESTIGATOR: COL William Benson, MC

PROFESSIONAL ASSISTANTS: MAJ Shannon Harrison, MC
MAJ James Higbee, MSC

WORK UNIT NO: 83/59

TECHNICAL OBJECTIVE

To compare the outcome of single drug therapy with Mezlocillin to a multiple drug regimen of ampicillin, gentamicin, and clindamycin in serious gynecological infections.

METHOD

Two hundred women with serious genital tract infections will be studied. Patients in which an anaerobic organism is suspected or in which patients are ill enough to indicate initial treatment with a drug directed at anaerobes will be included in the study unless they are allergic to penicillin. Patients who have been treated with an antibiotic within the past 7 days will not be entered in this study. All subject will have urine analysis and culture, CBC, SMA-20, chest x-ray, and aerobic and anaerobic cultures of blood and presumed site of infection done as appropriate. Patients will be randomly assigned to one of the two treatment groups: Group I: Mezlocillin, 300 mg/kg/day, IV, divided into 6 doses or Group II: ampicillin, 2 gms q. 4 hrs, clindamycin, 600 mgs q. 8 hrs, gentamicin, 2 mg/kg loading dose, then 1.5 mg/kg q. 8 hrs VI. Subjects will have temperatures taken at 4 hour intervals. All patients will have a CBC and ESR daily and a serum creatinine biweekly. Patients in Group II will have gentamicin levels determined at 24-36 hrs and biweekly with gentamicin dose adjusted to produce peak levels at 5-8 mcg/ml and trough levels less than 2 mcg/ml. Treatment will be continued for 5 days unless terminated earlier because of drug reaction or toxicity; pathogens resistant to the antibiotic are documented, worsening in condition requires change in antibiotic, addition of heparin, or surgery. The treatment will be considered successful if, by completion of 5 days of therapy, the patient has been afebrile for 48 hours and has a normal examination. Following successful treatment, the patient will be followed at weekly intervals for three weeks.

PROGRESS

(83 04 - 83 09) Twenty-eight patients have been entered. Data is being collected, but no analysis is planned until 50 eligible patients have been entered.

STATUS: (0)

TITLE: The Detection of Fetal Maternal Hemorrhage in External Version and OCT via Alpha-feto-protein.

PRINCIPAL INVESTIGATOR: LTC Fred H. Coleman, MC

PROFESSIONAL ASSISTANTS: LTC Edward E. Dashow, MC
LTC John A. Read, MC

WORK UNIT NO: 83/12

TECHNICAL OBJECTIVE

To test for possible fetal-maternal bleeding during external cephalic version and oxytocin challenge testing using serum alpha-feto-protein and Kleihauer-Betke tests.

METHOD

Patients will be selected for oxytocin challenge testing or version by current management criteria used in the OB/GYN Department. Fifty patients reporting for versions and 100 patients reporting for oxytocin challenge testing will have pre and post blood samples drawn. The AFP levels will be determined via AFP radioimmunoassay kit and the Kleihauer-Betke via standard kit. The results will be correlated with each other and the procedures performed to determine the rate of fetal maternal bleeding.

PROGRESS

(82 10 - 83 09) Only two patients have been available and willing to participate in the study. No lab tests or alpha-feto-protein assays have been done to this date.

STATUS: (0)

TITLE: Ritodrine Hydrochloride Applications to Fetal Distress

PRINCIPAL INVESTIGATOR: LTC Edward Dashow, MC

PROFESSIONAL ASSISTANTS: COL Joseph Sakakini, MC
LTC Roger A. Spencer, MC

WORK UNIT NO: 81-17

TECHNICAL OBJECTIVE

To determine if ritodrine hydrochloride in arresting labor will interrupt fetal distress, reduce fetal acidosis, and result in healthier infants with less requirement for neonatal intensive care with consequent reduced hospital costs.

METHOD

Phase I (pilot study): Subjects will be patients in whom fetal monitoring indicates fetal distress and a decision is made to perform cesarean section. Subjects will receive 250 micrograms per minute ritodrine hydrochloride IV or sterile saline in equal volume in a random double-blind method. No attempt will be made to delay cesarean section. If after this infusion labor has stopped and fetal distress is no longer in evidence, the patient will be observed for 30 minutes, after which cesarean section will be performed. If fetal distress reoccurs, cesarean section or the best treatment for the patient will be performed immediately. At cesarean section, umbilical artery and vein pH will be measured from a sample obtained immediately after passing the infant to the pediatrician in attendance. Apgar scores at 1, 5, and 10 minutes and duration of intensive care will be recorded. At the end of Phase I the code will be broken and the groups compared according to parameters of Apgar score, umbilical artery and vein pH, duration of neonatal intensive care, and hospital costs. Phase II: If the study group shows no harmful effects compared to the control group, 70 additional patients will be studied and further analyzed.

PROGRESS

(82 09 - 83 09) Only two patients have been entered into this protocol, both in FY 81. The two patients entered had unremarkable postpartum courses along with their infants. No further work was done on this protocol because both professional assistants departed the Command.

STATUS: (D)

TITLE: Management of Intractable Postpartum Hemorrhage by the
Use of 15-Methyl Prostaglandin F2 Alpha-Tromethamine Salt

PRINCIPAL INVESTIGATOR: LTC Edward E. Dashow, MC

PROFESSIONAL ASSISTANT: COL Joseph Sakakini, MC

WORK UNIT NO: 81/36

TECHNICAL OBJECTIVE

To study the effects of 15-methyl prostaglandin F2 Alpha-THAM given IM to individuals having postpartum hemorrhage secondary to uterine atony that have been treated with all other conventional methods.

METHOD

This drug will only be utilized after the conservative management has failed and the patient is then considered for a surgical procedure to stop the severe postpartum hemorrhage and only if the use of the drug is not contraindicated by asthma, hypersensitivity to the drug, active cardiac, pulmonary, renal, or hepatic disease, or a history of these conditions or anemia, jaundice, or epilepsy. At the time of infusion, the IV infusion of oxytocin will be discontinued. The IV fluids will be continued and no further methergine will be given. Vital signs will be monitored and recorded every 15 min and continued for two hours after the final injection. Hemoglobin and hematocrit will be checked at 24 and 48 hours after the last injection. The volume of blood loss after delivery and the amount of blood loss after the initial injection will be estimated and recorded. The degree of contraction of the uterus will be determined by palpation before and one-half hour after each injection. The rate of hemorrhage will be estimated one-half hour after each injection and recorded as either increased, unchanged, or stopped. The presence of lacerations of the genital tract and retained placental fragments will be ruled out prior to entrance in the study.

PROGRESS

(82 10 - 83 09) Eight patients have been entered. Early results were not thought to be reliable due to a possible impotent batch of medicine. In the last three patients the drug appeared to be excellent for refractory post-partum hemorrhage except with advanced uterine infection. The medication has had no adverse effect in any of the patients.

STATUS: (0)

TITLE: Management of Premature Rupture of Membranes in Patients at 34-40 Weeks Gestation

PRINCIPAL INVESTIGATOR: LTC Edward E. Dashow, MC

PROFESSIONAL ASSISTANTS: COL Joseph Sakarini, MC
MAJ Alexander E. Smythe, MC

WORK UNIT No: 81255

TECHNICAL OBJECTIVE

(1) To ascertain whether a decreased caesarean section rate will result with conservation management in the patient with rupture of membranes and an "unripe" cervix at 34-40 weeks gestation; and (2) to judge whether a decreased infection rate will result with conservation management in the above patient group as opposed to those where labor is medically initiated immediately in spite of the unprepared cervix.

METHOD

Following initial evaluation, patients who are ≥ 34 weeks gestation will be placed in three groups. Group A (Bishop's inducibility score ≥ 7) will be induced and/or augmented as expeditiously as possible and evaluated per usual obstetrical guidelines. Group B (Bishop's score < 7 and odd terminal SSN digit) will be placed under observation using standard obstetrical monitoring and treated according to the progress of each patient. Group C (Bishop's score < 7 and even terminal SSN digit) will be induced or augmented as soon as possible following admission to the labor and delivery unit.

PROGRESS

(82 10 - 83 09) Additional subjects have been entered for a total of approximately 60 subjects. There appears to be no significant difference between waiting or immediate delivery in the 34-40 week pregnancy with rupture of membranes. The investigators anticipate that the study will be concluded in the next fiscal year.

STATUS: 00

TITLE: Comparison Study of Intrauterine Irrigation with Moxalactam Disodium, Cephapirin Sodium, Cefamandole Nafate, and Ampicillin During Cesarean Sections

PRINCIPAL INVESTIGATOR: LTC Edward E. Dashow, MC

PROFESSIONAL ASSISTANTS: LTC John A. Read, MC
MAJ Fred H. Coleman, MC

WORK UNIT NO: 83401

TECHNICAL OBJECTIVE

To compare the effects of moxalactam disodium, cephapirin sodium, cefamandole nafate, and ampicillin in reducing febrile morbidity and the incidence of endomyometritis following cesarean section.

METHOD

All patients undergoing cesarean section without a history of allergic reactions to cephalosporins and penicillin, without evidence of clinical chorioamnionitis, and not on antibiotic therapy will be eligible. Patients will be randomly assigned to one of five groups. All patients will receive endometrial cultures prior to irrigation and two days post-operative.

Group 1: After removal of the placenta, the uterine cavity will be cleaned manually with a wet sponge and the uterus will be delivered onto the anterior abdominal wall. A bulb syringe with 2 grams cefamandole nafate in 800 cc of saline will be used. Instillation of the irrigant solution will be performed using 400 cc in the endometrial cavity. Suction of the irrigation fluid will be performed simultaneously using a standard pool tip suction apparatus. Following uterine irrigation, repair of the uterine incision will be performed in the usual manner. The area under the bladder flap will then be irrigated with 50 cc of solution after which the flap will be closed in the standard manner. The cul de sac will then be irrigated with 50 cc of solution and the uterus replaced in the abdomen. The gutters will then be irrigated by instillation of approximately 200 cc of irrigation fluid. This will then be suctioned. Debris and clots will be removed at this time. Closure of the abdominal incision will be done in the standard fashion decided upon by the operating physician. The remaining 100 cc of irrigation solution will be utilized during this time for wound irrigation.

Group 2: will receive the same treatment as Group 1; however, moxalactam will be used in a dosage of 2 gm/800 cc of saline.

Group 3: will be similar to the previous groups, except that cephapirin in a dosage of 2 gm/800 cc of saline will be used.

Comparison Study of Intrauterine Irrigation with Moxalactam Disodium, Cephapirin Sodium, Cefomandole Nafate, and Ampicillin During Cesarean Sections - Dashow

Group 4: 2 grams of ampicillin will be placed in 800 cc of saline and irrigated as in the other groups.

Group 5: 800 cc of normal saline will be used as an irrigant.

No additional antibiotics will be given, unless indicated for complications. A vitamin solution (Solu-B-Forte) will be added to each solution such as the identity of the solution is unknown to the operator. All patients will receive aerobic and anaerobic endometrial cultures at the time of cesarean section prior to irrigation. Two days following cesarean they will again receive aerobic and anaerobic cultures of the endometrial cavity. Patients will be followed at two and six weeks post-op.

Measurement of Effect - A fever index as described by ledger 14 will be utilized to measure the febrile morbidity. Oral temperatures will be recorded every four hours. The quantity of fever will be expressed in degree hours and will represent that area above the baseline of 99 degrees Fahrenheit. Post-operative course will be reviewed with regard to the sequela associated with endomyometritis, post-operative total hospital days, and cost of total antibiotic therapy during hospitalization.

PROGRESS

(83 10 - 83 09) Two hundred seventy subjects have been entered. Data for the first 160 have been analyzed and show a trend toward decreased morbidity with cephalosporin irrigation. This is not yet statistically significant and other subjects will be entered.

STATUS: (0)

TITLE: Gynecological Oncology Procedure Training

PRINCIPAL INVESTIGATOR: COL Roger B. Lee, MC

PROFESSIONAL ASSISTANTS: LTC Richard Belts, MC
LTC George Ward, MC

WORK UNIT NO: 81/42

TECHNICAL OBJECTIVE

To provide training to OB-GYN residents in the technical aspects of various types of abdominal resections and anastomoses, to include training in the use of stapling instruments.

METHOD

Each resident participating will be provided with a large anesthetized dog. Under staff supervision, the following procedures will be accomplished on each animal:

1. exploratory laparotomy
2. resection and end to end anastomosis of small bowel
3. resection and end to side anastomosis of small bowel to colon
4. side to side anastomosis using the GIA stapler
5. end to end bowel anastomosis using the EEA stapler.

At the completion of each session, the animal will be sacrificed.

PROGRESS

(82 10 - 83 09) This protocol was used as a training model.

STATUS: (C)

TITLE: External Cephalic Version with Tocolysis Using Ritodrine

PRINCIPAL INVESTIGATOR: MAJ David J. Magelssen, MC

PROFESSIONAL ASSISTANTS: LTC Edward E. Dashow, MC
LTC John A. Read, MC

WORK UNIT NO: 83/17

TECHNICAL OBJECTIVE

To determine if the incidence of breech birth can be decreased by external cephalic version using Ritodrine to relax the uterus.

METHOD

One hundred gravidas with breech presentation > 36 wks weeks gestation will be studied. Ultrasonography will be performed to confirm the breech presentation; measure biparietal fetal diameter to assess gestational age; quantify amount of amniotic fluid; rule out fetal cephalic anomalies and/or hyperextension; localize placenta. If the mother is Rh negative, a Kleihauer-Betke test on blood samples will be done pre and post procedure. Rhogam will be administered if indicated. A pre and post procedure fetal activity determination test will be done by external fetal monitoring. At this point the subjects will be randomized to a treatment group and a control group. The treatment group will be administered Ritodrine by IV infusion at 200 µg/min for 20 min. External cephalic version will then be attempted and a successful procedure will be confirmed by ultrasonography. The treatment group will go straight to the external cephalic version. Any patients with evidence of a compromised fetus with a non-reactive fetal activity determination test; congenital anomalies by ultrasonography; oligohydramnios; or placenta previa will be excluded.

PROGRESS

(82 11 - 83 09) Fifteen subjects have been entered. The number of subjects is too small for any meaningful data, although the use of Ritodrine has seemed to be helpful. No adverse reactions have been noted and several successful versions have been accomplished.

STATUS: (0)

TITLE: Effects of Pure HCG, Progesterone, HPL, Estradiol 17-B,
and Estriol on Migration Inhibition Factor *In Vitro*

PRINCIPAL INVESTIGATOR: CPT Arthur S. Maslow, MC

PROFESSIONAL ASSISTANTS: COL Stephen R. Plymate, MC

WORK UNIT NO: 81/94

TECHNICAL OBJECTIVE

To determine what effect(s) various concentrations of pure progesterone, HPL, estradiol 17-B, and estriol have on migration inhibition factor (MIF), one of the potent soluble factors produced by lymphocytes during the immune reaction.

METHOD

Blood will be obtained from five pregnant patients in the first trimester. Lymphocyte stimulation assay (comparing PHA and poke-weed) will be run parallel with MIF assay to test effects of various concentrations of the individual hormones tested on MIF. If inhibitory effects are noted, assays will then be attempted of the hormones used in conjunction with one another. Guinea pigs will be injected with a substance to produce monocytes in the abdominal cavity. They will then be sacrificed and the monocytes will be harvested and used in a study to determine beta hCG on migration inhibition factor. The guinea pig monocytes will be used because they are produced in abundance and are easily harvested as opposed to human monocytes. The experiment is designed to test the function of migration inhibition factor produced by human lymphocytes and the effect of migration inhibition factor on the monocytes (in this case guinea pig monocytes).

PROGRESS

(82 10 - 83 09) Distance of migration of WBC's from an agarose microdrop was used to determine the effects of pure hCG and progesterone on MIF. In microtiter wells containing no immunogen mean migration was maximal, while in wells containing immunogen, mean migration was minimal, demonstrating the presence of MIF. In those wells containing both immunogen and varying concentrations of hCG and progesterone, significant migration occurred. These data confirm the inhibitory capabilities of hCG and progesterone on MIF and suggest a modulating role for progesterone by facilitating the effects of hCG at higher levels of progesterone. A paper has been submitted for consideration for publication.

STATUS: (C)

TITLE: Randomized Trial of Ambulation vs Oxytocin for Labor Enhancement

PRINCIPAL INVESTIGATOR: LTC John A. Read, MC

PROFESSIONAL ASSISTANTS: LTC Edward E. Dashow, MC
MAJ Frederick H. Coleman, MC

WORK UNIT NO: 83/02

TECHNICAL OBJECTIVE

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

METHOD

Approximately 100 patients with demonstrated failure to progress in labor for one hour, at least 4 cm dilated, and who are felt to require augmentation of labor are eligible for the study. The membranes shall have been ruptured and direct internal fetal monitoring in use. The vertex shall be applied to the cervix and there will be no evidence of fetal distress. The patient should not have received analgesia or sedations for at least one hour and should not be drowsy or exhausted. The patient will be placed on the fetal monitor in the right or left lateral decubitus position. A 30-minute observation period will be undertaken 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 (ambulation): Using either a cable or 2-channel telemetry the patient will assume the vertical position. She will be able to walk at will within the range of the cable or telemetry, and will be able to sit or visit the bathroom as required. Exams will be conducted at the end of one and two hours. The parameters stated above will be noted. The study will be interrupted for delivery, maternal or fetal distress, or maternal exhaustion. If after 2 hours no progress has occurred, the patient will be returned to bed and oxytocin utilized. If good progress is being accomplished and patient wishes to continue ambulation, she may do so.

Group II (oxytocin): Continuous IV infusion of oxytocin will begin at 0.5 mu/min and be 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 above noted parameters 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.

Randomized Trial of Ambulation vs Oxytocin for Labor Enhancement -
Read

Length of labor, time from study entry to delivery, type delivery, 1 and 5 min Apgar scores, cord blood gasses, maternal pain perception, newborn weight and neonatal problems will be noted in addition to previously mentioned parameters. Appropriate statistical analysis will be performed.

PROGRESS

(82 10 - 83 09) No patients have been entered. Subject entry will begin in November 1983.

STATUS: (0)

TITLE: Impact on Fetal Monitoring on the Premature Infant

PRINCIPAL INVESTIGATOR: COL David Sa'Adah, MC

PROFESSIONAL ASSISTANTS: COL Joseph Sakakini, MC
MAJ Alexander Smythe, MC
D. A. Luthy, M.D.
E. B. Larson, M.D.
K. K. Shy, M.D.
G. VanBelle, M.D.

WORK UNIT NO: 80/48

TECHNICAL OBJECTIVE

To analyze the effects of electronic fetal monitoring versus traditional auscultation in infants of very low birth weight with respect to the following endpoints: (1) perinatal mortality; (2) perinatal morbidity including Apgar scores, acid-base status at birth, and frequency of intracranial hemorrhage; (3) maternal morbidity including rates of cesarean section; (4) infant neurological and psychomotor development to one year of age; (5) provider satisfaction; (6) consumer satisfaction; (7) medical decision making; and (8) cost effectiveness analysis.

METHOD

Follow-up will be performed on infants who have had fetal monitoring. Those fetuses which have had electronic fetal monitoring and fetal scalp blood sampling done will be followed and compared to randomized traditional auscultation fetal heart rate. Comparisons of fetal outcome and well-being will be made. A comparison will be made of infants <1100 gm and >1100 gm. Infants will be followed and evaluated for evidence of retardation, cerebral palsy, and hearing loss at 6 months, 1 year, 1 1/2 years, and 2 years.

PROGRESS

(82 10 - 83 09) This protocol is being done in conjunction with several other hospitals. Subject entry has been completed, and the subjects are now in the follow-up period which will continue for approximately 18 more months.

STATUS: (0)

TITLE: Fetal-Maternal Hemorrhage in First Trimester Abortion

PRINCIPAL INVESTIGATOR: CPT Andrew P. Soisson, MC

PROFESSIONAL ASSISTANTS: LTC Edward E. Dashow, MC
CPT William J. Watson, MC

WORK UNIT NO: 83/49

TECHNICAL OBJECTIVE

To compare the Kleihauer Betke (KB) technique versus the maternal serum alpha fetal protein level in determining the incidence of fetal maternal hemorrhage in first trimester abortions and whether this hemorrhage is increased by suction curettage.

METHOD

Sixty (60) consecutive patients admitted for spontaneous abortion will be enrolled in the study. Presuction blood draw (15-20 ml) will include a maternal serum alpha fetal protein level as well as a sample for KB analysis. This will be repeated 30 minutes after suction curettage. An alpha fetal protein level will be obtained three months post abortion. This study will include only those women in the first 12 weeks or the first trimester of pregnancy. The only patients excluded from this study will be those past 12 weeks gestation.

PROGRESS

(83 03 - 83 06) This protocol was terminated due to an inability to obtain the three month post abortion samples.

(T)

TITLE: Maternal Unconjugated Estriol as a Predictor of Fetal Lung Maturity

PRINCIPAL INVESTIGATOR: CPT William S. Stovall, MC

PROFESSIONAL ASSISTANT: LTC Edward E. Dashow, MC

WORK UNIT NO: 83-03

TECHNICAL OBJECTIVE

To determine if there is a correlation between maternal levels of unconjugated estriol and fetal lung maturity as determined by L/S ratio.

METHOD

A maternal blood unconjugated estriol level will be obtained on all obstetrical patients who have amniocentesis for routine obstetric indications, determining fetal lung maturity by L/S measurements in patients with premature labor or prior to elective repeat cesarean sections. This will be done with approximately 30 or more patients and the data analyzed to see if there is a significant correlation between maternal estriol levels and L/S ratio.

PROGRESS

(82 10 - 83 09) A total of 141 patients who met the criteria has been entered. Estimated gestational age has been determined from first and second trimester ultrasounds. Biparietal diameters obtained at the time of amniocentesis have been collected for correlation with E_3 and L/S ratios. The preliminary data show that patients fall into one of three categories:

mature, L/S ($\geq 2/1$)/ $E_3 \geq 15$, n=44

mature, L/S ($\geq 2/1$)/ $E_3 < 15$, n=70

immature, L/S ($< 2/1$)/ $E_3 < 15$, n=27.

There have been no patients with an immature L/S and in $E_3 \geq 15$.

At this point the following conclusions can be made concerning the patients studied. (1) An $E_3 \geq 15$ is 100% predictive of an L/S ratio of 2/1 or greater. (2) An $E_3 < 15$ is useless for determination/prediction of L/S ratio.

STATUS: (0)

TITLE: The Effect of Maternal Glucose Administration on Neonatal Hypoglycemia

PRINCIPAL INVESTIGATOR: CPT William J. Watson, MC

PROFESSIONAL ASSISTANTS: COL Stephen R. Plymate, MC
LTC Edward E. Dashow, MC
CPT Donald Trippel, MC

WORK UNIT NO: 83/10

TECHNICAL OBJECTIVE

To determine whether glucose solution given to a patient in labor (now standard practice) results in significant hypoglycemia in the immediate newborn period.

METHOD

Sixty (60) normal term patients without complications who are in active labor will be enrolled in this study. A history of food intake during the past 6 hours will be taken. Those patients who wish to eat during labor will be excluded from or removed from the study. An initial serum glucose hemoglobin A_{1c} and basal insulin will be obtained. The patient will then be randomized to receive Ringer's lactated solution, Ringer's dextros lactated solution, or normal saline (control group). The fluids will be administered in the usual manner with monitoring of the total intake and urinary output. At the time of delivery, a cord blood will be obtained for glucose, insulin, and lactate. Maternal blood glucose will also be obtained on the mother while still in the delivery room. A heel-stick glucose determination will be obtained on each newborn at 45 and 90 minutes after delivery.

PROGRESS

(83 10 - 83 12) Eight patients were entered with no adverse reactions. The protocol was then terminated because the exact same study was published in the literature.

STATUS: (T)

DETAIL SHEETS
FOR
PROTOCOLS

DEPARTMENT OF PATHOLOGY

TITLE: Use of a Syringe and Blood Filter for Neonatal Transfusions.

PRINCIPAL INVESTIGATOR: CPT Dennis Urban, MSC

PROFESSIONAL ASSISTANTS: Marlene Bartram, M.T.
Delores Dilks, M.T.
Hollis Smith, M.T.

WORK UNIT NO: 82/04

TECHNICAL OBJECTIVE

To provide better utilization of Group O, Rh negative red blood cells, when small amounts (10-20 ml) are needed for neonatal replacement transfusions. The investigators will attempt to obtain (a) the incidence of culture positive fresh frozen plasma (FFP) on whole blood; (b) correlation with neonatal bacteremia/septicemia; and (c) comparison of blood utilization rate with new and old methods.

METHOD

Thirty (30) ml syringes will be filled with 8 ml fresh AB plasma and frozen in a sealed plastic bag. When blood is needed, syringe will be thawed and 16 ml of O negative packed red blood cells will be added and mixed. Syringe will be issued with an 18-micron syringe blood filter. Exact amount of FFP and packed red blood cells may be adjusted to provide whole blood with a hematocrit of 65%. All syringes of thawed FFP or units of reconstituted whole blood will be cultured for sterility and the NICU notified immediately of positive culture results. All transfused infants would be evaluated when FFP or reconstituted blood is culture positive.

PROGRESS

(82 09 - 83 09) This study showed that the use of a syringe and blood filter was a satisfactory method for neonatal transfusion when a small amount is needed.

STATUS: (C)

DETAIL SHEETS
FOR
PROTOCOLS

DEPARTMENT OF PEDIATRICS

TITLE: Social Support Resources and the Impact of A Child's
Illness or Disability on the Family

PRINCIPAL INVESTIGATOR: MAJ Heather S. Daniels, MC

PROFESSIONAL ASSISTANTS: Denise L. Schutte, Ph.D.
Pacific Lutheran University

WORK UNIT NO: 83/39

TECHNICAL OBJECTIVES

To assess the impact of the child's chronic illness or disability on the family; to assess the extent of the social support available to parents in this situation; to assess the relationship between the availability of social support and the impact of illness on the family; and to compare the levels of support and coping in military and civilian families as it relates to adjustment to the child's stability.

METHOD

Thirty families will be followed over the first three months after the initial diagnosis of a child's illness or disability. To serve as a control group, 30 families with children matched as to age, sex, number of siblings, and socioeconomic status will also be followed. The following instruments will be used to collect data: a demographic data sheet; a social relationships scale, an L-22 to assess parents' emotion and physical stress reactions; a dyadic adjustment scale; a social competence scale, Conner's Teacher Rating Scale, and a patient adjustment rating. Three months after the initial contact, subjects will be asked to complete the instruments a second time. After completion of the second contact, staff members will be asked to complete the patient adjustment ratings.

PROGRESS

(83 02 - 83 09) This protocol was terminated because of an inability to find local patients fitting the restrictions in an adequate number.

STATUS: (T)

TITLE: Phototherapy for Idiopathic Hyperbilirubinemia of the Newborn: Comparison of Patient Response to Different Irradiance Doses

PRINCIPAL INVESTIGATOR: CPT Alan G. Getts, MC

PROFESSIONAL ASSISTANTS: LTC Gary Pettett, MC
MAJ Philip V. Marinelli, MC
CPT Angelina LePage, MC

WORK UNIT NO: 83/74

TECHNICAL OBJECTIVE

To compare two phototherapy regimens in the treatment of idiopathic hyperbilirubinemia of the newborn (IHN). Items to be compared are: serum bilirubin decrease during phototherapy, duration of phototherapy required to resolve IHN, and complications of phototherapy. The specific goal is to determine a preferred regimen.

METHOD

Fifty (50) infants, >37 weeks gestation, appropriate for gestational age, who develop idiopathic hyperbilirubinemia, will be studied. Hyperbilirubinemia needing treatment will be defined as total serum bilirubin greater than 10.0 mg/dl within the first 48 hours of life or greater than 12.0 within the first 72 hours of life. Infants with other medical problems will be excluded from the study. Infants will be randomized into two treatment groups.

Group I patients will receive phototherapy in a dosage of 4-6 microwatts/cm²/nm at the specific wave lengths that are active.

Group II patients will receive between 10 and 12 microwatts/cm²/nm. Phototherapy will be delivered using two identical Olympic Bili-Lites.

Dosage delivered will be changed by varying the combinations of fluorescent bulbs in the two bili-lites. The dosage delivered will be measured using the Air Shields PR III Phototherapy Radiometer. Measurements will be made every eight hours. Laboratory data to be collected will be an initial total and direct bilirubin, hematocrit, direct Coombs' and blood type. Serial total and direct bilirubins will be drawn 4, 12, 24, 48, and 72 hours after the initiation of phototherapy. All samples will be drawn by heelstick.

PROGRESS

(83 09 - 83 09) Three patients were studied. No problems have been encountered.

STATUS: (0)

TITLE: Use of Folinic Acid in Prevention of Neutropenia and
Thrombocytopenia Secondary to Trimethoprim-sulfamethoxazole.

PRINCIPAL INVESTIGATOR: CPT G. William Letson, MC

PROFESSIONAL ASSISTANTS: LTC Alan D. Mease, MC
CPT Joseph High, MSC
CPT Merlin L. Robb, MC
CPT Philip L. Rogers, MC

WORK UNIT NO: 82/38

TECHNICAL OBJECTIVE

To establish whether or not folinic acid can significantly reduce reported incidence of 34% neutropenia and 12% thrombocytopenia in children treated with Trimethoprim-sulfamethoxazole.

METHOD

Pediatric patients diagnosed as having acute otitis media or urinary tract infections would be treated with Trimethoprim-sulfamethoxazole (T-S) in one group and T-S plus folinic acid in a second group. Dosage would be 40 mg/kg per day for T-S and 0.5 mg/kg per day for folinic acid divided in two daily doses and given over a ten day period. Patients would be randomized and selected to be in one or the other group with the T-S plus folinic acid as an experimental group. Drugs would be given in such a fashion as to achieve a double blind study. Results would be obtained by drawing a baseline CBC and another on the final day of treatment. Anyone developing neutropenia would be followed further with CBC's until resolution of neutropenia. Count of medication left over would be undertaken at the end of treatment to determine compliance level. The final step would be statistical analysis of data. A minimum of 30 subjects would be studied in each group.

PROGRESS

(82 03 - 82 09) Seven patients in the folinic acid group and 12 patients in the control group have completed the study. All patients responded satisfactorily to therapy. Platelet counts were normal before and after therapy in both groups. The control group demonstrated a mean decrease in absolute neutrophil count (ANC) of 61.9% with a 50% incidence of neutropenia. Two patients developed an ANC < 1000. The test group demonstrated only a 24.5% decline (mean) in ANC with a 14% incidence of neutropenia.

A paper presenting the results of this study to date has been selected as a finalist in the Howard Johnson Award for Housestaff Research to be presented at the Annual Tri-Service Pediatric Conference in March 1984.

STATUS: (0)

TITLE: Mechanical Ventilation of Newborn Premature Lambs: The Effect of Frequency, I:E Ratio, PIP, and PEEP on Oxygenation and Ventilation

PRINCIPAL INVESTIGATOR: MAJ Philip V. Marinelli, MC

PROFESSIONAL ASSISTANTS: LTC Gary Pettett, MC
MAJ Stanley P. Liebenberg, VC
CPT Richard Meidell, MC

WORK UNIT NO: 82/26

TECHNICAL OBJECTIVE

To prospectively evaluate the effect of ventilator setting, specifically frequency, I:E ratio, PIP, and PEEP, on arterial oxygenation and minute ventilation in premature newborn lambs.

METHOD

Premature or term lambs (125-135 days gestation) will be delivered via C-section, intubated with cuffed endotracheal tubes, paralyzed with Pavulon, and ventilated with the Sechrist ventilator. All animals will have prophylactic chest tubes inserted bilaterally to prevent symptomatic pneumothoraces during the experiment. Catheters will be placed in the descending aorta through femoral artery cutdowns. The aortic blood pressure will be maintained at 50-70 mm of mercury by infusions of maternal blood and/or lactated Ringer's solution. Initially, ventilator settings will be a rate of 30, inspiratory time of 1 sec, expiratory time of 1 sec, and sufficient PIP and PEEP to deliver an adequate tidal volume while maintaining a normal P_{aO_2} and P_{aCO_2} . The sequential changes in rate will be made, maintaining the baseline PIP and PEEP. At the completion of each change, the fetus will be returned to baseline until values are stabilized before proceeding to the next step. Subsequent changes in I:E ratio, maintaining a constant rate PIP and PEEP, will be studied. The fetus will be returned to baseline settings between each step. Third, changes in PIP will be employed with a constant rate, constant I:E ratio, and a constant PEEP. Finally, changes in PEEP will be determined by maintaining a constant rate, a constant I:E ratio, and a fixed peak inspiratory pressure. Arterial blood gases will be determined prior to and immediately following each portion of the experiment. Lung tissue will be obtained from each lamb for microscopic examination.

