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DEPARTMENT OF CLINICAL INVESTIGATION
WALTER REED ARMY MEDICAL CENTER
WASHINGTON, DC 20307-5001

CLINICAL INVESTIGATION PROGRAM
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REPORT DATE: 02/16/94 WORK UNIT # 1400-88

DETAIL SUMMARY SHEET

TITLE: A Pilot Study Evaluating Intestinal and Serum Immunoglobulin Levels in Patients with Acquired Hypogammaglobulinemia and Recurrent/Chronic Diarrhea of Undefined Etiology

KEYWORDS: immunoglobulin, hypogammaglobulinemia, diarrhea

PRINCIPAL INVESTIGATOR: Engler, Renata COL MC
ASSOCIATES: Kikendall, James COL MC; Martinez, Miguel MAJ MC

SERVICE: Allergy-Immunology Service

STATUS: Completed
APPROVAL DATE: Feb 1988

FUNDING: Current FY: $ 0 Previous FYs: $ 2,658 Total: $ 2,658

STUDY OBJECTIVE

To develop an IgG-subclass specific ELISA for measurement of G1/G2/G3 and G4 levels in intestinal secretions, and to measure quantitative immunoglobulin levels, particularly IgG subclasses, in the intestinal secretions of patients with common variable hypogammaglobulinemia (CVID) and compare these with normal levels.

TECHNICAL APPROACH

Secretions previously collected under protocol #1453 (normals) and those stored from medically indicated evaluations (hypogammaglobulinemic patients with diarrhea) will be utilized for study. An ELISA utilizing highly specific monoclonal antibodies to human G subclasses will be developed. Results are to be standardized to a uniform reference and quantitated in nanograms per ml. It is anticipated that additional samples will be collected on patients presenting for the problem of diarrhea and hypogammaglobulinemia, as well as normals, under protocol W.U. No. 1453.

PRIOR AND CURRENT PROGRESS

A total of three patients with CVID were enrolled, and eight controls. No additional samples were collected or assayed this past year due to personnel retraining and shortages. Initial baseline experiments were performed, but were complicated by low level detection requirements which have since been overcome by the availability of purified subclass reagents.

CONCLUSIONS

This study is closed. When personnel time and materials are not so limited, it will be resubmitted for activation.

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REPORT DATE: 11/29/93 WORK UNIT # 3336

DETAIL SUMMARY SHEET

TITLE: The Effect of Human Breast Milk Cell Supernatants on In Vitro Immunoglobulin Secretion

KEYWORDS: breast milk, immunoglobulin

PRINCIPAL INVESTIGATOR: Engler, Renata COL MC
ASSOCIATES: Carregal, Valerie CPT MC; McCormack, Emma CPT MC

SERVICE: Allergy-Immunology Service

STATUS: Completed
APPROVAL DATE: Nov 1987

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To evaluate the ability of human breast milk cells in culture to continue to secrete human immunoglobulin (Ig) of all isotypes. To evaluate human breast milk cells (HBMC) supernatants (derived from cultured HBMC) in their ability to stimulate Ig secretion by peripheral blood lymphocytes (PBL).

TECHNICAL APPROACH

Human breast milk (HBM) is collected with a breast pump at 48 hours and 2-3 weeks after delivery. HMBC are separated and placed in culture for 7 days. Supernatants are harvested and assayed by isotype specific ELISA for quantitative Ig. HBMC supernatants are co-cultured with peripheral blood lymphocytes from normal donors for 8 days, and supernatants are again assayed for Ig production.

PRIOR AND CURRENT PROGRESS

A total of 10 subjects have been enrolled. The study has attempted to define optimal conditions for the assays as well as adequate internal controls. Lack of technical support and increased clinical responsibilities have resulted in no progress during the past year. Breast milk cell supernatants will continue to be stored so that this protocol may be resubmitted when more support is available.

CONCLUSIONS

Cells derived from HBM (colostrum) continue to release IgA over 7 days of culture even in the absence of any non-specific stimulation. Although IgA levels increase significantly in the first 24 hours, the HBM cells continue to secrete variable amounts of IgA over 7 days, even in serum free media. The role of lymphokines has yet to be elucidated.

REPORT DATE: 10/15/93 WORK UNIT # 3343

DETAIL SUMMARY SHEET

TITLE: Standardized Vs. Nonstandardized Allergen Products Containing Dust Mite Antigens

KEYWORDS: dust mite, potency, allergens

PRINCIPAL INVESTIGATOR: Salata, Kalman PhD
ASSOCIATES: Hershey, Joyce BA

SERVICE: Allergy-Immunology Service STATUS: Completed
APPROVAL DATE: Oct 1988

FUNDING: Current FY: $ 0 Previous FYs: $ 737 Total: $ 737

STUDY OBJECTIVE
To compare standardized and nonstandardized house dust mite allergen extracts for potency and allergen content.

TECHNICAL APPROACH
Fluorescent enzyme linked immunosorbent assay (FELISA) inhibition tests, sodium dodecylsulfate polyacrylamide gel electrophoresis (SDS-PAGE), isoelectric focusing (IEF), immunoblotting, and titrated skin prick testing are used to compare commercial allergen extracts prepared from Dermatophagoides farinae and Dermatophagoides pteronyssinus for potency and allergen content.

PRIOR AND CURRENT PROGRESS
Methods have been developed to analyze house dust mite allergens using SDS-PAGE, IEF, immunoblotting, FELISA, FELISA inhibition, and titrated house skin prick testing. A total of 14 subjects have been enrolled (none this past year); 5 mite allergic subjects and 9 normal subjects. There were no adverse reactions, no patients withdrew, and there was no benefit to the patients. None of the serum samples collected so far contained measurable IgE against mite proteins. All of the products appeared, in initial studies, to have the same popreagents are being prepared. All of the products appeared, in initial studies, to have the same potency in skin tests.

CONCLUSIONS
Substantial differences exist between extracts from different companies. There were differences in protein content and spectrum of extract proteins, yet the skin test activity was similar. This study is completed.

REPORT DATE: 06/17/94 WORK UNIT # 3346

DETAIL SUMMARY SHEET

TITLE: Comparison of Three Methods of Assessing Induction of Mitogen and Allergen Specific Lymphocyte Proliferation

KEYWORDS: lymphocyte, proliferation, fluorescence

PRINCIPAL INVESTIGATOR: Salata, Kalman PhD
ASSOCIATES: Hershey, Joyce BA

SERVICE: Allergy-Immunology Service STATUS: Completed
APPROVAL DATE: Jun 1989

FUNDING: Current FY: $ 20 Previous FYs: $ 1,630 Total: $ 1,650

STUDY OBJECTIVE
To compare three methods of measuring lymphocyte proliferation induced by dust mite allergens and lymphocyte mitogens.

TECHNICAL APPROACH
Cell counting with a Coulter counter, fluorescein release and 3H-thymidine incorporation are used to measure lymphocyte proliferation in response to allergens and mitogens. The methods are compared for sensitivity; 3H-thymidine acts as the gold standard.

PRIOR AND CURRENT PROGRESS
A method was developed to quantitate cells in culture which is based on fluorescein diacetate. This assay can be performed directly on cell cultures and requires no cell washing. The color of the plate used in the assay is important; white plates perform about 32 times better than black or clear plastic plates. A method to detect lymphocyte activation was developed using a cell counter that uses size to measure activation. Two subjects have been enrolled; none in this reporting period. No one has withdrawn, and there have been no adverse reactions. This study is completed.

CONCLUSIONS
3H-thymidine is probably the best method for measuring lymphocyte proliferation. An assay based on cell size appears usable, and it requires little post-culture manipulation. A simple fluorescent assay for quantitating cultured cells was established. A way of greatly increasing the sensitivity of 96 well plate assays was shown. This study is completed.

REPORT DATE: 11/29/93 WORK UNIT # 3348

DETAIL SUMMARY SHEET

TITLE: Immunotherapy Reactions

KEYWORDS: allergy immunotherapy, venom immunotherapy, adverse reactions

PRINCIPAL INVESTIGATOR: Engler, Renata COL MC
ASSOCIATES: McCormack, Emma CPT MC; Smith, Laurie MD

SERVICE: Allergy-Immunology Service STATUS: Ongoing
APPROVAL DATE: Nov 1989

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To maintain a data base of the results of an ongoing chart audit of all patients receiving immunotherapy (IT) at Walter Reed Army Medical Center since 1986, and to establish the incidence of different types of adverse reactions in relation to the following parameters: number of injections received of increasing or maintenance IT, specific extract contents, nature of all reactions, and underlying patient factors (e.g., beta blockers).

TECHNICAL APPROACH
A weekly chart review will be conducted of all patients having received IT at WRAMC Allergy Clinic. Reactions are categorized into three levels of local reactions, as well as cutaneous/systemic anaphylaxis. Data is entered into a computer data base for analysis.

PRIOR AND CURRENT PROGRESS
Chart review and data tabulation for 1989-present is ongoing. Due to variations in charting techniques of data collectors, repeating medical chart reviews began in August 1992. By November 1992, a total of 404 charts had been reviewed. During this past year, another 125 charts were reviewed for a total of 529. This represents approximately three-quarters of the charts to be analyzed. The principal chart reviewer has been on sick leave for more than 5 months and is just now resuming work half-time. She hopes to finish the chart reviews this next year.

CONCLUSIONS
1) Increasing IT had significantly more systemic reactions than maintenance IT for both inhalant allergens and venom. 2) Specific aeroallergen (AA) IT reactions were not correlated to extract type/content. Venom IT had a significantly lower rate of reaction for all three categories of local reactions (compared to AA IT, $p</=0.001$) but was not statistically different for systemic reactions.

REPORT DATE: 12/16/93 WORK UNIT # 3349

DETAIL SUMMARY SHEET

TITLE: Mitogen-Inducible T Suppressor Cell Assay by Flow Cytometry

KEYWORDS: activation, flow cytometry, suppressor

PRINCIPAL INVESTIGATOR: Salata, Kalman PhD
ASSOCIATES: Hershey, Joyce BA

SERVICE: Allergy-Immunology Service STATUS: Completed
APPROVAL DATE: Dec 1989

FUNDING: Current FY: $ 0 Previous FYs: $ 2,763 Total: $ 2,763

STUDY OBJECTIVE

To measure T cell suppression using a lymphocyte activation marker. To measure the suppression of mitogen-stimulated lymphocytes of concanavalin-A-induced lymphocyte proliferation by two-color flow cytometry.

TECHNICAL APPROACH

Suppression will be measured by culturing activated suppressor lymphocytes (effectors) with target lymphocytes and then measuring a parameter of activation of the targets. Lymphocyte activation will be assessed by measuring CD69 expression on the lymphocyte membrane using a monoclonal antibody. Target cells will be stained with a fluorescent vita stain, DIO, to identify them. CD69 expression will be used to assess suppression of lymphocyte activation caused by mitogen-induced suppressor cells. Flow cytometry will be used to make these measurements.

PRIOR AND CURRENT PROGRESS

A two-color flow cytometric method was developed to measure mitogen-induced suppressor cell function. DIO is a useful reagent for use in assays which involve mixes of more than one group of cells which must be monitored individually. CD69 in lymphocyte expression begins to appear within hours of stimulation, peaks at 18 hours, and remains elevated. Suppressor cell function was measured in a number of normal subjects. Seventeen subjects were enrolled; none since the last progress report. There have been no adverse reactions.

CONCLUSIONS

This assay greatly improves and expands activated suppressor cell function compared to older methods. Harsh treatments of effectors and radioactive materials are avoided. The cells are allowed to function in a more natural way. This method allows other parameters of the lymphocytes to be measured simultaneously.

REPORT DATE: 01/18/94 WORK UNIT # 3350

DETAIL SUMMARY SHEET

TITLE: Flow Cytometric Analysis of Natural Killer Cell Activity and Antibody-Dependent Cell-Mediated Cytotoxicity

KEYWORDS: flow cytometry, natural killer cells, cytotoxicity

PRINCIPAL INVESTIGATOR: Salata, Kalman PhD
ASSOCIATES: Hershey, Joyce BA

SERVICE: Allergy-Immunology Service STATUS: Completed
APPROVAL DATE: Jan 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 48 Total: $ 48

STUDY OBJECTIVE
To measure in vitro natural killer (NK) cell activity and antibody-dependent cell cytotoxicity (ADCC) against cultured tumor cell lines using a two-color flow cytometric assay.

TECHNICAL APPROACH
The assay uses peripheral blood mononuclear cells from normal subjects as effector cells and tumor cells as target cells. Target cells are stained with a fluorescent dye, 3,3'-dioctadecyloxacarbocyanine perchlorate, to distinguish them from effector cells. Killed cells are identified using propidium iodide, which stains dead cells. ADCC is measured using antibody coated cells; NK activity is measured using uncoated cells. Measurements are performed with a flow cytometer; forward light scatter, side scatter, and two colors of fluorescent light are measured.

PRIOR AND CURRENT PROGRESS
A total of seven patients have been enrolled; none during the past year. There have been no adverse reactions, and no one has withdrawn. This study is now closed. A natural killer assay has been devised with an intubation time much shorter than the traditional, 4-hour one. Past problems with the ADCC assay appeared to have been caused by the length of the 4-hour assay, which disintegrated the targets in addition to killing them. The shorter incubation period worked out well; it was possible to measure both dead target cells and residual intact target cells. Also, it appears that simple vortexing of the cell pellets and chilling the incubations act to stop the killing action. This is a simple way to stop the assays.

CONCLUSIONS
A killer cell assay has been developed which is faster than the traditional 51Cr method. This method avoids radioactive materials and allows the quality of the cells to be assessed. The flow cytometer gives much more information than older methods of measuring killer cell activity.

REPORT DATE: 01/18/94 WORK UNIT # 3351

DETAIL SUMMARY SHEET

TITLE: In Vitro House Dust Mite Allergy Assays: Comparison of a Monoclonal Antibody/Allergen Capture Method with a Fluorescent Allergosorbant Test

KEYWORDS: allergy, IgE, monoclonal

PRINCIPAL INVESTIGATOR: Salata, Kalman PhD
ASSOCIATES: Hershey, Joyce BA

SERVICE: Allergy-Immunology Service STATUS: Completed
APPROVAL DATE: Jan 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 331 Total: $ 331

STUDY OBJECTIVE

To compare two in vitro methods of detecting house dust mite allergy in normal and proven allergic subjects; and to measure IgE directed against D. farinae F1 and D. pteronyssinus P1 proteins by monoclonal antibody/allergen capture and mite specific IgE by a FAST method.