PROGRESS

(82 09 - 83 09) Four sets of twins were lost secondary to maternal anesthesia. Five term sheep were utilized; no premature sheep were used because of mating-time schedule difficulties. Only rudimentary data were collected. Procedures performed were cannulation of vessels, blood pressure recording, heart rate, transthoracic manometrics, and placement of intravascular Clark electrodes.

STATUS: (O)

TITLE: Mean Airway Pressure: Significance During Mechanical Ventilation in Neonates

PRINCIPAL INVESTIGATOR: MAJ Philip V. Marinelli, MC

PROFESSIONAL ASSISTANTS: LTC Gary Pettett, MC
CPT Richard Meldell, MC

WORK UNIT NO: 82/27

TECHNICAL OBJECTIVE

The specific aspects of the respiratory cycle during mechanical ventilation which allow optimal gas exchange are controversial. Recently, the concept of mean airway pressure as a composite of all pressures has been employed. It has been shown that mean airway pressure correlates directly with oxygenation. The purpose of this study is to examine the effect of various ventilator settings on gas exchange while maintaining a constant mean airway pressure.

METHOD

All neonates requiring intermittent mandatory ventilation will be eligible for the study. Indications for mechanical ventilation will be based on the standard criteria ($P_aCO_2 > 60$ Torr, $pH < 7.25$ and/or $P_aO_2 < 50$ Torr, $F_iO_2 > 0.6$). A pressure limited time-cycled ventilator will be used. PIP, PEEP, inspiratory time, flow rate, ventilator rate, and F_iO_2 will be adjusted to provide a P_aO_2 of 50-80 Torr and a $P_aCO_2 < 60$ Torr, pH of 7.30-7.40. The initial combination of settings producing these values will be taken as the baseline ventilator settings. Mean airway pressure will be measured from the T piece of the ventilator circuit using a proximal airway ventilator monitoring system which provides a constant digital display of the mean airway pressure by sampling proximal airway pressures every 10 msec and averaging these values over time. After achieving a steady state on baseline ventilator settings, an arterial blood sample will be obtained and the following sequential changes will be made on the ventilator:

Experiment I: PIP increased by 20% of baseline value and duration of positive pressure (inspiratory time) will be decreased in order to achieve the same baseline mean airway pressure. The other ventilator settings will be maintained at baseline value. All settings will then be returned to the initial baseline values.

Experiment II: PIP will be decreased by 20% of baseline value and inspiratory time will be increased to maintain a constant mean airway pressure; the other ventilator settings will be held constant.

Following a 10 min equilibration period, arterial blood gas will be sampled. Vital signs will be continuously monitored. In

Mean Airway Pressure: Significance During Mechanical Ventilation
in Neonates - Marinelli

addition, a transcutaneous PO_2 monitor will be used to insure that no detrimental increase or decrease in PaO_2 occurs as the result of experimental changes. This sequence will be followed in the first 24 hours of the infant's life and repeated during the second and third day in order to observe whether the natural change in compliance of the lungs will change the significance of mean airway pressure.

Each of the infants will serve as its own control. Statistical analysis of pH and PaO_2 and $PaCO_2$ will be performed utilizing Student's t test for paired data. The $aAPO_2$ gradient will be calculated from each of the blood gas results in order to standardize PaO_2 values over a range of F_iO_2 concentrations. These ratios will be analyzed by the means of the t test for paired data.

PROGRESS

(82 09 - 83 09) Data was collected on 15 infants with no adverse effects. No data analysis has been done.

STATUS: (0)

TITLE: Modified Immune Serum Globulin in Neonates

PRINCIPAL INVESTIGATOR: MAJ Philip V. Marinelli, MC

PROFESSIONAL ASSISTANTS: LTC G. Fischer, MC
LTC Gary Pettett, MC
LTC J. Pierce, MC
MAJ Robert M. Skarin, MC
CPT Richard Meidell, MC

WORK UNIT NO: 82/28

TECHNICAL OBJECTIVE

To evaluate Modified Immune Serum Globulin (MISG) as an adjunct to antimicrobial therapy in the treatment of neonatal Group B streptococci (GBS) disease. This protocol will analyze the ability of MISG to elevate neonatal IgG levels and will specifically look at pre and post MISG sera for evidence of increased activity against Group B streptococci using *in vitro* assays for opsonic antibody.

METHOD

Human MISG will be screened to ensure activity against several strains of GBS and one lot of 5% MISG will be selected and used throughout the study. Neonates who have a clinical diagnosis of suspected or proven sepsis will be evaluated and treated in the standard fashion and will also receive MISG. Infants thought to be in need of blood products will be excluded from the study. All infants will have cultures for bacterial pathogens taken prior to antibiotic or MISG therapy which will include umbilical, gastric aspirate, urine, blood, and cerebral spinal fluid. A 2.0 ml blood sample (prespecimen) will be obtained just prior to starting antibiotics and MISG therapy. A second 2.0 ml specimen will be obtained 2 hours after the completion of MISG infusion and again at 1, 2, 3, and 6 weeks after the infusion. The material will be given as 5% human MISG in a 10% maltose solution. The dose will be 250 mg/kg or 5 ml/kg to be given as a 30 minute infusion. Standard supportive care will be given to all other neonates treated for proven or suspected sepsis. All patients receiving MISG will be required to have constant temperature, heart rate, and respiratory monitoring. Patients with an umbilical artery catheter will have continuous BP monitoring. If not, BP by the Doppler method will be obtained before infusion, every 15 minutes after infusion for at least 2 hours, and then every hour for at least 24 hours. Urine volume, protein, and reducing substances will be measured at each void for the first 24 hours after MISG administration. Serum sodium, potassium, BUN, chloride, calcium, glucose, and osmolality along with hematocrit, hemoglobin, platelets and white blood cell count with differential will be

Modified Immune Serum Globulin in Neonates - Marinelli

obtained before, 2 hours after, and twice weekly for 2 weeks following the infusion. After the blood specimen is obtained, the serum will be separated and stored at -70°C . Immunoglobulin levels will be determined by standard immunodiffusion assay and opsonic antibody to GBS will be measured using the bactericidal opsonophagocytic assay currently used in the MAMC lab. In addition, a chemiluminescent assay, which measures activation of the hexose-monophosphate shunt, is being developed and will be utilized to measure functional antibody to GBS. All patients will be followed for a minimum of 6 weeks. The infants will be evaluated for growth and development and will receive all standard immunizations and care.

PROGRESS

(82 09 - 83 09) Data has been collected on four patients at MAMC and forwarded to WRAMC for analysis.

Group-wide, 22 neonates were randomly assigned to receive either 250 mg/kg or 500 mg/kg intravenous immunoglobulin. Both groups received antibiotics and supportive care. Specific activity against GBS was detected in intravenous immunoglobulin using several assays. Serum was analyzed for IgG and GBS specific IgG by comparing pre and post infusion samples. The 500 mg/kg dose gave a sustained increase in total and GBS specific IgG, while 250 mg/kg produced only a small and transient rise. No toxicity was observed. Further studies seem warranted to determine the value of intravenous immunoglobulin in neonates.

PUBLICATION: Weissman, L, Fischer, G, Marinelli, P: Intravenous Immunoglobulin Therapy in the Neonate. A Study of Pharmacokinetics and Safety. *Pediatric Research* 17(4): 341, 1983.

PRESENTATION: A paper has been accepted for presentation at the American Academy of Pediatrics, New York, New York, Oct 83

STATUS: (0)

TITLE: Hydrogen Breath Analysis After First Feedings in Infants
in Intensive Care Nursery

PRINCIPAL INVESTIGATOR: COL Charles Mitchell, MC

PROFESSIONAL ASSISTANTS: MAJ James Little, MSC
CPT Richard Meidell, MC

WORK UNIT NO: 81/107

TECHNICAL OBJECTIVE

To determine if there is malabsorption in infants in the intensive care nursery after first feedings and if there is predictive value of impending necrotizing enterocolitis in those infants who have malabsorption.

METHOD

A minimum of 20 patients will be studied before and after one of the initial feedings of formula. Expired air will be obtained at 0, 2, and 4 hours. In infants mechanically ventilated, the air may be obtained via a one-way volume. Non-ventilated infants will have sampling obtained from a catheter nasal apparatus connected to a syringe. Breath hydrogen will be measured by gas chromatograph equipped with a reduction gas detector.

PROGRESS

(82 09 - 83 09) The majority of time has been devoted to setting up equipment and standardization of procedures. Ten infants are scheduled to be entered in the protocol in October 1983.

STATUS: (0)

TITLE: Hydrogen Breath Analysis in Normal Newborns

PRINCIPAL INVESTIGATOR: COL Charles Mitchell, MC

PROFESSIONAL ASSISTANTS: MAJ James S. Little, MSC
CPT Richard Meidell, MC

WORK UNIT NO: 81/108

TECHNICAL OBJECTIVE

To determine if normal newborns malabsorb any of their formula feedings.

METHOD

A minimum of 30 patients will have samples taken of expired air. This will be done using a painless catheter apparatus in one anterior nares. The samples will be taken before the first feeding, at 2 hours and 4 hours. Breath hydrogen will be measured by gas chromatograph equipped with a reduction gas detector.

PROGRESS

(82 09 - 83 09) The majority of time has been devoted to setting up equipment and standardization of procedures. No infants have been entered on the protocol.

STATUS: (0)

TITLE: Hydrogen Breath Analysis in Children with Chronic
Nonspecific Diarrhea

PRINCIPAL INVESTIGATOR: COL Charles Mitchell, MC

PROFESSIONAL ASSISTANTS: MAJ James S. Little, MSC
MAJ Marsha Van Wagner, ANC

WORK UNIT NO: 81/109

TECHNICAL OBJECTIVE

To determine if ingestion of various carbohydrates is related to the chronic non-specific diarrhea syndrome; the hypothesis being that malabsorbed carbohydrates act osmotically to increase the fluid content of stools and that malabsorbed molecules are fermented by clonic bacteria producing hydrogen; therefore, hydrogen detected in the breath of previously fasting patients implicates malabsorption and subsequent diarrhea.

METHOD

Subject will be tested, fasting, on three different mornings. First test - cereal given without milk, using water as the fluid; second test - lactose as 20% solution; third test - sucrose. After the feeding the breath will be sampled at 0, 60, and 120 minutes. The breath will be sampled by a large catheter inserted into the anterior nares, a finger pressed against the opposite nares. A smaller tube will be inserted into the larger and attached to a syringe. At midexpiration, a few ml will be aspirated to a total of approximately 20 ml and insufflated into a vacuum test tube. Breath hydrogen will be measured by gas chromatograph equipped with a reduction gas detector.

PROGRESS

(82 09 - 83 09) The majority of time has been devoted to setting up equipment and standardization of procedures. Six infants have been entered on the protocol with no adverse effects.

STATUS: (0)

TITLE: Prevalence of Thyroid Dysfunction in Juvenile Onset
Diabetic Children and Its Relationship to Immunotype

PRINCIPAL INVESTIGATOR: MAJ Dan C. Moore, MC

PROFESSIONAL ASSISTANTS: None

WORK UNIT NO: 81/88

TECHNICAL OBJECTIVE

To define the percentage of juvenile onset diabetic children who have thyroid dysfunction as assessed by measurement of thyroid antibodies, T₄, T₃RU, and TSH response to TRH infusion. HLA typing will be done and a correlation made between those patients with evidence of thyroid autoimmunity and dysfunction and their immunotype to see if a subgroup of patients with juvenile onset diabetes can be identified by HLA typing who will be at risk for development of thyroid dysfunction in later life.

METHOD

Twenty-five patients, 18 years of age or less, will have a TRH test which will consist of three blood samples taken as follows:

- a. Baseline - for TSH, T₄, T₃U, thyroid antibodies, HLA type and hemoglobin A₁C.
- b. Injection of TRH, 7 ug/kg IV
- c. 30 minutes - blood sample for TSH
- d. 60 minutes - blood sample for TSH

Measurement of TSH, T₄, T₃U, thyroid antibodies, HLA type and hemoglobin A₁C are accepted tests in the management of the diabetic. The TRH test is a standard test to evaluate thyroid function.

PROGRESS

(82 09 - 83 09) Three patients were entered in this study in FY 83 for a total of eight subjects. One of eight diabetics was found to have thyroid antibodies. No abnormalities were found in thyroid function. Five of eight patients had B8 or B15 hapto-type; however, the inability to obtain DR typing limited the usefulness of HLA typing. Somatomedin-C was low in one of the eight patients but did not correlate with thyroid or nutritional status. No more studies are planned due to a lack of useful information and the low number of patients willing to participate.

STATUS: (C)

TITLE: Somatomedin-C and Gonadal Hormones in Precocious Sexual Development and in Relation to Medroxyprogesterone Treatment

PRINCIPAL INVESTIGATOR: LTC Dan C. Moore, MC

PROFESSIONAL ASSISTANTS: COL Stephen R. Plymate, MC
Vincent C. Kelley, M.D.

WORK UNIT NO: 31/113

TECHNICAL OBJECTIVE

To define the abnormalities of pituitary, adrenal, and gonadal function in patients with precocious sexual development in order to discern whether certain laboratory determinations correlate with clinical stages of sexual precocity and can be predictive of subsequent course; to discern whether any of these same parameters can be used to predict response to medroxyprogesterone therapy; and to assess the relative effect of medroxyprogesterone in suppressing somatomedin-C and sex steroids of gonadal vs adrenal origin.

METHOD

Thirty patients with precocious sexual development (males under 9 years and females under 8 years) will be given a physical examination rating of puberty status according to the system of Tanner. Plasma LH, FSH, E₁, E₂, T, DHEAS, bone age films, and skull films will be done. Blood samples will be drawn for somatomedin-C, somatomedin bioassay, Δ^4 -androstenedione and SHBG. Once a diagnosis is made, patients will be followed at 3 month intervals according to standard procedure. Those patients in whom it is clinically indicated will be placed on medroxyprogesterone therapy (100-200 mg IM every 2 weeks). Those patients placed on medroxyprogesterone will have initial blood tests repeated at 3 and 6 months to assess effect of therapy.

PROGRESS

(82-09 - 83-09) Ten additional subjects were entered in this protocol during FY 83. The investigator is in the process of assembling the data and analysis is to commence shortly.

STATUS: (0)

TITLE: A Teaching Model for Pediatric Intubation Utilizing
Ketamine-Sedated Kittens

PRINCIPAL INVESTIGATOR: LTC Gary Pettett, MC

PROFESSIONAL ASSISTANTS: COL Errol R. Alden, MC
LTC Ronald W. Brenz, MC
LTC Paul B. Jennings, VC

WORK UNIT NO: 74/19

TECHNICAL OBJECTIVE

To teach infant resuscitation procedures to nurses, nurse clinicians, OB-GYN residents, and other nonpediatric physicians who may be called upon to treat pediatric emergencies. Many physicians and paramedics have never had the training opportunity to attempt intubation of an awake living creature. The kitten, immobilized with ketamine hydrochloride, gives the student the opportunity to visualize vocal cords, precipitate laryngospasm, and learn the difficulties associated with emergency intubation.

METHOD

Weaned kittens, weighing 0.5 to 1.0 kg will be used in these teaching sessions. Ketamine hydrochloride (22 mg/kg) plus atropine sulfate (0.04 mg/kg) will be administered intramuscularly to each kitten. Intubation will be performed with the kittens on their backs, using a pediatric laryngoscope, and sizes 8-14 French endotracheal tubes. Kittens may be used for several consecutive weekly sessions until they grow too large to be utilized. The procedure is not harmful to the kittens.

PROGRESS

(82 09 - 83 09) This course was given on three occasions during FY 83.

PUBLICATION: Jennings, P.B., Alden, E.R., and Brenz, R.W.:
A Teaching Model for Pediatric Intubation
Utilizing Ketamine-Sedated Kittens.
Pediatrics 53:283-84, 1974.

A Teaching Model for Pediatric Intubation Utilizing Ketamine-Sedated Kittens - Pettett

EXHIBIT: Alden, E.R. and Jennings, P.B.: Animal Models for Neonatal Resuscitation.

- a. Annual Meeting of the American Academy of Pediatrics, Chicago, IL, Oct 1976.
Gold Award for Outstanding Exhibit for Teaching Value.
- b. Annual Meeting of the American Medical Association, San Francisco, CA, Jun 1977.
Certificate of Merit
- c. American Veterinary Association
Atlanta, GA, Jul 1977.
- d. Annual Meeting of the Association of Military Surgeons, Washington, DC, Nov 1977.

STATUS: (O)

TITLE: Techniques of Advanced Life Support

PRINCIPAL INVESTIGATOR: LTC Philip G. Pettett, MC

PROFESSIONAL ASSISTANTS: COL Barry Wolcott, MC
LTC Stan Harris, MC
LTC William A. Madden, MC
MAJ Steve Dronen, MC
MAJ Philip V. Marinelli, MC
MAJ Stanley P. Liebenberg, VC

WORK UNIT NO: 83/35

TECHNICAL OBJECTIVE

To provide experience for physicians/nurse personnel in the techniques of advanced life support. This program will provide the student with familiarity in the skills of thoracotomy, percutaneous/venous puncture, arterial venous cutdown, vascular line insertion and tracheostomy placement.

METHOD

The animal models will be mongrel dogs. Each animal will be properly prepared for standard surgical techniques by shaving and scrubbing. Surgical procedures will be performed in a sterile manner with the animal fully anesthetized and supported by proper ventilatory technique. Each animal will then undergo the following surgical procedures using techniques currently in hospital practice for humans:

- (1) thoracotomy with pleural tube insertion
- (2) percutaneous arterial and venous cannulation with IV lines
- (3) arterial and venous cutdown with IV line insertion
- (4) tracheostomy insertion

At the conclusion of the experiment, surgical sites will be properly closed and the animal given a lethal dose of barbiturate without being allowed to regain consciousness.

PROGRESS

(83 01 - 83 09) This is a teaching protocol and is given to all Pediatric residents on an annual basis.

STATUS: (0)

TITLE: Neonatal Hydrotherapy: An Adjunct to Developmental Early Intervention in an Intensive Care Nursery Setting

PRINCIPAL INVESTIGATOR: MAJ Jane K. Sweeney, AMSC

PROFESSIONAL ASSTS: LTC Gary Pettett, MC
CPT Carolyn Talentino, ANC

WORK UNIT NO: 83/16

TECHNICAL OBJECTIVE

To describe the use of hydrotherapy for infants at high risk for neurological impairment and developmental delay in an intensive care nursery; measure the physiologic parameters and behavioral state changes before, during, and after aquatic intervention; and analyze the potential physiologic risks versus therapeutic musculoskeletal and behavioral benefits in the use of hydrotherapy as an adjunct to an individualized developmental intervention program in the neonatal ICU.

METHOD

Twenty (20) medically stable infants ≥ 36 weeks gestation will be studied. Randomization will not be used in the selection process; rather, the total caseload will be screened for medically stable infants with abnormalities in muscle tone and/or in behavioral state control when handled.

A standard plastic bassinet will be used as the neonatal hydrotherapy tub with the water temperature prepared at $37.2-38.3^{\circ}\text{C}$. An overhead radiant heater will be placed over the tub to decrease temperature loss in the undressed infant. Mean blood pressure, mean heart rate, and behavioral state will be measured at 5 min intervals during the 20 min period before aquatic intervention, at 5 min intervals during aquatic intervention, at 5 min intervals during the 20 min period after aquatic intervention. The methods of aquatic intervention will be compared in each subject: warm water immersion by one examiner and warm water immersion and hydrotherapy techniques by two examiners (one at head/shoulder region and one at pelvis/lower extremity region). The hydrotherapy techniques consistent with the Neurodevelopment Treatment Approach will involve midline positioning of the head, graded muscle tone normalizing movements of the trunk and extremities, and proximal hand placement. The behavioral state of the infants will be evaluated and coded from the standardized scoring system in the Brazelton Neonatal Behavioral Assessment Scale.

TITLE: Neonatal Hydrotherapy: An Adjunct to Developmental Early Intervention in an Intensive Care Nursery Setting

PROGRESS

(82 11 - 83 09) Three infants were studied. A total of twenty observations were recorded from the three infants. This resulted in nine observations of water immersion only and eleven observations of water immersion and hydrotherapy. Collective data trends demonstrated the following: (a) increased blood pressure, heart rate, and behavioral state during both forms of aquatic intervention; (b) decreased heart rate after hydrotherapy with increased heart rate after the sessions of immersion only; (c) smaller increase in blood pressure after hydrotherapy than after immersion only; (d) maintenance of the quiet alert state following immersion only. Hydrotherapy utilizing NDT facilitation/inhibition principles with gentle graded flexion and rotary movements at shoulder and pelvic girdle regions with midline head position resulted in longer periods of sustained alertness and less change in physiologic variable than the ten minute sessions of warm water immersion only.

The risk-benefit relationship of the effects of hydrotherapy is noted in terms of potential physiologic complications to high risk infants versus therapeutic neuromusculoskeletal and behavioral benefits. These benefits included the following: (1) improvement in abnormal muscle tone; (2) enhancement of visual and auditory orientation responses; (3) improvement in feeding behavior; (4) contracture control; (5) parent participation in therapeutic bathing; (6) role release of hydrotherapy to the nursing staff for evening and weekend carryover; and (7) cost effectiveness in terms of equipment, time management, and personnel resources.

PUBLICATION: Sweeney, J.K.: Neonatal Hydrotherapy: An Adjunct to Developmental Intervention in an Intensive Care Nursery Setting; in Aquatics: A Revised Approach to Pediatric Management, The Haworth Press, 1983, pp 39-52.

PRESENTATIONS: Sweeney, J.K.: Neonatal Hydrotherapy: An Adjunct to Developmental Intervention in an Intensive Care Nursery Setting.

- a. American Physical Therapy Association Combined Section Meeting, Nashville, TN, Feb 83.
- b. American Physical Therapy Association Annual Conference, Kansas City, MO, Jun 83.
- c. Eastern Regional Neurodevelopmental Therapy Conference, National Children's Hospital, Washington, DC, Nov 83.

STATUS: (C)

TITLE: Descriptive Study of Characteristics of Adolescent Women Who Have Had Unplanned Pregnancies with a Comparison Study of Those Who Have Not

PRINCIPAL INVESTIGATOR: LTC Gentry Yeatman, MC

PROFESSIONAL ASSISTANTS: Juvann M. Wolff, R.N.

WORK UNIT NO: 83/80

TECHNICAL OBJECTIVE

To identify the high risk and the low risk parameters for teenage pregnancies in order to better educate teenage girls in the area of avoiding unplanned pregnancies.

METHOD

A minimum of 100 adolescent women ages 14-19 will be provided with a cover letter and a questionnaire. A quiet, private location will be provided in which to complete the questionnaire.

After completion, the questionnaire will be placed in a sealed envelope by the participant and returned to the researcher or receptionist. The questionnaires will be collected and analyzed.

The questionnaire consists of 32 items, divided into eight categories: demographic, attitude toward contraception, knowledge of contraception, reproductive knowledge, perceived severity, perceived susceptibility, perceived benefits of action, and a self-esteem scale.

PROGRESS

(83 09 - 83 09) This is a new study. The logistics are being worked out. No patients have been entered.

STATUS: (0)

DETAIL SHEETS
FOR
PROTOCOLS

PHYSICAL MEDICINE AND REHABILITATION SERVICE

TITLE: Analysis of Thigh Girth Measurement as an Evaluative Tool

PRINCIPAL INVESTIGATOR: 1LT Stephen C. Allison, AMSC

PROFESSIONAL ASSISTANT: CPT Kathleen A. Westphal, AMSC

WORK UNIT NO: 83/14

TECHNICAL OBJECTIVE

To determine the value of human thigh girth measurement as an evaluative tool in predicting asymmetry in the function of knee flexors and extensors and to determine if there exists an optimal site for girth measurement in terms of predicting muscle function.

METHOD

Thirty adult will be studied. This patient must have 2 cm or more asymmetry in thigh girth as measured 15 cm proximal to the superior border of the patella. Patients with acute injury, acute pain, acute knee joint effusion or limitation of active motion exceeding 10° of knee extension or 100° of knee flexion will be excluded. The data to be gathered will include sex, dominant limb, a brief history, thigh girth measurements of both lower extremities, and isokinetic testing of both knees for flexion and extension. Girth measurements will be taken of both thighs at 1 cm increments, beginning 1 cm proximal to the superior patellar border and ending 20 cm proximal to the superior patellar border. Measurements will be recorded to the nearest half centimeter. Isokinetic testing will be done on both knees using the Cybex II dynamometer and associated testing apparatus currently in use in the Physical Therapy Clinic. Each test will be standardized according to the Cybex testing manual. Data to be obtained from the Cybex graph readouts will include peak quadriceps and hamstring torques at 60°/second and number of repetitions to 50% quadriceps fatigue at 180°/second. Measurements will be recorded to the nearest foot-pound. Pearson correlation coefficients will be obtained for the 30 sets of paired data representing each of the 20 thigh girth levels measured. Asymmetry at each of the 20 levels of thigh girths will be tested for correlation with loss of quadriceps strength, hamstring strength, and quadriceps endurance. T-tests for significant difference between coefficients of correlation will then be applied to determine relative strengths of correlation.

PROGRESS

(82 11 - 83 09) Approximately 15 subjects were entered in this protocol. The protocol has been closed at MAMC due to the departure of the principal investigator. CPT Allison has had the protocol approved at Ft Riley, Kansas, and will continue to enter patients into the study there.

STATUS: (C)

DETAIL SHEETS
FOR
PROTOCOLS

DEPARTMENT OF PSYCHIATRY

TITLE: The Neuropsychological Correlates of Hyperthyroidism
and Its Treatment

PRINCIPAL INVESTIGATOR: MAJ Lloyd I. Cripe, MSC

PROFESSIONAL ASSISTANTS: LTC Gary Treece, MC
MAJ Louis Panjaro, MC
MAJ Raymond Parker, MC

WORK UNIT NO: 81/75

TECHNICAL OBJECTIVE

To determine the neuropsychological correlates of hyperthyroidism and the effects of treatment.

METHOD

Approximately 30 subjects presenting with a diagnosis of spontaneous hyperthyroidism, whose management and treatment have been decided by the primary physician, will be entered in the study. Phase I - will include the administration of the entire Halstead-Reitan Neuropsychological Test Battery during the physician's initial diagnostic work-up. Phase II - Patients will be randomly assigned to receive either propranolol, 40 mg q.i.d. or a placebo. After 7-10 days of drug therapy patients will again be given the Halstead Reitan Battery and blood levels will be checked. Phase III - the test battery will be administered for the third time after the patient has been euthyroid for one month as determined by TFT. Thirty controls without psychiatric, neurological, or thyroid disease will be matched with the experimental group for age, sex, intelligence, and education. They will be administered the Halstead-Reitan Battery on the same schedule as the experimental group. Thyroid status would be determined at each testing by blood levels for hormones. Hotelling's Multiple t-tests for multi-variant data will be utilized to make comparisons between the groups for the three testings. Correlations with test measures and blood levels will also be made.

PROGRESS

(82 09 - 83 09) Two subjects were entered during FY 83 for a total of eight subjects. The investigators will continue to enter subjects.

STATUS: (0)

TITLE: Psychological Variables Related to Childbirth and Early Infant Development

PRINCIPAL INVESTIGATOR: MAJ Anthony C. Zold, MSC

PROFESSIONAL ASSISTANTS: CPT Richard H. Rubes, MSC
CPT (USAR) Maren Stavig, ANC

WORK UNIT NO: 81/59

TECHNICAL OBJECTIVE

To study selected psychological and behavioral variables during pregnancy which may affect ease of delivery, medical complications, and early growth and development of the infant. Specifically, the independent variables to be investigated are: (1) maternal expectations of delivery and of the infant; (2) mother's perception of her husband's emotional support; (3) orgasmic history of the mother; (4) mother's participation in various childbirth preparation programs; (5) mother's history of depression during pregnancy.

... from volunteers at ... recontact mother for ... mother's subjective rating ... record search for ... of complications, ... between mother and ... request mother ... and do a record ... analysis will ... and contingency

... birth, and six ... assessment tools ... we plan to start in

... of depression ... satisfaction are ... birth complications ... for the newborn.

STATE :

DETAIL SHEETS
FOR
PROTOCOLS

DEPARTMENT OF SURGERY

TITLE: Implantation of Intraocular Lenses

PRINCIPAL INVESTIGATOR: COL Stanley C. Allison, MC

PROFESSIONAL ASSISTANTS: COL Stanley C. Sellie, MC
LTC Christopher G. Knight, MC
MAJ Bruce D. Bellin, MC
CPT Lawrence E. Hannon, MC
LTC John C. Goodin, MC

WORK UNIT: 79764

TECHNICAL OBJECTIVE

To become proficient in intraocular lens implantation and to gain investigator status with FDA requirements, thereby providing a new technique in ophthalmic surgical care for our patients.

METHOD

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

(82 10 - 83 09) Lenses were implanted in 238 patients during FY 83 with no adverse reactions. The ophthalmologic community is progressing towards accepting the intraocular lenses as a standard part of the surgical armamentarium of this specialty. Special status as a research tool should be obviated within two to three years.

STATUS: (0)

TITLE: The Evaluation of Synthetic and Autologous Grafts in an Acute Wound

PRINCIPAL INVESTIGATOR: COL Charles Andersen, MC

PROFESSIONAL ASSISTANTS: MAJ Eddie J. Reddick, MC
Linda Bickerstaff, M.D., DAC

WORK UNIT NO: 83/65

TECHNICAL OBJECTIVE

To determine the most appropriate arterial replacement in an acute wound by comparing autologous saphenous vein, Gortex PFEF graft, and Meadox Biograft.

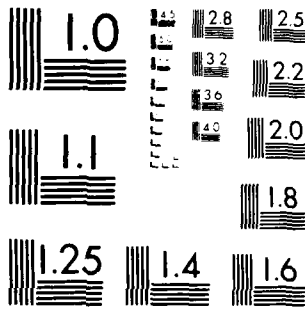
METHOD

Eighteen (18) adult mongrel dogs will be divided into three groups of six with each group having arterial replacement with either autogenous saphenous vein, Meadox Biograft, or Gortex PFEF Graft. After adequate general anesthesia, a standard, reproducible wound will be made in the hind leg near the area of the femoral artery using a captive bolt gun. The animals will be kept under anesthesia for three hours. The wounds will be debrided, the arterial graft will be inserted under sterile conditions, and the wound will be primarily closed. Blood cultures and wound cultures will be taken at the time of debridement and at the time of graft sacrifice. This will result in two aerobic and two anaerobic blood cultures and two aerobic and two anaerobic tissue cultures being performed on each animal. The wound will be observed daily for ten days and weekly thereafter for evidence of wound infection. At two months post injury, an arteriogram will be performed, the wound will be re-explored and the graft removed. The graft will be inspected for pseudoaneurysm formation, neo-intimal formation, obvious sites of breakdown, patency, and evidence of distal embolization. Animals which die prior to two-months will be autopsied and the graft will be inspected as above. If an animal becomes septic, it will be euthanized.

PROGRESS

(83 07 - 83 09) This protocol has not been started.

STATUS: ()



MICROCOPY RESOLUTION TEST CHART
NATIONAL BUREAU OF STANDARDS-1963-A

TITLE: Treatment of Recurrent Otitis Media: Chemoprophylaxis
Versus Tympanostomy Tubes

PRINCIPAL INVESTIGATOR: MAJ James E. Arnold, MC

PROFESSIONAL ASSISTANTS: CPT James B. Erhart, MC
CPT Alan G. Getts, MC
CPT Stephen R. Pratt, MC

WORK UNIT NO: 83/33

TECHNICAL OBJECTIVE

To compare the effectiveness of treatment with PE tubes or antibiotic prophylaxis in children with recurrent otitis media.

METHOD

Children with recurrent otitis media will be randomly assigned to:

Group A: Bilateral myringotomies with placement of PE tubes.

Group B: Prophylactic antibiotic regimen consisting of Gantrisin, 500 mg for six months.

Group C: A placebo will be given for six months.

They will be followed for six months to determine the most effective treatment modality.

During an episode of acute otitis media, patients will be treated with appropriate antibiotics, and the study medicine will be discontinued until the episode is resolved.

A failure will be defined as two or more episodes of recurrent otitis media within a three month period after entering the study. Those patients who fail will be treated in the following manner:

Patients in Group A will be treated with the Gantrisin regimen. Patients in Groups B & C will then undergo myringotomy and PE tube placement.

PROGRESS

(83 01 - 83 09) Ten subjects have been entered. As this is a double blind study and the code has not been broken, no results are available.

STATUS: (O)

TITLE: The Effect of Dimethyl Sulfoxide on the Uptake of Cisplatin
From the Urinary Bladder of the Dog

PRINCIPAL INVESTIGATOR: LTC William Belville, MC

PROFESSIONAL ASSISTANTS: LTC Samuel J. Insalaco, MC
LTC George S. Ward, VC
MAJ Eduardo S. Blum, MC
MAJ Carl F. Cricco, MC
MAJ Willis H. Jacob, MSC
MAJ Roger Schoenfeld, MC

WORK UNIT: 79/57

NOTE: Thio-TEPA was the original drug to be utilized in this study. Being unable to develop a successful thio-TEPA assay, cisplatin was used in the study due to the ease of measurement by atomic absorption spectrometry and because its medium-sized molecular weight avoids excessive absorption. The original protocol is listed below.

TECHNICAL OBJECTIVE

Thio-TEPA has been used in the management of various types of neoplasias for almost two decades. However, its use in the management of urinary bladder carcinoma has had mixed results. In addition, the cytotoxic effect of thio-TEPA on the hematopoietic tissues are a severe side effect in its use. The objective of this study is to determine if intravesicular thio-TEPA can be more effectively transported through the urinary bladder wall using DMSO as a carrier.

METHOD

Ten dogs will be divided into groups I and II (4 dogs each and Group III (2 dogs). The test solution (50 ml) will be instilled into the urinary bladder of each animal and maintained there for one hour. The test solutions are: Group I 45 mg thio-TEPA in 50% DMSO; Group II - 45 mg thio-TEPA in an isotonic salt solution; and Group III - 50% DMSO in an isotonic salt solution. The Group III animals are to verify that DMSO does not interfere with thio-TEPA identification.

Blood samples will be obtained from the caudal vena cava and the external jugular vein immediately before instillation of the test solution and at 5, 10, 20, 40, and 60 min after instillation. One blood sample will be taken from a small vein on the bladder surface at 15 min and the test solution will be withdrawn from the bladder at 60 minutes.

The Effect of Dimethyl Sulfoxide - Belville

Two dogs from Groups I and II will be studied for toxicity following a complete treatment regime, consisting of four weekly treatments as described above. These animals will have bone marrow, liver, kidney, and spleen biopsies before the first treatment. One week following the last treatment, the dogs will be sacrificed and tissue sections of the same organs plus the urinary bladder and lens will be taken. These tissues will be examined histopathologically for evidence of toxic changes. Complete blood counts will also be performed at weekly intervals.

The remaining two dogs in Groups I and II will have a section of urinary bladder removed following the test solution instillation. This tissue section will be divided and one part homogenized and extracted for thio-TEPA analysis and the other section evaluated histopathologically.

The withdrawn test solution, blood samples, and bladder tissue extracts will be analyzed by spectrophotometry to determine levels of thio-TEPA. The results will be compared to determine effectiveness of DMSO in increasing absorption of thio-TEPA.

PROGRESS

(82 10 - 83 09) Cis-platinum was used in this study rather than Thio-TEPA. The results of the study suggest that DMSO is useful by transporting cis-platin into the muscle layer of the canine bladder. Serum levels of cis-platin can be monitored and dosages can be adjusted to avoid untoward side effects, with an acceptable assay. A larger series is necessary to solidify and extend these observations. No laboratory work was done in FY 83 due to personnel shortages. It is anticipated that further work will be accomplished in FY 84.

PRESENTATION: Schoenfeld, R.H., Belville, W.D., Jacob, W.H., Buck, A.S., Dresner, M.L., Insalaco, S.J., and Ward, G.S.: The Effect of Dimethyl Sulfoxide on the Uptake of Cisplatin From the Urinary Bladder of the Dog. Kimbrough Urologic Seminar, Denver, November 1981.

PUBLICATION: Schoenfeld, R.H., Belville, W.D., Jacob, W.H., Buck, A.S., Dresner, M.L., Insalaco, S.J., and Ward, G.S.: The Effect of Dimethyl Sulfoxide on the Uptake of Cisplatin From the Urinary Bladder of the Dog: A Pilot Study. J Amer Osteopath Assoc 82: 570-753, 1983.

STATUS: (0)

TITLE: Early Definitive Treatment of Pilonidal Abscess vs Delayed Definitive Treatment. A Prospective Randomized Study.

PRINCIPAL INVESTIGATOR: LTC Preston Carter, MC

PROFESSIONAL ASSISTANTS: LTC James F. Bascom, MC
CPT Robert B. Freeman, MC
CPT Edward Pullen, MC

WORK UNIT NO: 81/104

TECHNICAL OBJECTIVE

Conventional treatment of pilonidal abscess has consisted of incision and drainage over a point of fluctuance lateral to the midline, followed at a variable interval by definitive excision of the midline tracts. A proposed alternative method is to perform the incision and drainage in the midline with excision of the midline tracts in the process. The objective of this study is to study the two methods to see if there is any advantage in terms of minimizing the patient morbidity of one method over the other.

METHOD

Patients who have had previous surgical treatment of pilonidal disease and minors will be excluded. Patients will be randomized to one of the two treatment methods outlined above and will be followed until complete healing has occurred. Hospitalization time, if any; loss of time from work; healing time; and complications related to either treatment method will be studied. A minimum of ten patients per group will be studied.

PROGRESS

(82 10 - 83 09) Fifteen patients were entered into the study. Early definitive excision of the pilonidal sinuses appears to be an effective method of treatment. This method spares the patient the necessity of a secondary procedure which is required if pilonidal abscess is treated with an initial incision and drainage without excision.

PRESENTATION: Gary Wratten Surgical Symposium, Augusta, GA,
April 1983

STATUS: (C)

TITLE: A Protocol to Compare Segmental Mastectomy and Axillary Dissection With and Without Radiation of the Breast and Total Mastectomy and Axillary Dissection.

PRINCIPAL INVESTIGATOR: LTC Preston Carter, MC

PROFESSIONAL ASSISTANTS: LTC James F. Bascom, MC
LTC Stanley C. Harris, MC
LTC Dick R. Smith, MC

WORK UNIT NO: 82/02

TECHNICAL OBJECTIVE

To begin participation by MAMC in an established national cooperative study comparing the survival, treatment failure, and cosmetic results of partial mastectomy with and without radiation compared to modified radical mastectomy.

METHOD

Patients with breast cancers under two inches in size and without fixation to the chest wall or skin will be offered randomization to three treatment arms: (a) segmental mastectomy, axillary dissection; (b) segmental mastectomy, radiation, axillary dissection; (c) total mastectomy, axillary dissection. Patients with positive axillary nodes will, regardless of the primary treatment, be given L-PAM and 5-FU chemotherapy as further treatment.

PROGRESS

(82 10 - 83 09) Eight patients at MAMC have been entered into the study. None of the patients who have had a partial mastectomy has had any local recurrence of the tumor in the breast.

STATUS: (0)

TITLE: Intravenous Dexamethasone to Control Post Operative Pain
in Orthopedic Patients

PRINCIPAL INVESTIGATOR: CPT Michael Q. Cosio, MC

PROFESSIONAL ASSISTANTS: COL Richard Camp, MC
LTC Thomas J. Parr, MC
MAJ Douglas Beirne, MC

WORK UNIT NO: 82/29

TECHNICAL OBJECTIVE

To determine whether intravenous dexamethasone can decrease the severity of post-operative pain in orthopedic patients.

METHOD

Patients undergoing elective surgery will be studied with the following exceptions: history of altered immune response or delayed wound healing; steroid use in past 6 months; open wounds or fractures, infected wounds/joints or abscesses; open growth plates; total joint, hip, and spine surgery, history of malignancy; pregnant or lactating female. In a prospective, randomized, double-blind study, dexamethasone or placebo (D₅W) will be given IV slow push in 3 doses: 12 mg in the OR prior to surgery, then 4 mg 6 hours and 14 hours after the first dose. The patient will fill out a questionnaire regarding his pain level throughout the hospital stay. Pain medications will be standardized as follows: Morphine 4 or 8 mg IM q 3 hr and codeine 30 or 60 mg po q 4 hr prn pain. If allergic to codeine, Zomax 1 or 2 tabs po q 4 hr prn will be used. If allergic to morphine, Stadol 1 or 2 mg IM q 3 hr with Zomax will be used. The use of antipyretics and salicylates will be withheld for one week to insure detection of fever and possible infection as early as possible. Since some surgery is more painful than others, the patients will be subdivided into groups by regions of pain. Patients will be followed until the sutures are removed, usually two weeks later.

PROGRESS

(82 10 - 83 09) Seventy-three patients have been entered in the following groups: foot (11), ankle (3), shoulder (12), knee (13), hand (28), fracture (2), metal removal (4). One infection occurred and resolved with local wound care and antibiotics. One GI bleed occurred but the patient was not on dexamethasone. In order to have numbers large enough to demonstrate statistical significance approximately 50 patients per group are needed and 100 patients for the hand group. Investigators will continue to enter patients on the study in the next year.

TITLE: Incidence and Natural History of Deep Venous Thrombosis
in Patients Undergoing Elective Knee Surgery

PRINCIPAL INVESTIGATOR: CPT Michael Q. Cosio, MC

PROFESSIONAL ASSISTANTS: COL Stanton Brown, MC
COL Joel Sim, MC
LTC Thomas J. Parr, MC
Denise Anderson, R.N.

WORK UNIT NO: 82/57

TECHNICAL OBJECTIVE

To determine the true incidence, natural history, and response to therapy and prophylaxis of DVT in patients undergoing elective knee surgery.

METHOD

Approximately 100 patients undergoing elective surgery about the knee, except for knee ligament reconstruction, total knee replacement, or pediatric patients, will have daily clinical evaluation for DVT and PE following surgery. If a patient develops signs and symptoms of DVT or PE, an immediate Doppler and venogram and/or lung scan will be performed as appropriate. Otherwise, a venogram will be performed following a Doppler evaluation of both limbs 7-10 days post op. If the incidence of DVT in the nonoperated leg is found to be <5%, venography will be done only on the operated leg. Those patients who have DVT will undergo a perfusion lung scan immediately after the venogram, at four and eight days after detection of the DVT. Those who have CVT confined to the calf will not receive any therapy. Those with DVT of the calf with proximal extension will receive a 10 day course of IV heparin. The heparin will always be given by continuous IV infusion, maintaining the PTT between one and a half to two times normal.

PROGRESS

(82 10 - 83 09) Of the 21 subjects entered into the study, 14 have had arthroscopic surgery only, 7 have had arthroscopic surgery combined with a second operative procedure on the same knee. Ten patients have had bilateral venograms, all of which have been negative with no adverse reactions. The remaining 11 patients have had venograms performed on the operated limb only; all of them have been negative. Two allergic reactions in the form of hives have been encountered; each resolving after IM benadryl. The rate of DVT in elective knee arthroscopic surgery appears to be quite low. Thus far, there have been no instances of documented DVT in the operated limb of 21 patients or the nonoperated limb in 10 patients.

STATUS: (C)

TITLE: Bulbocavernosus Reflex and Conduction Velocity of Dorsal Penile Nerve in Normal Men

PRINCIPAL INVESTIGATOR: COL Martin L. Dresner, MC

PROFESSIONAL ASSISTANT: MAJ Mohammad A. Saeed, MC

WORK UNIT NO: 80/67

TECHNICAL OBJECTIVE

To determine the normal values of the bulbocavernosus reflex arc as transmitted through the dorsal penile nerve as an indicator of peripheral neuropathy. Peripheral neuropathy is one of the causes of organic impotence.

METHOD

Approximately 25 men will be studied with electrophysiological testing of the bulbocavernosus reflex to determine reflex latency and conduction velocity of the dorsal penile nerve. Subjects will have no history or clinical evidence of any disorder which would affect the peripheral nervous system and sural nerve conduction will be tested to rule out subclinical peripheral neuropathy. A monopolar teflon coated needle electrode will be placed in either the right or left bulbocavernosus muscle and the dorsal penile nerve will be stimulated with bipolar stimulator electrode at the base of the penis and the glans penis using TECA TE4 electromyogram. These stimuli will be delivered with a frequency of 1/second and a pulse duration of 0.5 msec. At least five identical responses will be recorded. Motor unit action potential of bulbocavernosus muscles, recruitment pattern in bulbocavernosus muscles, reflex latency, wave form, and dorsal penile nerve conduction velocity will be evaluated.

PROGRESS

(82 10 - 83 09) Approximately 200 subjects were studied. The investigators found that the bulbocavernosus reflex was slightly higher in patients when stimulation was done at the glans penis. No further subjects were entered in FY 84. The protocol has been closed due to the departure of the investigators.

PRESENTATIONS: Singh, S., Dresner, M., and Saeed, M.: Bulbocavernosus Reflex in Men with Impotence. Amer Assoc of Electromyography and Electrodiagnosis, 26 Sep 80. Philadelphia.

Dresner, M.L., Saeed, M.A., Belville, W.D., and Buck, A.S.: Evaluation of Impotence. NY Section of the American Urological Assoc, 16 Oct 82, Rome, Italy.

STATUS: (C)

TITLE: An Evaluation of the Safety and Efficacy of Cyanoacrylate Ester in Ossicular Reconstruction and Nerve Graft Anastomosis in the Guinea Pig Middle Ear

PRINCIPAL INVESTIGATOR: COL William H. Gernon, MC

PROFESSIONAL ASSISTANTS: CPT Roy Kim Davis, MC

WORK UNIT NO: 77/88

TECHNICAL OBJECTIVE

To determine the safety and efficacy of cyanoacrylate ester in the middle ear; specifically, for ossicular reconstruction for histological changes in the oval window area and in the facial nerve. In addition, the use of this compound in tympanoplasty would be a natural extension of this project. The intended purpose of this study is to open the door for the use of cyanoacrylate ester in human surgery, initially on an experimental basis.

METHOD

The investigators propose to use Histoacryl and Crazy Glue to do interpositions (incus) on a test group of guinea pigs as well as place glue on the facial nerve, perhaps to do facial nerve anastomoses, and to place the glue in the oval window area. Approximately 39 animals would be utilized. At 3, 6, and 12 months, 12 experimental animals and one control animal would be sacrificed. Histological temporal bone studies would then be conducted at AFIP.

PROGRESS

(82 10 - 83 09) The temporal bones were completed at the AFIP and review of these is in process. Findings show that the cyanoacrylate causes considerable bony overgrowth. There is no evidence of toxicity to inner ear structures.

PRESENTATION: Wells, J., Gernon, W.H., Ward, G.S., Davis, R.K., and Hays, L.L.: Otosurgical Model in the Guinea Pig (*Cavia porcellus*). American Academy of Otolaryngology, Head and Neck Surgery, Sep 81, New Orleans, LA.

STATUS: (O)

TITLE: Advanced Trauma Life Support Course

PRINCIPAL INVESTIGATOR: LTC Stanley C. Harris, MC

PROFESSIONAL ASSISTANTS: LTC Terence L. Babcock, MC
MAJ Kenneth Frumkin, MC
MAJ Stanley P. Liebenberg, VC

WORK UNIT: 82/32

TECHNICAL OBJECTIVE

To provide training to General Surgery, Emergency Medicine, and Family Practice residents in the proper management of the patient in the initial one hour after major trauma.

METHOD

At least twice a year, the Advanced Trauma Life Support Course as designed by the American College of Surgeons will be conducted. The course involves a hands on training session in the placement of chest tubes, tracheostomy, pericardiocentesis, peritoneal lavage, and venous cutdown utilizing the dog as the animal model.

PROGRESS

(82 10 - 82 10) This protocol was replaced by MAMC 83/08 with LTC Stanley C. Harris as the principal investigator. No training sessions were held under this protocol number.

STATUS: (C)

TITLE: Advanced Trauma Life Support Course

PRINCIPAL INVESTIGATOR: LTC Stanley C. Harris, MC

PROFESSIONAL ASSISTANTS: MAJ Stanley P. Liebenberg, VC

WORK UNIT NO: 83/08

TECHNICAL OBJECTIVE

To provide training to general surgery, emergency medicine, and family practice residents in proper management of the initial one hour after major trauma.

METHOD

This course as designed by the American College of Surgeons will be given at MAMC one to two times per year. The course includes hands-on training using dogs as the experimental model. Each student will be directly involved in the performance of a venous cutdown, cricothyroidotomy, tube thoracostomy, peritoneal lavage, and pericardiocentesis.

PROGRESS

(82 10 - 83 09) This course was completed twice during FY 83. A display of Advanced Trauma Life Support objectives at MAMC was given at the Tacoma Surgical Society Meeting.

STATUS: (O)

TITLE: Medical Treatment of the Frey Syndrome

PRINCIPAL INVESTIGATOR: COL Leonard L. Hays, MC

PROFESSIONAL ASSISTANTS: Alvin J. Novack, M.D.
University of Washington

WORK UNIT NO: 76/06

TECHNICAL OBJECTIVE

1. To study objectively the true incidence of the Frey syndrome in post-parotidectomy patients by means of the Minor Starch Iodine Test.
2. To determine the effect of, and patient satisfaction with, medical management comparing on a double blind basis topical use of a placebo, varying concentrations of scopolamine hydrobromide, and the newer anticholinergic agent, glycopyrrolate.
3. To investigate the value and practicality of iontophoresis of the above agents to increase the duration of satisfactory control of sweating.
4. To compare the topical use of a patient's most effective antiperspirant on the involved facial skin with the result from the topical use of the most effective agent in the double blind series for that patient.

METHOD

Phase I - Double-blind treatment with 1/4%, 1%, and 3% scopolamine hydrobromide cream, 0.1% glycopyrrolate, and a placebo; comparison by the patient as to effectiveness; and retreatment after drug dosage adjustment if the patient fails to respond.

Phase II - Utilize iontophoretic introduction of the best anticholinergic agent to a group of volunteers with significant sweating symptoms and to a group who are medical failures and compare action and duration of action with iontophoretic introduction using tap water, Ringer's lactate, or saline.

Phase III - Patients who fail medical treatment or have become dissatisfied with the medical treatment and have significant symptoms confirmed on minor starch-iodine testing will be offered surgery such as flap elevation or tympanic neurectomy.

Medical Treatment of the Frey Syndrome - Hays

PROGRESS

(82 10 - 83 09) Four new patients were entered in FY 83, for a total of 26 patients studied. The use of topical glycopyrrolate remains a highly effective means to control gustatory sweating with rare minor side effects such as dry eyes or oral dryness. The investigators plan to study more patients.

PUBLICATION: Hays, L.L.: The Frey Syndrome: A Review and Double Blind Evaluation of the Topical Use of a New Anticholinergic Agent. Laryngoscope 88:1796-1824, 1978.

PUBLICATION: Hays, L.L.: The Frey Syndrome. News Bulletin, The American Acad Otolaryngology-Head and Neck Surgery, 20 Sep 81.

PRESENTATION: Hays, L.L., Novack, A.J., and Worsham, J.C.: The Frey Syndrome, A Simple Effective Treatment. American Academy of Otolaryngology Meeting, New Orleans, LA, Sep 81.

PUBLICATION: Hays, L.L., Novack, A.J., and Worsham, J.C.: The Frey Syndrome, A Simple Effective Treatment. Otolaryngol Head Neck Surg 90:419-25, 1982.

STATUS: (0)

TITLE: Teaching Program for Practical Microsurgery

PRINCIPAL INVESTIGATOR: LTC Stanley Jackson, MC

PROFESSIONAL ASSISTANTS: COL Leonard L. Hays, MC
LTC Preston L. Carter, MC
LTC Thomas G. Griffith, MC
MAJ Stanley P. Liebenberg, VC

WORK UNIT NO: 82/35

TECHNICAL OBJECTIVE

To establish a formal training program in clinical microsurgery at MAMC for use of surgeons desiring to develop this expertise.

METHOD

In order to perfect the techniques needed to perform clinical microsurgery, extensive practice is needed in the research laboratory. The teaching program will be established at the Department of Clinical Investigation, and a room will be set aside for the project where equipment for the microsurgery can be housed. A schedule of two afternoons per week will be set aside for teaching sessions. Animal model preparations (cadaver and live) will be developed by the veterinary surgical consultant with the support of the clinical teaching staff. Sessions will begin with lectures, followed by practical exercises in anatomy and step-by-step instruction in the surgical techniques.

PROGRESS

(82 10 - 83 09) There was minimal participation during FY 83 due to time restrictions on the Plastic Surgery Service. Time has been scheduled for each Thursday afternoon for four hours of microvascular practice and teaching. Tentative plans are to prepare for free flap transfers.

STATUS: (O)

TITLE: Evaluation of a Short Course of Prednisone in the Treatment of Serous Otitis Media: A Double Blind Crossover Study

PRINCIPAL INVESTIGATOR: MAJ Del Ray Maughan, MC

PROFESSIONAL ASSISTANTS: COL William Gernon, MC
LTC William Harpster, MC

WORK UNIT NO: 82/01

TECHNICAL OBJECTIVE

To evaluate the effect of a brief course of prednisone on the course of serous otitis media.

METHOD

Population: Patients diagnosed as having unilateral or bilateral serous otitis media by clinical microscopic exam; type B tympanogram must be present; effusion must be unresponsive to standard medical therapy, using decongestants, for at least three weeks; adult and pediatric patients will be studied.

Double blind protocol: Group I (25 patients) - placebo
Group II (25 patients) - prednisone
1 mg/kg for 2 days; 0.75 mg/kg
for 2 days, and 5 mg/day for 3 days.

Follow-up clinical exam after one week and crossover then performed for patients with a persistent effusion. Patients clearing their effusion would be followed with periodic clinical exam and tympanometry for one year (every 3 months). Any patient developing acute otitis media would have his medication discontinued, be removed from the study, and receive standard therapy.

PROGRESS

(82 10 - 83 09) The investigators had revised this protocol in FY 82 to use dexamethasone. However, they were able to obtain the prednisone and the study was started using prednisone. Ten patients were entered in the protocol. No adverse reactions were reported at MAMC. However, two cases have been reported in the literature of patients developing meningitis when treated with prednisone for serous otitis media. Dr. Maughan feels, in light of these reports, that proceeding with the study is not safe. Dr. Harpster, the original principal investigator who is now at FAMC concurs with this decision.

STATUS: (T)

TITLE: Evaluation of Calcium Sulfate (Plaster of Paris) as
an Alloplastic Implant in Mandible Reconstruction

PRINCIPAL INVESTIGATOR: MAJ Del Ray Maughan, MC

PROFESSIONAL ASSISTANTS: COL Leonard L. Hays, MC
MAJ Stanley P. Liebenberg, VC
CPT John H. McGath, MC
CPT Wallace E. Taylor, MC

WORK UNIT NO: 82/34

TECHNICAL OBJECTIVE

To evaluate the use of calcium sulfate as an alloplastic implant material in reconstruction of surgical defects of the mandible.

METHOD

Six mongrel dogs will undergo unilateral partial mandibulectomies (2-4 cm segments of hemi-mandible, depending upon dog size) under endotracheal halothane anesthesia. Three will have periosteum preserved and three will have periosteum removed. Each dog will undergo immediate reconstruction utilizing calcium sulfate as an alloplastic implant. Stabilization will be accomplished utilizing standard ASIF fixation bone plates applied to the lateral aspect of proximal and distal segments. Each animal will be placed on liquids postoperatively until intraoral mucosa is sealed and then on a soft diet for four to six weeks. Each dog will be followed with monthly roentgenograms to determine calcium sulfate resorption and osteoneogenesis. Two dogs (one with periosteum intact and one with periosteum removed) will be sacrificed at two, four, and six months postop and the reconstructed mandibles examined histologically for bone formation.

PROGRESS

(82 10 - 83 09) Five animals underwent mandible reconstruction with calcium sulfate and have been sacrificed. Gross evaluation of study animals showed solid union of mandible in four of five animals. One animal had a fibrous union. Mandibles are undergoing decalcification for histological evaluation. Histology is pending to confirm bone presence/absence.

STATUS: (O)

TITLE: Immunologically Mediated Persistent Infertility in
Patients Following Vasovasotomy

PRINCIPAL INVESTIGATOR: LTC Michael R. Moon, MC

PROFESSIONAL ASSISTANTS: COL Stephen R. Plymate, MC
LTC William E. Belville, MC
MAJ James W. Higbee, MSC

WORK UNIT NO: 82/68

TECHNICAL OBJECTIVE

To investigate the relationship between immunologically mediated infertility in patients after vasovasotomy and its treatment by corticosteroids.

METHOD

Thirty males who are going to have vasovasotomies performed will, prior to surgery, have serum samples analyzed for antisperm antibodies using the Isojima and Kibrick techniques as described by Linnet. They will have two serum samples measured at least one week apart. Following vasovasotomy, monthly semen analyses will be performed, and upon the first appearance of sperm in the ejaculate, serum and semen will be analyzed by the Isojima and Kibrick technique for antisperm antibodies. Monthly semen analyses will be followed, and, when sperm samples for two consecutive months are >20 million/ml with >20% motility, a sperm penetration assay (SPA) will be performed as well as a repeat antibody study. If the SPA is negative, patients will be treated with 1 mg dexamethasone three times a day for one month. One month following the dexamethasone treatment, a repeat SPA will be performed as well as serum drawn for antibodies. If the patient's spouse becomes pregnant during the study, serum and semen antibodies will be drawn and a SPA performed as soon as the pregnancy is recognized.

PROGRESS

(82 10 - 83 09) Six patients have been entered on this project. Data collection is ongoing.

STATUS: (0)

TITLE: A Prospective Clinical Trial Comparing Drainage or no Drainage After Acute Cholecystectomy

PRINCIPAL INVESTIGATOR: CPT Michael J. O'Reilly, MC

PROFESSIONAL ASSISTANT: LTC Preston L. Carter, MC

WORK UNIT NO: 82/58

TECHNICAL OBJECTIVE

To determine the long term sequelae of repair of peripheral meniscal tears.

METHOD

This study will be a randomized prospective clinical trial. Patients presenting with signs and symptoms consistent with acute cholecystitis to include right upper quadrant pain, fever, and leukocytosis will have diagnosis confirmed by histological examination of the gallbladder. Cholecystectomy will be performed according to standard technique through a subcostal incision. If the surgeon determines that the patient has no contraindications for inclusion in the study, the patient will be randomly assigned to have drainage of the gallbladder bed with a Jackson-Pratt drainage system brought out through a lateral stab wound or no drainage of the gallbladder bed. A bile culture will be taken and an intraoperative cholangiogram performed when possible. Visible bile in the peritoneal cavity following cholecystectomy, presence of a frank abscess cavity in the gallbladder bed, or a common bile duct exploration will be cause for exclusion from the study. Postoperative management and follow-up will be identical in both groups. Parameters to be followed include: postoperative fever, wound infection, return of gastrointestinal tract function, and length of stay in the hospital. A SMAC-20 will be drawn on all patients on postoperative day number two.

PROGRESS

(82 10 - 83 09) No patients have been entered in this study due to time constraints on the investigators. However, the principal investigator plans to start entering patients within the next month.

STATUS: (0)

TITLE: Repair of Peripherally Torn

PRINCIPAL INVESTIGATOR: J. D. [REDACTED]

PROFESSIONAL ASSISTANTS: C. P. [REDACTED]

WORK UNIT NO: 82/45

TECHNICAL OBJECTIVE

To determine the long term sequelae of repair of peripherally torn meniscal tears.

METHOD

PATIENT POPULATION: Patients who have had symptoms of a torn meniscus for at least four months and who subsequently are found to have a peripherally torn meniscus. Patients will be excluded who have undergone a previous meniscectomy, who have a torn anterior or posterior cruciate ligament, or who have worse than Grade II osteoarthritis.

If the meniscus is detached from its capsular attachment, it will be reattached with 2-0 Dexon suture going through the capsule, grabbing at least 1 mm of the body of the meniscus, then back out of the capsule and tied. If there is a tear of the body of the meniscus paralleling the capsular edge of the meniscus and leaving no more than 2 mm of meniscus still attached to the capsule, this capsular remnant will be excised, the edge of the meniscus will be abraded, and the meniscus reattached to the capsule as above. Both groups of patients will be placed in a long leg bent knee cast, partial weight bearing on crutches for six weeks before beginning knee rehabilitation. Follow-up will be every three months for the first year, six months the second year, then annually for subsequent years up to ten years. If the patient develops recurrence of the symptoms despite vigorous physical therapy and anti-inflammatory medication, he will be rearthroscoped for inspection of the repair. A final evaluation of the knee will be made at ten years that will include x-rays of the knees, assessment of the level of activity, and knee function.

PROGRESS

(82 10 - 83 09) Six patients have been entered. The sample size is still too small to reach adequate conclusions. Each case has been successful to this date, with no failures in the program.

STATUS: (0)

TITLE: Ultrasonic Localization of Internal Fixation Devices
Within Connective Tissues

PRINCIPAL INVESTIGATOR: CPT Davis C. Peterson, MC

PROFESSIONAL ASSISTANTS: LTC Thomas J. Parr, MC
MAJ William Fill, MC
MAJ Stanley P. Liebenberg, VC

WORK UNIT NO: 83/75

TECHNICAL OBJECTIVE

To determine the feasibility of A-mode ultrasonography in determining the extent of hardware penetration during internal fixation procedures.

METHOD

PHASE I: A 3.5 MHz ultrasonic transducer with a rapid sweep oscilloscope monitor will be coupled through a glycerin contact with a machined 5/32" diameter stainless steel Steinman pin with 90° + 2 minute faces via a machined brass jig incorporating an air chamber to minimize noise as well as shear wave interference in the near field and a 90° centered contact with respect to the transducer face. The exact length will allow calculation of the sound conduction velocity by measuring the time delay from initial to the reflected wave from the distal face. The reflected wave form characteristics will also be determined. The initial phase will be conducted in air and fluid media. A stainless steel reflector plate will then be positioned at 1 mm increments from the pin tip in a saline bath to determine the effect of acoustic impedance and beam attenuation on the reflected waveform. An attenuation coefficient will be determined as a reference for tissue comparison. Connective tissue samples will then be interposed to again determine the wave patterns and attenuation coefficients. Should the bone/metal acoustic impedance interface difference be too great to allow resolution of reflected waves from bone media through stainless steel, metals such as vitallium and titanium with density and elastic moduli nearer that bone will be used.

PHASE II: Phase I will be repeated using machined pins with 45° tetrahedral tips and 90° faces with precise length measurements with the intent of maximizing the amplitude of the reflected wave and minimizing base width in a cutting tip.

PHASE III: Clinical feasibility will be determined by using previously designed and tested hardware in an articular tissue block stratified with perpendicular planes of cancellous bone,

Ultrasonic Localization of Internal Fixation Devices Within
Connective Tissues - Peterson

subchondral bone, and articular cartilage. Correlation of the strata level by direct mapping of a cross section will be compared with depth measurement determined directly from a machined nylon core guide. Patterns of reflection will be recorded in the previous manner with progressive advancement of the pin to correlate wave form with level of penetration.

PROGRESS

(83 09 - 83 09) The protocol has been developed and materials list completed. Initial machining of parts is complete with additional parts to be designed following preliminary work. Connective tissue specimens are yet to be obtained.

STATUS: (0)

TITLE: Replacement of Inferior Vena Cava With Small Bowel Interposition Graft

PRINCIPAL INVESTIGATOR: MAJ Eddie J. Reddick, MC

PROFESSIONAL ASSISTANT: MAJ Stanley P. Liebenberg, VC

WORK UNIT NO: 83/04

TECHNICAL OBJECTIVE

To demonstrate the feasibility of replacing a traumatically injured segment of inferior vena cava with a small bowel interposition graft.

METHOD

Laparotomy will be performed on six sheep and 6 cm sections of infrarenal vena cava will be excised and replaced with segments of small bowel approximately 40 cm from ligament of Treitz. Supply to bowel segment will be preserved.

Two weeks postop, venogram of infrarenal vena cava will be performed to assess patency.

The sheep will be re-explored after venogram, and bowel segments will be removed and studied histologically and grossly. Specific histological points of interest are: neo-intimal formation, adherence of clot, and mucosal changes.

This will be a pilot study. If this project is successful, a long term study (approximately 6 months) will be performed to assist in the assessment of aneurysmal formation of the small bowel in the vena system.