TECHNICAL APPROACH

The FAST assay uses antigen coated plates in a fluorescent enzyme-linked immunosorbent assay. The capture assay employs monoclonal antibodies directed against allergen proteins. These monoclonal antibodies are used to capture allergens from a complex extract. Serum from volunteers is exposed to these immobilized allergens to detect the presence of anti-house dust mite IgE.

PRIOR AND CURRENT PROGRESS

Methods have been developed to analyze IgE directed against house dust mite allergens F1 and P1 using a fluorescent enzyme-linked immunosorbent assay and a monoclonal antibody capture method. None of the serum samples collected so far contained measurable IgE against mite proteins. A new, more sensitive, microtiter plate fluorimeter is being procured to improve the sensitivity of the tests. No subjects were enrolled in the last reporting period. A total of 23 subjects have been enrolled. There were no adverse reactions or benefit to the patients, and no patients withdrew. This study is completed.

CONCLUSIONS

Two in vitro methods were used to measure IgE specific to mite allergens. None of the mite sensitive-patients had any measurable serum anti-mite IgE. Whether this is due to the sensitivity of the tests or because the IgE is sequestered on mast cells is unclear. New reagents and experimental strategies are being established to improve the sensitivity of these tests.

REPORT DATE: 02/28/94 WORK UNIT # 3352

DETAIL SUMMARY SHEET

TITLE: Use of Steroid Sparing Agents Among Asthmatics Doing Poorly on Corticosteroids: A Pilot Study

KEYWORDS: asthma, methotrexate

PRINCIPAL INVESTIGATOR: Squire, Edward LTC MC

SERVICE: Allergy-Immunology Service STATUS: Ongoing
APPROVAL DATE: Jan 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 2,357 Total: $ 2,357

STUDY OBJECTIVE
To establish a consensus as to a rational treatment approach for severe, steroid-dependent asthma at Walter Reed Army Medical Center.

TECHNICAL APPROACH
The definition of success/failure of asthma control will be based upon seven indicators: symptoms; mini-peak flows; PRN use of bronchodilators; lung function; asthma admissions; quality of life; and willingness of physician/patient to continue treatment. This definition will be used to prospectively judge the outcome of 42 open-treatment trials among 19 steroid-dependent asthmatics, all of whom are doing poorly with conventional management. The three treatment regimens will be: 3 months of weekly methotrexate (MTX), 10-30 mg IM or PO; qid maintenance TAO, 250 mg/4 mg PO; and up to 6 months of daily Gold 3 mg PO bid.

PRIOR AND CURRENT PROGRESS
Seven patients were enrolled this past year. Seventeen of the total 34 patients responded successfully to MTX. All reduced their need for oral steroids by 50% or more, had no hospitalizations, and enjoyed 8 or more months of equal or better asthma control. TAO proved toxic (hepatitis and not steroid-sparing); TAO and Gold both proved poorly effective (4/12 and 1/3 respectively); and each was therefore dropped from the protocol. Of the 17 patients who did not benefit from methotrexate, 12 went on to be treated with other agents. Seven of these patients were treated successfully; five were continued failures. This outcome still establishes the fact that even those patients whose asthma fails to respond to MTX may still be successfully treated.

CONCLUSIONS
Better therapy for severe asthma continues to be sorely and urgently needed. Improved protocols with alternative and multiple agents are likely to be useful. Different protocols for induction of asthma control, and for maintenance of adequate asthma control, once established, are also needed.

REPORT DATE: 03/15/94 WORK UNIT # 3353

DETAIL SUMMARY SHEET

TITLE: Contrasuppressor Cells in Allergy Immunotherapy

KEYWORDS: flow cytometry, contrasuppressor, immunotherapy

PRINCIPAL INVESTIGATOR: Salata, Kalman PhD
ASSOCIATES: Hershey, Joyce BA

SERVICE: Allergy-Immunology Service STATUS: Ongoing
APPROVAL DATE: Mar 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 530 Total: $ 530

STUDY OBJECTIVE
To measure contrasuppressor T cells in individuals with multiple allergies who are also on high and low dose immunotherapy with allergen extracts. Measurements will also be performed on cells from normal and untreated allergic subjects.

TECHNICAL APPROACH
Flow cytometry will be used to measure fluorescently labeled V. villosa lectin to lymphocytes.

PRIOR AND CURRENT PROGRESS
In preliminary studies using cells on hand, lectin bound to all lymphocytes. Recent studies with lectins in another protocol have shown that lectins often bind to cells extensively in a nonspecific manner. Specific binding can be demonstrated using a blocking sugar to which the lectin binds. This approach will be tried, and if the results are no different the study will be concluded. No subjects have been enrolled in this study.

CONCLUSIONS
Reports in the literature describe a small population of lymphocytes, contrasuppressors, which bind V. villosa lectin. In preliminary studies, FITC-labeled lectin bound to all lymphocytes. Lectins appear to bind to cells nonspecifically. Blocking sugars suppress background binding by lectins. It is possible that V. villosa lectin does not identify a separate lymphocyte subpopulation.

REPORT DATE: 04/19/94 WORK UNIT # 3354

DETAIL SUMMARY SHEET

TITLE: Two Way Mixed Lymphocyte Culture: Analysis by Two Color Flow Cytometry

KEYWORDS: MLC, flow cytometry, DIO

PRINCIPAL INVESTIGATOR: Salata, Kalman PhD
ASSOCIATES: Hershey, Joyce BA; Berger, Teresa BSc(MT)

SERVICE: Allergy-Immunology Service STATUS: Completed
APPROVAL DATE: Apr 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 4,403 Total: $ 4,403

STUDY OBJECTIVE
To devise a two-color, simultaneous, two-way mix lymphocyte culture (MLC) assay.

TECHNICAL APPROACH
Flow cytometry will be used to measure lymphocyte activation in two-way mixed lymphocyte cultures. Cell surface expression of CD69 will be used as a measure of lymphocyte activation. A fluorescent vital stain, 3,3'-dioctadecyloxacarbocyanine perchlorate, will be used to differentiate the cell populations.

PRIOR AND CURRENT PROGRESS
A flow cytometric MLC assay has been devised. Little expression of CD59 or transferrin receptor has been seen in response to allogeneic stimulation. A lot of cell death takes place during the assay. In addition, little reaction was seen using a thymidine incorporation assay. Changes in serum made no difference to the assay. A total of 19 subjects have been enrolled; none in the last reporting period. There have been no adverse reactions, and no subjects have withdrawn. This protocol is completed.

CONCLUSIONS
An assay of the mixed lymphocyte reaction based on flow cytometry and a fluorescent vital stain has been devised. Unlike other methods, both cell populations may be analyzed simultaneously, avoiding the harshness treatments of current methods. The cells are allowed to function in a more natural fashion, and additional analyses (not possible using current methods) are achievable. No expression of lymphocyte activation markers, either early or late, was seen.

REPORT DATE: 05/13/94 WORK UNIT # 3355

DETAIL SUMMARY SHEET

TITLE: Effect of Methotrexate on Expression of Intercellular Adhesion Molecule I in Interleukin-1 Stimulated Cultured Human Cells

KEYWORDS: methotrexate, interleukin-1, ICAM-1

PRINCIPAL INVESTIGATOR: Salata, Kalman PhD
ASSOCIATES: Hershey, Joyce BA

SERVICE: Allergy-Immunology Service STATUS: Completed
APPROVAL DATE: May 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 655 Total: $ 655

STUDY OBJECTIVE
To measure the effect of methotrexate on interleukin-1 (IL-1) induced ICAM-1 expression in cultured human fibroblasts and adenocarcinoma cells.

TECHNICAL APPROACH
Expression of ICAM-1 will be measured using monoclonal antibodies, flow cytometry, and enzyme-linked immunosorbent assay.

PRIOR AND CURRENT PROGRESS
Cultured cells were incubated with IL-1 to stimulate ICAM-1 expression. In general, the cells responded well. ICAM-1 was readily detectable with monoclonal antibodies and flow cytometry. Concurrent incubation of cells with methotrexate did not affect IL-1 induced ICAM-1 expression. Endotoxin, a potent stimulator of ICAM-1 expression, is a ubiquitous contaminant of chemical preparations. A preparation of methotrexate for parenteral administration which is endotoxin-free will be tested. This study does not use any human subjects. This project is completed.

CONCLUSIONS
ICAM-1 expression on human lung epithelioid cells in culture has been measured by flow cytometry. Methotrexate does not appear to inhibit ICAM-1 expression in these cells. The anti-inflammatory actions of methotrexate do appear to be mediated by inhibition of IL-1-induced ICAM-1 expression.

REPORT DATE: 09/21/94 WORK UNIT # 3357

DETAIL SUMMARY SHEET

TITLE: Serum and Secretory Immune Status of Patients with Chronic Sinusitis and Normals

KEYWORDS: sinusitis, immunodeficiency, mucosal immunity

PRINCIPAL INVESTIGATOR: Engler, Renata COL MC

SERVICE: Allergy-Immunology Service STATUS: Ongoing
APPROVAL DATE: Sep 1990

FUNDING: Current FY: $ 526 Previous FYs: $ 13,444 Total: $ 13,970

STUDY OBJECTIVE
To evaluate the humoral, cellular, and mucosal immune responses of patients with chronic sinusitis in comparison with normal controls.

TECHNICAL APPROACH
Functional humoral immunity will be assessed by measuring total and antigen-specific antibody levels. Pre/post-immunization with tetanus/diphtheria/H influenza type b and Pneumovax will be given. Cellular immune function will be evaluated using delayed hypersensitivity skin testing, lymphocyte phenotyping and in vitro lymphocyte functional assays; mucosal immune function will be measured by collection of nasal secretions in response to methacholine and histamine; and IgG, IgA, secretory IgA, lactoferrin, lysozyme and albumin measurements will be analyzed.

PRIOR AND CURRENT PROGRESS
A total of 41 subjects have been enrolled in this study, none this past year. There have been no adverse reactions. In addition to the above assays, some of which were repeated this year to clarify results, IL-2 and IL-4 levels in nasal secretions and saliva were measured by ELISA in a representative group of patients. The remaining patient samples will be analyzed for IL-2 and IL-4 when assay kits are procured. Results have been entered in a computer data base and await analysis.

CONCLUSIONS
Study is ongoing; data analysis is planned this coming year.

REPORT DATE: 09/15/94 WORK UNIT # 3358

DETAIL SUMMARY SHEET

TITLE: Plasma Level of Mast Cell Tryptase in Patients Undergoing Immunodiagnostic or Immunotherapy Procedures who Experience Adverse Reactions

KEYWORDS: tryptase, anaphylaxis, mast cell

PRINCIPAL INVESTIGATOR: Salata, Kalman PhD
ASSOCIATES: Hershey, Joyce BA

SERVICE: Allergy-Immunology Service STATUS: Completed
APPROVAL DATE: Sep 1990

FUNDING: Current FY: $ 320 Previous FYs: $ 6,362 Total: $ 6,682

STUDY OBJECTIVE
To measure tryptase levels in blood samples from patients in the Allergy/Immunology Clinic who experience local or systemic reactions in response to diagnostic or immunotherapy procedures.

TECHNICAL APPROACH
Immunoassays will be used to measure mast cell tryptase levels in blood samples from subjects who have experienced a reaction, as well as from subjects who have not had a reaction. Samples are drawn at the time of the reaction and a period of days later. The second sample acts as a baseline sample. Control subjects will have the blood samples drawn in a similar manner with a similar time period between samples.

PRIOR AND CURRENT PROGRESS
The immunoassay works well. To date, all but two samples have been negative for tryptase. There have been no false positives. The assay is a very simple radioimmunoassay which works well with controls and standards. One subject has been enrolled this year, for a total of 52. Subjects with a wide variety of reactions, as well as control subjects, have been enrolled. There have been no adverse reactions, and no subject has withdrawn from the study. The recruitment phase is finished, and the testing of samples was completed this past year. No more subjects will be enrolled.

CONCLUSIONS
A mast cell tryptase radioimmunoassay has been established in the laboratory. All but two samples from subjects who suffered a reaction have been negative for tryptase. There have been no false positives. It appears that only vigorous anaphylactic reactions produce measureable levels of tryptase in the blood. This test does not appear to be of much utility in diagnosing the milder systemic allergic reactions.

REPORT DATE: 11/16/93 WORK UNIT # 3359

DETAIL SUMMARY SHEET

TITLE: Leukotriene B4 Receptor Downregulation: Flow Cytometry Analysis

KEYWORDS: leukotriene B4, flow cytometry, downregulation

PRINCIPAL INVESTIGATOR: Salata, Kalman PhD
ASSOCIATES: Hershey, Joyce BA

SERVICE: Allergy-Immunology Service STATUS: Completed
APPROVAL DATE: Nov 1990

FUNDING: Current FY: $ 20 Previous FYs: $ 834 Total: $ 854

STUDY OBJECTIVE
To measure leukotriene B4 (LTB4) binding and calcium ion (CA++) release after an initial challenge with LTB4 in granulocytes from normal subjects using a flow cytometric assay.

TECHNICAL APPROACH
Two-color flow cytometry will be used with a fluorescein isothiocyanate (FITC) labeled LTB4 to measure receptor downregulation in granulocytes. A calcium indicator, FLUO-3AM, will be used to measure cytosolic calcium levels during stimulation.

PRIOR AND CURRENT PROGRESS
LTB4-FITC binds to granulocytes. Brief pre-incubation with LTB4 results in receptor downregulation. LTB4 also competitively inhibits LTB4-FITC binding. A flow cytometric assay has been developed to measure LTB4-FITC binding to granulocytes. No subjects have been enrolled this reporting period; two subjects have been enrolled altogether. No subject has withdrawn or had an adverse reaction. There were no benefits to patients. This study is completed.