PROGRESS

(82 10 - 83 09) Six animals were studied. The small bowel was removed from its blood supply and inverted and the mucosa was stripped and sewn end-to-end as an interposition graft in the inferior vena cava. Five of the animals died from massive pulmonary emboli from clots in the grafted area. The other animal was sacrificed at the end of two weeks. The graft on this animal was clotted. It was concluded that replacement of the inferior vena cava with a reverse segment of small bowel carries an excessively high mortality from pulmonary embolism and the procedure should not be further pursued.

STATUS: (C)

TITLE: Evaluation of the Arc Electrocoagulator (Davol System 5000)
in the Management of Splenic Trauma

PRINCIPAL INVESTIGATOR: MAJ Eddie J. Reddick, MC

PROFESSIONAL ASSISTANTS: MAJ Stanley P. Liebenberg, VC
CPT Stephen H. Koopmeiners, MC

WORK UNIT NO: 83/70

TECHNICAL OBJECTIVE

To determine if the arc electrocoagulator will decrease the blood loss and operating time during the repair of splenic lacerations when compared with standard methods of treatment.

METHOD

SPLenic LACERATION: A laceration 3 cm long and 1/2 cm deep will be made in the upper pole of the spleen, utilizing a #15 blade. The laceration will then be repaired utilizing the arc coagulator and two standard methods of repair. Eighteen dogs will be used; six dogs each will be repaired with the arc system, a standard solid-state electrocoagulator, and a combination suture/chemical hemostat technique. Prior to the procedure, the spleen will be packed with pre-weighed dry sponges. Blood loss will be determined by weight after the procedure. Time of procedure will be determined from the time of splenic laceration until bleeding is stopped. All dogs will be re-explored at 7 days. The spleen will be removed and sectioned for histologic study. Depth of burn/necrosis will be determined.

SPLenic AVULSION: To simulate a splenic avulsion, the lower pole of the spleen in each dog will be finger fractured from the upper pole and removed at the initial surgery after the above experiment has been completed. Each splenic avulsion will be managed in a similar manner to the laceration of the upper pole described above. Histologic studies will be done as above.

LIVER LACERATION/AVULSION: Liver laceration and avulsion will be done in the same manner as for the spleen.

PROGRESS

(83 08 - 83 09) Eighteen mongrel dogs were divided into groups of six each. Each group had a splenic transection, a splenic laceration, and a liver transection. These injuries were repaired using standard suture repair, standard solid state electrocoagulation, and the Davol System 5000 Arc Electrocoagulator. A comparison was made using total blood loss for each procedure and total time required for each procedure. There was no statistical difference between the amount of blood lost among the different groups; however, the Davol System 5000 was somewhat faster than the other two methods at repairing splenic and liver trauma.

STATUS: (C)

TITLE: Use of Brainstem Evoked Response (B.S.E.R.) in
Identification of Learning Disabilities

PRINCIPAL INVESTIGATOR: CPT Wallace E. Taylor, MC

PROFESSIONAL ASSISTANTS: MAJ Carl F. Loovis, MSC
MAJ A. W. Atkinson, MC
Mary W. Loovis, M.S.
Susan Boyce, M.S.

WORK UNIT: 81/97

TECHNICAL OBJECTIVE

To determine if significant differences exist in auditory evoked response between children with auditory processing problems and normal children randomly selected.

METHOD

Ten randomly selected 8 and 9-year old Caucasian males will be subjected to puretone and speech audiometry, tympanometry, and B.S.E.R. audiometry. Ten Caucasian males, 8 and 9-year olds, suspected of having auditory-related learning disabilities by review of school achievement testing will be given the sections of the Illinois Test of Psycholinguistic Abilities, subserving audition, and auditory processing. Those children scoring less than 25th percentile in at least one subtest will be given the same battery of audiologic tests as the control group. The choice of Caucasian males was made on the basis of evidence which suggests that B.S.E.R. potentials differ from sex to sex, race to race, and with age. By limiting the make-up of the group, these differences will be eliminated. Questionnaires will also be answered by parents involving history of potential risk. Statistical analysis will be by t-test. If difference exists, but is not statistically significant, additional numbers of children will be studied.

PROGRESS

(82 10 - 83 09) No patients have been entered in this study. Discussion with several leading researchers in the field of learning disabilities and auditory evoked response led the investigators to the conclusion that several modifications in the design of the study would have to be made. The protocol was terminated due to the departure of the principal investigator.

STATUS: (T)

TITLE: Canine Training Model for Endoscopic Laryngeal Surgery
Using the CO₂ Laser

PRINCIPAL INVESTIGATOR: CPT Wallace E. Taylor, MC

PROFESSIONAL ASSISTANTS: COL Leonard L. Hays, MC
MAJ Stanley P. Liebenberg, VC
MAJ Del Ray Maughan, MC

WORK UNIT: 82/55

TECHNICAL OBJECTIVE

To train ENT residents in the use of the CO₂ laser in a non-human subject in a controlled setting simulating a human situation prior to performing in an actual clinical setting.

METHOD

Twelve large mongrel dogs will be anesthetized with ultra-short acting barbiturate and placed in dorsal recumbancy. Suspension laryngoscopy will then be employed to visualize the larynx. ENT residents will use the CO₂ laser to perform a partial laryngectomy. Supplemental oxygen will be administered to the animal using the Saunders jet ventilating device to displace CO₂ from the lower airways and to facilitate viewing of the operative site during actual tissue removal with the laser. The opposite hemilarynx will be left unoperated to serve as a control. Each dog will be placed on a liquid diet for 24 hours post-op and will then be fed a semi-soft diet for the next 5 days. Each dog will be endoscoped at weekly intervals until healing is completed. The dogs will then be used in conjunction with the protocol "Use of the CO₂ Laser in Pharyngeal Surgery in the Dog"; LTC Stanley P. Liebenberg, Principal Investigator.

PROGRESS

(82 10 - 83 09) No further work has been done on this protocol. The investigators plan to continue work on it in the forthcoming year.

STATUS: (O)

TITLE: Defining Blood Gas Parameters Using the Saunders Jet Ventilating Device in the Dog in Conjunction with Endoscopic Laryngeal Surgery

PRINCIPAL INVESTIGATOR: CPT Wallace E. Taylor, MC

PROFESSIONAL ASSISTANTS: COL Leonard L. Hays, MC
MAJ Willis H. Jacob, MSC
MAJ Stanley P. Liebenberg, VC
MAJ Del Ray Maughan, MC

WORK UNIT: 82/56

TECHNICAL OBJECTIVE

To define blood gas and blood pH levels in the dog using the Saunders jet ventilating device.

METHOD

A total of six dogs will be included in this study. After each dog has been anesthetized with ultrashort-acting barbiturate and before actual tissue excision with the CO₂ laser commences, a femoral arterial cutdown will be performed. Arterial catheterization will be made under direct visualization by insertion of an Intracath. After ligatures are securely placed around the Intracath to prevent accidental withdrawal, a 3-way stopcock will be placed on the end of the catheter, the catheter will be flushed with 10% heparinized saline to prevent clot formation, and then the catheter will be connected to a Hewlett-Packard Model 7700 8-channel physiograph machine for blood pressure and EKG monitoring. Ventilation with the Saunders device will be performed at varying rates (4, 5, 7.5, 12, and 30 times/minute) for 5 minutes each. The duration of each burst of oxygen will be approximately one second. An initial arterial blood sample will be drawn for O₂, CO₂, and pH determinations prior to any ventilation with the Saunders device. Further blood samples for the same parameters will be drawn at the end of each 5 minute ventilation period. The study will commence with the most rapid rate (30/minute) and proceed in order to the slowest rate (4/minute). After completion of all ventilation periods, the Intracath will be withdrawn. This protocol will be done in conjunction with the protocol "Use of the CO₂ Laser in Pharyngeal Surgery in the Dog"; LTC Stanley P. Liebenberg, Principal Investigator.

PROGRESS

(82 10 - 83 09) Due to the transfer of the principal investigator, no work was conducted on this project during FY 83. MAJ Stanley Liebenberg has agreed to become the principal investigator and will attempt to complete the project prior to his transfer in August 1984.

STATUS: (0)

DETAIL SHEETS
FOR
PROTOCOLS

CHILDRENS CANCER STUDY GROUP PROTOCOLS

TITLE: CCG 191P - Total Sanctuary vs Conventional CNS Treatment of Newly Diagnosed Acute Lymphoblastic Leukemia for Patients with "Average Risk" and "High Risk" Prognostic Characteristics, Phase III

PRINCIPAL INVESTIGATOR: MAJ Allen R. Potter, MC

PROFESSIONAL ASSISTANTS: LTC Charlene P. Holt, MC
LTC Alan D. Mease, MC

WORK UNIT NO: 79/89

TECHNICAL OBJECTIVES

To compare the effects of high-dose, protracted IV methotrexate infusion vs standard cranial irradiation plus IT methotrexate on: (1) central nervous system relapse; (2) central nervous system toxicity - both acute and delayed; (3) hematologic remission induction and duration; (4) non-CNS extramedullary relapse (e.g. testes); and (5) survival.

METHOD

Previously untreated patients <21 years of age with acute lymphoblastic leukemia who are <3 years old, ≥7 or have an initial WBC of greater than 10,000/ μ l will be eligible. Patients with the diagnosis of acute undifferentiated leukemia on any initial WBC will be treated on this protocol but analyzed as a separate group. Patients will be treated initially with prednisone, vincristine, L-asparaginase, daunomycin, and central nervous system prophylaxis. The type of CNS prophylaxis will be determined by randomization and will consist either of very high doses of methotrexate IV or cranial radiation plus IT methotrexate. Most of the CNS therapy will be given during the second month of treatment, during which 6-MP will replace the daunomycin and L-asparaginase. From the third month on, remission will be maintained by a sequence of multiple drug administrations, including vincristine, prednisone, L-asparaginase, daunomycin, methotrexate, cyclophosphamide, and 6-MP. M₃ bone marrow or extramedullary leukemia at any time will be cause for removal from the study.

PROGRESS

(82 10 - 83 09) One patient was entered on study during FY 83 and developed hepatotoxicity which was reversible. One patient with Down's syndrome who was entered during the previous year expired from severe marrow hypoplasia and renal toxicity from methotrexate.

Patients are no longer being randomized. All patients with "average risk" are treated with total sanctuary because this arm is definitely superior as far as decreasing bone marrow relapses. CNS relapse rate appears to be not significantly different between the two groups.

STATUS: (0)

TITLE: CCG #251: Treatment of Newly Diagnosed Acute
Non-Lymphocytic Leukemia with Multiagent Chemotherapy
(Cyclic Versus Continuous) or Bone Marrow Transplantation
Following Total Body Irradiation

PRINCIPAL INVESTIGATOR: MAJ Allen R. Potter, MC

PROFESSIONAL ASSISTANT: LTC Alan D. Mease, MC

WORK UNIT NO: 81/103

TECHNICAL OBJECTIVES

To improve remission duration and survival in children with previously untreated acute non-lymphocytic leukemia using Cytoxan and total body irradiation followed by bone marrow transplantation with compatible donor marrow for those children who achieve a complete remission with induction therapy; to compare two intensive maintenance regimens; continuous 6-thioguanine with monthly courses of Cytoxan, vincristine, 5-azacytidine, and cytosine arabinoside vs repeated cycles of 6-thioguanine and cytosine arabinoside; adriamycin and cytosine arabinoside; prednisolone, vincristine, methotrexate, and 6-mercaptopurine; 5-azacytidine and adriamycin; and BCNU and cyclophosphamide; to evaluate the induction capabilities of adriamycin and cytosine arabinoside; and to evaluate the prognostic significance of any chromosomal abnormalities in leukemic cell lines.

METHOD

Induction therapy will consist of adriamycin and ARA-C given IV. When the bone marrow by aspiration is M-1 (day 29) or M-2 (day 57), subjects will receive one of the two intensive maintenance regimens listed above with concomitant radiotherapy or bone marrow transplant preceded by two successive days of Cytoxan therapy, followed four days later by total body irradiation. Patients 21 years of age at diagnosis who have previously untreated acute non-lymphocytic leukemia will be eligible.

PROGRESS

(82 10 - 83 09) One patient has been entered (FY 83) with good results. The patient is still on chemotherapy.

STATUS: (0)

TITLE: CCG 372 - Evaluation of Cis-Platinum Diamine Dichloride (CPDD) and 4'-Demethyl-Epidophyllotoxin-*B*-D-Thenylidene Glucoside (VM-26) for the Treatment of Recurrent Stage IV Neuroblastoma of Childhood, Phase II

PRINCIPAL INVESTIGATOR: MAJ Allen R. Potter, MC

PROFESSIONAL ASSISTANTS: LTC Charlene P. Holt, MC
LTC Alan D. Mease, MC

WORK UNIT NO: 79/35

TECHNICAL OBJECTIVES

To determine if CPDD and VM-26, both of which have been reported to produce responses in recurrent Stage IV neuroblastoma as single agents, are efficacious when given in combination.

METHOD

Patients, to be eligible, must have Stage IV neuroblastoma, i.e., remote disease involving skeleton, marrow, soft tissues, distant lymph nodes, etc. Patients previously treated with CPDD and/or VM-26 are not eligible. VM-26, 150 mg/M² IV, will be administered on days 1, 8, and 15. CPDD, 4.5 mg/kg IV, will be administered on day 2 (24 hours after day 1 dose of VM-26). Patients will be hospitalized. Cycles will be repeated every three weeks. Two complete cycles will be considered an adequate trial. If a complete or partial response is noted, cycles will be continued until progressive disease ensues.

PROGRESS

(78 11 - 83 05) No entries at MAMC.

STATUS: (T)

TITLE: CCG #551: A Trial of Memorial Hospital LSA₂-L₂ Treatment Regimen (Modified) Cyclophosphamide, Vincristine, Prednisone, Methotrexate, and Daunomycin for Induction; Cytosine, Arabinoside, 6-Thioguanine, L-Asparaginase, Methotrexate, and BCNU for Consolidation; and 6-Thioguanine, Hydroxyurea, Cytosine Arabinoside, and Methotrexate for Maintenance vs Intermittent High Dose Cyclophosphamide, Moderate Dose Methotrexate, Vincristine, and Prednisone (COMP) and Radiation Therapy for the Treatment of Non-Hodgkin's Lymphoma in Children, With A Study of Disease Characterization, Phase III.

PRINCIPAL INVESTIGATOR: MAJ Allen R. Potter, MC

PROFESSIONAL ASSISTANTS: LTC Charlene P. Holt, MC
LTC Alan D. Mease, MC

WORK UNIT NO: 79/36

TECHNICAL OBJECTIVES

To study the classification and biology of that group of childhood neoplasms included in the non-Hodgkin's lymphomas. To compare the effectiveness of two combination chemotherapy programs (Memorial Hospital LSA₂-L₂ and COMP) in the control of all forms of childhood non-Hodgkin's lymphoma. To determine for each of the two treatment regimens the effectiveness of standardized IT methotrexate without radiation for the control of occult CNS disease. To determine for each of the treatment regimens the effectiveness of standardized irradiation of bulk disease.

METHOD

All newly diagnosed and previously untreated patients with non-Hodgkin's lymphoma will be eligible. Multi-disciplinary treatment of the patient is required in this study. Surgical treatment will be undertaken first. For most patients this will be a biopsy procedure, but for abdominal presentation, major tumor resection may be necessary. Following the surgical phase of treatment and the initial evaluation, treatment will commence with combined chemotherapy and irradiation by random choice between Regimen I or Regimen II (see title for drugs in each regimen). Irradiation will commence during induction upon bone marrow recovery. In general, irradiation will be completed before consolidation or maintenance has commenced according to regimen. Treatment will terminate on completion of 18 months of treatment. All patients will be followed for a minimum of 5 years or until death.

PROGRESS

(78 11 - 83 05) Three patients were entered during previous years, all males. One is followed elsewhere. Two are off therapy without evidence of disease two years after therapy. Overall group results within CCG have been good with "good prognosis" patients and fair with "poor prognosis" patients.

STATUS: (C)

TITLE: CCG #861: Surgery, Radiation Therapy, and Chemotherapy with Bleomycin, Vinblastine, Cis-Platinum Diamine Dichloride, Actinomycin-D, Cyclophosphamide, and Adriamycin in the Treatment of Local and Metastatic Malignant Germ Cell Ovarian Tumors of Childhood (Phase II Study)

PRINCIPAL INVESTIGATOR: MAJ Allen R. Potter, MC

PROFESSIONAL ASSISTANTS: LTC Charlene Holt, MC
LTC Alan Mease, MC

WORK UNIT NO: 79/46

TECHNICAL OBJECTIVES

To determine, in patients with germ cell ovarian malignancy which has been completely excised by surgery, treated with 6-drug chemotherapy, and perhaps with radiation therapy, the length of disease free interval and the percentage of patients having long term survival; to determine, in patients with residual or metastatic disease treated with surgery, 6-drug chemotherapy, and radiation therapy, the effectiveness of the treatment program as indicated by percent of patients experiencing CR or PR and the length of the remission periods; to examine the relationship between age, tumor type, staging, and pathology with prognosis; and to determine if a single arm study of an infrequent childhood tumor is practical and produces significant conclusions.

METHOD

Patients will be treated with chemotherapy for 18 weeks. At week 18, a second look laparotomy is performed. If there is residual or persistent tumor present, radiation therapy will be given. If there is no residual or persistent tumor at this time, radiation therapy will not be administered. If at 24 weeks the patient has progressive disease, the patient will be taken off the study. Patients on the study will continue chemotherapy until week 102. The patient will be taken off the study if there is progressive disease after 24 weeks of therapy or if recurrent or metastatic disease appears after six months of therapy.

PROGRESS

(78 11 - 83 09) No entries at MAMC.

STATUS: (0)

DETAIL SHEETS
FOR
PROTOCOLS

FRED HUTCHINSON CANCER RESEARCH CENTER GROUP PROTOCOLS

TITLE: FHCRC #11 - Protocol for Treatment of Adult Acute
Nonlymphocytic Leukemia, Study V.

PRINCIPAL INVESTIGATOR: LTC Irwin B. Dabe, MC

PROFESSIONAL ASSISTANTS: COL Friedrich H. Stutz, MC
LTC James E. Congdon, MC
MAJ Thomas M. Baker, MC
MAJ Alfred H. Chan, MC
MAJ Howard Davidson, MC
MAJ Timothy J. O'Rourke, MC

WORK UNIT NO: 83/30

TECHNICAL OBJECTIVES

To determine the complete remission rate with intensive induction in patients with ANL; to determine if therapy with high-dose Ara-C, Asparaginase, AMSA, and VP-16 will decrease the rate of leukemic relapse; to determine whether the wider application of marrow transplantation using allogeneic, partially-matched, unrelated, and autologous marrow will increase the cure rate of ANL in patients less than 30 years of age; and to determine if marrow transplantation should be carried out in first remission or at first sign of relapse in patients age 30-50.

METHOD

All Patients <75 years with adult nonlymphocytic leukemia, previously untreated except for the administration of hydroxyurea are eligible. Diagnoses to be included: acute myelocytic, promyelocytic, monocytic, myelomonocytic, acute undifferentiated, and erythroleukemic. Daunomycin, Ara-C, 6-thioguanine, vincristine, and prednisone will be used in Cycle I as the induction regimen; Cycle 2 will be high-dose Ara-C and asparaginase; Cycle III - same as Cycle I; Cycle IV will be high dose AMSA and VP-16; cycle V - same as Cycle I, Cycle VI will be vincristine, prednisone, 6-mercaptopurine, and methotrexate. Regardless of remission status, patients <30 will be offered bone marrow transplantation after Cycle 2. Patients 30-50 years of age who have not achieved complete remission after two courses or who relapse after remission will be offered transplantation. Patients >50 will receive chemotherapy only. All patients will continue on chemotherapy, regardless of transplantation status.

PROGRESS

(83 01 - 83 09) No patients entered.

STATUS: (0)

TITLE: FHCRC 102 - Protocol for the Treatment of Adult Acute Lymphoblastic Leukemia (ALL)

PRINCIPAL INVESTIGATOR: LTC Irwin B. Dabe, MC

PROFESSIONAL ASSISTANTS: COL Friedrich H. Stutz, MC
LTC James E. Congdon, MC
MAJ Thomas M. Baker, MC
MAJ Alfred H. Chan, MC
MAJ Howard Davidson, MC
MAJ Timothy J. O'Rourke, MC

WORK UNIT NO: 83/53

TECHNICAL OBJECTIVES

To determine the complete remission rate with intensive induction in adults with ALL; to determine the overall survival of patients treated with this intensive consolidation and maintenance therapy; and to determine the remission duration and overall survival of patients treated with CY and TBI and a HLA matched sibling bone marrow transplant while in first remission and to compare the results with those patients who achieve a remission and are continued on chemotherapy.

METHOD

All patients with acute lymphoblastic leukemia over the age of 18 and less than age 50 who are previously untreated except for the administration of hydroxyurea, prednisone, and vincristine are eligible. Also included will be young adults with lymphoblastic lymphoma (T cell variant). Individuals will be treated with one or two cycles of a four-drug regimen. Those not achieving a remission after two cycles of induction therapy will be taken off study and treated with other drugs. Those who have a tissue match with a donor will be followed by no further leukemic treatment unless they relapse. Those without a tissue match will be treated with further drug treatment for 15 ten-week cycles at which time therapy will be stopped and they will be followed closely. Spinal taps and bone marrow exams will be done periodically during consolidation and maintenance drug therapy.

PROGRESS

(83 03 - 83 09) No patients have been entered.

STATUS: (0)

TITLE: FHCRC #143: Treatment of Relapsed Acute Nonlymphocytic Leukemia with AMSA, and Use of in Vitro Studies (Stem Cell Assay) to Predict a Response in Vivo.

PRINCIPAL INVESTIGATOR: LTC Irwin B. Dabe, MC

PROFESSIONAL ASSISTANTS: COL Friedrich H. Stutz, MC
LTC James E. Congdon, MC
MAJ Thomas M. Baker, MC
MAJ Alfred H. Chan, MC
MAJ Howard Davidson, MC
MAJ Timothy J. O'Rourke, MC

WORK UNIT NO: 83/48

TECHNICAL OBJECTIVE

To determine the ability of AMSA to induce remission for patients with acute nonlymphoblastic leukemia in relapse.

METHOD

Patients who have relapsed after successful induction of remission with daunomycin and cytosine arabinoside, as well as patients who have failed two cycles of remission induction therapy, are eligible for this study. The factors that will be analyzed include duration of first remission, nature and amount of previous chemotherapy received, age and number of cycles of therapy to first complete remission. Patients will receive AMSA 120 mg/M² for five days. A bone marrow exam will be done on day 14. If the marrow has more than 30% blasts when the marrow is hypocellular or more than 10% when the marrow is normocellular, a second induction course will be given. A minimum of two courses is needed to evaluate response. If after two courses a complete remission is not reached and the patient has not had undue toxicity, a third course may be given.

PROGRESS

(83 02 - 83 09) No patients entered.

STATUS: (0)

TITLE: FHCRC #152: Combined Modality Treatment for Non-Hodgkin's Lymphomas of Intermediate and High-Grade Malignancy

PRINCIPAL INVESTIGATOR: LTC James E. Congdon, MC

PROFESSIONAL ASSISTANTS: COL Friedrich H. Stutz, MC
LTC Irwin B. Dabe, MC
MAJ Thomas M. Baker, MC
MAJ Alfred H. Chan, MC
MAJ Howard Davidson, MC
MAJ Timothy J. O'Rourke, MC

WORK UNIT NO: 83/47

TECHNICAL 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.

METHOD

After appropriate tests to determine the extent of the lymphomas, patients will receive 4 cycles of multi-agent chemotherapy to include cytoxan, adriamycin, oncovin and prednisone. At the end of 4 cycles of chemotherapy, given 4 weeks 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

(83 02 - 83 09) Three patients have been entered. Two patients experienced vincristine toxicity requiring decreased dosage or discontinuation, two patients experienced some gastritis (one related to adriamycin), and one patient experienced prolonged myelotoxicity after hemibody radiation.

STATUS: (0)

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

F O R

P R O T O C O L S

G Y N E C O L O G Y O N C O L O G Y G R O U P P R O T O C O L S

FILE: GOG #26C: A Phase II Trial of Cis-Platinum Diamminedichloride

PRINCIPAL INVESTIGATOR: COL Roger B. Lee, MC

PROFESSIONAL ASSISTANTS: COL William L. Benson, MC

WORK UNIT NO: 82/07

TECHNICAL OBJECTIVE

To determine the efficacy of cis-platinum diamminedichloride in patients whose advanced malignancies have been resistant to higher priority methods of treatment.

METHOD

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

(82 10 - 83 09) Two patients have been entered on this protocol in previous years; one had progression of disease.

STATUS: (0)

TITLE: GOG #26D: A Phase II Trial of VP-16 in Patients with
Advanced Pelvic Malignancies

PRINCIPAL INVESTIGATOR: COL Roger B. Lee, MC

PROFESSIONAL ASSISTANT: COL William L. Benson, MC

WORK UNIT NO: 83/18

TECHNICAL OBJECTIVE

To determine the efficacy of VP-16 in patients whose advanced malignancies have been resistant to higher priority methods of treatment.

METHOD

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

(82 11 - 83 09) No patients entered.

STATUS: (0)

TITLE: GOG #26E: A Phase II Trial of Glactitol 1,2:5,6-Dianhydro
in Patients with Advanced Pelvic Malignancies

PRINCIPAL INVESTIGATOR: COL Roger B. Lee, MC

PROFESSIONAL ASSISTANTS: COL William L. Benson, MC

WORK UNIT NO: 83-19

TECHNICAL 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.

METHOD

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

(82-11 - 83-09) No patients entered.

STATUS: (0)

TITLE: GOG #26G: A Phase II Trial of ICRF-159 in Patients with
Advanced Pelvic Malignancies

PRINCIPAL INVESTIGATOR: COL Roger B. Lee, MC

PROFESSIONAL ASSISTANT: COL William L. Benson, MC

WORK UNIT NO: 83/20

TECHNICAL OBJECTIVE

To determine the efficacy of ICRF-159 in patients whose advanced malignancies have been resistant to higher priority methods of treatment.

METHOD

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

(82 11 - 83 09) One patient was entered and had progression of disease.

STATUS: (0)

TITLE: GOG #261: A Phase II Trial of AMSA in Patients with Advanced
Pelvic Malignancies

PRINCIPAL INVESTIGATOR: COL Roger B. Lee, MC

PROFESSIONAL ASSISTANT: COL William L. Benson, MC

WORK UNIT NO: 83/21

TECHNICAL OBJECTIVE

To determine the efficacy of AMSA in patients whose advanced malignancies have been resistant to higher priority methods of treatment.

METHOD

All patients with measurable gynecological cancer who have failed higher prior therapies will be offered AMSA as a Phase II drug to determine its efficacy. The drug will be given as 60 mg/M² I.V. once every 28 days. Patients will continue to receive the agent until progression occurs.

PROGRESS

(82 11 - 83 09) No patients entered.

STATUS: (0)

TITLE: GOG #26J: A Phase II Trial of Yoshi 864 in Patients with
Advanced Pelvic Malignancies

PRINCIPAL INVESTIGATOR: COL Roger B. Lee, MC

PROFESSIONAL ASSISTANT: COL William L. Benson, MC

WORK UNIT NO: 83/22

TECHNICAL OBJECTIVE

To determine the efficacy of Yoshi 864 in patients whose advanced malignancies have been resistant to higher priority methods of treatment.

METHOD

All patients with measurable gynecological cancer who have failed higher prior therapies will be offered Yoshi 864 as a Phase II drug to determine its efficacy. The drug will be given as 1.5 mg/kg/d x 5 I.V. every six weeks. Patients will continue to receive the agent until progression occurs.

PROGRESS

83 11 - 83 091 No patients entered.

STAT 83 11 11

TITLE: GOG #26L: A Phase II Trial of Tamoxifen (NSC 180793) in
Patients with Advanced Epithelial Ovarian Carcinoma,
Part II

PRINCIPAL INVESTIGATOR: COL Roger B. Lee, MC

PROFESSIONAL ASSISTANTS: COL William Benson, MC

WORK UNIT NO: 83/52

TECHNICAL OBJECTIVE

To determine the efficacy of tamoxifen in patients whose advanced malignancies have been resistant to higher priority methods of treatment.

METHOD

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

(83 03 - 83 09) No patients entered.

STATUS: (0)

TITLE: GOG #26M: A Phase II Trial of PALA in Patients with Advanced Pelvic Malignancies

PRINCIPAL INVESTIGATOR: COL Roger B. Lee, MC

PROFESSIONAL ASSISTANT: COL William L. Benson, MC

WORK UNIT NO: 83/23

TECHNICAL OBJECTIVE

To determine the efficacy of PALA in patients whose advanced malignancies have been resistant to higher priority methods of treatment.

METHOD

All patients with measurable gynecological cancer who have failed higher prior therapies will be offered PALA as a Phase II drug to determine its efficacy. The drug will be given as 5.0 mg/M² I.V. every three weeks. Patients will continue to receive the agent until progression or adverse effects prohibit further therapy.

PROGRESS

(82 11 - 83 09) No patients entered.

STATUS: (0)

TITLE: GOG #26N: A Phase II Trial of Dihydroxyanthracenedione
(DHAD) in Patients with Advanced Pelvic Malignancies

PRINCIPAL INVESTIGATOR: COL Roger B. Lee, MC

PROFESSIONAL ASSISTANT: COL William L. Benson, MC

WORK UNIT NO: 83/24

TECHNICAL OBJECTIVE

To determine the efficacy of DHAD in patients whose advanced malignancies have been resistant to higher priority methods of treatment.

METHOD

All patients with measurable gynecological cancer who have failed higher prior therapies will be offered DHAD as a Phase II drug to 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.

PROGRESS

(82 11 - 83 09) One patient was entered with progression of disease.

STATUS: (0)

TITLE: GOG #26-O: A Phase II Trial of Aziridinylbenzoquinone
(AZQ) in Patients with Advanced Malignancies

PRINCIPAL INVESTIGATOR: COL Roger B. Lee, MC

PROFESSIONAL ASSISTANTS: COL William L. Benson, MC

WORK UNIT NO: 82/30

TECHNICAL OBJECTIVE

To determine the efficacy of AZQ in patients whose advanced malignancies have been resistant to high priority methods of treatment.

METHOD

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

(82 10 - 83 09) No patients entered at MAMC.

STATUS: (O)

TITLE: GOG #26P: A Phase II Trial of AT-125 in Patients with
Advanced Pelvic Malignancies

PRINCIPAL INVESTIGATOR: COL Roger B. Lee, MC

PROFESSIONAL ASSISTANT: COL William L. Benson, MC

WORK UNIT NO: 83/25

TECHNICAL OBJECTIVE

To determine the efficacy of AT-125 in patients whose advanced malignancies have been resistant to high priority methods of treatment.

METHOD

All patients with measurable gynecological cancer who have failed higher prior therapies will be offered AT-125 as a Phase II drug to determine its efficacy. The drug will be given as 12-15 mg/M² I.V. daily for five days every three weeks. Patients will continue to receive the agent until progression or adverse effects prohibit further therapy.

PROGRESS

(82 11 - 83 09) No patients entered at MAMC.

STATUS: (0)

TITLE: GOG #26Q: A Phase II Trial of Aminothiadiazole in
Patients with Advanced Pelvic Malignancies

PRINCIPAL INVESTIGATOR: COL Roger B. Lee, MC

PROFESSIONAL ASSISTANT: COL William L. Benson, MC

WORK UNIT NO: 83/26

TECHNICAL OBJECTIVE

To determine the efficacy of aminothiadiazole in patients whose advanced malignancies have been resistant to high priority methods of treatment.

METHOD

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

(82 11 - 83 09) No patients entered at MAMC.

STATUS: (0)

TITLE: GOG #33: A Clinical Pathologic Study of Stages I and II
Carcinoma of the Endometrium

PRINCIPAL INVESTIGATOR: COL Roger B. Lee, MC

PROFESSIONAL ASSISTANT: COL William L. Benson, MC

WORK UNIT NO: 81/12

TECHNICAL 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.

METHOD

These 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

(82 10 - 83 09) Six patients have been entered on the protocol one of these during FY 83. All show no evidence of disease at this time.

STATUS: (0)

TITLE: GOG #34: A Randomized Study of Adriamycin as an Adjuvant After Surgery and Radiation Therapy in Patients with HighRisk Endometrial Carcinoma Stage I and Occult Stage II

PRINCIPAL INVESTIGATOR: COL Roger B. Lee, MC

PROFESSIONAL ASSISTANT: COL William L. Benson, MC

WORK UNIT NO: 81/24

TECHNICAL OBJECTIVES

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.

METHOD

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

(82 10 - 83 09) Three patients have been entered, one during FY 83, with no progression of disease.

STATUS: (0)

TITLE: GOG #36: Surgical-Pathologic Study of Women with Squamous Cell Carcinoma of the Vulva

PRINCIPAL INVESTIGATOR: COL Roger B. Lee, MC

PROFESSIONAL ASSISTANT: COL William L. Benson, MC

WORK UNIT NO: 31767

TECHNICAL OBJECTIVES

To determine by observations of 5-year survival and disease-free interval the validity of current FIGO staging to the histopathologic prognostic factors of size of lesion, location of lesion, depth of invasion of tumor in millimeters, histologic grade, and site and number of positive lymph nodes in Stages I-IV carcinoma of the vulva; to rapidly accumulate prospectively significant surgical pathologic data which would expedite development of further protocols for subsets of disease identified; to determine morbidity of primary radical surgical therapy.

METHOD

Eligible patients are those with primary, previously untreated histologically confirmed invasive squamous cell carcinoma of the vulva clinically determined to be Stage I through IV. Patients will be treated with radical vulvectomy plus bilateral groin dissection. The patients will undergo a thorough pelvic examination under anesthesia to assess pelvic structures and evaluate possible pelvic node disease. Those with negative groin nodes will be followed for 5 years without therapy. Those with positive groin nodes will be transferred to GOG #37. Relevant pathologic specimens will be studied.

PROGRESS

(81-03 - 83-09) No entries at MAMC.

STATUS: (0)

TITLE: GOG #37: A Randomized Study of Radiation Therapy Versus
Pelvic Node Resection for Patients with Invasive Squamous
Cell Carcinoma of the Vulva Having Positive Groin Nodes

PRINCIPAL INVESTIGATOR: COL Roger B. Lee, MC

PROFESSIONAL ASSISTANT: COL William L. Benson, MC

WORK UNIT NO: 81 68

TECHNICAL OBJECTIVES

To determine the benefit and morbidity of adding adjunctive radiation therapy to pelvis and groin for patients found to have positive groin nodes at the time of radical vulvectomy and bilateral groin dissection.

METHOD

Eligible patients are those with primary previously untreated histologically confirmed invasive squamous cell carcinoma of the vulva, such that radical vulvectomy suffices to remove all of the local lesion, and whose surgery revealed that there were nodes in the groin on one or both sides containing metastatic carcinoma. Patients will be randomized to receive pelvic node dissection (the dissection will be carried out only on the side containing positive groin nodes or a bilateral if both sides are positive) or to receive bilateral groin and pelvic node irradiation. Major parameters to be studied are survival and time to recurrence. Patients will be followed quarterly for 3 years and every 6 months thereafter.

PROGRESS

(81 03 - 83 09) No entries at MAMC.

STATUS: (0)

TITLE: DOD #49: A Clinical-Pathologic Study of Stages I and II Uterine Sarcomas

PRINCIPAL INVESTIGATOR: COL Roger B. Lee, MC

PROFESSIONAL ASSISTANT: COL William L. Benson, MC

WDBK UNIT NO: 81779

TECHNICAL OBJECTIVES

The purpose of this study is 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.

METHOD

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:

1. Peritoneal cytology will be evaluated for malignant cells.
2. 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.
3. The adnexa will be evaluated for presence of metastasis.
4. The lymph nodes will be evaluated as to metastasis and:
 - (1) location of involved lymph nodes and (2) number involved.

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

(32 10 - 83 09) One patient entered during FY 83 with progression and death from metastatic sarcoma.

STATUS: (0)

TITLE: GOG #41: Surgical Staging of Ovarian Carcinoma

PRINCIPAL INVESTIGATOR: COL Roger B. Lee, MC

PROFESSIONAL ASSISTANT: COL William L. Benson, MC

WORK UNIT NO: 81/35

TECHNICAL OBJECTIVES

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.

METHOD

There will be no change in the surgical procedures performed. This protocol is being performed as a statistical protocol. These will be patients who have surgery as standard treatment. Eligible patients will be those who have Stages I, II, or III (optimal) 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 further treatment will be at the discretion of the investigator if no protocol is available.

PROGRESS

(82 10 - 83 09) Two new patients entered during FY 83 with no adverse reactions.

STATUS: (0)

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

PRINCIPAL INVESTIGATOR: COL Roger B. Lee, MC

PROFESSIONAL ASSISTANT: COL William L. Benson, MC

WORK UNIT NO: 81/25

TECHNICAL OBJECTIVES

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.

METHOD

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

(80 12 - 83 09) No entries at MAMC.

STATUS: (0)

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)

PRINCIPAL INVESTIGATOR: COL Roger B. Lee, MC

PROFESSIONAL ASSISTANT: COL William L. Benson, MC

WORK UNIT NO: 81/43

TECHNICAL OBJECTIVES

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.

METHOD

Patients with documented primary Stage III, Primary Stage 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 for this study. Patients who have received previous chemotherapy are ineligible. Patients will be randomized.

Regimen 1: adriamycin 60 mg/M² IV q 3 weeks x 8 courses. Responders will have follow-up only. Those with progression will be transferred to Protocol #26.

Regimen 2: adriamycin 60 mg/M² IV q 3 weeks 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. Those 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

(82 10 - 83 09) Two patients have progressed with Provera; both have responded to Cytosan-Adriamycin.

STATUS: (0)

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

PRINCIPAL INVESTIGATOR: COL Roger B. Lee, MC

PROFESSIONAL ASSISTANT: COL William L. Benson, MC

WORK UNIT NO: 81/70

TECHNICAL OBJECTIVES

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.

METHOD

Patients with primary, previously untreated histologically confirmed invasive Stage I_B (invasion of 3 mm or greater of lymphatic invasion) carcinoma of the cervix (squamous cell, adenocarcinoma, or adenosquamous) will be eligible. Patients must have undergone exploratory laparotomy, peritoneal fluid sampling, bilateral pelvic and paraaortic 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. Those with positive pelvic nodes, unilateral metastasis, 3 or fewer 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

(82 10 - 83 09) Eight patients have been entered, four during FY 83. Three are stable, two have recurred, two have died from carcinoma, and one has been lost to follow-up.

STATUS: (0)

TITLE: GOG #50: A Study of Adriamycin as Postoperative Therapy for Ovarian Sarcoma, Primary or Recurrent, With no Prior Chemotherapy

PRINCIPAL INVESTIGATOR: COL Roger B. Lee, MC

PROFESSIONAL ASSISTANT: COL William L. Benson, MC

WORK UNIT NO: 81/71

TECHNICAL OBJECTIVES

To evaluate the efficacy of adriamycin in the treatment of primary ovarian sarcomas, primary or recurrent, through historic controls; and to accumulate additional surgical-pathological data relative to ovarian sarcomas.

METHOD

Patients must have histologically confirmed primary Stage I-IV or recurrent ovarian sarcoma. Cases without histologic confirmation of recurrence must be documented by submission of original slides. Optimal reductive surgery is required for cases with advanced disease, whether primary or recurrent. Patients may have measurable disease, nonmeasurable disease, or no residual disease postoperatively. The endometrium must be examined to exclude an endometrial origin of the tumor. Patients with prior chemotherapy are ineligible. All patients will receive chemotherapy as soon as the acute effects of surgery have resolved. After completion of a total cumulative dose of 550 mg/M², patients with clinically complete responses or detectable disease which is thought to be resectable will undergo second look surgery. Those patients with progression will be entered on Protocol #26. At second look those with NED will have no further therapy and follow-up for five years; those with stable disease or progression will be entered on Protocol #26.

PROGRESS

(81 03 - 83 09) No entries at MAMC.

STATUS: (0)

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

PRINCIPAL INVESTIGATOR: COL Roger B. Lee, MC

PROFESSIONAL ASSISTANT: COL William L. Benson, MC

WORK UNIT NO: 81/105

TECHNICAL OBJECTIVES

To determine, in "optimal" Stage III ovarian adenocarcinoma, if the addition of adriamycin to cyclophosphamide plus cis-platinum (Platinol) improves progression-free interval, frequency of negative second-look laparotomy and survival. This protocol replaces GOG #25.

METHOD

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

(82 10 - 83 09) One patient was entered in FY 83 for a total of three entries. One patient died of disease and two are alive without disease.

STATUS: (0)

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

PRINCIPAL INVESTIGATOR: COL Roger B. Lee, MC

PROFESSIONAL ASSISTANT: COL William L. Benson, MC

WORK UNIT NO: 81/116

TECHNICAL OBJECTIVES

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.

METHOD

Eligible patients must have histologically confirmed malignant tumors of the ovarian stroma (granulosa cell tumor, granulosa-theca cell tumor, Sertoli-Leydig cell tumor, androblastoma, gynandroblastoma, unclassified sex cord-stromal tumor, sex cord tumor with annular tubules) not amenable to cure by further surgery or radiation therapy. Patients who have received chemotherapy at any time or those who have received radiotherapy less than four weeks prior to entry are ineligible for study. Patients admitted to this study will have undergone an exploratory laparotomy with removal of as much tumor as is prudent. Chemotherapy will be followed within four weeks and not later than six weeks following surgery. Patients must have recovered from surgery. All patients will receive VAC for a minimum of three cycles or a maximum of ten cycles. Patients who exhibit a complete response or a partial response after ten 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, patient will be removed from study. Patients who exhibit progression of disease after three cycles of VAC will receive adriamycin. If further progression is observed on adriamycin therapy, the patient will be removed from the study. All patients will be followed for five years or until death.

PROGRESS

(81 09 - 83 09) No entries at MAMC.

STATUS: (0)

TITLE: GOG #55: Hormonal Contraception and Trophoblastic Sequelae
After Hydatidiform Mole, Phase III

PRINCIPAL INVESTIGATOR: COL Roger B. Lee, MC

PROFESSIONAL ASSISTANT: COL William L. Benson, MC

WORK UNIT NO: 81/44

TECHNICAL OBJECTIVES

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.

METHOD

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

(82 09 - 83 09) No entries in FY 83. Two patients were entered in FY 81 and are alive without tumor.

STATUS: (0)

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)

PRINCIPAL INVESTIGATOR: COL Roger B. Lee, MC

PROFESSIONAL ASSISTANTS: COL William L. Benson, MC
COL Donald Kull, MC

WORK UNIT NO: 82/08

TECHNICAL 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.

METHOD

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

(81 11 - 83 09) No entries at MAMC.

STATUS: (0)

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)

PRINCIPAL INVESTIGATOR: COL Roger B. Lee, MC

PROFESSIONAL ASSISTANTS: COL William L. Benson, MC

WORK UNIT NO: 82/31

TECHNICAL 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).

METHOD

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

(82 10 - 83 09) One patient has been entered (FY 83) with a complete response to the Bagshawe regimen.

STATUS: (0)

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

PRINCIPAL INVESTIGATOR: COL Roger B. Lee, MC

PROFESSIONAL ASSISTANT: COL William L. Benson, MC
COL Donald Kull, MC

WORK UNIT NO: 81/117

TECHNICAL OBJECTIVES

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 highrisk group of patients to expedite development of further protocols.

METHOD

Eligibility: All 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. Patients will undergo preoperative clinical staging (stages defined in protocol) utilizing lymphangiography, computerized axial tomography, and/or sonography as well as traditional methods. Subsequently, the 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 extra-pelvic nodes. All patients with para-aortic 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 four weeks, or survival of eight weeks after radiation therapy for the no-further-treatment regimen. Patients will be followed quarterly for two years and every six months for three additional years.

PROGRESS

(81 09 - 83 09) No entries at MAMC.

STATUS: (0)

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, Stage III and IV.

PRINCIPAL INVESTIGATOR: COL Roger B. Lee, MC

PROFESSIONAL ASSISTANT: COL William L. Benson, MC

WORK UNIT NO: 31/118

TECHNICAL OBJECTIVES

To determine if the addition of BCG to doxorubicin plus cyclophosphamide plus cisplatin improves remission rate, remission duration, or survival in suboptimal Stage III and Stage IV ovarian adenocarcinoma; to determine the frequency and duration of true complete remission using these regimens as judged at second-look laparotomy.

METHOD

Eligibility: Patients with established suboptimal 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 or 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

(82 09 - 83 09) One patient was entered in FY 83 for a total of four entries. One patient expired from a pulmonary embolus, one refused BCG after scarifications after two separate times and has recurrent carcinoma, and the other two patients are alive without disease.

STATUS: (0)

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.

PRINCIPAL INVESTIGATOR: COL Roger B. Lee, MC

PROFESSIONAL ASSISTANT: COL William L. Benson, MC

WORK UNIT NO: 82709

TECHNICAL 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.

METHOD

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

(82-10 - 83-09) One patient entered at MAMC for a total of two entries. One patient is alive with disease and the other is alive without disease.

STATUS: (0)

TITLE: GOG #63: A Clinical-Pathologic Study of Stages II_B, III, and IV_A Carcinoma of the Cervix

PRINCIPAL INVESTIGATOR: COL. ROBERT B. LEE, MC

PROFESSIONAL ASSISTANT: COL. WILLIAM L. BENSON, MC

WORK UNIT NO: 82-36

TECHNICAL OBJECTIVES

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.

METHOD

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

(82-03 - 83-09) No entries at MAMC.

STATUS: (0)

TITLE: GOG #64: A Randomized Comparison of Intravenous Cisplatin (24-Hour) Infusion of 75 mg/m² versus Intravenous Cisplatin Cell Carcinoma of the Cervix.

PRINCIPAL INVESTIGATOR: COL. Roger W. Lee, MD

PROFESSIONAL ASSISTANT: COL. William L. Benson, MD

WORK UNIT NO: 82/37

TECHNICAL OBJECTIVES

(1) To determine whether the frequency and duration of objective response of squamous cell carcinoma of the cervix is altered significantly by prolonging to 24 hours the duration of the infusion of a dose of cisplatin as compared to administration at a rate of 1 mg/minute; and (2) to determine whether the administration of a dose of cisplatin as a continuous 24-hour infusion alters the frequency and/or severity of drug-related nausea and vomiting; as compared to the administration of the same dose at a rate of 1 mg/minute.

METHOD

Eligible patients are those with histologically confirmed, locally advanced, recurrent, persistent, or metastatic squamous cell carcinoma of the cervix which is resistant to curative treatment with surgery or radiotherapy. Cis-platinum (50 mg/M²) will be given as a 24-hour infusion or at a rate of 1 mg/minute IV once every three weeks. Treatment will be repeated every three weeks for eight courses unless disease progression or adverse effects dictate cessation.

PROGRESS

(82 10 - 83 09) One patient was entered in FY 83. There were no adverse reactions and the patient has stable disease.

STATUS: (0)

FILE: GOG #66: Ultrastructural, Staging, and Therapeutic Considerations in Small Cell Carcinoma of the Cervix, Phase II

PRINCIPAL INVESTIGATOR: COL Roger B. Lee, MC

PROFESSIONAL ASSISTANTS: COL William Benson, MC

WORK UNIT NO: 83740

TECHNICAL 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 IVB small cell carcinoma of the cervix or progressive local disease after radiation therapy.

METHOD

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 non-keratinizing carcinoma or adenocarcinoma are eligible, providing that the small cell elements comprise 50% of the tumor. Only patients with primary Stage IVB 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, intravenously every 21 days. Patients with previous irradiation will receive vincristine, 2 mg, doxorubicin, 40 mg/M², and cyclophosphamide, 600 mg/M², intravenously 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) intravenously 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 IVB on the basis of brain metastasis alone, patients will be given whole brain irradiation to a dose of 3000 rads in 10 fractions.

PROGRESS

(83-02 - 83-09) No entries at MAMC.

STATUS: (0)

TITLE: GOG #70: A Randomized Comparison of Single Agent Chemotherapy (Methotrexate and Methotrexate with Folinic Acid Rescue) in "Good Prognosis" Metastatic Gestational Trophoblastic Disease

PRINCIPAL INVESTIGATOR: COL Roger B. Lee, MC

PROFESSIONAL ASSISTANTS: COL William Benson, MC

WORK UNIT NO: 83/63

TECHNICAL OBJECTIVES

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.

METHOD

Eligible patients: those with metastatic gestational trophoblastic disease who are "good prognosis" with duration of disease <4 months from antecedent pregnancy, serum β -hcg titer <42,000 mIU/ml, no liver or brain metastasis, no prior chemotherapy, and antecedent molar pregnancy, ectopic pregnancy, or abortion.

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 she attains remission, 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

(83 05 - 83 09) One patient has been entered. She was treated with methotrexate for three courses and has had a complete response.

STATUS: (0)

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

PRINCIPAL INVESTIGATOR: COL Roger B. Lee, MC

PROFESSIONAL ASSISTANTS: COL William Benson, MC
COL Donald Kull, MC

WORK UNIT NO: 83/41

TECHNICAL OBJECTIVES

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.

METHOD

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

(83 02 - 83 09) No entries at MAMC.

STATUS: (0)

DETAIL SHEETS

FOR

PROJECTS

NATIONAL ANCESTRAL HEALTH PROJECT

TITLE: NCI #178-4: Guidelines for the Clinical Use of
Streptozotocin (Group C Guidelines)

PRINCIPAL INVESTIGATOR: COL Friedrich H. Stutz, MC

PROFESSIONAL ASSISTANTS: LTC Irwin B. Dabe, MC
LTC Archie W. Brown, MC

WORK UNIT: 81/18

TECHNICAL OBJECTIVE

To provide an investigational drug of proven efficacy, not previously released for general use, to MAMC patients under Group C NCI Guidelines. Also, to determine extent and variety of side effects with streptozotocin that have not been previously described.

METHOD

Streptozotocin will be used for patients with malignant islet cell tumor (response rate 70%) and in metastatic carcinoid. Streptozotocin will be given IV either daily for 5 days every 4-6 weeks or weekly for approximately 4 weeks. Careful pre-treatment evaluation will be accomplished and any untoward or unexpected side effects will be reported to the National Cancer Institute.

PROGRESS

(80-12 - 83 09) No entries at MAMC.

STATUS: (0)

TITLE: NCI #178-10: Guidelines for the Clinical Use of
Hexamethylmelamine (Group C Guidelines)

PRINCIPAL INVESTIGATOR: COL Friedrich H. Stutz, MC

PROFESSIONAL ASSISTANTS: COL Roger B. Lee, MC
LTC Archie W. Brown, MC
LTC Irwin B. Dabe, MC

WORK UNIT: 81/19

TECHNICAL OBJECTIVE

To provide an investigational drug of proven efficacy, not previously released for general use, to MAMC patients under Group C NCI Guidelines. Also to determine the extent and variety of side effects with hexamethylmelamine that have not been previously described.

METHOD

Hexamethylmelamine will be used in patients whose cancer of the ovary has become refractory to therapy with alkylating agents or in patients where therapy with alkylating agents is contra-indicated. Hexamethylmelamine will be given daily by mouth, either continuously or intermittently depending on response, toxicity, and other drugs which the patient may be taking concomitantly. The treatment will continue for as long as the disease is stable or the tumor shrinks.

PROGRESS

(82 10 - 83 09) Two patients were entered on this protocol in FY 83 for a total of eight entries. Nausea and neutropenia were reported as adverse reactions.

STATUS: (0)

TITLE: NCI #180-11: VP-16-312 For Small Cell Carcinoma of
The Lung (Group C Guidelines)

PRINCIPAL INVESTIGATOR: COL Friedrich H. Stutz, MC

PROFESSIONAL ASSISTANTS: LTC Irwin B. Dade, MC
LTC Archie W. Brown, MC

WORK UNIT: 31/20

TECHNICAL OBJECTIVE

To provide an investigational drug of proven efficacy, not previously released for general use, to MAMC patients under Group C NCI Guidelines. To determine extent and variety of side effects with VP-16-312 that have not been previously described.

METHOD

VP 16-312 will be used in refractory or recurrent small cell cancer of the lung, usually in combination with other effective chemotherapeutic drugs. It will be administered IV over a 30-minute period either daily for 5 days every 2-3 weeks or on days 1, 3, and 5 every 4-5 weeks. The exact interval between subsequent courses will be modified, depending on the time required for recovery from toxic manifestations. Careful pre-treatment evaluation and follow-up will be done. Any untoward or unexpected side effects will be reported to the NCI. The treatment will be continued for as long as the patient's tumor responds or remains stable.

PROGRESS

(82 10 - 83 09) Three patients were entered on this protocol in FY 83 for a total of 14 entries. Neutropenia, thrombocytopenia, hair loss, anemia, and fatigue (expected side effects of the small cell carcinoma of the lung and the chemotherapy) were reported.

STATUS: (0)

TITLE: NCI #180-12: Group C Guidelines for the Use of Delta-9-Tetrahydrocannabinol

PRINCIPAL INVESTIGATOR: COL Friedrich H. Sautz, MC

PROFESSIONAL ASSISTANTS: LTC Irwin B. Dabe, MC
LTC Alan D. Mease, MC
MAJ Lauren K. Colman, MC

WORK UNIT: 81/102

TECHNICAL OBJECTIVE

To determine untoward side effects not previously described with THC and to make available this anti-nausea drug to patients on chemotherapy.

METHOD

Delta-9-THC will be used as an antiemetic therapy in cancer chemotherapy patients refractory to standard antiemetic agents. It will be administered at a starting dose of 5 mg/m² p.o., 6-8 hours prior to the administration of chemotherapy and for 12 hours thereafter. Should the 5 mg/m² dose prove to be ineffective, and in the absence of significant side effects, the dose may be escalated to 7.5 mg/m². Any untoward side effects will be reported to the NCI.

PROGRESS

(82 10 - 83 09) Four patients were entered in this protocol in FY 83 for a total of 11 entries. Drowsiness was the only reported side effect.

STATUS: (0)

TITLE: NCI #7601 - Selected Stage I_A - I_{B1} Ovarian Cancer
(Well and Moderately Differentiated)

PRINCIPAL INVESTIGATOR: COL Roger B. Lee, MC

PROFESSIONAL ASSISTANTS: COL William L. Benson, MC

WORK UNIT: 31745

TECHNICAL OBJECTIVE

To define the natural history of patients treated by surgery; to determine whether prophylactic, adjuvant chemotherapy with melphalan alters the natural history; to study the effect of various potential prognostic factors on the natural history of patients treated by each form of therapy; to establish the value of various staging parameters on the stage of disease and its natural history.

METHOD

To be eligible, patients must have a histopathologic diagnosis of common epithelial ovarian cancer, either serous, mucinous, or other (endometrioid, transitional, mesonephroid, adenocanthoma, mixtures and intermediate types, and unclassifiable). Patients will be stratified by histology, histologic grade, and stage. After staging laparotomy and total abdominal hysterectomy or bilateral salpingo-oophorectomy, patients will be randomized to observation with no chemotherapy or to a chemotherapy regimen of melphalan (0.2 mg/kg/day PO for 5 days). The chemotherapy will be repeated every four weeks for 18 months or after 12 cycles of therapy, whichever comes first. Chemotherapy will be discontinued for unacceptable toxicity or at 18 months if the patient is free of disease at that time. If patient relapses, she will be taken off study at that time. Second-look will occur at 18 months after randomization using peritoneoscopy or laparotomy.

PROGRESS

(31-12-83-99) No entries at MAMC.

STATUS: (0)

TITLE: NCI #7602: All Stage Ic and II (A, B, C) and Selected Stage IAii and IBii Ovarian Cancer

PRINCIPAL INVESTIGATOR: COL Roger B. Lee, MC

PROFESSIONAL ASSISTANTS: COL William L. Benson, MC

WORK UNIT: 81/33

TECHNICAL OBJECTIVE

To define the natural history of patients treated by 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.

METHOD

All patients with common epithelial ovarian cancer are eligible, if after definitive staging procedures the patient is zoned to be in Stages 2A, 2B, 2C, IAii, IBii, or IAi or IBi 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 IIB, IIC, residual disease is found, patient 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

(81-01 - 82-19) No patients entered during FY 83. One patient entered during FY 81 and is alive at present time.

STATUS: (0)

DETAILED SHEETS
FOR
PROTOCOLS

PEDIATRIC ONCOLOGY BRANCH PROTOCOLS

TITLE: Intrathecal Aminopterin, NSC # 739-NB, Clinical Studies

PRINCIPAL INVESTIGATOR: MAJ Allen R. Potter, MC

PROFESSIONAL ASSISTANTS: LTC Charlene P. Holt, MC
LTC Alan D. Mease, MC

WORK UNIT NO: 80750

TECHNICAL OBJECTIVES

To demonstrate that IT aminopterin is less neurotoxic in man than IT methotrexate. To show that IT aminopterin requires fewer lumbar punctures for an equivalent therapeutic effect than IT methotrexate. To compare the pharmacokinetics in man of IT aminopterin and IT methotrexate.

METHOD

Any patient with a CNS neoplasm, primary or metastatic will be eligible provided IT methotrexate is an accepted treatment for the neoplasm. Patients with acute leukemia or non-Hodgkin's lymphoma scheduled to receive preventive IT chemotherapy will be eligible. Patients with a prior history of IT methotrexate arachnoiditis will be eligible, but patients with a prior history of myelopathy or encephalopathy associated with IT methotrexate therapy will not be eligible. Eligible patients will receive intrathecal AMT at a dose of 2.0 mg per injection at weekly intervals. For prophylaxis, six injections will be given. For treatment of established disease, the injections will be continued until the CNS is free of blast cells by cytocentrifuge analysis. Thereafter, the injections will be given weekly x 2, then q 2 weeks x 2, then monthly for 2 years.

PROGRESS

130 06 - 83 093 No entries at MAMC.

STATUS: CF

TITLE: POB #76-04: Combined Modality Treatment of Rhabdomyosarcoma

PRINCIPAL INVESTIGATOR: MAURITZ R. POTTER, MD

PROFESSIONAL ASSISTANTS: LTC CHARLENE R. BOLT, MD
LTC ALICE H. MERRILL, MD

WORK UNIT NO: 50163

TECHNICAL OBJECTIVES

To answer the following questions: (1) Can the functional impairments of surgery be reduced by primary chemotherapy and can "rational" surgical procedures be avoided? (2) Does early use of intensive chemotherapy enhance survival for patients presenting with metastatic disease? (3) What can be learned about the kinetics, biochemistry, immunology, and etiology of childhood rhabdomyosarcoma?

METHOD

Patients <25 years with rhabdomyosarcoma or undifferentiated sarcoma who have not had prior surgical debulking, radiotherapy, or chemotherapy will be eligible. STAGING: Stage I - disease limited to a single anatomic structure; Stage II - local contiguous spread (with or without involvement of regional nodes); Stage III - metastatic disease. Stages I and II will be randomized to either Group I or Group II. Group I will initially receive surgery followed by chemotherapy (vincristine, actinomycin, and cyclophosphamide) and radiotherapy. Group II will initially receive the same chemotherapy as above and radiotherapy. After hematologic recovery from chemotherapy, patients will undergo surgical exploration and residual tumor will be excised. Stage III patients will be randomized to receive a standard regimen of chemotherapy or to receive an intensive regimen which is the same as standard with an extra day of chemotherapy added. Both groups will receive radiotherapy during the chemotherapy and will be evaluated for surgical excision of remaining bulk disease after recovery from chemotherapy. All patients who attain CR or PR will receive maintenance chemotherapy.

PROGRESS

Case # - 44-011. No outflow of MAMC.

1977: (1)

TITLE: POB 77/03 - Treatment of Metastatic Osteosarcoma

PRINCIPAL INVESTIGATOR: MAJ Allen R. Potter, MC

PROFESSIONAL ASSISTANTS: LTC Charlene P. Holt, MC
LTC Alan D. Mease, MC

WORK UNIT NO: 80751

TECHNICAL OBJECTIVES

To determine the differences in tumor response rates and drug toxicities when high dose methotrexate is given as a 6-hour bolus infusion or as a 42-hour infusion. To determine if the use of intensive chemotherapy given when tumor burden is minimal results in the complete eradication of all microscopic foci of metastatic osteosarcoma.

METHOD

Patients <30 years of age with no evidence of serious infection, active bleeding disorders, or concomitant significant complications and biopsy-proven osteosarcoma are eligible. Patients must have pathologic or radiologic evidence of overt metastatic disease and must have received no previous chemotherapy, radiotherapy or surgical therapy for metastatic disease. Patients presenting with metastatic osteosarcoma will enter a first phase which is designed to create a state in which there is no evidence of disease (NED). If possible, this will be achieved by surgery alone; if surgery alone cannot achieve NED, then chemotherapy will be used initially rather than surgery. Patients in this latter category will be randomized to receive weekly vincristine plus high dose MTX-CF given over 6 hours or methotrexate given as a 42-hour infusion. Patients who respond to this phase of methotrexate may become candidates for surgery even though resection was not possible initially. If NED can be achieved in this way, patients will proceed to Phase 2. Patients achieving NED with surgery and/or chemotherapy will enter Phase 2 of the protocol and be treated with intensive combination chemotherapy employing agents known to be active against overt metastatic disease (methotrexate, citrovorum factor, vincristine, adriamycin, cyclophosphamide, phenylalanine mustard, DTIC, cisplatin).

PROGRESS

(80 06 - 83 09) No entries at MAMC.

STATUS: (1)

FILE: 908 #7704: Childhood Non-Hodgkin's Lymphoma

PRINCIPAL INVESTIGATOR: MAJ Allen R. Potter, MC

PROFESSIONAL ASSISTANTS: LTC Charlene P. Holt, MC
LTC Alan D. Mease, MC

WORK UNIT NO: 80-62

TECHNICAL OBJECTIVES

To treat patients in as uniform manner as possible while studying the spectrum of diseases in as much detail as possible, including clinical features, histology and cytology, surface markers, induction of differentiation in vitro, functional potential of tumor cells, distribution patterns of DNA and protein pre- and post-treatment, and possible tumor markers. From such studies, it is hoped that insights into classification and rational approaches to therapy will be forthcoming.

METHOD

Untreated patients with non-Hodgkin's lymphoma <25 years of age or with Burkitt's lymphoma at any age, who consent to a second biopsy procedure are eligible. Patients in whom a diagnosis of non-Hodgkin's lymphoma is strongly suspected will be admitted as soon as possible. Treatment will be commenced as soon as initial studies and biopsy have been completed and therapy should begin within 48-72 hours. Therapy will include total surgical resection wherever possible. The backbone of therapy, however, will be chemotherapy, since childhood non-Hodgkin's lymphoma is rarely a localized tumor. Drug therapy will be intensive utilizing cyclophosphamide, vincristine, adriamycin, methotrexate, and prednisone. These will be used in a sequence which should result in drugs being administered every 10 days. We propose a somewhat different approach to prophylactic therapy, in that first, an IT methotrexate boost will be given during IV 42 hour methotrexate infusion; second, Ara-C will be used as a second drug in combination with methotrexate, and third, prophylaxis will begin at the same time as systemic therapy since it is more likely that tumor cells enter the sanctuary at a time when the systemic tumor burden is high. Irradiation as part of CNS prophylactic therapy is not planned.

PROGRESS

(80-07 - 83-09) No entries at MAMC.

STATUS: (T)

TITLE: POB #7705 - Treatment of Metastatic and High Risk Ewing's Sarcoma

PRINCIPAL INVESTIGATOR: MAJ Allen R. Potter, MC

PROFESSIONAL ASSISTANTS: LTC Charlene P. Holt, MC
LT Alan D. Mease, MC

WORK UNIT NO: 30752

TECHNICAL OBJECTIVES

To examine the efficacy of total body irradiation in combination with high dose chemotherapy in the treatment of metastatic or high-risk Ewing's sarcoma. To examine the immunological status of patients receiving total body irradiation as a function of time. To examine the utility of autologous marrow infusion in patients receiving high-dose chemotherapy who do not have marrow disease at presentation but who may have metastatic disease in other sites.

METHOD

Patients with a pathologically proven diagnosis of Ewing's sarcoma presenting with metastatic disease or with a pelvic or vertebral primary lesion, without prior radiation or chemotherapy, will be eligible. Chemotherapy to include vincristine, actinomycin D, and cyclophosphamide will be given for four weeks concomitant with irradiation to the primary site for 5 weeks. Total body irradiation will then be given weeks 6-10. High dose therapy of vincristine, adriamycin, cyclophosphamide, and DTIC will then be given for 3 days. Maintenance chemotherapy to include vincristine, adriamycin, cyclophosphamide, and DTIC will be given once every 6 weeks for 12 cycles.