CONCLUSIONS
LTB4 receptor downregulation can be measured by flow cytometry using an FITC labeled LTB4 conjugate. Brief incubation with LTB4 leads to downregulation of the LTB4 receptor.

REPORT DATE: 11/16/93 WORK UNIT # 3360

DETAIL SUMMARY SHEET

TITLE: 3,3'-Dioctadecyloxacarbocyanine (DiO) Induced Immunosuppression: Inhibition of Mitogen, Antigen and Alloantigen Stimulated CD69 Expression

KEYWORDS: carbocyanine (DIO), CD69, immunosuppression

PRINCIPAL INVESTIGATOR: Salata, Kalman PhD
ASSOCIATES: Hershey, Joyce BA

SERVICE: Allergy-Immunology Service STATUS: Completed
APPROVAL DATE: Nov 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 632 Total: $ 632

STUDY OBJECTIVE
To measure inhibition by 3,3'-dioctadecyloxacarbocyanine perchlorate (DIO) of lymphocyte activation in lymphocytes stimulated with mitogens and antigens using an antibody directed against a lymphocyte activation marker.

TECHNICAL APPROACH
Two-color flow cytometry will be used with activation marker analysis to measure the immunosuppressive effect of 3,3'-dioctadecyloxacarbocyanine perchlorate (DIO).

PRIOR AND CURRENT PROGRESS
DIO inhibits mitogen-stimulated lymphocyte activation. The assay used is very simple and rapid; an answer can be obtained in less than 24 hours. Complete and irreversible inhibition of lymphocyte activation was achieved with brief exposure to luM DIO. The dye does not appear to interfere with measurement of constitutively expressed cell surface antigens. No subjects have been enrolled since the last report, for a total of 18 subjects. No subject has withdrawn or had an adverse reaction. There were no benefits to patients.

CONCLUSIONS
DIO is a lipid-soluble vital stain with little or no reported toxicities and is a potent inhibitor of CD69 expression and lymphocyte activation. DIO, at 1 uM, completely inhibits mitogen-induced activation of lymphocytes.

REPORT DATE: 01/18/94 WORK UNIT # 3362

DETAIL SUMMARY SHEET

TITLE: Immunologic Evaluation of Acute and Persistent Ectopic Gestation: A Collaborative Project with Portsmouth Naval Hospital

KEYWORDS: immunologic, ectopic, gestation

PRINCIPAL INVESTIGATOR: Salata, Kalman PhD
ASSOCIATES: Hershey, Joyce BA

SERVICE: Allergy-Immunology Service STATUS: Ongoing
APPROVAL DATE: Jan 1991

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To evaluate the immunologic systems of women with normal, acute ectopic, and persistent ectopic gestations.

TECHNICAL APPROACH
Subjects will be enrolled at Portsmouth Naval Hospital. Blood samples will be collected there and distributed to the laboratories conducting tests. WRAMC will perform lymphocyte subset analysis using monoclonal antibodies and two-color flow cytometry. HLA typing will be performed by a cytotoxicity assay with microscopic examination.

PRIOR AND CURRENT PROGRESS
Lymphocyte subset analysis has been performed on 28 samples, none since the last report. HLA typing has been performed on 11 samples, none since the last report. There has been no progress during the past year since WRAMC investigators did not receive any blood samples from Portsmouth Naval Hospital during that time. The data on lymphocytes and HLA typing has been submitted to Dr. Hansen at Portsmouth Naval Hospital. This study should be completed within the next reporting period.

CONCLUSIONS
The study is in the data collection stage, and no conclusions have been drawn yet. Lymphocyte subset analysis and HLA typing methods are working well. When all the data from the various participating groups is collected, final conclusions will be drawn.

REPORT DATE: 04/15/94 WORK UNIT # 3363

DETAIL SUMMARY SHEET

TITLE: Stability of Cat and House Dust Mite Allergens in Allergy Immunotherapy Preparations

KEYWORDS: allergens, stability, ELISA

PRINCIPAL INVESTIGATOR: Salata, Kalman PhD
ASSOCIATES: Hershey, Joyce BA

SERVICE: Allergy-Immunology Service STATUS: Ongoing
APPROVAL DATE: Apr 1991

FUNDING: Current FY: $ 690 Previous FYs: $ 1,154 Total: $ 1,844

STUDY OBJECTIVE
To measure at intervals over a year, fel d1, F1, and P1, in mixtures of cat or house dust mites with WRAMC grass, tree, weed, and mold groups of antigens.

TECHNICAL APPROACH
House dust mite or cat allergen extracts are combined with various mixtures of commonly used allergen immunotherapy preparations to test the effect these preparations have on levels of specific allergen proteins, fel d1, F1, and P1. The specific allergen proteins are measured with monoclonal antibody based enzyme-linked immunosorbent assays (ELISA).

PRIOR AND CURRENT PROGRESS
Preliminary studies are finished, and the study is underway. Two site capture assays have been established and work well. The house dust mite phase of this study is well underway; it is in the seventh month of stability testing. Fungal extracts appear to degrade the major mite allergen Der F1 even when stored at 4 degrees C. So far, the other mixtures of allergen extracts do not appear to affect Der F1 levels. No human subjects are involved in this study.

CONCLUSIONS
The study is ongoing; no conclusions on degradation of specific allergens by proteolytic or physical processes can be drawn yet. It does appear that mold extracts may degrade mite allergen protein in allergen extract mixtures.

REPORT DATE: 05/13/94 WORK UNIT # 3364

DETAIL SUMMARY SHEET

TITLE: Effect of N-(Fluorenyl-9-methoxycarbonyl)-L-Leucine (FMOC-LEU) on Neutrophil Activation

KEYWORDS: flow cytometry, neutrophil, FMOC-Leu

PRINCIPAL INVESTIGATOR: Salata, Kalman PhD
ASSOCIATES: Hershey, Joyce BA

SERVICE: Allergy-Immunology Service

STATUS: Completed
APPROVAL DATE: May 1991

FUNDING: Current FY: $ 1,386 Previous FYs: $ 3,509 Total: $ 4,895

STUDY OBJECTIVE
To measure the effect of N-(Fluorenyl-9-methoxycarbonyl)-L-leucine (FMOC-Leu) on CD11b expression in neutrophils activated with chemotactic agents by flow cytometry.

TECHNICAL APPROACH
The assay will use whole blood and isolated granulocytes from normal subjects. Neutrophils will be activated with chemotactic agents, with and without FMOC-Leu. Measurements will be performed with a flow cytometer, forward light scatter, side scatter, and fluorescent light. Changes in chemotactic-induced CD11b expression caused by FMOC-Leu will be determined.

PRIOR AND CURRENT PROGRESS
Whole blood and isolated granulocyte assays of chemotactic agent-induced CD11b expression have been established. FMOC-Leu appears to inhibit CD11b expression induced by FMLP but does not inhibit the size change induced by this stimulator. Some variability was seen between assays. Isolated granulocytes were activated by the isolation procedure, while it appeared that plasma proteins might interfere with the whole blood assay. An alternative procedure using dextran sedimentation alone in which the granuloctyes are kept at 4 degrees C was employed. The problems of premature neutrophil activation and plasma proteins were avoided. A total of 14 subjects have been enrolled (none in this last reporting period). There have been no adverse reactions, and no subjects have withdrawn from the study. This project is completed.

CONCLUSIONS
Whole blood and isolated granuloctye assays of chemotactic agent-induced CD11b expression have been established. FMOC-Leu does inhibit expression on granulocytes of the adhesion protein CD11b. The compound may exert its anti-inflammatory effect in part by interfering with cellular adhesion.

REPORT DATE: 07/15/94 WORK UNIT # 3365

DETAIL SUMMARY SHEET

TITLE: Leucocyte Subset Analysis in Patients Treated with Intravenous Immunoglobulin (IVIG)

KEYWORDS: IVIG, phenotypic changes, immunological changes

PRINCIPAL INVESTIGATOR: Salata, Kalman PhD
ASSOCIATES: Huh, Michael LCDR MC

SERVICE: Allergy-Immunology Service STATUS: Completed
APPROVAL DATE: Jul 1991

FUNDING: Current FY: $ 708 Previous FYs: $ 11,276 Total: $ 11,984

STUDY OBJECTIVE
To further define the mechanism of high dose intravenous immunoglobulin (IVIG) in inflammatory and immunologic disorders.

TECHNICAL APPROACH
To sequentially measure lymphocyte phenotypes in patients treated with high dose IVIG, observe changes, and correlate these phenotypic changes with clinical response.

PRIOR AND CURRENT PROGRESS
This study was closed to new subject enrollment in the last reporting period. Nine patients were enrolled; none this reporting period. An interesting transient reversal of the CD4/CD8 lymphocyte ratio was seen. There have been no unexpected adverse reactions, and no patients have withdrawn from the study.

CONCLUSIONS
The major finding has been that in some patients a single dose of IVIG is safe and potentially more effective than divided doses. A reversible inversion of the CD4/CD8 ratio that appears to correlate with clinical response has been noted in some patients.

REPORT DATE: 08/17/94 WORK UNIT # 3366

DETAIL SUMMARY SHEET

TITLE: Bird Antigen Detection in the Home and IgG and IgG Subclass Titers in Healthy Bird Owners Versus Those With Hypersensitivity Pneumonitis

KEYWORDS: hypersensitivity, bird, immunoglobulin

PRINCIPAL INVESTIGATOR: Salata, Kalman PhD
ASSOCIATES: Hershey, Joyce BA

SERVICE: Allergy-Immunology Service STATUS: Ongoing
APPROVAL DATE: Aug 1991

FUNDING: Current FY: $ 47 Previous FYs: $ 4,505 Total: $ 4,552

STUDY OBJECTIVE
To measure bird antigen levels in the homes of pet bird owners, and to determine the persistence of bird antigen after the bird(s) is (are) removed from the home.

TECHNICAL APPROACH
Enzyme linked immunosorbent inhibition assays are used to measure bird antigen levels in samples of dust collected from several rooms in the home, including the room where the bird was kept.

PRIOR AND CURRENT PROGRESS
Methods have been developed to measure bird antigen in immunoassay techniques. Subjects continue to be enrolled as they are identified. Since this disease is reasonably uncommon, and strict enrollment criteria are being used, it is taking time to enroll the required number of subjects. A total of 11 subjects have been enrolled; none in this reporting period. None have withdrawn, and there were no adverse reactions. This project will be wrapped up during the next reporting period.

CONCLUSIONS
Methods have been developed to quantitate bird antigen samples collected in homes. Bird antigen persists for up to 18 months after removal of the bird(s). This may partly explain the persistence of symptoms in patients with bird fancier's hypersensitivity pneumonitis despite aggressive medical therapy. Final conclusions will be drawn when the study is finished.

REPORT DATE: 06/30/94 WORK UNIT # 3367

DETAIL SUMMARY SHEET

TITLE: Naive Versus Memory T Lymphocytes in Patients Undergoing Aeroallergen Immunotherapy

KEYWORDS: lymphocyte, aeroallergen, immunotherapy

PRINCIPAL INVESTIGATOR: Carregal, Valerie CPT MC
ASSOCIATES: Davis, William MAJ MC

SERVICE: Allergy-Immunology Service STATUS: Completed
APPROVAL DATE: Jun 1992

FUNDING: Current FY: $ 62 Previous FYs: $ 14,074 Total: $ 14,136

STUDY OBJECTIVE
To measure memory and naive T cell subsets in patients undergoing aeroallergen immunotherapy and compare with age- and sex-matched allergic controls.

TECHNICAL APPROACH
These subjects of T lumphocytes, as well as basic cell surface markers, will be measured by flow cytometry before and at intervals during immunotherapy.

PRIOR AND CURRENT PROGRESS
A total of 14 subjects have been enrolled (7 patients and 7 controls). No new subjects have been enrolled during the past year. A total of 10 subjects completed the protocol (5 patients and 5 controls). One study pair (patient and control) did not complete the study due to difficulty with progression on allergy immunotherapy. Another pair dropped out due to non-compliance with instructions. Data is being reviewed, and a manuscript is being prepared.

CONCLUSIONS
No noted appreciable changes were noted over time in the allergy immunotherapy patients as compared with the controls in CD45 RA and RO CD markers on CD3 T cells. CD4 and CD8 T cell subsets did not change as well. Notably, there is a large variation of normal in both study groups.

REPORT DATE: 09/21/94 WORK UNIT # 3368

DETAIL SUMMARY SHEET

TITLE: ELISA Measurement of the Humoral Immune Response to a Primary Rabies Vaccine Series

KEYWORDS: vaccination, immune response, immunodeficiency

PRINCIPAL INVESTIGATOR: Engler, Renata COL MC

SERVICE: Allergy-Immunology Service STATUS: Ongoing
APPROVAL DATE: Sep 1992

FUNDING: Current FY: $ 479 Previous FYs: $ 3,167 Total: $ 3,646

STUDY OBJECTIVE
To measure antibody production in patients immunized with the rabies vaccine. A detailed measurement will be useful both as an indicator of rabies protection, and as an aid in the evaluation of a patient's ability to respond to new antigens. This will be most useful when patients with possible immunodeficiences are considered.

TECHNICAL APPROACH
A group of about 35 subjects will be recruited to this study, consisting of patients undergoing a primary pre-exposure rabies vaccine series. Blood samples will be obtained on three occasions: prior to immunization, 40 days later (10 days after the completed series), and 60 days later (30 days after the completed series). A series of ELISA assays will be run to determine the specific antibody responses (IgG, IgA, IgM, IgG1, IgG2, IgG3, or IgG4) to the two major antigenic epitopes of the rabies vaccine.

PRIOR AND CURRENT PROGRESS
A total of 29 subjects were enrolled in this study; none this past year. There have been no serious or unexpected adverse reactions. A total of 2 blood samples have been obtained from 18 subjects, and 3 samples from 16. Refinements in an IgG ELISA were made, but further standardization is necessary. Before testing can continue, a shipment of antigen from the CDC must be received.

CONCLUSIONS
Study is ongoing. A moderate IgG response to the rabies nucleoprotein was seen after three doses of vaccine. IgA and IgM responses have yet to be determined.