PROGRESS

(80 06 - 83 09) No entries at MAMC.

STATUS: (1)

TITLE: POB #77/06: Treatment of Low Risk Ewing's Sarcoma

PRINCIPAL INVESTIGATOR: MAJ Allen R. Potter, MC

PROFESSIONAL ASSISTANTS: LTC Charlene P. Holt, MC
LTC Alan D. Mease, MC

WORK UNIT NO: 80/53

TECHNICAL OBJECTIVES

To evaluate the efficacy of prophylactic pulmonary irradiation in conjunction with combination chemotherapy in the treatment of low risk Ewing's sarcoma. To evaluate the immunologic status and competence of patients with Ewing's sarcoma as a function of time.

METHOD

Patients with a pathologically proven diagnosis of Ewing's sarcoma presenting with distal primary lesions (but not in the pelvis or spine) without evidence of metastatic disease are eligible for this study. Patients with prior chemotherapy, radiation therapy, or surgical resection procedures other than biopsies are ineligible for the study. For initial therapy, patients will receive vincristine, actinomycin D, and cyclophosphamide (given week 1 and 4), radiation therapy to the primary site (5 treatments/week for 5 weeks), and subsequent to the completion of radiation to the primary site, pulmonary irradiation (5 treatments/week for 2 weeks). Maintenance chemotherapy will begin subsequent to pulmonary irradiation consisting of vincristine, adriamycin, and cyclophosphamide every 4 weeks for a total of 12 courses.

PROGRESS

(80 06 - 83 09) No entries at MAMC.

STATUS: (T)

TITLE: BOB 47711: A Prospective Study of the Efficacy of HLA-Matched Platelet Transfusions for Platelet Support in Hematopoietic Cancer Patients

PRINCIPAL INVESTIGATOR: MAJ Allen E. Potter, MC

PROFESSIONAL ASSISTANTS: LTC Charlene P. Holt, MC
LTC Alan D. Meyer, MC

WORK UNIT NO: 80/54

TECHNICAL OBJECTIVES

To determine what differences exist between patients initially treated with HLA-matched or HLA-mismatched platelets in the number and frequency of transfusions required; mean increments of those transfusions; frequency of transfusion reactions; number of bleeding episodes; development of anti-HLA antibodies; and length of time until patients become refractory to the treatment strategy employed; to determine how often patients refractory to one strategy will respond to the other and what differences will exist in those subsequent responses; to determine if the order of strategy makes a difference in the total length of time patients respond to platelet transfusions; to determine if the type of platelets transfused in those patients refractory to both matched and mismatched platelet transfusions makes a difference in the number of transfusions required, the mean increments of those transfusions, and the frequency and time to the development of significant bleeding episodes.

METHOD

ELIGIBILITY: All pediatric patients admitted to Madigan.

EXCLUSIONS: >5 blood component transfusions, if cannot be HLA typed, or if there is an inadequate number of HLA-matched donors to provide HLA-matched platelet support. RANDOMIZATION: 2 groups by diagnostic categories; further, patients within each diagnostic category will be divided into those with or without known bone marrow involvement. Group 1 patients will receive platelet transfusions with matched platelets. Group 2 will receive mismatched platelets. The indications for transfusion will be the same in both groups. Patients in both groups will continue to receive platelet transfusions until the patient is judged to be refractory and then crossed into the opposite group. When patients are considered refractory to matched and mismatched platelets, they shall be randomized to receive either matched or mismatched platelets for the remainder of the study. Following randomization, the patients will continue to receive the assigned platelet preparation until the development of a significant bleeding problem. Patients refractory to both matched and mismatched platelets who develop significant bleeding problems will be considered off-study and will be supported with the best available platelet support.

PROGRESS

(80 06 - 83 09) No entries at MAMC.

STATUS: (1)

TITLE: POB #78/06 - Treatment of Recurrent Lymphoma

PRINCIPAL INVESTIGATOR: MAJ Allen R. Potter, MC

PROFESSIONAL ASSISTANTS: LTC Charlene P. Holt, MC
LTC Alan D. Mease, MC

WORK UNIT NO: 80/55

TECHNICAL OBJECTIVES

To investigate the utility of a combination of aggressive chemotherapy and total body irradiation (TBI) in the treatment of recurrent disseminated non-Hodgkin's lymphoma. To study the utility of flow-micro-fluorimetric techniques as a potential means of individualizing timed-sequence chemotherapy scheduling. To study the value of supplementary irradiation to apparently localized recurrent tumor. To study recurrent tumor for changes in morphology, surface receptors, EBV genome, and cell surface micro-viscosity as compared to the patient's primary tumor.

METHOD

Patients with recurrent non-Hodgkin's lymphoma who have relapsed on other protocols in whom autologous marrow has been stored at least 2 months prior to relapse and whose disease is not defined as small volume, local relapse will be eligible for the study. The presence of complicating factors (renal failure, infection, etc.) which constitute relative contraindications to the initiation of CARAT therapy (Cytosan, ARA-C, TBI) will be considered individually for eligibility. Patients with prior CNS disease of proven resistance to chemotherapy and cranial or craniospinal irradiation will normally be ineligible for CARAT therapy. All patients will be treated in laminar flow rooms if available. Normally, chemotherapy will not commence until the total WBC is >4000 and granulocyte count >1500 in order to keep the period of granulocytopenia to a minimum. All patients will be vigorously hydrated prior to therapy. Treatment schemas are: cytosan; 45 mg/kg days 1, 2, 3, 4, (IV in 100 cc D5W over 30 min); TBI: 15 rads daily x 8 commencing on day 1 omitting weekends or 400 rads on days 6 and 8; ARA-C: 300 mg/M² 24 hours by continuous infusion days 9, 10, 11, 12, given in 5% dextrose/water; autologous marrow infusion: day 13. In the presence of CNS disease, intrathecal or intraventricular therapy will be administered. Patients also may be randomized to receive hyperalimentation.

PROGRESS

(80 06 - 83 09) No entries at MAMC.

STATUS: (T)

TITLE: POB #78/10 - A Phase II Study of *Achromobacter* Glutaminase
in Acute Leukemia

PRINCIPAL INVESTIGATOR: MAJ Allen R. Potter, MC

PROFESSIONAL ASSISTANTS: LTC Charlene F. Holt, MC
LTC Alan D. Mease, MC

WORK UNIT NO: 80/56

TECHNICAL OBJECTIVES

To determine the therapeutic efficacy of glutaminase against acute leukemia refractory to standard agents. To determine the toxicity of glutaminase administered in a fixed dosage schedule.

METHOD

Patients must have a life expectancy of at least 4 weeks and cytologically documented acute lymphocytic, acute myelocytic, or acute undifferentiated leukemia (on bone marrow aspirate or the biopsy specimen). In addition, patients must be proven refractory to conventional drugs considered active against their disease and must have recovered from the toxic effects of any previous therapy. The drug will be administered as a continuous infusion (10,000 IU/M²/day) for at least 14 days with re-evaluation of the leukemia at that time. If no beneficial effect has been seen the trial will be discontinued. If there is evidence of improvement, the infusion will be continued for a total of 28 days.

PROGRESS

(80 06 - 83 99) No entries at MAMC.

STATUS: (1)

TITLE: POB #78/13 - Fever and Antimicrobial Therapy, Study II

PRINCIPAL INVESTIGATOR: MAJ Allen R. Potter, MC

PROFESSIONAL ASSISTANTS: LTC Charlene P. Holt, MC
LTC Alan D. Mease, MC

WORK UNIT NO: 80/61

TECHNICAL OBJECTIVES

To evaluate the role of empiric antibiotic therapy in granulocytopenic cancer patients. To reduce the incidence of fever and infection in patients for whom treatment-related granulocytopenia is anticipated. To evaluate and treat the granulocytopenic patient colonized with fungi.

METHOD

Patients in this study will be treated in three distinct groups. Group I (Treatment of Granulocytopenic Patients Prior to the Onset of Fever) will consist of afebrile patients receiving chemotherapy anticipated to produce granulocytopenia, irrespective of the projected duration of granulocytopenia. These patients will be randomized to a double blind study of either erythromycin and bactrim or a placebo. Group II (Evaluation and Treatment of Granulocytopenic Patients who Become Febrile) will consist of patients with granulocytopenia who are febrile with either a documented infection or a fever of undetermined origin. Those with documented infection will receive either broad spectrum antibiotics or specific therapy based on sensitivity testing. FUO patients will be treated with empiric antibiotics for 7 days and then managed according to their status (febrile/afebrile). Group III (Evaluation and Treatment of the Granulocytopenic Patient Colonized with Fungi) after 7 days of KGC will be randomized to receive amphotericin or not receive amphotericin.

PROGRESS

(80 07 - 83 09) No entries at MAMC.

STATUS: (T)

TITLE: POB #79/01 - Evaluation of Human Lymphoblastoid Interferon and Poly I:C (Stabilized with Poly-L-Lysine and Carboxymethyl Cellulose [Poly(ICLC)]) in the Treatment of Acute Myelocytic Leukemia, CLL, and Various Solid Tumors, Phase II.

PRINCIPAL INVESTIGATOR: MAJ Allen R. Potter, MC

PROFESSIONAL ASSISTANTS: LTC Charlene P. Holt, MC
LTC Alan D. Mease, MC

WORK UNIT No: 80157

TECHNICAL OBJECTIVES

To determine the therapeutic efficacy of human lymphoblastoid interferon and stabilized polyribonucleic acid-polyribocytidylic acid (poly[ICLC]) in patients with acute myelocytic leukemia (who are in their first bone marrow relapse and have received no previous induction treatment for this relapse), and in patients with various solid tumors in relapse.

METHOD

Patients ≥ 16 years with acute myelocytic leukemia who are in their first bone marrow relapse after having been treated with standard drugs and who have not received any other induction treatment for this relapse are eligible. Solid tumor patients in relapse are eligible as determined by the specific protocol priority scheme for that tumor type. Patients will be randomized to receive either lymphoblastoid interferon or Poly(ICLC). An adequate trial will consist of a minimum of one month of treatment. A second month of induction with the same agent on the same schedule will be given if marrow improves by day 30 from M_3 to M_2 in the case of AML, or if, in the case of solid tumor patients, the disease is stable or improved. In no case will induction continue beyond two months. Patients with stable or improving disease at the end of two months will begin a maintenance schedule with the same agent; patients with progressive disease at the end of one or two months may, if their condition permits, cross-over to an induction attempt with the other agent.

PROGRESS

(80 06 - 83 09) No entries at MAMC.

STATUS: (1)

TITLE: POB #79/03: Phase II Study of 2'-Deoxycoformycin in
Acute Lymphoblastic Leukemia

PRINCIPAL INVESTIGATOR: MAJ Allen R. Potter, MC

PROFESSIONAL ASSISTANTS: LTC Charlene P. Holt, MC
LTC Alan D. Mease, MC

WORK UNIT NO: 80/58

TECHNICAL OBJECTIVES

To determine the therapeutic efficacy of 2'-deoxycoformycin (2'dCF) against acute lymphoblastic leukemia refractory to standard agents; to determine the toxicity of 2'dCF administered in a fixed dosage schedule.

METHOD

Patients with a life expectancy of at least 4 weeks who have cytologically documented acute lymphoblastic leukemia on bone marrow aspirate or biopsy specimen are eligible. Patients must be proven refractory to those conventional drugs considered active against ALL. This protocol will investigate a dose of 0.25 mg/kg 2'dCF given IV daily for 3 consecutive days. Each patient will receive at least 2 courses of 2'dCF (toxicity permitting). The second course of 2'dCF will be given 14 days following the initial treatment. If there is no evidence of improvement on day 28 the patient will be removed from the study. Patients who have achieved either a complete or partial response after the second course will continue to receive treatment on this protocol until M₃ marrow status occurs. Upon entrance to the protocol, cell surface marker studies will be obtained on the lymphoblasts from each patient. The ALL patients will be treated and analyzed separately according to whether they have T cell or non-T cell ALL.

PROGRESS

(80 06 - 83 09) No entries at MAMC.

STATUS: (T)

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

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SOUTHWEST ONCOLOGY GROUP PROTOCOLS

TITLE: SWOG 2804: Adjuvant Chemotherapy with 5-Fluorouracil, Adriamycin, and Mitomycin-C (FAM) vs Surgery Alone for Patients with Locally Advanced Gastric Adenocarcinoma

PRINCIPAL INVESTIGATOR: COL Friedrich H. Stutz, MC

PROFESSIONAL ASSISTANTS: LTC James E. Congdon, MC
LTC Irwin B. Dobb, MC

WORK UNIT NO: 73742

TECHNICAL OBJECTIVE

To determine the efficacy of adjuvant chemotherapy with FAM on the disease-free interval and survival of patients with T₁N₁ stage-groups I_B, I_C, II and III gastric adenocarcinoma compared to potentially curative surgery alone.

METHOD

Patient Eligibility: patients must have T₁N₁ stage-group I_B, I_C, II, or III gastric adenocarcinoma and no microscopic or gross residual postoperatively; no prior chemo- or radiotherapy; no medical contraindications to chemotherapy with FAM; serum bilirubin <2.0 mg/100 ml; SGOT and SGPT less than three times the upper limit of normal values; creatinine clearance >75 cc/min; BUN <25 mg%; serum creatinine <1.5 mg%; WBC >4,000; and 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 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

(78 06 - 83 09) No entries at MAMC.

STAFF: /00

TITLE: SWOG 7808, Combination Modality Treatment for Stages III and IV Hodgkin's Disease, MOPP #6

PRINCIPAL INVESTIGATOR: COL Friedrich H. Stutz, MC

PROFESSIONAL ASSISTANTS: LTC James E. Congdon, MC
LTC Irwin B. Dabe, MC

WORK UNIT NO: 78747

TECHNICAL 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.

METHOD

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.

Treatment 1: Normal marrow patients will receive 6 cycles of MOP-BAP.

Treatment 2: Impaired bone marrow patients will receive 6 cycles of MOP-BAP with dose modifications.

Complete remission (CR) patients with prior radiotherapy will be randomized between Treatment 3 (no treatment) and 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 MOPBAP therapy at the discretion of the investigator).

PROGRESS

(82 10 - 83 09) No entries in FY 83. Three patients entered in previous years remain in complete remission 29, 31, and 47 months after diagnosis. The fourth patient had a recurrence 16 months after diagnosis.

STATS: (0)

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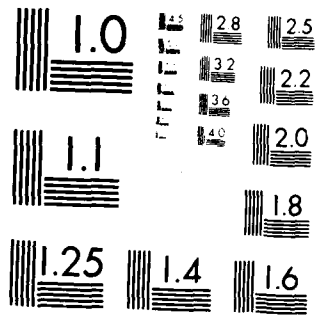
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TITLE: SWOG 7823/24/25/26: ROAD-AdOAP in Acute Leukemia,
Phase III

PRINCIPAL INVESTIGATOR: COL Friedrich H. Stutz, MC

PROFESSIONAL ASSISTANTS: LTC James E. Congdon, MC
LTC Irwin B. Dabe, MC

WORK UNIT NO: 79/02

TECHNICAL OBJECTIVE

To compare the efficacy of the 4-drug combination chemotherapy regimen, ROAP (Rubidazone, Vincristine, Arabinosyl Cytosine, and Prednisone) to AdOAP (the same combination using Adriamycin in place of Rubidazone) in adult acute leukemia, as determined by remission duration and survival; to determine the comparative toxicity of these regimens; to determine whether late intensification therapy at 9 months after complete remission will improve long-term, disease free survival; to determine whether immunotherapy using Levamisole for 6 months after 12 months of complete remission on chemotherapy improves disease-free survival; to determine the effects of intrathecal Ara-C on the incidence of CNS leukemia; to determine reproducibility of the FAB/histologic classification and correlation to response to therapy in 200 consecutive cases of acute leukemia; and to study the effects of intensive supportive care in the management of acute leukemia.

METHOD

For remission induction, Group A will receive ROAP and Group B will receive AdOAP. When leukemic cells are no longer visible in the bone marrow, consolidation therapy will begin with one-half the patients receiving RAOP in reduced dosage. The other one-half will receive AdOAP with the addition of cytosine arabinoside in the spinal fluid at weekly intervals for 8 weeks. If a complete remission persists, maintenance therapy will be given consisting of vincristine, cytosine arabinoside, and prednisone for 5 days at monthly intervals for 9 months. One half of these patients will then receive late intensification therapy consisting of a combination of vincristine, prednisone, and methotrexate plus 6-mercaptopurine for 5 days. The other one-half will receive 3 additional months of maintenance therapy, at which time all patients will be randomized into one group receiving no further treatment and another group receiving levamisole for 2 days of each week for 6 months.

PROGRESS

(82 10 - 83 09) No new entries at MAMC. Of five patients entered in previous years, three died after partial response and two have been lost to follow-up.

STATUS: (0)

TITLE: SWOG 7827: Combined Modality Therapy for Breast Carcinoma,
Phase III

PRINCIPAL INVESTIGATOR: COL Friedrich H. Stutz, MC

PROFESSIONAL ASSISTANTS: LTC James E. Congdon, MC
LTC Irwin B. Dabe, MC

WORK UNIT NO: 79/96

TECHNICAL OBJECTIVE

To compare the disease-free interval and recurrence rates in:
(1) estrogen receptor positive premenopausal patients with Stage II disease using combination chemotherapy alone vs combination chemotherapy and oophorectomy; (2) estrogen receptor positive postmenopausal patients with Stage II disease using combination chemotherapy plus tamoxifen vs tamoxifen alone vs combination chemotherapy alone; (3) estrogen receptor negative patients with Stage II disease using one vs two years of combination chemotherapy; and 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.

METHOD

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-fluorouracil, 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

(82 10 - 83 09) Two new patients were entered in FY 83 for a total of 16 entries. These 16 patients received various treatments according to their ER and menopausal status. Of the 16 patients, 11 are alive and well without evidence of recurrent breast cancer. Four patients are doing well on alternative treatments after they had a recurrence, and one patient is dead of aggressive, rapidly progressive, widely metastatic breast cancer.

STATUS: (0)

TITLE: SWOG 7916: Phase II Evaluation of Gallium Nitrate in
Metastatic Urological Malignancies: Testicular, Bladder,
Prostate, and Kidney

PRINCIPAL INVESTIGATOR: COL Friedrich H. Stutz, MC

PROFESSIONAL ASSISTANTS: LTC James E. Congdon, MC
LTC Irwin B. Dabe, MC

WORK UNIT NO: 80/23

TECHNICAL OBJECTIVES

To determine the efficacy of gallium nitrate as determined by response and survival in patients with metastatic urological malignancies which include: testicular, bladder, prostate, and kidney; who have failed on higher priority treatment.

METHOD

Patients are eligible who are not candidates for studies of higher priority and who have histologically proven incurable advanced metastatic testicular carcinoma, bladder carcinoma, prostate or kidney carcinoma. Patients should not have had more than two previous types of combination or single agent chemotherapy trials.

All patients will be treated at a dose of 700 mg/m² given as a 30 minute IV infusion in 200 ml of normal saline. Course will be repeated every two weeks if blood counts, and liver and renal functions permit. An adequate trial will consist of two courses of therapy.

PROGRESS

(80 02 - 83 09) Study is now open only to bladder patients. No entries at MAMC.

STATUS: (0)

TITLE: SWOG 7924: Multimodal Therapy for Limited Small Cell Carcinoma of the Lung, Phase III

PRINCIPAL INVESTIGATOR: COL Friedrich H. Stutz, MC

PROFESSIONAL ASSISTANTS: LTC James E. Congdon, MC
LTC Irwin B. Dabe, MC

WORK UNIT NO: 80/26

TECHNICAL OBJECTIVES

To determine the efficacy of sequentially alternating mutually noncross-resistant, multidrug regimens in remission induction and intensification therapy in patients with limited small cell lung carcinoma; to determine the value of chest radiotherapy added to intensive systemic chemotherapy in reducing chest recurrences and in improvement of survival; to determine the relative efficacy and toxicity of low-dose, extensive chest radiation when used in close chronologic sequence with systemic multiagent chemotherapeutic regimens; to determine whether radiotherapy ports should be set according to tumor size prior to or after induction chemotherapy; and to determine the value of combined systemic chemotherapy and radiotherapy in the control of bulky chest disease.

METHOD

Patients with histologically or cytologically confirmed small cell carcinoma of the lung are eligible. Patients will be treated for 8 weeks with combination chemotherapy of methotrexate, vincristine, VP-16, adriamycin, and cyclophosphamide. Following the completion of induction chemotherapy, patients will be treated as follows: (1) Complete remission: patients will be randomized to receive either chest and whole brain radiotherapy followed by chemotherapy or whole brain radiotherapy alone followed by chemotherapy. (2) Partial remission or stabilized disease: patients will be randomized to receive either extended field and whole brain radiotherapy followed by chemotherapy or involved field and whole brain radiotherapy followed by chemotherapy. Patients with progressive disease after induction chemotherapy will go off study.

PROGRESS

(82 10 - 83 09) No new entries at MAMC in FY 83. None of the seven patients entered in previous years survived. However, significant prolongation of life was noted when compared to historical controls. Small cell carcinoma of the lung is a very aggressive cancer and ultimately fatal.

STATUS: (C)

TITLE: SWOG 7927/28: Chemotherapy for Multiple Myeloma,
Phase III

PRINCIPAL INVESTIGATOR: COL Friedrich H. Stutz, MC

PROFESSIONAL ASSISTANTS: LTC James E. Congdon, MC
LTC Irwin B. Dabe, MC

WORK UNIT NO: 80/27

TECHNICAL OBJECTIVES

To compare the effectiveness of four different drug combinations for remission induction in previously untreated patients with multiple myeloma; and, for patients with a 75% tumor reduction, to evaluate the role of 12 months of chemotherapy maintenance with vincristine, cyclophosphamide, and prednisone vs these drugs plus levamisole, when compared with previous experiences.

METHOD

Patients previously untreated with chemotherapy (except prednisone) with a diagnosis of multiple myeloma, Stages I, II, or III, will be eligible for the study. Patients will receive remission induction treatment with one of the following: (1) vincristine, melphalan, cyclophosphamide, and prednisone (VMCP) for 3 courses followed by vincristine, BCNU, adriamycin, and prednisone (VBAP) for 3 courses, every 3 weeks; (2) VMCP for 3 courses followed by VBAP for 3 courses every 3 weeks plus levamisole; (3) vincristine, cyclophosphamide, and prednisone (VCP) every 3 weeks; or (4) VCP every 3 weeks plus levamisole. Treatment will continue on all regimens for a minimum of 6 months, until a 75% tumor reduction has occurred, but no longer than 18 months in the absence of remission. Patients who are responsive to remission induction with Treatments 1 or 3 will receive maintenance treatment with VCP. Patients responsive to induction therapy with Treatments 2 or 4 will receive maintenance treatment with VCP plus levamisole. Treatment cycles are repeated at 21 day intervals for 12 months provided the absolute granulocyte count is at least 1,000 and the platelet count is at least 80,000.

PROGRESS

(82 10 - 83 09) No new entries in FY 83. One patient was entered in FY 81 and was treated for 7 months with some disease stabilization before subsequent progression of disease and death. One patient was entered in FY 82 and treated for 8 months before subsequent progression of disease and death.

STATUS: (C)

TITLE: SWOG 7958: Evaluation of m-AMSA in Metastatic or Recurrent Epithelial Carcinoma of the Female Genital Tract, Phase II

PRINCIPAL INVESTIGATOR: COL Friedrich H. Stutz, MC

PROFESSIONAL ASSISTANTS: LTC James E. Congdon, MC
LTC Irwin B. Dabe, MC

WORK UNIT NO: 80/37

TECHNICAL OBJECTIVES

To determine the antitumor activity of AMSA in patient with metastatic or recurrent epithelial carcinomas of the ovary, endometrium, cervix, vagina, or vulva who have failed on higher priority treatment protocols; and to determine the nature and degree of toxicity of AMSA in patients treated by the split-course three-day schedule.

METHOD

Patients are eligible who have a histologically proven diagnosis of incurable advanced metastatic or recurrent epithelial carcinoma of the ovary, endometrium, cervix, vagina, or vulva. The patients will be divided into two treatment groups; good risk patients and poor risk patients. All patients will be treated by a split dose, 3-day schedule. Dose for good risk: 40 mg/M²/day, IV, for three days. Dose for poor risk: 30 mg/M²/day, IV, for three days. Total daily dose will be dissolved in 250-500 ml of D/W and given IV over one hour. Repeat courses of AMSA will be given at 21 day intervals. In the event that myelosuppression persists at day 21, biweekly WBC and platelet counts will be done and subsequent courses of AMSA will be given only when there is bone marrow recovery.

PROGRESS

(82 10 - 83 09) No new patients in FY 83. The one patient entered previously had an unusually long good partial regression of her metastatic ovarian cancer. She experienced pain in the veins proximal to the infusion requiring placement of a Hickman catheter. This eliminated the problem and the patient was able to continue her treatment until the tumor progressed.

STATUS: (C)

TITLE: SWOG 7984: The Treatment of Chronic Stage CML with
Pulse, Intermittent Busulfan Therapy with or without
Oral Vitamin-A, Phase III

PRINCIPAL INVESTIGATOR: LTC Irwin B. Dabe, MC

PROFESSIONAL ASSISTANTS: COL F. H. Stutz, MC
MAJ Lauren K. Colman, MC

WORK UNIT NO: 81/80

TECHNICAL OBJECTIVES

To determine the efficacy of standard pulse, intermittent busulfan therapy plus oral vitamin A in prolonging the chronic phase of CML, and hence in prolonging survival.

METHOD

Patients with a diagnosis of chronic stage CML for one year or less with no prior therapy are eligible. Patients will be stratified into those who had a splenectomy and those who did not. Randomization will be to busulfan alone or busulfan plus oral vitamin A. Stratification is also by age, <20 or >20 years. Treatment will continue for as long as the patient responds to the treatment and does not have unacceptable toxicity.

PROGRESS

(81 05 - 83 09) No entries at MAMC.

STATUS: (O)

TITLE: SWOG 7990: Intergroup Testicular Study

PRINCIPAL INVESTIGATOR: COL Friedrich H. Stutz, MC

PROFESSIONAL ASSISTANTS: LTC James E. Congdon, MC
LTC Irwin Dabe, MC

WORK UNIT NO: 80/33

TECHNICAL OBJECTIVES

To compare the disease-free survival and overall survival for surgery alone (with chemotherapy for relapsers) vs surgery plus early adjuvant chemotherapy in patients with resectable Stage II testicular cancer; to register and follow patients with nonseminoma, nonchoriocarcinoma Stage I testicular cancer to define prognostic variables which may predict recurrence in this stage group; to define the difference in disease-free rates and patterns of recurrence, based upon histologic subtypes and extent of disease on initial presentation; to evaluate the role of marker substances such as HCG, alpha-fetoprotein, and lactic dehydrogenase in the early detection and management of recurrence in patients with Stage I and Stage II testicular carcinoma; to evaluate the accuracy of lymphangiograms, CAT scans, and ultrasound studies for staging of retroperitoneal nodal involvement.

METHOD

Patients with histologically confirmed carcinoma (not pure seminoma or choriocarcinoma) of the testis Stage I or Stage II who have had an orchiectomy will be eligible. Patients will undergo bipedal lymphangiogram with the intent of retroperitoneal node dissection. Serum markers will be obtained orchiectomy and must be obtained prior to lymphadenectomy and one to two weeks after. If at two weeks any marker is positive but falling, markers will be repeated at 3-4 weeks and the 4-week value must be normal or serial determinations must be declining with time at a rate predicted by the known serum halflife of the marker. Entry will be at 2-4 weeks postoperatively. Stage I patients will be followed routinely and tumor markers should be negative 4 weeks postop. Stage II unresectable patients are not eligible. Stage II resectable patients will be treated in two treatment groups. Group I: no adjuvant chemotherapy with monthly follow-up until recurrence. Group II: adjuvant chemotherapy with vinblastine, bleomycin, and cis-platinum. Stages I and II who were originally randomized to the follow-up group and Stage II relapsing after chemotherapy will be further treated with vinblastine, bleomycin, and cis-platinum. Patients in complete or partial remission or showing improvement after relapse induction will receive maintenance treatment with vinblastine, repeated every 4 weeks until complete remissions have received 104 weeks of therapy and partial remissions and improvements may continue indefinitely. All other patients will go off study.

PROGRESS

(80 02 - 83 09) No entries at MAMC.

STATUS: (0)

TITLE: SWOG 8012: Treatment for Advanced Adenocarcinoma and Large Cell Carcinoma of the Lung: FOMi vs. CAP vs. FOMi/CAP, Phase III

PRINCIPAL INVESTIGATOR: COL Friedrich H. Stutz, MC

PROFESSIONAL ASSISTANTS: LTC Archie W. Brown, MC
LTC Irwin B. Dabe, MC

WORK UNIT: 81/21

TECHNICAL OBJECTIVES

To evaluate by pairwise comparison the response rate, duration of response, and survival of three regimes, FOMi, CAP, and FOMi/CAP, in patients with advanced (TMN Stage III M₁) adenocarcinoma and large cell undifferentiated carcinoma of the lung; to evaluate the degree of non-cross resistance of FOMi in CAP failures and of CAP on FOMi failures; to compare the toxicities and side effects of FOMi and CAP.

METHOD

Patients with histologically confirmed diagnosis of adenocarcinoma of the lung or large cell undifferentiated carcinoma of the lung will be eligible for this protocol. Alveolar cell carcinoma patients will also be eligible but will be treated under the FOMi arm only. Patients with metastatic disease (TNM Stage III M₁) are eligible. This excludes patients who have metastases only to ipsilateral hilar nodes (N₁) and/or mediastinal nodes (N₂). Patients whose disease can be encompassed within a single radiation port are not eligible. Prior chemotherapy patients are ineligible; however prior radiation therapy is acceptable as long as the patient has measurable disease outside the radiation field. Patients with brain metastases are eligible and can receive concomitant radiation to the brain. Patients will be stratified prior to randomization by cell type, performance status, presence or absence of bone metastasis. Randomization is to Arm I (FOMi) and Arm 2 (CAP) and an alternating regimen (Arm 3) utilizing FOMi and CAP as described in the protocol. If the patients on Arm 3 (alternating FOMi/CAP) relapse on FOMi, CAP will be continued and FOMi discontinued. If there is a relapse on CAP, FOMi will be continued as a single arm. Patients will be treated for as long as the disease remains stable or regresses. Other reasons for discontinuation of the protocol are patient refusal or intolerable side effects.

PROGRESS

(82 10 - 83 09) No new entries at MAMC in FY 83. Seven subjects had previously been entered. All patients expired with the longest response being 5 months.

STATUS: (C)

TITLE: SWOG 8015: Evaluation of Two Combination Chemotherapy Programs, Adriamycin and Cis-Platinum (AP) versus Adriamycin, Cis-Platinum plus VP 16-213 (VAP), in the Treatment of Extensive Squamous Cell Carcinoma of the Lung, Phase III

PRINCIPAL INVESTIGATOR: COL Friedrich H. Stutz, MC

PROFESSIONAL ASSISTANTS: LTC Archie W. Brown, MC
LTC Irwin B. Dabe, MC

WORK UNIT: 81/22

TECHNICAL OBJECTIVES

To determine the activity, in terms of response rate, remission duration, and survival in patients with extensive squamous cell (epidermoid) carcinoma of the lung, for two combination chemotherapy programs; Adriamycin and Cis-platinum (AP) versus VP 16-213, Adriamycin and Cisplatinum (VAP); to evaluate the relative toxicities of these respective regimens; to assess the feasibility and reliance of applying "measurable versus evaluable" criteria of tumor regression in determining therapeutical response; to correlate tumor grade with response and survival.

METHOD

Patients with extensive squamous cell (epidermoid) lung cancer which has spread beyond the hemithorax and ipsilateral scalene, supraclavicular and mediastinal lymph nodes, equivalent with TNM Stage III class M₁ or with any T or N other than mediastinal, supraclavicular scalene node involvement, or patients with evidence of disease beyond the confines of a single radiation therapy port are eligible. Patients who were initially treated with radiation but failed and have a measurable lesion are eligible as well. Patients with prior chemo or immunotherapy are not eligible. Patients must have pathologic proof of squamous cell carcinoma of the lung and a measurable lesion. Patients must meet other criteria as well as outlined in the protocol. Patients will be stratified to good risk and poor risk patients. They will be randomized to treatment with adriamycin/platinum or VP 16/adriamycin/platinum and followed on treatment. Reasons for removal from the protocol are patient refusal and intolerable side effects.