REPORT DATE: 05/11/94 WORK UNIT # 3369

DETAIL SUMMARY SHEET

TITLE: Survey of Prevalent Pollen and Fungal Aeroallergens in the Washington DC Area

KEYWORDS: pollen, aeroallergen, fungal

PRINCIPAL INVESTIGATOR: Kosisky, Susan
ASSOCIATES: Carpenter, Gary COL MC

SERVICE: Allergy-Immunology Service STATUS: Ongoing
APPROVAL DATE: May 1993

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To identify the predominant aeroallergen in the Washington, D.C. area. Identification of prevalent trees, weeds, and grasses are essential to the effective treatment and diagnosis of the allergic patient. Daily volumetric samples will re veal peak concentrations and pollination periods for area allergenic aeroallergens. Seasonal definition of pollination periods for trees, weeds, grasses, and molds will allow for the development of a better patient treatment regimen.

TECHNICAL APPROACH

Daily volumetric sampling using a Rotorod Sampler is conducted. Two polyurethane "I" rods are exposed to the atmosphere for collection of aeroallergens. The rods are microscopically examined for pollen grains and mold spores. Counts are converted to a volumetric grains/cubic meter assessment. The Rotorod Sampler is on the roof of the hospital, Building 2. Counts are conducted daily, weather permitting.

PRIOR AND CURRENT PROGRESS

The Allergen Extract Laboratory has been certified by the American Academy of Allergy and Immunology's Aeroallergen Network for the last 7 years. Counts are sent to the Pollen and Mold Spore Report published by the Academy annually. The volumetric counts submitted are the only quality-assured counts for the Washington, D.C. area. The laboratory is now certified to count mold spores, and assessment of peak concentrations for these aeroallergens is currently underway. A 5-year survey for area trees, weeds, and grasses is currently being written. The purchase of a Burkhard Spore Trap for better assessment of mold spores is being considered.

CONCLUSIONS

This study is ongoing. Assessment of data for the last 5 years is near completion. The more years of data accumulated, the better the assessment will be in terms of an overall picture of the predominant tree, weed, and grass aeroallergens. The survey for these aeroallergens will continue. Mold spore aeroallergens will be better assessed by the purchase of a Burkhard Spore Trap.

REPORT DATE: 07/25/94 WORK UNIT # 3371

DETAIL SUMMARY SHEET

TITLE: The Effect of Acetylsalicylic Acid (ASA) and Hydrocortisone (HC) on Urushiol Stimulated Lymphocytes and Epithelial Cells In Vitro

KEYWORDS: urushiol, aspirin, immunology

PRINCIPAL INVESTIGATOR: Radford, Bennett MAJ MC
ASSOCIATES: Salata, Kalman PhD

SERVICE: Allergy-Immunology Service STATUS: Ongoing
APPROVAL DATE: Jul 1993

FUNDING: Current FY: $ 1,213 Previous FYs: $ 0 Total: $ 1,213

STUDY OBJECTIVE
To study the effects of aspirin and hydrocortisone on urushiol-stimulated lymphocytes and keritinocytes in culture.

TECHNICAL APPROACH
Keritinocytes in culture will be stimulated with urushiol activation markers identified by flow cytometry. Aspirin will be added to interfere with cytokines' or adhesion molecules' communication with lymphocytes.

PRIOR AND CURRENT PROGRESS
No progress has occurred due to lack of adequate supplies and insufficient time for PI to perform study.

CONCLUSIONS
No conclusions can be made.

REPORT DATE: 10/15/93 WORK UNIT # 4804

DETAIL SUMMARY SHEET

TITLE: Antigen Typing Reticulocytes in Mixed Red Blood Cell Populations by Flow Cytometry

KEYWORDS: flow cytometry, reticulocyte, red cell antigens

PRINCIPAL INVESTIGATOR: Salata, Kalman PhD

SERVICE: Allergy-Immunology Service STATUS: Completed
APPROVAL DATE: Oct 1989

FUNDING: Current FY: $ 1,143 Previous FYs: $ 0 Total: $ 1,143

STUDY OBJECTIVE

To develop a procedure to determine the red cell antigen phenotype of a recently transfused patient using a sample containing both patient and donor blood.

TECHNICAL APPROACH

The approach being developed is a dual staining technique followed by analysis with a flow cytometer. The presence or absence of a particular red cell antigen is detected using the fluorescent stain phycoerythrin (PE) in an indirect antiglobulin procedure. Reticulocytes are stained with a second fluorescent stain, thiazole orange (TO). If one assumes that the reticulocytes are from the patient, then the phenotype of the reticulocyte is the patient's phenotype.

PRIOR AND CURRENT PROGRESS

Antigen phenotyping and reticulocyte identification have been performed on 319 mixed red cell samples using a flow cytometric method developed in this project. No identification has been performed this past year. Antigen positive and negative cells in both mature red cell and reticulocyte populations could be readily differentiated. Excellent results were obtained with antisera to Rh0, K, Fya, Fyb, Jka, and c(hr'). The S antigen proved to be a difficult problem, probably because it is only sparsely expressed on red cells. Samples from 19 patients were tested, and in the vast majority of cases the results agreed with the manual method which was the gold standard. The few disagreements occurred when there were too few reticulocytes or if the S antigen was involved. No false positives were recorded.

CONCLUSIONS

A simple, two-color flow cytometric method to phenotype mature red cells and reticulocytes was developed. This method correctly identifies the red cell antigen phenotypes in transfused patients. The method was applied to samples from patients who had received one unit of blood or who were massively transfused or chronically transfused.

REPORT DATE: 07/15/94 WORK UNIT # 4815

DETAIL SUMMARY SHEET

TITLE: Preparation and Characterization of Antibodies Directed Toward Enzymatically Treated Type A1 Erythrocytes

KEYWORDS: antibody, blood type, glycosidase

PRINCIPAL INVESTIGATOR: Salata, Kalman Ph.D.

SERVICE: Allergy-Immunology Service STATUS: Ongoing
APPROVAL DATE: Jul 1993

FUNDING: Current FY: $ 643 Previous FYs: $ 0 Total: $ 643

STUDY OBJECTIVE
To produce antisera against the residual antigen sites of enzymatically treated type A1 red blood cells. These antisera will provide tools to evaluate anzymatic conversion procedures for extent of type A antigen removal from red blood cells.

TECHNICAL APPROACH
Antibody induction in rabbits will be performed using glycocidase-treated red cells. Analysis of the amount and specificity of anti-red cell antibodies will be accomplished using absorption with red cells of known antigen type and standard blood bank hemagglutination techniques.

PRIOR AND CURRENT PROGRESS
Four New Zealand white rabbits were immunized with enzymatically treated cells provided by the New York Blood Center. All the rabbits responded to immunization but only one rabbit produced antibody which specifically recognized the antigen A-line remnants on enzyme treated cells. This antibody was of low titer but produced good reactivity in agglutination assays. This study requires a little more time to finish and will probably be closed before the end of the next reporting period.

CONCLUSIONS
A useful polyclonal antibody that is specific for antigen A-like remnants on red cells treated with alpha-N-acetylgalactosaminidase has been produced. This tool will greatly aid efforts in evaluating methods of converting type A blood to type O blood.

REPORT DATE: 09/16/94 WORK UNIT # 4817

DETAIL SUMMARY SHEET

TITLE: Flow Cytometry Analysis of Plasma Factors Affecting Reticulocyte Maturation in Refrigerated Blood

KEYWORDS: reticulocyte, flow cytometry, maturation

PRINCIPAL INVESTIGATOR: Salata, Kalman PhD

SERVICE: Allergy-Immunology Service STATUS: Ongoing
APPROVAL DATE: Sep 1993

FUNDING: Current FY: $ 4,404 Previous FYs: $ 0 Total: $ 4,404

STUDY OBJECTIVE
To determine if reticulocyte maturation in stored blood is dependent on temperature or plasma factors or both.

TECHNICAL APPROACH
Flow cytometry and thiazole orange staining are used to quantitate reticulocytes. Reticulocytes will be incubated at 4 and 37 degrees C. Fractions of plasma will be purified by molecular weight separation.

PRIOR AND CURRENT PROGRESS
Sixteen subjects were enrolled. There were no adverse reactions, and no one withdrew from the protocol. Temperature had the most effect on reticulocyte maturation; at 4 degrees C there was little or no change in reticulocyte number through 21 days, while at 37 degrees C no reticulocytes were detected after 7 days. The presence of plasma or fractions of plasma had little or no effect on reticulocyte maturation.

CONCLUSIONS
Reticulocyte maturation, or the lack of it, in stored blood appears to be temperature-dependent.

REPORT DATE: 11/17/93 WORK UNIT # 6276

DETAIL SUMMARY SHEET

TITLE: In Vivo Persistence of Reticulocyte and Antigen Phenotype in Post-Transfusion Patients Analyzed by Flow Cytometry

KEYWORDS: reticulocyte, blood transfusion, flow cytometry

PRINCIPAL INVESTIGATOR: Salata, Kalman PhD
ASSOCIATES: Cooper, Louis CAPT MC; Billups, Lloyd MSc

SERVICE: Allergy-Immunology Service

STATUS: Completed
APPROVAL DATE: Nov 1990

FUNDING: Current FY: $ 50 Previous FYs: $ 2,374 Total: $ 2,424

STUDY OBJECTIVE
To determine the in vivo time course of homologous reticulocyte survival of recently transfused patients.

TECHNICAL APPROACH
Peripheral blood specimens will be collected from patients immediately before transfusion, immediately after completion of transfusion, and 3, 6, 12, 24, 48, and 72 hours later. Donor and recipient blood samples will be phenotyped for 12 different red cell antigens. The reticulocyte members for both antigen positive and antigen negative reticulocytes will be determined using a two-color flow cytometer procedure developed in our laboratory. The absolute reticulocyte numbers and relative proportions will be analyzed.

PRIOR AND CURRENT PROGRESS
A total of 17 subjects have been enrolled; 2 were enrolled this past year. In 50% of patients, donor reticulocytes persisted for 48 hours, and in two cases, donor reticulocytes were detected 72 hours after transfusion. In two patients with low pre-transfusion reticulocyte counts, the donor reticulocytes predominated. In patients receiving regular transfusions, it was not possible to distinguish host and donor reticulocytes due to difficulties in establishing the host antigens. There have been no adverse reactions, and no subject has withdrawn from the study. This study is completed.

CONCLUSIONS
Donor reticulocytes may represent a significant portion of total reticulocytes in post transfusion samples collected within 72 hours and, consequently, create potential for misinterpretation of post-transfusion reticulocyte testing.

REPORT DATE: 06/17/94 WORK UNIT # 9286

DETAIL SUMMARY SHEET

TITLE: Major Histocompatibility Complex DNA Typing of Hemophilia A Patients

KEYWORDS: Hemophilia A, HLA-DQ, inhibitor

PRINCIPAL INVESTIGATOR: Salata, Kalman, PhD
ASSOCIATES: Kapur, Janet BSc(MT); Billups, Lloyd MSc

SERVICE: Allergy-Immunology Service

STATUS: Ongoing
APPROVAL DATE: Jun 1992

FUNDING: Current FY: $ 1,750 Previous FYs: $ 8,272 Total: $ 10,022

STUDY OBJECTIVE
To establish a genetic marker that will identify the hemophilia A patients at risk for developing anti-factor VIII inhibitor antibodies (inhibitors) using recently developed typing techniques.

TECHNICAL APPROACH
Polymerase chain reaction (PCR), southern blotting, synthetic oligonucleotides, and dot blotting are to be used to examine HLA-DQ polymorphism.

PRIOR AND CURRENT PROGRESS
Genomic DNA has been amplified and tested on gels. Amplified DNA has been put on dot blots and tested with oligonucleotide probes, a consensus sequence, and four specific probes. Work on the HLA-DQ polymorphism is complete, and the HLA-DP studies remain. There are no human subjects in this protocol.

CONCLUSIONS
PCR methods for HLA typing have been established. Studies are still ongoing; no conclusions can be drawn at this time.

REPORT DATE: 10/18/93 WORK UNIT # 3709

DETAIL SUMMARY SHEET

TITLE: Pathogenesis of Systemic Sclerosis: Role of Transforming Growth Factor-Beta

KEYWORDS: systemic sclerosis, TGF-beta

PRINCIPAL INVESTIGATOR: Tsokos, George MAJ MC

DEPARTMENT: Department of Clinical Investigation STATUS: Ongoing
APPROVAL DATE: Oct 1991

FUNDING: Current FY: $ 6,419 Previous FYs: $ 56,711 Total: $ 63,130

STUDY OBJECTIVE
To establish (1) the presence of TGF-B in the skin of patients with systemic sclerosis (SSc); (2) establish that peripheral blood mononuclear cells (MNC) from patients with SSc express more TGF-B than normal MNC; (3) compare TGF-B levels among patients at various clinical phases, and (4) determine the type of MNC that is primarily responsible for the production of TGF-B.

TECHNICAL APPROACH
Patients with an established diagnosis of SSc will be enrolled in this study. MNC from these patients' blood will be isolated by gradient centrifugation, and RNA will be extracted, run on agarose gels, and hybridized with TGF-B probe. Skin biopsy specimens will be strained with anti-TGF-B antibodies. Perivascular areas will be evaluated carefully. Clinical information will be collected.

PRIOR AND CURRENT PROGRESS
To date, skin biopsies from 17 patients collected by a collaborator at the University of Athens have been used. Immunohistochemical techniques have shown that certain isoforms of TGFbeta display a distinct distribution in the skin of patients with systemic sclerosis. The deposition is specific and is important to the understanding of systemic sclerosis. A soluble form of the adhesion molecule ICAM-1 was found to be increased in the sera of patients with systemic sclerosis. Association was detected between the serum levels of ICAM-1 and certain clinical features.

CONCLUSIONS
Study of the expression of cytokines and adhesion molecules in the tissues and sera of patients with systemic sclerosis helps delineate the origin of the disease. A prospective study at WRAMC is planned.

REPORT DATE: 06/07/94 WORK UNIT # 3714

DETAIL SUMMARY SHEET

TITLE: Role of Adhesion Molecules in the Activation of T Cells From Patients with Systemic Lupus Erythematosus (SLE)

KEYWORDS: lupus, adhesion molecules, T lymphocytes

PRINCIPAL INVESTIGATOR: Tsokos, George MAJ MC

DEPARTMENT: Department of Clinical Investigation STATUS: Ongoing
APPROVAL DATE: Jun 1992

FUNDING: Current FY: $ 5,675 Previous FYs: $ 4,157 Total: $ 9,832

STUDY OBJECTIVE
To assess the role of adhesion molecules in the pathogenesis of systemic lupus erythematosus (SLE), and to determine whether deficient adhesion molecule expression and function are responsible for the inability of SLE T cells to respond to recall antigens.

TECHNICAL APPROACH
T cells will be obtained from the peripheral blood of patients with SLE by Ficoll gradient centrifugation and sheep erythrocyte rosetting. T cells will be cultured in the presence of recall antigens, and in the presence of functional adhesion molecules.

PRIOR AND CURRENT PROGRESS
T cells from patients with SLE have been stimulated with the nominal antigen tetanus toxoid or an anti-CD3 monoclonal antibody in the presence or absence of costimulatory molecules. Experiments performed this year showed that the BB1 adhesion molecule exerts its action by binding to the T cell surface molecule CD28. Five patients were studied during the last year (18 total). No side effects were noted. There was no benefit to the patients.

CONCLUSIONS
T cells from patients with SLE demonstrate decreased ability to antigens that can be restored in the presence of normal amounts of adhesion molecules.

REPORT DATE: 07/17/94 WORK UNIT # 3715

DETAIL SUMMARY SHEET

TITLE: Metabolic Parameters in Systemic Lupus Erythematosus with Neuropsychiatric Manifestations

KEYWORDS: Lupus erythematosus, neuropsychiatric, metabolic parameters

PRINCIPAL INVESTIGATOR: Tsokos, George MAJ MC

DEPARTMENT: Department of Clinical Investigation STATUS: Ongoing
APPROVAL DATE: Jul 1992

FUNDING: Current FY: $21,543 Previous FYs: $ 29,592 Total: $ 51,135

STUDY OBJECTIVE
To establish the value of cerebrospinal fluid (CSF) metabolic parameters in the diagnosis of active central nervous system (CNS) disease.

TECHNICAL APPROACH
Patients will be evaluated clinically, and a neuropsychiatric evaluation will be completed. Levels of C5b-9, C3a C4, antineuronal antibodies, antiphospholipid antibodies, quinolinic acid, and interleukin 6 will be determined in the cerebrospinal fluid (CSF) of patients with systemic lupus erythematosis (SLE). The diagnosis and prognostic value of these parameters will be determined.

PRIOR AND CURRENT PROGRESS
A total of 41 subjects have been enrolled. During the last year, 30 more CSF and serum samples were analyzed from patients with SLE. These samples were provided by Dr. West at Fitzsimmons Medical Center. The new data confirmed that quinolinic acid levels are elevated in a subgroup of SLE patients that have either seizures or neuritis. Serum levels correlated well with CSF levels. There have been no adverse reactions.

CONCLUSIONS
Quinolinic acid levels are elevated in patients with SLE who have seizures or neuritis. SLE patients who have other neuropyschiatric disorders do not have elevated levels of quinolinic acid.

REPORT DATE: 10/25/93 WORK UNIT # 9275

DETAIL SUMMARY SHEET

TITLE: Quantitation and Characterization of EGF Levels in Rat Milk

KEYWORDS: EGF, milk, rat

PRINCIPAL INVESTIGATOR: Schaudies, Paul MAJ MS

DEPARTMENT: Department of Clinical Investigation STATUS: Completed
APPROVAL DATE: Oct 1988

FUNDING: Current FY: $ 0 Previous FYs: $ 16,791 Total: $ 16,791

STUDY OBJECTIVE
To examine the levels of epidermal growth factor (EGF) present in rat milk. To identify immunoreactive species of EGF and determine relationship to standard r-EGF. To characterize forms regarding their biological activities in vitro. To determine the functional roles of the multiple forms of biologically active EGF present in normal rat milk.

TECHNICAL APPROACH
Radioimmunoassay of diluted whole rat milk. Generation of an affinity resin against rat EGF. Affinity extraction of immunoreactive material in milk. Native polyacrylamide gel electrophoresis of affinity purified materials. Extraction of activity from gels. Assay of activity for receptor binding and induction of DNA synthesis.

PRIOR AND CURRENT PROGRESS
No additional progress was done this year.

CONCLUSIONS
This study has determined that levels of EGF in the gastrointestinal tract of suckling rats is provided from mother's milk rather than through local synthesis. Results have demonstrated hormonal control of EGF levels within the pancreas and kidney of the suckling rat. T3 causes an increase in renal EGF levels, whereas cortisone causes an increase in EGF in the pancreas of suckling rats.

REPORT DATE: 04/12/94 WORK UNIT # 9284

DETAIL SUMMARY SHEET

TITLE: Comparison of the Hela Cell Monolayer Vs. the Toxi-titer System for Their Respective Ability to Detect Clostridium Difficile Toxin B in Stool Filtrate

KEYWORDS: C. difficile, toxin B, assay

PRINCIPAL INVESTIGATOR: Dobek, Arthur PhD
ASSOCIATES: Rothman, Sara PhD; McEvoy, Peter MAJ MC

DEPARTMENT: Department of Clinical Investigation

STATUS: Ongoing
APPROVAL DATE: Apr 1991

FUNDING: Current FY: $ 1,325 Previous FYs: $ 5,792 Total: $ 7,117

STUDY OBJECTIVE

To compare two diagnostic tests for reliability detecting Clostridium difficile toxin B in patient stool filtrates: a commercial human foreskin fibroblast cell assay (toxi-titer) and a cytotoxicity assay (an historical standard that can detect as little as 1 pg of toxin B) on HeLa cell monolayers cultured at WRAIR. Data will be compared with toxin A positive data detected by a commercial microtiter assay kit using the same stools.

TECHNICAL APPROACH

Stools sent to the Clinical Microbiology Laboratory, WRAIR, for C. difficile toxin assay are used. They were originally tested for toxin A by a commercial latex bead agglutination test, but this test was discontinued for failure to detect toxin A. To compensate, the DCI lab now uses a commercial microtiter plate assay for toxin A to test all frozen stool aliquots in batches of 89 specimens. Those found positive, as well as a negative series, will be tested as a batch for toxin B by HeLa cell and toxi-titer assays.

PRIOR AND CURRENT PROGRESS

A total of 801 samples from 643 patients (118 this past year) were tested. A total of 93 samples from 87 patients (13.5% of total population) were positive by ELISA toxin A kit; 73 (78.5%) were also positive by HeLa cell cytotoxin assay, but 20 (21.5%) were HeLa negative. Of 100 specimens negative by the toxin A kit, 94 (94%) were also negative by the HeLa cell assay, and 6 were HeLa positive. Statistical analysis at the 95% confidence interval (CI) indicates a positive predictive value of 78.5% at a CI of 68-86%, and a negative predictive value of 94% at a CI of 87-97%. Sensitivity of 95% CI for the 79 sample size (HeLa +) is 92.4% with a CI of 84-97%; specificity for a 114 sample size (HeLa -) is 82.5% with a CI of 74-89%. At the 95% CI, the 21.5% falsely positive by ELISA test have a CI of 14-31%, and the 6% falsely negative have a CI of 2.5-13%.

CONCLUSIONS

The high sensitivity (92.4%) of the toxi-titer test appears to be achieved at sacrifice to specificity (82.4%), a result published by others. The suggestion to use more than one test for presence of C. difficile toxin remains valid, as shown by 6% false negatives using only the toxi-titer method.

REPORT DATE: 01/14/94 WORK UNIT # 9285

DETAIL SUMMARY SHEET

TITLE: Honey: Antibacterial Activity Against Multiple Antibiotic Resistant Clinical Isolates In Vitro

KEYWORDS: antibacterial agent, clinical isolate, honey

PRINCIPAL INVESTIGATOR: Dobek, Arthur PhD
ASSOCIATES: Payne, Matthew CPT MC

DEPARTMENT: Department of Clinical Investigation

STATUS: Ongoing
APPROVAL DATE: Jan 1992

FUNDING: Current FY: $ 526 Previous FYs: $ 1,729 Total: $ 2,255

STUDY OBJECTIVE

To determine: (1) whether commercial honey and any of its specific components can inhibit clinical isolates in vitro, especially those resistant to one or several antibiotics; (2) the identity of the antibacterial agents in honey; and (3) whether honey from different plant sources have varying antibacterial activity based upon the concentration or presence of the inhibitory agents.

TECHNICAL APPROACH

Thirty-nine clinical isolates each of Escherichia coli, Proteus mirabilis, Enterobacter spp, Pseudomonas aeruginos, Klebsiella spp, and multiple antibiotic resistant Staphylococcus aureus will be tested for inhibition by commercial pure honey samples from four different plants (clover, alfalfa, orange blossom, and safflower) using agar well diffusion. In addition, a limited amount of sugar-free clover honey extract will be compared with pure clover honey for inhibition against five isolates of S. aureus and of E. coli. All tests will be done in duplicate with a range of honey concentrations from 80% to 0.625%. Cultures will be considered sensitive if the zones of inhibition are at least 10 mm in diameter.

PRIOR AND CURRENT PROGRESS

As previously reported, the extract of clover honey, provided by the late Dr. Klayman, inhibited S. aureus and E. coli isolates. Project chemist, CPT Payne, provided three separate extracts of clover honey for inhibition testing of the isolate collection. None of the isolates were inhibited by any of the extracts, even at approximately 3 times the concentration of the Klayman extract. The commercial clover honey from which these extracts were made did inhibit all of the S. aureus, E. coli, and Enterobacter spp. isolates, as has been previously found. As a noteworthy observation, the Klayman extract possessed the distinct odor of fresh apples, whereas none of the new extracts has that odor. The implication of this discrepancy is unknown.

CONCLUSIONS

Since the honey source of the new extracts inhibited the isolates, while the extracts themselves did not, the inhibitory agents may have been lost, altered, or reduced in concentration in the extraction procedure. A re-examination of the extraction procedure and a repeat of the extraction, or its modification, would be the next step prior to inhibition testing.

REPORT DATE: 01/06/94 WORK UNIT # 9287

DETAIL SUMMARY SHEET

TITLE: The Effect of Lipid Emulsion on the Duration of Ketamine/Xylazine Sedation in Rats

KEYWORDS: lipid, ketamine, xylazine

PRINCIPAL INVESTIGATOR: Bailey, Lynn

DEPARTMENT: Department of Clinical Investigation STATUS: Ongoing
APPROVAL DATE: Jan 1993

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine if rats treated with Intralipid remain sedated longer with ketamine and xylazine than non-treated rats.

TECHNICAL APPROACH
Part 1 rats will be randomized into three groups: saline and Intralipid, ketamine/xylazine and Intralipid, and ketamine/xylazine and saline. After treatment they will be evaluated every 30 minutes for depth of anesthesia. Part 2 will use the same animals in three different groups (Ketamine/xylazine 3 days after treatment of Intralipid, Intralipid after treatment of Ketamine/xylazine, and Ketamine and Intralipid), and will be evaluated in the same manner as Part 1.

PRIOR AND CURRENT PROGRESS
Eighteen animals were used, and both parts of the experiment were performed. There were no adverse reactions. However, there was some question about the reliability of data collected from Part 2 due to possible carry-over effects from Part 1. Therefore, this data will be considered but not used to draw specific conclusions.

CONCLUSIONS
The animals treated with lipid recovered from anesthesia on an average of 50% slower than non-treated animals. More study needs to be done to determine if the results are affected by the route of administration of the anesthetic and by use of ketamine without xylazine.

REPORT DATE: 06/28/94 WORK UNIT # 9288

DETAIL SUMMARY SHEET

TITLE: Effects of Trendelenburg Position on Cardiopulmonary Parameters During Sleep

KEYWORDS: sleep apnea, Trendelenburg, snoring

PRINCIPAL INVESTIGATOR: Hamm, Carolyn Ph.D.

DEPARTMENT: Department of Clinical Investigation STATUS: Ongoing
APPROVAL DATE: Jun 1993

FUNDING: Current FY: $ 1,750 Previous FYs: $ 0 Total: $ 1,750

STUDY OBJECTIVE

To: 1) determine the effects of Trendelenburg and reverse Trendelenburg positions on physiological parameters monitored during sleep in subjects with varying degrees of sleep-related respiratory disturbances; and 2) investigate the effects of a benzodizepine on respiratory and cardiovascular parameters during sleep.

TECHNICAL APPROACH

Plans are to enter 12 adult male subjects each into the following three groups: non-snorers, snorers with RDI less than 15, and apneics with RDI greater than 30 but less than 60. Five nocturnal polysomnograms will be taken including; baseline, horizontal, 7 degrees Trendelenburg, 7 degrees reverse Trendelenburg, and benzodiazepine. Sleep stages, snoring, respiratory disturbances, blood pressure, heart rate, oxyhemoglobin saturation, and upper airway resistances will be compared in a between within repeated measures ANOVA.

PRIOR AND CURRENT PROGRESS

Five subjects have been enrolled in the protocol. One has completed the five polysomnograms, and two are midway through the study. Two subjects are completing sleep diaries in preparation for the nocturnal studies. Three additional subjects have expressed interest and are being scheduled for sleep histories. There have been no serious or unexpected adverse reactions, and no subjects have been withdrawn. All subjects in the protocol have benefited from identification of an underlying sleep disorder.

CONCLUSIONS

Data from this study may pinpoint the site of collapse of the upper airway, providing greater therapeutic benefit from surgery or alternative treatment for obstructive sleep apnea.

REPORT DATE: 01/07/94 WORK UNIT # 9411

DETAIL SUMMARY SHEET

TITLE: Evaluation of Collagen Plugs to Prevent Localized Osteitis in the Sockets of Mandibular Third Molars Susceptible to Acute Pericornitis

KEYWORDS: collagen, plugs, osteitis

PRINCIPAL INVESTIGATOR: Patterson, Adrian COL DC
ASSOCIATES: Baumgartner, John DDS; Glenn, Roger MAJ DC

SERVICE: Dental Clinic STATUS: Completed
APPROVAL DATE: Jan 1991

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine if collagen plugs are useful in preventing postoperative alveolar osteitis in third molar tooth sockets susceptible to pericoronitis. To determine if collagen plugs are useful in preventing postoperative alveolar osteitis in third molar tooth sockets which were susceptible to pericoronitis.