PROGRESS

(82 10 - 83 09) One patient was entered in FY 83. He was treated for two months and expired from progression of disease two weeks post-treatment. Severe neutropenia and moderate thrombocytopenia were noted as adverse side effects. One patient was entered during FY 82, but was removed because the pathology review did not bear out the diagnosis of squamous cell carcinoma.

STATUS: (C)

TITLE: SWOG 8017: 5-FU, Adriamycin, Streptozotocin, and
Cyclophosphamide (FAC-S) in the Treatment of Metastatic
Carcinoid Tumors, Phase II

PRINCIPAL INVESTIGATOR: MAJ Alfred H. Chan, MC

PROFESSIONAL ASSISTANTS: COL Friedrich H. Stutz, MC
LTC James E. Congdon, MC
LTC Irwin B. Dabe, MC
MAJ Lauren K. Colman, MC
MAJ Howard Davidson,
MAJ Thomas M. Baker, C

WORK UNIT NO: 82/11

TECHNICAL OBJECTIVE

To determine whether combination chemotherapy employing 5-Fluorouracil, is effective in the management of metastatic carcinoid; to study the duration of survival of patients with metastatic carcinoid tumor treated with combination chemotherapy regimens; to provide further information concerning the response and/or survival of patients with metastatic carcinoid originating in different sites and having different metastatic patterns.

METHOD

All patients except those with cardiac disease will receive the combination of 5-FU, cyclophosphamide, adriamycin, and streptozotocin. Patients will be divided into good and poor risk groups with medication adjusted accordingly. Courses will be repeated at 28 day intervals as tolerated. Patients with carcinoid or other varieties of cardiac disease will not receive adriamycin. An adequate trial is considered two courses.

PROGRESS

(82 10 - 83 09) No new entries at MAMC In FY 83. One patient entered on study during FY 82 and expired after failing to respond after two courses of treatment.

STATUS: (O)

TITLE: SWOG 8020: Adriamycin + VP-16 vs Adriamycin Alone in Advanced Adenocarcinoma of the Breast, Phase II

PRINCIPAL INVESTIGATOR: COL Friedrich H. Stutz, MC

PROFESSIONAL ASSISTANTS: LTC Archie W. Brown, MC
LTC Irwin B. Dabe, MC

WORK UNIT: 81/23

TECHNICAL OBJECTIVES

To determine the efficacy of the Adriamycin and VP-16 combination in the treatment of previously treated patients with disseminated breast cancer, as determined by response rate, compared with Adriamycin alone; and to determine the length of the remission on VP-16 maintenance after an Adriamycin/VP-16 regimen.

METHOD

Patients with histologically proven breast cancer, stage 4, with measurable lesions who have previously become resistant to CMFVP will be eligible. They will be stratified by ER receptor status, ER positive, ER negative, or ER unknown. Patients with current congestive heart failure or prior adriamycin treatment are not eligible. Prior radiation, hormonal, or chemotherapy may be permitted; however, four weeks must have elapsed since prior hormonal therapy and two weeks since radiation or chemotherapy was administered. Patients must have recovered from previous treatment toxicities with evidence of hematologic recovery. These will be stratified into good and poor risk patients and randomized between adriamycin plus VP 16 (Arm 1) and adriamycin alone (Arm 2). Treatment will be given for as long as the disease remains stable or regresses and for as long as the patient tolerates the chemotherapy.

PROGRESS

(82 10 - 83 09) No new entries at MAMC in FY 83. Two patients were previously entered. One had a partial response for two months with death one month after relapse and the second refused treatment after one dose and expired three months later.

STATUS: (C)

TITLE: SWOG 8025: Combination Chemotherapy for Chronic Lymphocytic Leukemia, Phase II

PRINCIPAL INVESTIGATOR: LTC Irwin B. Dabe, MC

PROFESSIONAL ASSISTANTS: COL Friedrich H. Stutz, MC
MAJ Lauren K. Colman, MC

WORK UNIT: 31/81

TECHNICAL OBJECTIVES

To determine the response rate and duration of remission in patients with CLL treated with combination chemotherapy consisting of prednisone, vincristine, cytosine arabinoside, Cytoxan, and adriamycin; to correlate parameters obtained in the clinical, pathological, and immunological staging with response to treatment; to determine the effect of stopping chemotherapy after patients have achieved a complete remission plus 2 consolidation courses, in order to define a cured or stabilized fraction of patients.

METHOD

Patients with chronic lymphocytic leukemia fulfilling the criteria as outlined by the Rai classification of CLL (all stages) are eligible for this protocol. Patients who have been treated previously with a single alkylating agent are eligible but will be analyzed separately. Patients may not have received prior adriamycin or Ara-C; however, patients previously treated with radiation therapy alone are eligible, and these patients will also be analyzed separately. The protocol consists of Arm I which is applicable to Rai Classification, stages 1 and 2, which is registration only (no treatment) with careful documentation of the progression of the disease; and Arm II, Rai Classification 3-4, consisting of chemotherapy with a combination of prednisone, Oncovin, Ara-C, cyclophosphamide, and hydroxyduranubicin (adriamycin). Treatment will continue for as long as the patient responds on Arm II. Patients on Arm I at the time of progression to stage 3 or 4 will be eligible for treatment on the same combination chemotherapy regimen. Patients will be followed indefinitely or until death.

PROGRESS

(81 05 - 83 09) No patients registered on protocol at MAMC. Nationally, accrual has been slow with a significant morbidity and mortality rate associated with the therapy.

STATUS: (0)

TITLE: SWOG 8030: Evaluation of DHAD in Advanced Squamous Cell Carcinoma of the Head and Neck, Phase II

PRINCIPAL INVESTIGATOR: COL Friedrich H. Stutz, MC

PROFESSIONAL ASSISTANTS: LTC Archie W. Brown, MC
LTC Irwin B. Dabe, MC

WORK UNIT: 81/46

TECHNICAL OBJECTIVES

To determine the response rate and remission duration in patients with advanced squamous cell carcinoma of the head and neck treated with DHAD used in a single dose every-three-week schedule; to define further the qualitative and quantitative toxicities of DHAD.

METHOD

Patients with histologically confirmed diagnosis of squamous cell carcinoma of the neck or adenoid cystic carcinoma of the head and neck with measurable disease are eligible if they have become resistant to standard chemotherapy. Only patients with advanced disease not amenable to surgery or radiation are eligible. All patients must have measurable disease and have recovered from toxicities of previous therapies. Patients will be stratified according to prior chemotherapy or no prior chemotherapy and then will be treated with DHAD without randomization (12 mg/M² IV infusion in 100 cc D5W over 30 minutes, repeated every three weeks). Treatment will continue for as long as the tumor remains stable or shrinks. Treatment will be discontinued if the tumor progresses, if intolerable side effects occur, or if the patient refuses further treatment.

PROGRESS

(81 02 - 83 09) No patients registered on this protocol.

STATUS: (0)

TITLE: SWOG 8031: Evaluation of DHAD in Refractory Multiple Myeloma, Phase II

PRINCIPAL INVESTIGATOR: COL Friedrich H. Stutz, MC

PROFESSIONAL ASSISTANTS: LTC Irwin B. Dabe, MC
MAJ Lauren K. Colman, MC

WORK UNIT: 81/83

TECHNICAL OBJECTIVES

To determine the response rate and response duration of patients with refractory multiple myeloma treated with dihydroxyanthracenedione (DHAD) used in a single dose every-three-week schedule; to define the qualitative and quantitative toxicities of DHAD administered in a Phase II study.

METHOD

Patients with multiple myeloma refractory to standard treatment or protocols of higher priority are eligible for this protocol. Patients must have clearly measurable myeloma protein levels to be eligible. These patients must also meet other criteria as outlined in the protocol. Stratification will be done according to response to prior treatment and prior treatment with adriamycin. Initial dose is 9 mg/M^2 given as an IV infusion in 100 cc of D_5W over 30 minutes and repeated every 3 weeks. Treatment continues for as long as tumor remains stable or is improving. Patient refusal of further treatment and intolerable toxicity will cause discontinuation of the patient on the protocol.

PROGRESS

(81 05 - 83 09) No patients registered on this protocol at MAMC.

STATUS: (T)

TITLE: SWOG 8037: Combined Therapies for Squamous Cell Cancer
of the Esophagus, Phase II

PRINCIPAL INVESTIGATOR: LTC James E. Congdon, MC

PROFESSIONAL ASSISTANTS: COL Friedrich H. Stutz, MC
LTC Irwin B. Dabe, MC
MAJ Alfred H. Chan, MC
MAJ Howard Davidson, MC
MAJ Timothy J. O'Rourke, MC
MAJ Thomas M. Baker, MC

WORK UNIT NO: 82/69

TECHNICAL OBJECTIVE

To determine the feasibility and toxicity of combined radiotherapy and chemotherapy with 5-fluorouracil (5-FU) and cis-platinum followed by surgery in patients with epidermoid carcinoma of the middle or distal esophagus; to determine the time to local or distant progression in patients treated by these three combined modalities; to determine the survival of patients treated by these three combined modalities; and to determine the response rate by clinical and pathological staging at the time of surgery.

METHOD

After metastatic survey testing to determine that the patient has localized disease, the patient will be started on a simultaneous combination of chemotherapy and radiotherapy. The chemotherapy will consist of cis-platinum given through the side tubing of a freely running IV line over 2 hours followed by 5-FU given through a freely running IV by continuous infusion for 4 days. The patient will then be given a 4-week rest period and a similar chemotherapy regimen will be repeated. The exact dose of each chemotherapy agent will be determined by the patient's height and body weight. Simultaneous with the start of the chemotherapy, the patient will receive external beam radiation therapy to the esophagus in the region of the tumor. Approximately 2 weeks after the completion of the radiation and two courses of chemotherapy, the patient will be taken to surgery for definitive resection of the tumor. This will be followed by an anastomosis of the proximal remaining esophagus to the stomach.

PROGRESS

(82 09 - 83 09) No patients registered on this protocol at MAMC.

STATUS: (0)

TITLE: SWOG 8038: Vinblastine in Advanced Ovarian Cancer,
Phase II

PRINCIPAL INVESTIGATOR: COL Friedrich H. Stutz, MC

PROFESSIONAL ASSISTANTS: COL Roger B. Lee, MC
LTC Irwin B. Dabe, MC

WORK UNIT: 81/72

TECHNICAL OBJECTIVES

To determine the response rate and remission duration with intravenous therapy using Velban as a continuous infusion in patients with advanced ovarian cancer; to define further the qualitative and quantitative toxicity of the continuous infusion of Velban.

METHOD

This is a Phase II study using vinblastine infusion. Patients with extensive epithelial ovarian tumors with measurable disease are eligible. Patients must meet other criteria as outlined in the protocol. The Velban will be administered as a continuous 5-day infusion once every three weeks. This will be continued as long as the tumor remains stable or shrinks. Treatment will be discontinued for patient refusal of further treatment or intolerable toxicity. Patients will be stratified according to bilirubin, SGOT, and alkaline phosphatase status.

PROGRESS

(82 10 - 83 09) No new entries in FY 83. One patient registered (FY 82) with stable disease for two months and later expired. Patient had mild nausea, vomiting, and severe neutropenia.

STATUS: (0)

TITLE: SWOG 8040: Evaluation of Combination Chemotherapy (FAM-S)
vs a Phase II Drug in Pancreatic Adenocarcinoma, Phase II

PRINCIPAL INVESTIGATOR: COL Friedrich H. Stutz, MC

PROFESSIONAL ASSISTANTS: LTC Irwin B. Dabe, MC
MAJ Lauren K. Colman, MC

WORK UNIT: 81/84

TECHNICAL OBJECTIVES

To determine the response rate and survival in patients with advanced pancreatic adenocarcinoma treated with 5-FU, Adriamycin, Mitomycin-C, and Streptozotocin (FAM-S); to determine further the toxicity of the FAM-S regimen; to determine the activity of a Phase II drug in previously untreated patients with advanced adenocarcinoma of the pancreas by determination of response rate and duration of response and survival; to determine further the toxicity of each Phase II agent.

METHOD

Patients with histologically confirmed adenocarcinoma of the exocrine pancreas with distant metastasis (liver, peritoneum) and those with localized disease not amenable to curative surgery or radiotherapy are eligible. All patients must have objectively measurable disease and have not received any prior chemotherapy or radiation therapy. Patients must also meet other criteria as outlined in the protocol. Patients will be stratified according to biopsy only performed vs. palliative bypass procedures and performance status. Subsequently, the patient will be randomized to either a combination chemotherapy regimen consisting of 5-FU, adriamycin, mitomycin, and streptozotocin or a Phase II agent which will be changed periodically when sufficient patients are accumulated on one arm. If the patient fails or has a response and subsequently has increasing disease, a cross-over is recommended. Patients on FAM-S will cross over to the Phase II agent and vice versa. Chemotherapy will continue for as long as the disease remains stable or the tumor is shrinking. Progressive disease, patient refusal of further treatment, or intolerable side effects are criteria for discontinuation of the protocol.

PROGRESS

(82 10 - 83 09) One patient has been entered (FY 83). This patient received only one treatment course which had no effect on the progression of her disease. She refused any further chemotherapy and later expired.

STATUS: (0)

TITLE: SWOG 8043: Evaluation of DHAD in Pancreatic Adenocarcinoma,
Phase II

PRINCIPAL INVESTIGATOR: COL Friedrich H. Stutz, MC

PROFESSIONAL ASSISTANTS: LTC Irwin B. Dabe, MC
MAJ Lauren K. Colman, MC

WORK UNIT: 81/86

TECHNICAL OBJECTIVES

To determine the antitumor activity of DHAD, as determined by response rate and duration of response, used in a single dose schedule every three weeks in patients with advanced adenocarcinoma of the pancreas; to determine additional information concerning the nature and degree of toxicity of this drug.

METHOD

This protocol is an adjunct to SWOG 8040. In this protocol, MGBG is the Phase II Agent set forth in the master protocol; therefore, the methods of the protocol will be the same as for SWOG 80/40.

PROGRESS

(82 10 - 83 09) No new entries in FY 83. One patient was entered in FY 82 with stable disease for five months while on treatment. Severe neutropenia was noted as a side effect.

STATUS: (0)

TITLE: SWOG 8049: Treatment of Resected, Poor Prognosis
Malignant Melanoma: Stage I: Surgical Excision vs
Surgical Excision + Vitamin A

PRINCIPAL INVESTIGATOR: LTC James E. Congdon, MC

PROFESSIONAL ASSISTANTS: COL Friedrich H. Stutz, MC
LTC Irwin B. Dabe, MC
MAJ Thomas M. Baker, MC
MAJ Alfred H. Chan, MC
MAJ Lauren K. Colman, MC
MAJ Howard Davidson, MC

WORK UNIT NO: 82/13

TECHNICAL OBJECTIVE

To determine the efficacy of surgical excision or surgical excision plus vitamin A in preventing the recurrence of high risk, Stage I malignant melanoma by determination of remission or disease-free interval; to determine the immunocompetence of patients with malignant melanoma and to determine the influence of vitamin A upon that immunocompetence.

METHOD

Patients will be equally randomized between the two treatment arms: vitamin A versus no further treatment. Patients will be stratified by depth of invasion, sex, and type of surgery. Those patients randomized to receive vitamin A will receive a dose of 100,000 I.U. daily. Treatment will continue for 18 months. Patients who receive no treatment will be followed until relapse and removal from the study.

PROGRESS

(82 10 - 83 09) No new entries in FY 83. One patient entered study the study in FY 82. At present, patient is in complete remission and has been taken off the study.

STATUS: (0)

TITLE: SWOG 8051: Evaluation of L-Alanosine in Acute Leukemia,
Phase II

PRINCIPAL INVESTIGATOR: LTC James E. Congdon, MC

PROFESSIONAL ASSISTANTS: COL Friedrich H. Stutz, MC
LTC Irwin B. Dabe, MC
MAJ Thomas M. Baker, MC
MAJ Alfred H. Chan, MC
MAJ Lauren K. Colman, MC
MAJ Howard Davidson, MC

WORK UNIT NO: 82/53

TECHNICAL OBJECTIVE

To determine the antitumor activity of L-Alanosine as determined by response rate and duration of response in patients with acute leukemia who are ineligible for higher priority studies and to determine the nature and degree of toxicity of this drug.

METHOD

This is a Phase II clinical trial of a new chemotherapy agent and is to be used in patients with acute leukemia who have not responded to the standard forms of treatment. L-Alanosine has demonstrated moderate activity against both acute lymphocytic leukemia cells and acute myelogenous leukemia blast cells in cell culture work as well as a variety of laboratory animals. It has been tested in Phase I clinical trials in human beings and its toxicities, including temporary myelosuppression, temporary nausea and vomiting, and temporary gastrointestinal toxicity consisting mainly of stomatitis and diarrhea, as well as a rare case of idiosyncratic anaphylactoid reactions, have been recognized. The patients will have met a number of performance and laboratory eligibility criteria. L-Alanosine will be administered through a freely running IV line as a continuous infusion for 5 consecutive days. Bone marrow examinations will be performed at weekly intervals and, if the bone marrow blast count remains greater than 50% of the initial count by 3 weeks, a second course will be given. The amount of L-Alanosine will be determined by the patient's body surface area.

PROGRESS

(82 10 - 83 09) No new entries in FY 83. One patient entered study FY 82 with documented disease progression after two cycles. Patient died of acute leukemia relapse two months later.

STATUS: (C)

TITLE: SWOG 8077: Combined Chemotherapy and Hormonal Therapy
for Recurrent or Disseminated ER+ Breast Cancer, PACT
vs ACT, Phase II.

PRINCIPAL INVESTIGATOR: LTC James E. Congdon, MC

PROFESSIONAL ASSISTANTS: COL Friedrich H. Stutz, MC
LTC Irwin B. Dabe, MC
MAJ Thomas M. Baker, MC
MAJ Alfred H. Chan, MC
MAJ Lauren K. Colman, MC
MAJ Howard Davidson, MC

WORK UNIT NO: 82/14

TECHNICAL OBJECTIVE

To determine the response rate of a combined chemo-hormonal program in ER+ patients with metastatic breast cancer; to determine if the addition of prednisone will greatly increase the response rate.

METHOD

If regular menstrual periods are present, oophorectomy will be done followed within two weeks by chemotherapy. Twelve treatments, one every four weeks, with adriamycin and cyclophosphamide will be given. Half of the subjects will also receive prednisone immediately before each chemotherapy injection. After the first 12 treatments, medication will be adjusted because of the detrimental effects of adriamycin when given for longer than 12 months, and this regimen will be given once a month for 13 months. Those patients whose ovaries have been removed will receive the same regimens with the addition of tamoxifen throughout the study.

PROGRESS

(81 11 - 83 09) No patients registered on study at MAMC.

STATUS: (T)

TITLE: SWOG 8092: Use of Human Tumor Cloning System to Select
Chemotherapy for Patients with Ovarian Cancer Refractory
to Primary Therapy

PRINCIPAL INVESTIGATOR: COL Friedrich H. Stutz, MC

PROFESSIONAL ASSISTANTS: COL Roger B. Lee, MC
LTC Irwin B. Dabe, MC

WORK UNIT NO: 81/87

TECHNICAL OBJECTIVES

To utilize the human tumor cloning assay to select single agent chemotherapy for patients with epithelial-type ovarian cancer, refractory to standard therapy; to determine if the human tumor cloning system can be utilized to select the therapy of individual patients in a cooperative group setting.

METHOD

Patients with a pathologic diagnosis of epithelial-type ovarian cancer in pleural or peritoneal fluid or with solid tumor are eligible to have specimens sent to tumor cloning laboratories. These specimens will be cultured and incubated with antineoplastic agents to determine their sensitivity to these chemotherapeutic agents. In ovarian cancer resistant to standard treatment, treatment recommendations will be made. All these patients should have measurable disease. Other tumor specimens will be tested; however, no treatment recommendations will be made in these instances, especially when the patient was previously untreated with chemotherapy. This is an ancillary study and involves treatment only in patients with epithelial type ovarian cancer. This treatment continues for as long as the patient responds, tolerates the treatment, and continues to accept the investigational treatment.

PROGRESS

(82 10 - 83 09) No new entries at MAMC in FY 83. Two patients entered; one in FY 81, the other in FY 82. There was no growth from either patient's tumor. Both patients have expired since that time.

STATUS: (0)

TITLE: SWOG 8106: Evaluation of AZO (Carbamic Acid) in Central Nervous System Tumors, Phase II

PRINCIPAL INVESTIGATOR: LTC James E. Congdon, MC

PROFESSIONAL ASSISTANTS: COL Friedrich H. Stutz, MC
LTC Irwin B. Dabe, MC
MAJ Thomas M. Baker, MC
MAJ Alfred H. Chan, MC
MAJ Lauren K. Colman, MC
MAJ Howard Davidson, MC

WORK UNIT NO: 82739

TECHNICAL OBJECTIVE

To determine the efficacy of AZO given by intermittent bolus schedule in malignant gliomas by evaluation of response rate, duration, and survival; to determine the qualitative and quantitative toxicities of AZO given by this schedule in a Phase II setting.

METHOD

This is a Phase II clinical trial of Aziridinybenzoquinone (AZO) in patients with malignant, primary brain tumors who have not completely responded to surgery and/or radiation therapy. AZO has demonstrated considerable effectiveness in controlling primary brain neoplasms in a variety of laboratory animals. The drug has been tested in Phase I trials in humans, and its toxicities, including temporary marrow suppression, nausea, emesis, alopecia, and stomatitis have been recognized. All patients in this study will have met a number of performance and laboratory eligibility criteria as listed in the protocol. AZO will be administered through the side tubing of a freely flowing IV line in an amount determined by the patient's body surface area. The treatments will be repeated at three week intervals, unless unusual toxicities are encountered, for a minimum of two courses or until objective evidence of disease progression is ascertained.

PROGRESS

(82 03 - 83 09) No patients registered at MAMC.

STATUS: (T)

TITLE: SWOG 8107: Management of Disseminated Melanoma,
Master Protocol, Phase III/IV

PRINCIPAL INVESTIGATOR: LTC James E. Doolittle, MC

PROFESSIONAL ASSISTANTS: COL F. H. Stutz, MC
LTC Irwin B. Dade, MC
MAJ Thomas M. Baker, MC
MAJ Alfred H. Chan, MC
MAJ Howard Davidson, MC
MAJ Timothy J. O'Rourke, MC

WORK UNIT NO: 83/05

TECHNICAL OBJECTIVE

To determine the effectiveness of cranial irradiation given selectively in disseminated melanoma patients with lung and/or liver metastasis to prevent or delay the clinical appearance of brain metastasis and to determine the efficacy of high intermittent doses of cis-platinum with the use of IV hydration and mannitol diuresis in patients with advanced malignant melanoma refractory to higher priority protocols.

METHOD

This protocol employs some of the newer kinetic concepts of chemotherapy and radiation therapy. Patients will be randomized to receive 3000 rads of prophylactic whole brain radiation therapy versus close observation for the development of brain metastasis. Second randomization will be to one of three chemotherapy arms:

ARM 1 - DTIC and Actinomycin D.
ARM 2 - Cis-platinum, Velban and Bleomycin
ARM 3 - Cis-platinum

All chemotherapy agents will be given intravenously once every three weeks. Should there be objective evidence of disease progression during the course of the study, the patient will be crossed over to a treatment arm composed of drugs not used in the first treatment arm.

PROGRESS

(82 10 - 83 09) No entries at MAMC.

STATUS: (0)

TITLE: SWOG 8112: Combination Chemotherapy of Unfavorable Histology Non-Hodgkin's Lymphoma with CHOP and CVB, Phase III

PRINCIPAL INVESTIGATOR: LTC James E. Congdon, MC

PROFESSIONAL ASSISTANTS: COL Friedrich H. Stutz, MC
LTC Irwin B. Dabe, MC
MAJ Thomas M. Baker, MC
MAJ Alfred H. Chan, MC
MAJ Lauren K. Colman, MC
MAJ Howard Davidson, MC

WORK UNIT NO: 82/59

TECHNICAL OBJECTIVE

To gain experience with a treatment program utilizing a combination of two non-cross-resistant drug regimens in the treatment of "poor prognosis" lymphomas; to determine an approximate complete remission rate to the Cyclophosphamide, Adriamycin, Vincristine, and Prednisone (CHOP)/Cis-platinum, Vinblastine, and Bleomycin (CVB) treatment program prior to initiating a group wide Phase III study utilizing this program.

METHOD

Patients will initially receive 3 cycles of CHOP chemotherapy, which is the standard treatment for poor prognosis lymphoma. In addition, he will receive a small injection of intrathecal Methotrexate at the start of each new CHOP regimen. All of these drugs have been used extensively in lymphoma patients and their response rates and various toxicities are well known. All patients will have met a number of performance and laboratory eligibility criteria as outlined in the protocol. Most of these chemotherapy agents will be administered through the side tubing of a freely flowing IV line in an amount to be determined by the patient's body surface area. One agent, Prednisone, will be given by mouth daily for 5 days at the start of each CHOP treatment regimen and one final agent, Methotrexate, will be given directly into the spinal column via spinal tap. All patients will receive a minimum of 6 cycles of combination, cross-over type chemotherapy which will be given every 3 weeks unless unusual toxicities are encountered.

PROGRESS

(82 06 - 83 09) No patients registered on the protocol at MAMC. Group-wide treatment with CHOP x 3 cycles, then CVB x 3, then CHOP x 3 was active and tolerable.

STATUS: (C)

TITLE: SWOG 8116: Evaluation of Bisantrene Hydrochloride in Refractory Lymphoma, Phase II

PRINCIPAL INVESTIGATOR: LTC James E. Congdon, MC

PROFESSIONAL ASSISTANTS: COL Friedrich H. Stetzel, MC
LTC Irwin B. Dabe, MC
MAJ Thomas M. Baker, MC
MAJ Alfred H. Chan, MC
MAJ Lauren K. Colman, MC
MAJ Howard Davidson, MC

WORK UNIT NO: 82/48

TECHNICAL OBJECTIVE

To determine the response rate and response duration of malignant lymphoma treated with bisantrene hydrochloride used in a single dose, every-three-week schedule; to define the qualitative and quantitative toxicities of bisantrene administered in a Phase II study.

METHOD

This is a Phase II clinical trial of a new chemotherapy agent, bisantrene hydrochloride used in patients with malignant lymphomas of the Hodgkin's and non-Hodgkin's varieties that have not responded to standard treatment modalities. The drug has demonstrated some effectiveness in controlling lymphomas in a variety of laboratory animals. It has been tested in Phase I trials in humans, and its toxicities, including temporary bone marrow suppression, nausea, emesis, alopecia, transient hypotension, and pain at the injection site have been recognized. All patients in this study will have met a number of performance and laboratory eligibility criteria as listed in the protocol. Bisantrene hydrochloride will be administered through the side tubing of a freely flowing IV line in an amount determined by the patient's body surface area. The treatments will be repeated at three week intervals, unless unusual toxicities are encountered, for a minimum of two courses or until objective evidence of disease progression is ascertained.

PROGRESS

(82 05 - 83 09) No patients registered on the protocol at MAMC.

STATUS: (0)

TITLE: SWOG 8117: Evaluation of Bisantrone Hydrochloride in Refractory Ovarian Cancer, Phase II

PRINCIPAL INVESTIGATOR: LTC James E. Conjdon, MC

PROFESSIONAL ASSISTANTS: COL Friedrich H. Stutz, MC
LTC Irwin B. Dabe, MC
MAJ Thomas M. Baker, MC
MAJ Alfred H. Chan, MC
MAJ Lauren K. Colman, MC
MAJ Howard Davidson, MC

WORK UNIT NO: 82/49

TECHNICAL OBJECTIVE

To determine the response rate and response duration of refractory ovarian cancer treated with bisantrene hydrochloride used in a single dose, every-three-week schedule; to define the qualitative and quantitative toxicities of bisantrene administered in a Phase II study.

METHOD

This is a Phase II clinical trial evaluating a new chemotherapy agent, bisantrene hydrochloride, in the treatment of refractory ovarian carcinoma. Bisantrone is one of a series of new synthetic anticancer drugs in the hydrazone class which have demonstrated some in vitro activity in cell culture work against ovarian carcinoma as well as some in vivo efficacy in human volunteers. The clinical toxicities have been delineated in Phase I trials and include transient myelo suppression, nausea, emesis, transient alopecia, transient mild hypotension, and local superficial ulceration of the skin with extravasation of the drug at the IV site. The exact dosage of bisantrene that the patient will receive depends on several factors including the patient's height, body weight, and performance standards on several laboratory tests which evaluate bone marrow, hepatic, and renal function. The drug will be administered, dissolved in 500 cc of dextrose in water solution, through a freely flowing IV line over two hours. Unless unusual toxicities are encountered, the treatments will be repeated at three week intervals, for a minimum of two cycles or until objective evidence of disease progression is ascertained.

PROGRESS

(82 10 - 83 09) One patient was entered but not started on the drug because of rapidly worsening complications of disease.

STATUS: (0)

Protocol for Evaluation of Bisantrene Hydrochloride in
the Treatment of Malignant Melanoma, Phase II

Principal Investigator: LTJ James E. Congdon, MC
Sponsor: MAJ F. J. HANES: COL Friedrich H. Stutz, MC
LTC Irwin B. Dabe, MC
MAJ Thomas M. Baker, MC
MAJ Alfred H. Chan, MC
MAJ Lauren K. Colman, MC
MAJ Howard Davidson, MC

WORK UNIT NO: 82750

TECHNICAL OBJECTIVE

To determine the response rate and response duration of malignant melanoma treated with bisantrene hydrochloride used in a single dose, every-three-week schedule; to define the qualitative and quantitative toxicities of bisantrene administered in a Phase II study.

METHOD

This is a Phase II clinical trial evaluating a new chemotherapy agent, bisantrene hydrochloride, in the treatment of malignant melanoma which has become refractory to standard treatment modalities. This drug has demonstrated some effectiveness in controlling malignant melanoma neoplasms in cell cultures and in a variety of laboratory animals. The drug has been tested in Phase I clinical trials in human beings and its toxicities, including temporary bone marrow suppression, nausea, dizziness, alopecia, mild hypotension, and pain at the injection site, have been recognized. All patients entered into the study will have met a number of performance and laboratory eligibility criteria as outlined in the protocol. Bisantrene hydrochloride will be administered through the side tubing of a freely flowing IV line in an amount determined by the patient's body surface area. Unless unusual toxicities are encountered, the treatments will be repeated at three week intervals, for a minimum of two cycles or until objective evidence of disease progression is ascertained.

PROGRESS

(82 05 - 83 09) No patients registered on the protocol at MAMC.

STATUS: (0)

TITLE: SWOG 8119: Evaluation of Bisantrone Hydrochloride in Hepatoma, Phase II

PRINCIPAL INVESTIGATOR: LTC James E. Condon, MC

PROFESSIONAL ASSISTANTS: COL Friedrich H. Stutz, MC
LTC Irwin B. Dabe, MC
MAJ Thomas M. Baker, MC
MAJ Alfred H. Chan, MC
MAJ Lauren K. Colman, MC
MAJ Howard Davidson, MC

WORK UNIT NO: 82751

TECHNICAL OBJECTIVE

To determine the response rate and response duration of hepatomas treated with bisantrene hydrochloride used in a single dose, every-three-week schedule; to define the qualitative and quantitative toxicities of bisantrene administered in a Phase II study.

METHOD

This is a Phase II clinical trial evaluating a new chemotherapy agent, bisantrene hydrochloride, in the treatment of malignant primary carcinoma of the liver. The patients will have all failed on prior standard treatments including surgery, radiation therapy, and chemotherapy. This drug has demonstrated some effectiveness in controlling primary liver cancer in a variety of laboratory animals. The drug has been tested in Phase I clinical trials in human beings and its toxicities, including temporary nausea, emesis, alopecia, transient mild hypotension, transient mild myelosuppression, and localized pain at the injection site, have been recognized. All patients entered into the study will have met a number of performance and laboratory eligibility criteria as outlined in the protocol. Bisantrone hydrochloride will be administered through the side tubing of a freely flowing IV line in an amount determined by the patient's body surface area. Unless unusual toxicities are encountered, the treatments will be repeated at three week intervals, for a minimum of two cycles or until objective evidence of disease progression is ascertained.

PROGRESS

(82 05 - 83 09) No patients registered on the protocol at MAMC.