TECHNICAL APPROACH
This is a multi-center study. Each practitioner will extract approximately 100 third molars susceptible to pericoronitis. Patients will be randomly selected to either receive or not receive a collagen plug in the third molar socket after extraction. The patient will be evaluated 7 days post-surgery to determine if a dry socket or any other sequelae is present.

PRIOR AND CURRENT PROGRESS
A total of 162 patients have been enrolled; none since this past year. There has been no progress during the past year; this study is now closed.

CONCLUSIONS
Due to an inadequate number of patients in the study, no statistically significant conclusions could be drawn. However, the data suggest that the collagen plug may help to prevent dry socket.

REPORT DATE: 03/21/94 WORK UNIT # 9412

DETAIL SUMMARY SHEET

TITLE: Comparison of Presurgical and Postsurgical Condylar Measurements as a Function of Orthognathic Surgical Fixation Technique

KEYWORDS: condylar measurements, mandibular movement

PRINCIPAL INVESTIGATOR: Brousseau, Steven LTC DC

SERVICE: Dental Clinic STATUS: Completed
APPROVAL DATE: Mar 1991

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To measure changes in the temporomandibular joint (TMJ) that result from mandibular and/or mandibular-maxillary surgery, using presurgical and postsurgical (3-month, 6-month, 9-month) pantographic tracings to correlate clinical symptoms/signs with changes in condylar path tracings. The goal will be to try to use this information to predict problems with specific surgical movements and the use of rigid vs non-rigid fixation.

TECHNICAL APPROACH
Tracing of the condylar pathway during mandibular movement is a noninvasive diagnostic technique that allows quantitative and qualitative analysis of TMJ function. With a condylar path recording device, disk-condyle incoordination can be seen as a deviation or obstruction in the tracing pathway. The condylar path tracing can be translated into a PRI score, which can be used to compare and to correlate with clinical TMJ findings.

PRIOR AND CURRENT PROGRESS
No patients were seen last fiscal year; 16 have been enrolled altogether.

CONCLUSIONS
None.

REPORT DATE: 03/11/94 WORK UNIT # 9088

DETAIL SUMMARY SHEET

TITLE: Prevention of Low Back Pain in Military Basic Trainees

KEYWORDS: low back pain, prevention, smoking

PRINCIPAL INVESTIGATOR: O'Connor, Francis CPT MC
ASSOCIATES: Marlowe, Sarah CPT MC

SERVICE: Fort Dix, New Jersey STATUS: Completed
APPROVAL DATE: Mar 1991

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine the incidence and risk factors of low back pain (LBP) in military basic trainees; and to evaluate the role of exercise in preventing low back pain.

TECHNICAL APPROACH
Entry and exit survey questionnaires will be administered to evaluate subjective LBP in basic trainees, as well as detailed demographic data. Specific exercises will be introduced into a control basic training company, and then reevaluated through entry and exit survey.

PRIOR AND CURRENT PROGRESS
A total of 600 questionnaires were used in data analysis. The preliminary study on demographics was completed and published. The intervention study was completed; data was analyzed and is being prepared for presentation and publication.

CONCLUSIONS
Low back pain has an incidence of 15% in Army basic training. Smoking history is significantly associated with the onset of low back pain. A specific exercise intervention did not specifically prevent the onset of low back pain.

REPORT DATE: 01/21/94 WORK UNIT # 8200

DETAIL SUMMARY SHEET

TITLE: Prescribed Medication Use Among Troops Deploying and Deployed to Somalia: Pharmacoepidemiologic Analysis

KEYWORDS: pharmacy, pharmacoepidemiology, Somalia

PRINCIPAL INVESTIGATOR: Grabenstein, John EdM, MS
ASSOCIATES: Vauter, Robert RPh; Harris, Thomas SFC

SERVICE: Fort Drum, NY STATUS: Completed
APPROVAL DATE: Jan 1993

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To describe the frequency of chronic ambulatory prescriptions dispensed to troops deploying to Somalia for Operation Restore Hope, and to determine the incidence of medication-related hospital admissions in Somalia.

TECHNICAL APPROACH
A retrospective assessment of all prescriptions recorded in the pharmacy computer database, compared to the roster of troops deployed. Setting: Guthrie Army Health Clinic and Conner Troop Medical Clinic, 10th Mountain Division, Fort Drum, NY: 86th Evacuation Hospital, Mogadishu, Somalia. Subjects: All 3,701 soldiers of the 10th Mountain Division deploying between 24 November 1992 and 12 January 1993. The distribution of military rank was 85.5% enlisted soldiers, 2.8% warrant officers, and 11.6% commissioned officers. The analysis included combat arms, combat support, and combat service support troops, 93.2% of whom were male.

PRIOR AND CURRENT PROGRESS
Prescriptions for acute care (i.e., sick call) medications, immunizations, and malaria chemoprophylaxis were not included in this study. A total of 425 prescriptions were dispensed to 373 deploying soldiers (1.56 Rx per recipient). Of 3,701 troops, 7.4% had at least 1 prescription filled. For each 1,000 troops deployed, 114.8 prescriptions were dispensed. Of 273 prescription users, 69.9% received just 1 medication, and 7.0% received 4 or more. Of 333 presumptive diagnoses, inferred from usual medication indications, the most common diagnostic groups were contraceptive, musculoskeletal, dermatologic, respiratory, cardiovascular, allergic, and sedative/hypnotic. Women represented 6.8% of these troops and 31.5% of prescription recipients, and received 29.4% of prescriptions dispensed. Women were 6.5 times as likely to receive a prescription as men, or 3.4 times as likely if oral contraceptives were excluded.

CONCLUSIONS
Guthrie Health Clinic filled 1.15 ambulatory prescriptions for every 10 troops deployed overseas, primarily for contraceptive, musculoskeletal, dermatologic, respiratory, and cardiovascular diagnoses. Of 3,701 troops, 7.4% had 1 or more prescriptions filled. Soldiers with more time in military service were more likely to receive prescriptions than younger ones.

REPORT DATE: 01/12/94 WORK UNIT # 1952

DETAIL SUMMARY SHEET

TITLE: The Clinical Presentation of HIV Infected Patients at Walter Reed Army Medical Center

KEYWORDS: HIV, epidemiology, disease progression

PRINCIPAL INVESTIGATOR: Oster, Charles COL MC
ASSOCIATES: Chung, Raymond COL MC; Hicks, Charles LTC MC

SERVICE: HIV Research STATUS: Ongoing
APPROVAL DATE: Jan 1987

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To evaluate clinical and laboratory data on the first 402 adults seen in clinic at WRAMC who are infected with HIV-1.

TECHNICAL APPROACH
This will be a retrospective chart review of medical records and laboratory studies on HIV-infected patients. An addendum was submitted during the past year (FY93) requesting exception to policy to extend the duration of this study for 5 years (i.e., 1998).

PRIOR AND CURRENT PROGRESS
This is a retrospective protocol used with RV-1 Natural History of HIV Infection (W.U. #8804). Please refer to RV-1's Annual Progress Report. A total of 50 charts were reviewed in the last year as part of a bacteremia in HIV study; 22 altogether. Results of this study are still in analysis.

CONCLUSIONS
None.

REPORT DATE: 07/15/94 WORK UNIT # 2529

DETAIL SUMMARY SHEET

TITLE: Pharyngeal Tonsillar Biopsy Protocol: Feasibility Study

KEYWORDS: HIV RNA, lymph node biopsy, HIV viral load

PRINCIPAL INVESTIGATOR: Turnicky, Ronald LTC MC
ASSOCIATES: Anderson, David MD; Mann, Eric MD

SERVICE: HIV Research STATUS: Ongoing
APPROVAL DATE: Jun 1993

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine the feasibility of using lymphoid tissue biopcy (lymph node and tonsil) as a means to monitor therapeutic effectiveness and natural progression of HIV disease.

TECHNICAL APPROACH
Tonsilar tissue and anterior cervical lymph nodes are biopsied in early stage patients (WRS I-II). The tissues are placed in formalin, snap frozen in liquid nitrogen, and placed in RPMI solution. Morphology, immunologic parameters (quantitative phenotyping by image analysis), and in situ hybridization are performed. Flow cytometry is used to quality control research methodologies. Quantitative PCR in tissue is compared to viral burden in the peripheral blood.

PRIOR AND CURRENT PROGRESS
Four biopsies were obtained, and three patients enrolled. A total of six patients are expected. All patients demonstrated a marked expression of HIV RNA localized to the germinal centers of the lymphoid tissue. Within stage matched patients (WRS II) there is a morphologic and molecular difference among patients. Those without retrogressive changes of the lymphoid tissue demonstrate a HIV RNS distribution pattern along dendritic reticulum cells; those with retrogressive changes have a greater number of individually expressing cells. All HIV positive patients demonstrate a significantly increased number of cytotoxic T cells within all lymphoid tissue compartments when compared to controls. There were no serious or unexpected adverse reactions.

CONCLUSIONS
Differences exist in WRS II matched patients regarding HIV viral RNA distribution within lymphoid tissue. Immunologic profiles are similar among all HIV positive patients, but all show a significant increase in cytotoxic T cells over non-HIV controls. This may relate to eventual immunologic destruction of nodal and tonsilar tissue and eventual immune collapse of the host.

REPORT DATE: 07/08/94 WORK UNIT # 3370

DETAIL SUMMARY SHEET

TITLE: A Phase I Study of the Safety and Immunogenicity of MNrgp 120/HIV-1 Vaccine Comparing HIV-1 Seropositive Subjects Previously Immunized with IIIB rgp120/HIV-1 Vaccine on Protocol VO200g and HIV-1 Seropositive Subjects Who Have Not Previously Received HIV

KEYWORDS: vaccine, HIV seropositive, rgp 120 Genentech

PRINCIPAL INVESTIGATOR: Birx, Deborah LTC MC
ASSOCIATES: Redfield, Robert COL MC

SERVICE: HIV Research STATUS: Completed
APPROVAL DATE: Jun 1993

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To evaluate intraclade cross reactivity at the cellular and humoral immune response levels in order to determine the requirement for strand specificity.

TECHNICAL APPROACH
To immunize HIV-1 (IIIb) and have seropositives to HIV-1 (MN). To evaluate broadening to CD4 recognition and CD8 cytotoxicity as well as humoral response to HIV-1.

PRIOR AND CURRENT PROGRESS
This project was terminated prior to enrollment due to funding and priority changes along with reorganization within the MMCARR and Genentech.

CONCLUSIONS
Study not conducted.

REPORT DATE: 04/28/94 WORK UNIT # 6264

DETAIL SUMMARY SHEET

TITLE: Perinatal HIV Infection: Epidemiology and Natural History

KEYWORDS: natural history, perinatal HIV, epidemiology

PRINCIPAL INVESTIGATOR: Robb, Merlin LTC MC

SERVICE: HIV Research STATUS: Ongoing
APPROVAL DATE: Apr 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To develop a central perinatal program for the identification, evaluation, and follow-up of HIV-infected pregnant women and their newborn infants, and to describe the clinicopathologic correlates most predictive of perinatal transmission of HIV.

TECHNICAL APPROACH
High risk pregnant women and maternal-infant pairs are prospectively entered into a longitudinal study to evaluate immunologic status and detect vertical transmission of HIV infection in early infancy. Quarterly clinical examination and serologic/immunologic assays are utilized to fully characterize the immune status of all patients. Statistical analysis of clinical and laboratory results will be directed toward the identification of perinatal factors which are reliable predictors of vertical transmission.

PRIOR AND CURRENT PROGRESS
A total of 46 maternal-infant pairs (25 pairs during the past year) have been enrolled at 5 participating military medical centers: WRAMC (11); National Naval Medical Center (2); Madigan Army Medical Center (1); Wilford Hall (15), and San Diego Naval Medical Center (9). One of these women has yet to deliver. One death occurred in the last year; the cause of death was related to HIV. Ten families are no longer active in the protocol. Thirty-six families remain active on the protocol.

CONCLUSIONS
The apparent transmission rate based upon this experience is 25%. Patient enrollment is hampered by the geographic dispersion of HIV-infected pregnant women in the DOD. Also, the majority of HIV-infected women have HIV-uninfected spouses. As a consequence, HIV is usually discovered through screening in the prenatal clinics at DOD MTF's. Maternal disease stage is linked to the risk of HIV transmission with WR3-6 having almost twice the risk of transmission to infants.

REPORT DATE: 01/12/94 WORK UNIT # 6346

DETAIL SUMMARY SHEET

TITLE: Pediatric Vaccine Therapy: A Phase I, Feasibility Trial of Vaxsyn (rgp160 vaccine) in HIV Infected Symptomatic and Asymptomatic Children and Adolescents

KEYWORDS: MicroGeneSys rgp160, HIV, children

PRINCIPAL INVESTIGATOR: Robb, Merlin MAJ MC

SERVICE: HIV Research STATUS: Completed
APPROVAL DATE: Jan 1993

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine the feasibility, in terms of immunogenicity, practicality, and safety, of a recombinant HIV envelope virus vaccine, MicroGeneSys rgp 160, in infants and children with HIV infection. The study will assess the vaccine in patients who require antiretroviral therapy, as well as in infants and young children who do not require intervention at the time of enrollment.

TECHNICAL APPROACH
This Phase 1 study will have two parts: A and B. All patients will receive primary immunization over 12 months, and be followed for 6 months. In Part A, plans are to enroll about 30 children with perinatally acquired HIV at three military regional centers and at a collaborating civilian site. Patients in Part A must be asymptomatic or have mild symptoms of HIV. Patients must not be on nucleoside analogs or other potentially immunomodulatory agents (e.g., corticoseroids, interferons, or IVIG). In Part B, plans are to enroll another 30 patients 2 months-18 years old with major symptoms of HIV that define an immunosuppressed status, or who have CD4 counts which qualify them for antiretroviral therapy.

PRIOR AND CURRENT PROGRESS
Study was terminated prior to implementation due to lack of MMCARR funds for this project.

CONCLUSIONS
Same as above.

REPORT DATE: 04/12/94 WORK UNIT # 7243

DETAIL SUMMARY SHEET

TITLE: Psychiatric Natural History Study: Factors Related to Human Immunodeficiency Virus Transmission and Morbidity

KEYWORDS: HIV risk behaviors, early HIV disease, military performance

PRINCIPAL INVESTIGATOR: Tomoshok, Lydia PhD
ASSOCIATES: Nannis, Ellen PhD; Brandt, Ursula PhD

SERVICE: HIV Research STATUS: Ongoing
APPROVAL DATE: Apr 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine potential areas for effective interventions designed to reduce HIV transmission by HIV-infected military medical beneficiaries, and to reduce neuropsychiatric complications of HIV disease progression in infected military medical beneficiaries.

TECHNICAL APPROACH
Military medical beneficiaries from all three services [500 from Walter Reed Army Medical Center, 700 from Wilford Hall (WHMC), 300 from National Naval Medical Center (NNMC), and 400 from San Diego Naval Hospital] will be asked to complete anonymous risk behavior assessments. Smaller numbers of infected individuals will be recruited to participate in other non-anonymous protocol core areas; psychosocial (N=1,400), psychiatry (N=1,000), stress and coping (N=1,000), and neuropsychology (N=500). These non-anonymous but confidential portions of the protocol will be repeated at each patient's routine medical re-evaluation.

PRIOR AND CURRENT PROGRESS
Data collection for this protocol has been completed at all sites. A total of 273 HIV+ subjects have been enrolled at WRAMC, 262 at NNMC, 703 at WHMC, and 25 at WOMACK. A total of 100 HIV- controls have been enrolled in the neurobehavioral addendum. In-depth data analysis is ongoing. and scientific presentations and publications are in progress. There were no adverse reactions.

CONCLUSIONS
Preliminary data analyses have been completed. Two intervention protocols based on data from RV-26 have received approval by the USARMDC Retrovirus Clinical Research Committee. Upon receipt of full scientific approval, these protocols will be forwarded to the appropriate Human Use Committees.

REPORT DATE: 04/30/94 WORK UNIT # 8802

DETAIL SUMMARY SHEET

TITLE: VA Cooperative Study No. 298, Treatment of AIDS and AIDS Related Complex; Part I: Treatment of Patients with ARC (AZT Vs. Placebo)

KEYWORDS: zidovudine, HIV, ARC

PRINCIPAL INVESTIGATOR: Hawkes, Clifton LTC MC

SERVICE: HIV Research STATUS: Completed
APPROVAL DATE: Apr 1988

FUNDING: Current FY: $ 0 Previous FYs: $ 996 Total: $ 996

STUDY OBJECTIVE
To determine the effectiveness of AZT (zidovudine) on AIDS Related Complex (ARC) - Walter Reed Stages 2-4.

TECHNICAL APPROACH
This is a randomized double-blind placebo-controlled study. Subjects who meet the inclusion criteria, after screening, are randomized onto the study drug. Half of the subjects receive AZT 250 mg every 4 hours, while the other half receive a placebo. In January 1991, Part I was completed; all participants were informed of their original treatment assignment and given the opportunity to remain or be started on open-label zidovudine or placebo. In February 1991, an addendum was approved which allowed for extended follow-up for all participants who agreed to continue and sign a revised informed consent. The extension was granted for 3 years (i.e., April 1994).

PRIOR AND CURRENT PROGRESS
A total of 213 patients (9 from WRAMC) have been enrolled. There were no new patients enrolled since the last report. Part II of this study is now completed. No patients withdrew from the study because of adverse reactions. Unused drug (Zidovudine) was returned to the Veterans Administration Cooperative Studies Program in Albuquerque, New Mexico (per Ms. Janet Foster, Study Pharmacist).

CONCLUSIONS
Final analysis of data being conducted at this time. Conclusions regarding the effectiveness of early use of Zidovudine long-term will be made pending completion of statistical data analysis.

REPORT DATE: 05/24/94 WORK UNIT # 8803

DETAIL SUMMARY SHEET

TITLE: Core Protocol for HIV Developmental Diagnostics (Adults)

KEYWORDS: HIV, AIDS, virus culture

PRINCIPAL INVESTIGATOR: Chung, Raymond COL MC
ASSOCIATES: Oster, Charles COL MC

SERVICE: HIV Research STATUS: Ongoing
APPROVAL DATE: May 1988

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To develop and evaluate new and/or improved laboratory methods for establishing the diagnosis of HIV infection and for determining the stage of illness.

TECHNICAL APPROACH
Methods to detect replicating HIV virus, HIV antigens, and HIV nucleic acids will be used, including, for example, virus culture, antigen capture immunoassay, and polymerase chain reaction (PCR) amplification of HIV DNA.

PRIOR AND CURRENT PROGRESS
The total number of subjects enrolled is 822. As of 30 Apr 94, there were 500 active patients. During the past year, there were 73 new enrollments and 96 terminations (32 lost to follow-up, 6 patient withdrawals, 19 deaths, 18 transfers, and 21 other). The study continues to collect samples in conjunction with RV1 (W.U. #8804).

CONCLUSIONS
No conclusions at this time. Data still being collected in conjunction with Navy and Air Force.

REPORT DATE: 05/24/94 WORK UNIT # 8804

DETAIL SUMMARY SHEET

TITLE: The Natural History of HIV Infection and Disease in United States Military Beneficiaries

KEYWORDS: HIV, natural history, AIDS

PRINCIPAL INVESTIGATOR: Chung, Raymond COL MC

SERVICE: HIV Research STATUS: Ongoing
APPROVAL DATE: May 1988

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To systematically document the natural disease progression of HIV infection.

TECHNICAL APPROACH
Information already being routinely collected on HIV patients is being organized into a data base in such a way that more scientifically valid information will be forthcoming. Safeguards to patient confidentiality are met. This data base forms the core around which other specific protocols can be built.

PRIOR AND CURRENT PROGRESS
The total number of subjects enrolled is 864. As of 30 Apr 94, there were 530 active patients. During the past year, there were 75 new enrollments, and 226 terminations (117 lost to follow-up, 4 patient withdrawals, 51 deaths, 23 transfers, and 31 other). The protocol continues to collect natural history data.

CONCLUSIONS
No conclusions at this time. Data is still being collected in conjunction with the Navy and the Air Force.

REPORT DATE: 10/15/93 WORK UNIT # 8805

DETAIL SUMMARY SHEET

TITLE: Natural History of Oral Manifestations of HIV Infection in a United States Military Population

KEYWORDS: epidemiology, oral diseases, HIV

PRINCIPAL INVESTIGATOR: Konzelman, Joseph DDS
ASSOCIATES: Winn, Deborah PhD; Kleinman, Dushanka DDS MScD

SERVICE: HIV Research STATUS: Ongoing
APPROVAL DATE: Oct 1988

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To document the prevalence and incidence of oral manifestations of HIV infection in relation to the degree of immunodeficiency. Emphasis is given to oral pathologies, periodontal disease, oral candidal infections, and the effect of HIV on salivary constituents.

TECHNICAL APPROACH
Volunteers receive a comprehensive oral examination at entry and every 6 months thereafter. This evaluation includes clinical examinations for dental caries, periodontal disease, and oral mucosal pathologies. Dental plaque and saliva samples are collected for microbial and biochemical assays, and a questionnaire on oral health-related behaviors and history is administered. Data are analyzed in relation to subjects' medical condition and immune status.

PRIOR AND CURRENT PROGRESS
During the past year, 124 subjects have been enrolled; the current total is 1,070 enrollees (all of them are WRAMC patients). An initial baseline oral exam has been given to 784 subjects, and at least one 6-month follow-up exam has been given to 427 subjects. No adverse reactions have been reported, and no patients have withdrawn from the study. Benefits to subjects include early diagnosis of oral disease, dental prophylaxis, limited emergency care, and referral for appropriate treatment.

CONCLUSIONS
Prevalence of oral mucosal pathology was 32% at baseline and 44% after 6 months of follow-up. More than 30% of subjects initially free of mucosal pathology developed oral lesions within 6 months. Oral candidiasis was the condition that developed most frequently, with 70% of incident cases being of the erythematous form.

REPORT DATE: 11/18/93 WORK UNIT # 8806

DETAIL SUMMARY SHEET

TITLE: Active Immunization of HIV Infected Patients with Recombinant GP160 HIV Protein: Phase I Study of Immunotherapy, Immunogenicity and Toxicity

KEYWORDS: rgp160, vaccine therapy, HIV

PRINCIPAL INVESTIGATOR: Redfield, Robert LTC MC
ASSOCIATES: Birx, Deborah LTC MC; Johnson, Steven MAJ MC

SERVICE: HIV Research STATUS: Ongoing
APPROVAL DATE: Nov 1988

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To evaluate the long-term safety and immunogenicity of vaccine therapy in early stage HIV infected patients, to evaluate variable boosting schedules, and to evaluate in vitro assays with in vivo relevance for application to Phase II trials.

TECHNICAL APPROACH
During the primary extended immunization series, original trial responders will be vaccinated every 4 months (160 ug) and nonresponders at Day 0, 7, 30, 60, 90, and 120 (160 ug), and then every 4 months (160 ug). In March 1992, an addendum was approved by the HUC/IRB to vaccinate volunteers every month. Alterations in cellular and humoral immune responses to HIV specific proteins and changes in vivo and in vitro cellular immune function continue to be assessed.

PRIOR AND CURRENT PROGRESS
All 28 volunteers in initial extension trial re-enrolled into the continuation trial modifying vaccination schedule to every month. This was completed in July 1993; 27 of 28 volunteers completed portion of trial. To date, 26 have re-enrolled in continuation trial modifying vaccination schedule to every other month. To date, one subject has PCP, one thrush, and four have CD4 cell counts <200. Eight are receiving antiretroviral therapy (AZT/DDI) per primary physician. Long term safety and immunogenicity is in process. Mean trial follow-up in 47 months. Mean number of injections is 25; mean dose is 6500 ug of rgp160. Immunogenicity documented in 27 of 28 subjects; 24 of whom demonstrated evidence of long-term vaccine-induced immunogenicity. Long-term safety continues. Reactogenicity limited to local reaction. No evidence of in vitro or in vivo trial-associated immune dysfunction or increased in vivo HIV expression has been demonstrated.

CONCLUSIONS
The trial is ongoing. It continues to provide important sentinel safety information related to vaccine therapy. The observed experience to date continues to document the safety and immunogenicity of recurrent immunization with rgp160 in volunteers with HIV infection. A conclusion related to clinical efficacy must await completion of current and possibly future phase 2 trials.

REPORT DATE: 05/26/94 WORK UNIT # 8812

DETAIL SUMMARY SHEET

TITLE: The Investigation of the Cutaneous Manifestations of HIV Infection in Relation to the Onset, Severity and Progression of Disease, Dermatologic Natural History

KEYWORDS: HIV, dermatology, Walter Reed stage

PRINCIPAL INVESTIGATOR: Smith, Kathleen COL MC
ASSOCIATES: Skelton, Henry CDR MC USN

SERVICE: HIV Research STATUS: Completed
APPROVAL DATE: May 1989

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To study cutaneous manifestations, both histologically and clinically, in relation to disease onset and progression of disease.

TECHNICAL APPROACH
A complete dermatology examination, including a complete history, is performed. Lesional biopsies (4-6 mm punch) are performed, as needed, for diagnosis. Lesional biopsies may be split and half frozen for performing immunohistochemical markers of the inflammatory infiltrate. In addition, special stains are performed to rule out infections. Patients are followed every 6 months and may be seen for problems that develop between visits. Also, seven cutaneous sites are cultured for fungus and bacteria in all stages of disease; repeat cultures are performed if the stage changes.

PRIOR AND CURRENT PROGRESS
Preliminary evaluation of clinical data for demographic data, skin manifestations with increasing Walter Reed (WR) stage, and relation of different skin manifestations with WR stages has been completed through May 1993. Evaluation of data on cutaneous drug eruptions with disease progression has been completed. Evaluation of a portion of the immunohistochemical markers with disease progression has been completed. Manuscript on skin tumors in our HIV+ population has been published. Clinical protocol visits were stopped on 01 Oct 93. There were no adverse reactions from 27 May 93 through 26 May 94. A total of 681 patients enrolled at Walter Reed, and 508 patients enrolled at the National Naval Medical Center during the study. In the past year, 12 patients were enrolled at WRAMC and no patients were enrolled at NNMC.

CONCLUSIONS
The skin diseases and tumors which occur in different WR stages were determined, as well as their relationship to increasing WR stages. Patterns of immune dysregulation in the skin were also determined, based on immunohistochemical markers. Evaluation of clinical data is being completed to determine if any specific disease is predictive for disease progression. Evaluation of immunohistochemical markers is being completed to define patterns of immune dysregulation.

REPORT DATE: 08/09/94 WORK UNIT # 8814

DETAIL SUMMARY SHEET

TITLE: Pharmacoepidemiologic Study to Develop a Database to Document Variations in the Outcome of Illness Which May be Due to Drug Effects and To Document Patterns of Drug use in HIV Infected Patients

KEYWORDS: pharmacoepidemiology, data base, drug use

PRINCIPAL INVESTIGATOR: Cortese, Linda RPh, MS
ASSOCIATES: Oster, Charles COL MC; Hiner, William COL MS

SERVICE: HIV Research STATUS: Ongoing
APPROVAL DATE: Aug 1989

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To develop a data base to study outcomes of illness due to drug effects (both beneficial and adverse), and to gather useful information on drug use patterns of HIV infected patients.

TECHNICAL APPROACH
To develop a data base in conjunction with the Henry M. Jackson Foundation (HMJF) HIV data base which will allow for the retrospective and prospective collection and review of clinical data and prescription data on HIV infected patients.

PRIOR AND CURRENT PROGRESS
Data collection and analysis is being completed on "Zidovudine Usage: Patient Compliance and Associated Factors." This is a retrospective study involving 154 patients. A total of 593 patients have been enrolled into this protocol so far, with 88 added during this reporting year. There have been no adverse events.