STATUS: (0)

TITLE: SWOG 8120: Evaluation of Bisantrane Hydrochloride in Gastric Carcinoma, Phase II

PRINCIPAL INVESTIGATOR: LTC James E. Congdon, MC

PROFESSIONAL ASSISTANTS: COL Friedrich H. Stutz, MC
LTC Irwin B. Dade, MC
MAJ Thomas M. Baker, MC
MAJ Alfred H. Chan, MC
MAJ Lauren K. Colman, MC
MAJ Howard Davidson, MC

WORK UNIT NO: 82/52

TECHNICAL OBJECTIVE

To determine the response rate, response duration, and survival of gastric carcinoma treated with bisantrene hydrochloride used in a single dose, every-three-week schedule; to define the qualitative and quantitative toxicities of bisantrene administered

METHOD

This is a Phase II clinical trial evaluating a new chemotherapy agent, bisantrene hydrochloride, in the treatment of malignant primary gastric carcinoma. The patients will have all failed on prior standard treatments including surgery and standard chemotherapy agents. This drug has demonstrated some effectiveness in controlling the growth of primary gastric carcinomas in cell culture work and moderate effectiveness in several laboratory animals. The drug has been tested in Phase I clinical trials in human beings and its toxicities, including temporary nausea, emesis, alopecia, transient mild hypotension, transient mild myelosuppression, and localized pain at the injection site, have been recognized. All patients entered into the study will have met a number of performance and laboratory eligibility criteria as outlined in the protocol. Bisantrane hydrochloride will be administered through the side tubing of a freely flowing IV line in an amount determined by the patient's body surface area as well as the patient's overall performance status. Unless unusual toxicities are encountered, the treatments will be repeated at three week intervals, for a minimum of two cycles or until objective evidence of disease progression is ascertained.

PROGRESS

(82 10 - 83 09) One patient was entered in FY 83. The patient had nausea and vomiting after each of three courses. The nausea and vomiting were severe enough after the second course to admit the patient for hydration and parenteral anti-emetic regimen. It is too early to draw any conclusions regarding this regimen.

STATUS: (0)

TITLE: SWOG 8203/04: Randomized Comparison of Adriamycin, Mitoxantrone, and Bisantrone in Patients with Metastatic Breast Cancer Not Previously Exposed to Intercalating Chemotherapy, Phase III

PRINCIPAL INVESTIGATOR: LTC James E. Congdon, MC

PROFESSIONAL ASSISTANTS: COL Friedrich H. Stutz, MC
LTC Irwin B. Dabe, MC
MAJ Thomas M. Baker, MC
MAJ Alfred H. Chan, MC
MAJ Howard Davidson, MC
MAJ Timothy J. O'Rourke, MC

WORK UNIT NO: 83/13

TECHNICAL OBJECTIVES

To determine the comparative response rate, duration of response, and survival of equimyelosuppressive doses of Adriamycin, Mitoxantrone, and Bisantrone as single agents in breast cancer patients, not previously exposed to an intercalating agent, using a single dose, every-three-week schedule; to determine the salvage response rate of these agents in breast cancer patients failing one of these three agents; to assess the cardiotoxicity of these agents as determined by history, physical examination, and measurement of the left ventricular ejection fraction; to compare the relative noncardiac toxicities of these agents; to prospectively evaluate the *in vitro* effects of these drugs in the cloning assay and correlate them with *in vivo* activity in those patients with biopsiable disease; and to measure the peak plasma levels of each drug and correlate the levels with response and toxicity.

METHOD

Patients will be randomized to receive equivalent doses of either Adriamycin, Metoxantrone or Bisantrone intravenously once every 3 weeks as an out patient. The medicine will be continued until evidence of disease progression is noted or until maximum allowed dose of Adriamycin is achieved. Frequent studies including blood tests, x-rays and nuclear medicine scans will be performed on these patients in order to determine response to the treatment and spot early toxicities. At the first sign of documented disease progression, the patient will be re-randomized to receive one of the two other agents.

PROGRESS

(82 11 - 83 09) Two patients have been entered on the protocol. The patient who received Bisantrone had immediate local erythema with first course given via peripheral vein. She has also had leukopenia.

STATUS: (0)

TITLE: SWOG 8206: Evaluation of Aclacinomycin A in Colorectal Carcinoma, Phase II

PRINCIPAL INVESTIGATOR: LTC James E. Congdon, MC

PROFESSIONAL ASSISTANTS: COL Friedrich H. Stutz, MC
LTC Irwin B. Dabe, MC
MAJ Thomas M. Baker, MC
MAJ Alfred H. Chan, MC
MAJ Howard Davidson, MC
MAJ Timothy J. O'Rourke, MC

WORK UNIT NO: 82/70

TECHNICAL OBJECTIVE

To determine the antitumor activity of aclacinomycin A in previously untreated patients with colorectal carcinoma by determination of the response rate and remission duration of two dosage schedules: a single dose, every-three-week schedule and a weekly dosage schedule for four weeks out of six; and to further define the qualitative and quantitative toxicities of this drug for each of the two dosage schedules in a phase II study.

METHOD

This is a phase II study designed to determine the efficacy of a new agent, aclacinomycin A, in the treatment of disseminated or recurrent colon carcinoma. Aclacinomycin A is in the anthracycline derivative class of chemotherapeutic agents. It has seen limited in vitro and in vivo trials but has demonstrated activity in a number of hematologic and solid tumors. Aclacinomycin A will be given by IV infusion on one of two treatment schedules: either weekly (65 mg/M²) for four weeks followed by a two-week rest period or once every three weeks (100 mg/M²) for two cycles. At the end of the initial treatment phase, a repeat metastatic evaluation will be performed and, if there is evidence of tumor response, the treatments will continue. Treatment will be terminated at the first evidence of tumor progression or withdrawal of patient's permission.

PROGRESS

(82 10 - 83 09) No responses were observed in the five patients at MAMC nor any of the 80 patients entered group-wide. Aclacinomycin A, given either 100 mg/M² once every three weeks or as 65 mg/M² weekly x 4 then 2 weeks rest, was without activity in colorectal carcinoma.

STATUS: (C)

TITLE: SWOG 8207: AZQ in Advanced Renal Cell Carcinoma,
Phase II

PRINCIPAL INVESTIGATOR: LTC James E. Congdon, MC

PROFESSIONAL ASSISTANTS: COL Friedrich H. Stutz, MC
LTC Irwin B. Dabe, MC
MAJ Thomas M. Baker, MC
MAJ Alfred H. Chan, MC
MAJ Howard Davidson, MC
MAJ Timothy J. O'Rourke, MC

WORK UNIT NO: 82/71

TECHNICAL OBJECTIVE

To determine the response rate and duration of response in patients with advanced renal cell carcinoma treated with AZQ (aziridinybenzoquinone) used in a single dose, every-three-week schedule; and to define the qualitative and quantitative toxicities of AZQ administered in a phase II study.

METHOD

This is a phase II study designed to determine the efficacy of a new agent, AZQ, in the treatment of advanced renal cell carcinoma. It has shown promising in vitro and in vivo efficacy in a number of adenocarcinomas including renal cell carcinoma. The drug will be given through the side tubing of a freely running IV every 3 weeks (good risk: 40 mg/M², poor risk: 30 mg/M²). The treatments will be continued on a 3-week basis as long as there is objective evidence of disease stabilization or regressions. Treatment will be terminated if unacceptable side effects develop or if there is objective evidence of disease progression.

PROGRESS

(82 09 - 83 09) No patients registered at MAMC. In other institutions severe granulocytopenia and life-threatening thrombocytopenia were observed. This protocol was temporarily closed and then reopened in an amended form because of these complications.

STATUS: (0)

TITLE: SWOG 8211: Evaluation of cis-Diamminedichloroplatinum
in Disseminated Gastric Adenocarcinoma, Phase II

PRINCIPAL INVESTIGATOR: LTC James F. Condon, MC

PROFESSIONAL ASSISTANTS: COL Friedrich H. Stutz, MC
LTC Irwin B. Dabe, MC
MAJ Thomas M. Baker, MC
MAJ Alfred H. Chan, MC
MAJ Howard Davidson, MC
MAJ Timothy J. O'Rourke, MC

WORK UNIT NO. 83/43

TECHNICAL OBJECTIVES

To test the response rate of cis-diamminedichloroplatinum (DDP) in patients with disseminated and measurable adenocarcinoma of the stomach who are previously untreated, and to test the response rate of DDP in patients with disseminated adenocarcinoma of the stomach who have previously been treated with 5-fluorouracil, Adriamycin, and mitomycin-C (5-FAM) chemotherapy.

METHOD

Patients will be admitted to the hospital on a once every three weeks basis for overnight chemotherapy infusion. DDP will be given in a dose based on the patient's body height and weight. Treatment will continue on a once every three weeks basis for a minimum of one year or until evidence of objective disease progression has been determined.

PROGRESS

(83 03 - 83 09) No patients entered at MAMC.

STATUS: (O)

TITLE: SWOG 8215: Comparison of Combination Chemotherapy with VP-16 and Cis-Platinum vs BCNU, Thiotepa, Vincristine, and Cyclophosphamide in Patients with Small Cell Carcinoma of the Lung Who Have Failed or Relapsed Primary Chemotherapy, Phase III

PRINCIPAL INVESTIGATOR: MAJ Thomas M. Baker, MC

PROFESSIONAL ASSISTANTS: COL Friedrich H. Stutz, MC
LTC James E. Congdon, MC
LTC Irwin B. Dabe, MC
MAJ Alfred H. Chan, MC
MAJ Howard Davidson, MC
MAJ Manuel J. Martinez, MC
MAJ Timothy J. O'Rourke, MC

WORK UNIT NO: 83/67

TECHNICAL OBJECTIVES

To confirm the efficacy of combination VP-16-213 (VP-16) and Cis-diamminedichloroptinum (Cis-platinum) in the treatment of patients with small cell carcinoma of the lung who have failed or relapsed on firstline treatment protocols; and through a randomized trial, to compare the remission rate, duration of remission and toxicity between the combination of VP-16 plus Cis-platinum and the combination of bis-chloroethylnitrosourea (BCNU), triethylenethiophosphoramide (Thiotepa), Vincristine (Oncovin), and Cyclophosphamide (Cytosan) in the same group of patients.

METHOD

Patients will be randomized to either one of two treatments.

Arm I (BCNU, Thiotepa, Vincristine, and Cyclophosphamide): Both good and poor risk patients will receive Vincristine, 2 mg, Thiotepa, 20 mg/M², Cyclophosphamide, 500 mg/M², and BCNU, 100 mg/M², IV on days 1, 21, and 42. This therapy will be repeated every three weeks until progression of disease occurs.

Arm II (VP-16 and Cis-Platinum): Good risk patients will receive VP-16, 125 mg/M², IV, days 1, 3, and 4 and Cis-Platinum 75 mg/M², IV, day 2. For Poor risk patients, the dosages will be reduced to 100 mg/M² and 50 mg/M². Chemotherapy with VP-16 and Cis-platinum will be repeated every four weeks until progression occurs.

PROGRESS

(83 07 - 83 09) One patient was entered and expired after several weeks of therapy.

STATUS: (0)

TITLE: SWOG 8217: Evaluation of Spirogermanium (NSC-192965) in Adenocarcinoma of the Prostate, Phase II

PRINCIPAL INVESTIGATOR: LTC James E. Congdon, MC

PROFESSIONAL ASSISTANTS: COL Friedrich H. Stutz, MC
LTC Irwin B. Dabe, MC
MAJ Thomas M. Baker, MC
MAJ Alfred H. Chan, MC
MAJ Howard Davidson, MC
MAJ Timothy J. O'Rourke, MC

WORK UNIT #83/44

TECHNICAL OBJECTIVE

To determine the response rate and remission duration of adenocarcinoma of the prostate when treated with Spirogermanium used as a 60 minute infusion in a three times weekly schedule, and to define the qualitative and quantitative toxicities of Spirogermanium administered in a Phase II study.

METHOD

Patients will receive a dose of spirogermanium based upon their body height and weight, given IV on an outpatient basis, three times a week. This treatment regimen will continue for a period of one year, until unusual side effects develop, or until evidence of objective disease progression is noted.

PROGRESS

(83 02 - 83 09) One patient has been entered. It is too early to make conclusions.

STATUS: (0)

TITLE: SWOG 8213 - Evaluation of Spirogermanium (NSC-192965)
in Renal Cell Carcinoma, Phase II

PRINCIPAL INVESTIGATOR: LTC James E. Congdon, MC

PROFESSIONAL ASSISTANTS: COL Friedrich H. Stutz, MC
LTC Irwin B. Dabe, MC
MAJ Thomas M. Baker, MC
MAJ Alfred H. Chan, MC
MAJ Howard Davidson, MC
MAJ Timothy J. O'Rourke, MC

WORK UNIT NO: 83/54

TECHNICAL OBJECTIVES

To determine the response rate and remission of renal cell carcinoma when treated with spirogermanium used as a 60 minute infusion in a three times weekly schedule, and to define the qualitative and quantitative toxicities of spirogermanium administered in a Phase II study.

METHOD

Eligible patients will be treated at a dose of 80 mg/M², IV, three times a week. The dosage will be slowly escalated with weekly increments of 10 mg/M² to a total of 120 mg/M². The medicine will be continued on a three times a week basis until there is evidence of complete tumor remission or objective evidence of disease progression.

PROGRESS

(83 03 - 83 09) No patients entered at MAMC.

STATUS: (0)

TITLE: SWOG 8219: Evaluation of Combined or Sequential
Chemo-Endocrine Therapy in the Treatment of Advanced
Adenocarcinoma of the Prostate, Phase III

PRINCIPAL INVESTIGATOR: LTC James E. Condon, MC

PROFESSIONAL ASSISTANTS: COL Friedrich H. Stutz, MC
LTC Irwin B. Dabe, MC
MAJ Thomas M. Baker, MC
MAJ Alfred H. Chan, MC
MAJ Howard Davidson, MC
MAJ Timothy J. O'Rourke, MC

WORK UNIT No: 83-60

TECHNICAL OBJECTIVE

To compare the efficacy of the sequential use of endocrine therapy followed at the time of progression by cytotoxic chemotherapy (Adriamycin and cyclophosphamide) versus the combination of endocrine therapy and chemotherapy in the treatment of advanced adenocarcinoma of the prostate by determination of the response rate, response duration, and duration of survival.

METHOD

Patients will be stratified as to the type of endocrine therapy (Orchiectomy or diethylstilbestrol [DES]), performance status, and good risk or poor risk. Patients will be randomized to either Arm I (endocrine therapy followed at the time of progression by chemotherapy with cyclophosphamide and Adriamycin) or Arm II (endocrine therapy combined with cyclophosphamide and Adriamycin beginning two weeks after the orchiectomy or the initiation of DES). Endocrine therapy for both arms will consist of a bilateral orchiectomy or, if the patient refuses surgery, diethylstilbestrol, 1 mg po t.i.d. Good risk patients on both arms will receive adriamycin, 30 mg/M², IV, day 1, and cyclophosphamide, 650 mg/M², IV, day 1. Poor risk patients will receive adriamycin 20 mg/M² and cyclophosphamide 500 mg/M². Courses will be repeated every 21 days. A minimum of two cycles will be considered an adequate trial. When a total of 300 mg/M² adriamycin in good risk or 200 mg/M² in poor risk patients has been given, it will be discontinued and cyclophosphamide will be given alone at a dose of 1000 mg/M² (good risk) or 750 mg/M² (poor risk) every three weeks. Cyclophosphamide will be discontinued in patients who are in complete or partial remission or who have stable disease after one year of chemotherapy. Patients with progressive disease after the sequential or combined chemo-endocrine therapy will be treated on another protocol.

PROGRESS

(33 04 - 83 09) No entries at MAMC.

STATUS: (0)

TITLE: SWOG 8228 - Correlation Between Progesterone Receptor and Response to Tamoxifen in Patients with Newly Diagnosed Breast Disease, Phase II

PRINCIPAL INVESTIGATOR: LTC James E. Congdon, MC

PROFESSIONAL ASSISTANTS: COL Friedrich H. Stutz, MC
LTC Irwin B. Dabe, MC
MAJ Thomas M. Baker, MC
MAJ Alfred H. Chan, MC
MAJ Howard Davidson, MC
MAJ Timothy J. O'Rourke, MC

WORK UNIT NO: 83/55

TECHNICAL OBJECTIVE

To determine the prognostic role of progesterone receptor in patients with newly diagnosed metastatic breast disease by correlating progesterone receptor levels with objective response rates in women treated with tamoxifen.

METHOD

ER+, non-pregnant female patients with new metastatic breast carcinoma are eligible. Patients who have received prior hormonal adjuvant therapy are eligible provided that they have not failed during therapy and the therapy has been stopped for at least three months. Patients with adjuvant chemotherapy alone are eligible. Patients with massive liver involvement are not eligible.

Tamoxifen, 10 mg po, twice daily, will be given alone until there is documented progression of the disease. Clear cut response may not be observed until 6-12 weeks of tamoxifen therapy. Therefore, therapy will not be discontinued unless there is evidence of disease progression at four weeks or unsatisfactory stable disease after eight weeks of therapy.

PROGRESS

(83 03 - 83 09) No entries at MAMC.

STATUS: (0)

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

PRINCIPAL INVESTIGATOR: LTC James E. Congdon, MC

PROFESSIONAL ASSISTANTS: COL Friedrich H. Stutz, MC
LTC Irwin B. Dabe, MC
MAJ Thomas M. Baker, MC
MAJ Alfred H. Chan, MC
MAJ Howard Davidson, MC
MAJ Timothy J. O'Rourke, MC

WORK UNIT NO: 83761

TECHNICAL OBJECTIVES

To compare the effectiveness of two intermittent pulse schedules of the chemotherapy combination of vincristine, melphalan, cyclophosphamide and prednisone (VMCP) + vincristine, BCNU, ardiamycin and prednisone (VBAP) (alternating versus syncopated) for induction of remission in previously untreated patients with multiple myeloma. Results will also be compared with other combination chemotherapy treatments in previous SWOG studies. In patients proven to achieve remission, to compare the value of 12 months of chemo-immunotherapy maintenance, VMCP + levamisole, versus a consolidation program consisting of sequential half-body radiotherapy along with vincristine and prednisone followed by unmaintained remission. In patients who only achieve improvement to determine whether sequential halfbody radiotherapy along with vincristine and prednisone will increase the remission rate. To determine whether sequential half-body radiotherapy along with vincristine and prednisone can serve as an effective form of induction therapy for patients who fail to respond to chemotherapy or suffer early relapse.

METHOD

Only patients with previously untreated multiple myeloma are eligible. Patients will be stratified as to tumor mass status and then randomized to induction therapy on Arm I (VMCP alternated every three weeks with VBAP for a minimum of 6 months to a maximum of one year) or Arm II (VMCP for 3 cycles followed by 3 cycles of VBAP. Each course will be repeated every 3 weeks. Courses will be repeated 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 Arm III (VMCP + levamisole, repeated every three weeks) or Arm IV (sequential half-body radiotherapy and concomitant vincristine and prednisone). Patients who are partial responders (50-75% regression) or non-responders (<50% or early relapse) following induction

SWOG 8229/30 - Congdon

therapy will receive Arm V (sequential half-body radiotherapy and concomitant vincristine and prednisone for six weeks).

PROGRESS

(83 04 - 83 09) One patient has been entered. Adverse reactions noted include neutropenia (mild), one episode of diaphoresis, chills, and jittery feeling during BCNU, and cutaneous disseminated herpes zoster which was resolved without problem.

STAT's: 10

TITLE: SWOG 8231: Chemotherapy of Extragonadal Germinal Cell Neoplasms, Phase III

PRINCIPAL INVESTIGATOR: MAJ Howard Davidson, MC

PROFESSIONAL ASSISTANTS: COL Friedrich H. Stutz, MC
LTC William Belville, MC
LTC Irwin B. Dabe, MC
MAJ Thomas M. Baker, MC
MAJ Alfred H. Chan, MC
MAJ Timothy J. O'Rourke, MC
CPT Michael Stone, MC

WORK UNIT NO: 83/68

TECHNICAL OBJECTIVES

To determine the effectiveness of alternating combination chemotherapy consisting of VBP (vinblastine, bleomycin and cis-platinum) and EBAP (bleomycin, adriamycin, cis-platinum and VP-16) in patients with metastatic germinal cell neoplasms arising in extragonadal sites; to determine the overall toxicity of the alternating combination of VBP and EBAP; to determine the role of surgical removal of residual disease following this drug combination in partially responding patients; to compare the response rates observed in this study with those reported by other investigators.

METHOD

This study will utilize alternating combination chemotherapy, with first and third cycles consisting of VBP and the second and fourth cycles consisting of EBAP. There are reduced "poor risk" doses for patients who are over 65 or have neutropenia, thrombocytopenia, markedly abnormal liver function, or prior radiation therapy.

Following completion of the four cycles, those patients with a complete response will be observed; those with stable disease, minimal response, or partial response will have surgical resection of residual disease, if possible, followed by 2 more cycles of chemotherapy if malignant tumor is found at surgery.

PROGRESS

(83 07 - 83 09) No entries at MAMC.

STATUS: (0)

TITLE: SWOG 8232: Treatment of Limited Small Cell Lung Cancer with VP-16/Cis-Platinum Alternating with Vincristine/Adriamycin/Cyclophosphamide and Radiation Therapy versus Concurrent VP-16/Vincristine/Adriamycin/Cyclophosphamide and Radiation Therapy, Phase III

PRINCIPAL INVESTIGATOR: LTC James E. Congdon, MC

PROFESSIONAL ASSISTANTS: COL Friedrich H. Stutz, MC
LTC Irwin B. Dabe, MC
MAJ Thomas M. Baker, MC
MAJ Alfred H. Chan, MC
MAJ Howard Davidson, MC
MAJ Timothy J. O'Rourke, MC

WORK UNIT NO: 83/45

TECHNICAL OBJECTIVES

To compare the efficacy of alternating non-cross-resistant, multidrug regimens with concurrent combination chemotherapy as remission induction in patients with limited small cell lung carcinoma and to determine the toxicity of these treatment programs.

METHOD

After appropriate laboratory tests to determine that the patient has limited disease, the patient will be randomized to one of two treatment arms: ARM 1 - includes 4 agents, VP-16, vincristine, adriamycin and cyclophosphamide. These agents will be given IV every 3 weeks for a total of 6 courses. ARM 2 - consists of VP-16 and cis-platinum alternating every 3 weeks with vincristine, adriamycin, and cyclophosphamide. These regimens will be repeated for a total of 6 treatments or 3 treatments of each group of drugs. At the end of 6 cycles of therapy, the patients will be restaged. For those patients with no evidence of disease remaining or those who have had a large decrease in the size of their tumor with only residual tumor remaining in the chest will receive radiation therapy to mediastinal and hilar regions and prophylactic whole brain radiation therapy. At the completion of this phase of treatment, the patients will receive 6 more cycles of the same chemotherapy regimen that they received prior to radiation therapy.

PROGRESS

(83 02 - 83 09) One patient has been entered at MAMC. In patients treated group-wide severe and life-threatening granulocytopenia has been observed. However, a high response rate is being seen with both regimens. No survival data is available at this time.

STATUS: (0)

TITLE: SWOG 8237: Evaluation of Continuous Infusion Vinblastine Sulfate in Pancreatic Adenocarcinoma, Phase II

PRINCIPAL INVESTIGATOR: MAJ Thomas M. Baker, MC

PROFESSIONAL ASSISTANTS: COL Friedrich H. Stutz, MC
LTC Irwin B. Dabe, MC
MAJ Alfred H. Chan, MC
MAJ Howard Davidson, MC
MAJ Timothy J. O'Rourke, MC
CPT Michael D. Stone, MC

WORK UNIT NO: 83/72

TECHNICAL OBJECTIVE

To determine the clinical response rate of a five-day continuous infusion of vinblastine sulfate in pancreatic adenocarcinoma.

METHOD

Patients will be treated with vinblastine sulfate at a starting dose of 1.4 mg/M²/day by continuous infusion for five days. Vinblastine sulfate will be repeated every three weeks provided granulocyte and platelet counts are satisfactory. If the counts do not recover until four weeks, the chemotherapy will be given on a four week cycle at the same dose. If the counts have not recovered within four weeks, vinblastine sulfate will be given at a one dose level of reduction when the counts have recovered. Therapy will be continued as long as there is stable disease, partial response, or complete response and acceptable clinical toxicity. An adequate trial will be defined as two cycles of continuous infusion vinblastine therapy.

PROGRESS

(83 08 - 83 09) No entries at MAMC.

STATUS: (0)

TITLE: SWOG 8241: Treatment for Advanced Non-Small Cell Lung
Cancer: PVp Versus PVpM Versus PVE Versus PVeMi Versus
FOMi/CAP, Phase III

PRINCIPAL INVESTIGATOR: LTC James E. Congdon, MC

PROFESSIONAL ASSISTANTS: COL Friedrich H. Stutz, MC
LTC Irwin B. Dabe, MC
MAJ Thomas M. Baker, MC
MAJ Alfred H. Chan, MC
MAJ Howard Davidson, MC
MAJ Timothy J. O'Rourke, MC

WORK UNIT NO: 83/46

TECHNICAL OBJECTIVES

To directly compare the efficacy and toxicity of cis-platinum plus VP-16 (PVp) versus cis-platinum plus vinblastine (PVE) in patients with advanced non-small cell lung cancer; to compare the response rate, response duration, survival, and toxicity of PVp to cis-platinum plus VP-16 plus MGBM (PVpM); to compare the response rate, response duration, survival and toxicity of PVE to cis-platinum plus Vinblastine plus Mitomycin-C (PVeMi); to re-evaluate and compare the activity of FOMi/CAP to PVp, PVpM, PVE and PVeMi using a five arm, randomized study design; to evaluate differences in response rates among patients with squamous cell carcinoma, adenocarcinoma or large cell undifferentiated carcinoma of the lung.

METHOD

After adequate laboratory tests to determine extent of disease, patients will be randomized to 1 of 5 treatment arms. ARM 1 consists of cis-platinum plus VP-16 every 4 weeks for 3 courses, then every 6 weeks thereafter. ARM 2 consists of cis-platinum plus VP-16 plus MGBG to be repeated at 4 weeks times 2 cycles and thereafter every 6 weeks. ARM 3 consists of cis-platinum and vinblastine to be repeated every 7 weeks. ARM 4 consists of cis-platinum plus mitomycin C to be repeated every 7 weeks. ARM 5 consists of 6 drugs on an alternating schedule, 5-fluorouracil plus vincristine, plus mitomycin C will be alternated every 4 weeks with cyclophosphamide plus adriamycin, plus cis-platinum. These complete cycles will be repeated every 8 weeks. Treatment of all 5 ARMS may be discontinued after 12 months in patients achieving a complete remission status. The patients will be removed from the study at the first objective evidence of disease progression.

PROGRESS

(83 02 - 83 09) Four patients were entered with no severe side effects.

STATUS: (0)

TITLE: SWOG 8272: Treatment of Primary Brain Tumors with
Adjuvant Chemotherapy and Radiation Therapy Utilizing
Intra-Arterial Cis-Platinum and CCNU, Phase I-II, Pilot

PRINCIPAL INVESTIGATOR: MAJ Howard Davidson, MC

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LTC Irwin B. Dabe, MC
LTC E. Neal Gunby, MC
MAJ Thomas M. Baker, MC
MAJ Alfred H. Chan, MC
MAJ Timothy J. O'Rourke, MC
CPT Michael Stone, MC

WORK UNIT NO: 83/69

TECHNICAL OBJECTIVES

To determine whether the severe or worse toxicity rate of the proposed therapy (surgery plus radiation therapy plus CCNU plus intra-arterial cis-platinum) is "acceptable" (i.e., 1% or less) or "not acceptable" (i.e., 15% or more) in patients with malignant gliomas of the brain and to estimate rates (e.g., six month survival rate, response rate, etc.) with a standard error no more than 10%.

METHOD

Treatment consists of intra-arterial cis-platinum starting within four weeks of craniotomy. Three to five days later, radiotherapy will be started (5580 rads over 6 to 7 weeks) and oral CCNU will be given daily for 2 days, every 6 weeks for up to one year. Cis-platinum will be repeated once on day 28 of radiotherapy.

PROGRESS

(83 07 - 83 09) No entries at MAMC. Of 22 patients entered group-wide, two patients with large residual tumors post-operatively experienced expressive apraxia and hemiparesis post-infusion and one patient had transient exacerbation of focal seizures.

STATUS: (C)

TITLE: SWOG 8294 - Evaluation of Adjuvant Therapy and Biological Parameters in Node Negative Operable Female Breast Cancer (ECOG, EST-1180), Intergroup Study

PRINCIPAL INVESTIGATOR: LTC James E. Congdon, MC

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WORK UNIT NO: 83/56

TECHNICAL OBJECTIVES

To assess the impact of short-term intensive chemotherapy with CMEP 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 greater >3 cm; to assess the impact of surgical procedure, estrogen receptor status, menopausal status and tumor size; to develop guidelines referable to hispathological features of node negative tumors which are reporducible 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).

METHOD

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

(83 03 - 83 09) One patient has been entered in the observation only group.

STATUS: (0)

TITLE: SWOG 8304: Phase II Evaluation of L-Alanosine in
Metastatic Carcinoma of the Breast

PRINCIPAL INVESTIGATOR: MAJ Thomas M. Baker, MC

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CPT Michael D. Stone, MC

WORK UNIT NO: 83/73

TECHNICAL OBJECTIVES

To determine the antitumor activity as determined by response rate and duration of response of L-alanosine used on a three day, every three week schedule in patients with metastatic carcinoma of the breast who have failed on standard therapy and to determine the nature and degree of toxicity of L-alanosine.

METHOD

Patients will be stratified as to prior chemotherapy (minimal or extensive). L-alanosine will be given at a dose of 250 mg/M²/day. Courses of therapy will be repeated at three week intervals. An adequate trial of therapy is defined as two courses of therapy (six weeks) with follow-up tumor measurement or progression after one course of therapy. Therapy will be continued until progression of disease, relapse after attainment of remission, or unacceptable toxicity.

PROGRESS

(83 08 - 83 09) No entries at MAMC.

STATUS: (0)

APPENDIX I

GUIDING PRINCIPLES OF THE CARE AND USE OF ANIMALS

Approved by the
Council of the American Physiological Society

Only animals that are lawfully acquired shall be used in this laboratory, and their retention and use shall be in every case in strict compliance with state and local laws and regulations.

Animals in the laboratory must receive every consideration for their bodily comfort; they must be kindly treated, properly fed, and their surroundings kept in a sanitary condition.

Appropriate anesthetics must be used to eliminate sensibility to pain during operative procedures. Where recovery from anesthesia is necessary during the study, acceptable technic to minimize pain must be followed. Curarizing agents are not anesthetics. Where the study does not require recovery from anesthesia, the animal must be killed in a humane manner at the conclusion of the observations.

The postoperative care of animals shall be such as to minimize discomfort and pain and in any case shall be equivalent to accepted practices in schools of veterinary medicine.

When animals are used by students for their education or the advancement of science, such work shall be under the direct supervision of an experienced teacher or investigator. The rules for the care of such animals must be the same as for animals used for research.

APPENDIX II

Recommendations From the Declaration of Helsinki

I. Basic Principles

1. Clinical research must conform to the moral and scientific principles that justify medical research and should be based on laboratory and animal experiments or other scientifically established facts.

2. Clinical research should be conducted only by scientifically qualified persons and under the supervision of a qualified medical man.

3. Clinical research cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.

4. Every clinical research project should be preceded by careful assessment of inherent risks in comparison to foreseeable benefits to the subject or to others.

5. Special caution should be exercised by the doctor in performing clinical research in which the personality of the subject is liable to be altered by drugs or experimental procedure.

II. Clinical Research Combined with Professional Care

1. In the treatment of the sick person, the doctor must be free to use a new therapeutic measure, if in his judgment it offers hope of saving life, reestablishing health, or alleviating suffering.

If at all possible, consistent with patient psychology, the doctor should obtain the patient's freely given consent after the patient has been given a full explanation. In case of legal incapacity, consent should also be procured from the legal guardian; in case of physical incapacity, the permission of the legal guardian replaces that of the patient.

2. The nature, the purpose, and the risk of clinical research must be explained to the subject by the doctor.

3. a. Clinical research on a human being cannot be undertaken without his free consent after he has been informed; if he is legally incompetent, the consent of the legal guardian should be procured.

b. The subject of clinical research should be in such a mental, physical, and legal state as to be able to exercise fully his power of choice.

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