CONCLUSIONS
Analysis of the data for "Zidovudine Usage: Patient Compliance and Associated Factors" is not complete. Data collection of patients' perceptions of zidovudine usage is in process. The pharmacoepidemiologic study is ongoing.

REPORT DATE: 05/05/94 WORK UNIT # 8817

DETAIL SUMMARY SHEET

TITLE: The Effect of HIV Infection on the Initial Manifestations and Response to Treatment of Syphilis

KEYWORDS: HIV, syphilis, treatment

PRINCIPAL INVESTIGATOR: Johnson, Steven MAJ MC
ASSOCIATES: Hicks, Charles LTC MC

SERVICE: HIV Research STATUS: Completed
APPROVAL DATE: Nov 1989

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To compare current therapy of syphilis with a more intensive regimen in patients with and without HIV infection.

TECHNICAL APPROACH
Randomized double-blind placebo-controlled comparison of two antibiotic treatment regimens for HIV-infected patients with syphilis.

PRIOR AND CURRENT PROGRESS
This is a CDC-sponsored multi-center trial. At WRAMC, 12 patients were enrolled in the trial between 01 Jan 91 and 31 Dec 93. All study visits had been completed by 29 Nov 93. On 31 Dec 93, enrollment officially stopped for the protocol. For the whole study, approximately 600 patients were enrolled. Data analysis is currently underway.

CONCLUSIONS
Preliminary results are available. Final results should be available in late 1994.

REPORT DATE: 06/22/94 WORK UNIT # 8818

DETAIL SUMMARY SHEET

TITLE: Prospective Study of the Emergence of Zidovudine Resistance in Patients Infected with the Human Immunodeficiency Virus who are Treated with Zidovudine

KEYWORDS: AZT resistance, virus culture, HIV

PRINCIPAL INVESTIGATOR: Mayers, Douglas CDR MC
ASSOCIATES: Oster, Charles COL MC; Wagner, Kenneth MD

SERVICE: HIV Research STATUS: Ongoing
APPROVAL DATE: Jun 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine if there exists a level of AZT resistance, measured in vitro, which correlates with clinical deterioration in patients receiving AZT. Secondarily, to determine the time course, frequency and clinical parameters associated with development of AZT resistance, and to develop a repository of HIV-infected PBMC and plasma for future studies of AZT resistance.

TECHNICAL APPROACH
HIV-infected patients taking AZT will be clinically evaluated every 3 months. Blood will be drawn at each evaluation for HIV-culture, p24Ag, T cell subsets, and AZT levels. Aliquots of PBMC and plasma will be stored in liquid nitrogen. HIV isolates will be evaluated for susceptibility to AZT, DDC, and DDL. Genotypic analysis of the HIV reverse transcriptase gene will be performed on selected patient isolates. Primary clinical endpoints are death or development of a new opportunistic infection. Data will be evaluated using a Mantel-Haenszel survival analysis with transition states.

PRIOR AND CURRENT PROGRESS
The study closed to accrual with 100 patients in late 1991. To date, there have been 27 HIV related deaths, 66 primary study endpoints, 72 patients with CD4 decline below 200 CD4 cells, 51 patients with anergy, and 20 patients with wasting. Sixteen patients withdrew prior to study completion. A total of 41 patients are currently active on study. A total of 59 patients developed AZT resistance. AZT resistance develops more rapidly in patients with low CD4 cell counts, high plasma HIV RNA levels, and synctium-inducing virus by culture. Development of the AZT resistance-associated mutation at RT codon 215 appears to precede clinical decline, while phenotypic drug resistance (IC>1uM) appears after CD4 decline in these patients. Factors associated with new OI or death include: Hct<35, low CD4 cell counts, plasma HIV RNA>3000,000 copies/ml, and AZT-resistant virus.

CONCLUSIONS
Cox modeling of the study data is currently in progress.

REPORT DATE: 10/10/94 WORK UNIT # 8819

DETAIL SUMMARY SHEET

TITLE: Active Immunization of Early HIV Infected Patients with Recombinant GP160 HIV Protein: Phase II Study of Toxicity, Immunotherapy, In Vivo Immunoregulation and Clinical Efficacy

KEYWORDS: rgp160, HIV infection, vaccine therapy

PRINCIPAL INVESTIGATOR: Redfield, Robert LTC MC
ASSOCIATES: Birx, Deborah LTC MC; Johnson, Steven MAJ MC

SERVICE: HIV Research STATUS: Ongoing
APPROVAL DATE: Sep 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To evaluate the efficacy of recombinant gp160 (rgp160) in the treatment of patients with early HIV infection.

TECHNICAL APPROACH
This placebo-controlled, double-blind Phase II study will consist of 600 patients overall: 300 to be enrolled within the Department of Defense and 300 to be enrolled in sponsor supported civilian sites. Patients will be equally randomized to vaccine or placebo. All volunteers will receive intramuscular injections of 160 ug on days 0, 7, 30, 60, 120, 180 and then at 2 month intervals through the completion of the trial. Changes in cellular and humoral immune responses, toxicity to rgp160, changes in CD4 counts, and shifts in viral burden will all be explored.

PRIOR AND CURRENT PROGRESS
Enrollment was completed and closed in November 1992. Seventeen study sites are participating in this multi-center trial. A total of 608 volunteers were randomized to receive rgp160 or a placebo. Currently, 562 volunteers remain on the trial. WRAMC randomized 93 volunteers; 11 have discontinued the trial. Two HIV-related deaths have occurred in WRAMC volunteers in August 1993. Trial-wide, eight deaths have occurred. Eleven WRAMC volunteers have reached primary endpoints, and 28 secondary endpoints have occurred. Of note is that three lymphomas have occurred at the WRAMC study site. A total of 14 WRAMC volunteers are receiving AZT, 8 are receiving DDL, and 1 is receiving DDC.

CONCLUSIONS
The projected completion date of this study is November 1995. Integrity continues to be maintained. Minimal conclusions can be drawn at this time since the trial remains double-blinded. Progress is monitored by an independent DSMB chaired by Dr. J.P. Standord. The initial efficacy analysis was conducted in October 1993 in a blinded fashion. Based on its review, the DSMB recommended that the trial continue as planned.

REPORT DATE: 10/10/94 WORK UNIT # 8820

DETAIL SUMMARY SHEET

TITLE: A Phase I Study of the Safety and Immunogenicity of rgp120/HIV-1-111B Vaccine in HIV-1 Seropositive Adult Volunteers

KEYWORDS: gp120, vaccine therapy, HIV infection

PRINCIPAL INVESTIGATOR: Redfield, Robert LTC MC
ASSOCIATES: Birx, Deborah LTC MC; Johnson, Steven MAJ MC

SERVICE: HIV Research STATUS: Ongoing
APPROVAL DATE: Sep 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To assess the safety and immunogencitiy of rgp120 vaccine in asymptomatic HIV-1 infected volunteers, compare the effectiveness of a 3-injection vs. 5-injection schedule, and compare the effect of variable dose levels of rgp120 vaccine.

TECHNICAL APPROACH
This Phase I trial will consist of four groups: three open label (100, 300, 600 ug), with 5-10 patients each; and one placebo controlled (20 300 ug vaccine, 5 placebo). All volunteers will be vaccinated at 0, 1, 4, 8, 16 weeks. Alterations in cellular and humoral immune response to HIV specific proteins and changes in vivo and in vitro cellular immune function will be assessed. The continuation trial consists of four groups (all open label). Groups as follows: 300 ug q 1 month (15 volunteers); 300 ug q 3 months (15 patients); 600 ug q 3 months (10 volunteers); and 600 ug per original schedule (initial trial placebos).

PRIOR AND CURRENT PROGRESS
This study is closed to patient accrual. A total of 36 volunteers continued this year in the extended immunization protocol (dosage 600 ug q2months for 12 additional months). Five volunteers have discontinued the trial this year (two for advanced CD4 depletion, two for non-compliance, and one for personal reasons). On the extended trial, two volunteers developed thrush and three developed CD4 cell counts less than 200. Two volunteers currently on the trial are receiving antiretroviral therapy of AZT/DDI per primary physician. The trial is scheduled for completion this year, and analysis should be completed by mid-1995.

CONCLUSIONS
This trial is ongoing; the extended trial will be completed this winter. Analysis is expected to be completed by mid-1995.

REPORT DATE: 10/25/93 WORK UNIT # 8825

DETAIL SUMMARY SHEET

TITLE: Role of Accessory Cells in Hematopoietic Suppression After HIV-Infection

KEYWORDS: HIV-1, bone marrow, myelopoiesis

PRINCIPAL INVESTIGATOR: Burrell, Linda MAJ MC
ASSOCIATES: Schwartz, Gretchen PhD; Oster, Charles COL MC

SERVICE: HIV Research STATUS: Completed
APPROVAL DATE: Oct 1991

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To study whether the decreased numbers of mature blood cells seen in HIV-infected people relate to decreased production of bone marrow progenitor cells that produce the blood cells, abnormal responses of the progenitor cells to growth factors, or impaired production of growth inhibitory and growth stimulatory cytokines from accessory cells in the bone marrow microenvironment that regulates the production of mature blood cells and their progenitor cells.

TECHNICAL APPROACH

Human bone marrow long-term cultures (LTC) will be used to study how HIV-infected accessory cells effect production of mature blood cells and their progenitor cells. The stromal cell layer (an adherent layer of cells that forms in LTC) is used to simulate the bone marrow microenvironment. Stromal cells layers are begun by culturing bone marrow of noninfected people for 4 weeks, and then infecting the layers with HIV-1. Autologous CD34+ marrow cells, enriched for primitive cells that produce progenitor cells for mature blood cells, are then added. The effect of HIV-infection on myeloid and erythroid progenitor cell production is monitored by colony-forming assays.

PRIOR AND CURRENT PROGRESS

A reproducible and productive 0.5 ml bone marrow LTC system was developed. Results demonstrate that some cells in the stromal cell layers of LTC were targets for HIV-1ADA, a monotytotropic strain of HIV-1, and that a productive infection was maintained for at least 8 weeks in HIV-infected stromal cell layers. Within 1 week post infection, 50-70% fewer progenitor cells were produced in HIV-infected LTC than in noninfected LTC. In preliminary studies, addition of G-CSF did not further stimulate progenitor cell production. Production of myeloid progenitor cells was increased, however, when neutralizing antibodies to TNF-alpha or IL-4 were added to HIV-infected LTC.

CONCLUSIONS

Results suggest that HIV-infected bone marrow accessory cells suppress the production of erythroid and myeloid progenitor cells that produce mature blood cells, and that this suppression may be mediated by growth inhibitory cytokines. The small LTC system developed provides a reproducible system that may help identify therapeutic strategies to overcome or prevent severe hematopoietic suppression in AIDS patients.

REPORT DATE: 07/13/94 WORK UNIT # 8826

DETAIL SUMMARY SHEET

TITLE: A Double-Blind, Placebo Controlled, Parallel Group, Multicenter Study of the Use of Weekly Azithromycin as Prophylaxis Against the Development of Mycobactrium avium Complex Disease in HIV Infected People

KEYWORDS: azithromycin

PRINCIPAL INVESTIGATOR: Chung, Raymond COL MC

SERVICE: HIV Research STATUS: Ongoing
APPROVAL DATE: Jul 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To test the hypothesis that Mycobacterium avium complex disease can be prevented in late stage HIV disease by the use of azithromycin once a week.

TECHNICAL APPROACH
This is a multi-center placebo controlled study, in which volunteers with HIV and T helper cell counts below 100 receive either placebo or azithromycin once a week. The patients are monitored monthly for symptoms, signs, and laboratory findings suggestive of or diagnostic of Mycobacterium avium infection.

PRIOR AND CURRENT PROGRESS
Total number of patients screened for study: 13. Total number of patients enrolled in study: 12. Number of patients enrolled this year: 0. Total number of patients disenrolled from study: 5. Number of patients disenrolled this year: 5 (all of them during this past year). Total number of patients who died while on the study: 1 (not study-related). All disenrollments were due to patients' requests: 2 for convenience, and 3 for progression of HIV disease. No patient has developed MAC while on the study. There have been no adverse reactions.

CONCLUSIONS
There are no conclusions at this point in the study.

REPORT DATE: 09/01/94 WORK UNIT # 8827

DETAIL SUMMARY SHEET

TITLE: Active Immunization of AZT-Treated HIV-Infected Patients with Recombinant GP160 HIV Protein: Phase I/II Study of Immunogenicity Toxicity, and Effect in In Vivo Immunoregulation

KEYWORDS: HIV infection, vaccine therapy, gp160 vaccine

PRINCIPAL INVESTIGATOR: Redfield, Robert LTC MC

SERVICE: HIV Research STATUS: Completed
APPROVAL DATE: Aug 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To conduct a Phase I/II trial of the recombinant human immunodeficiency virus (HIV) envelope glycoprotein, gp160 candidate vaccine in patients who are HIV infected (Walter Reed Stage 1-2). Specific objectives include: 1) to evaluate the immunogenicity and toxicity of this product in HIV-infected individuals on AZT; and 2) to determine the parameters predictive of immune responsiveness.

TECHNICAL APPROACH
This is a multi-center, tri-service HIV research protocol conducted at Walter Reed Army Medical Center, National Naval Medical Center, and Wilford Hall Medical Center within the Military Medical Consortium for Applied Retroviral Research. Volunteers initially have HIV infection stage WR1-2. They will receive AZT (at least 500 mg/day for 12 weeks) statified by baseline CD4 count, and then 160 ug intramuscular injections of this vaccine on days 0 and 7, and at months 1, 2, 4, 6, and 10. Safety parameters, adaptive anti-HIV immune responses, and parameters of HIV in vivo regulation will be monitored. Volunteers will be eligible for standard of care intervention under the direction of their physicians.

PRIOR AND CURRENT PROGRESS
Overall, 78 volunteers were enrolled; 64 were randomized and vaccinated. A total of 37 volunteers were enrolled at WRAMC; 29 were randomized and immunized per the protocol. All 29 completed the trial. Enrollment was closed in April 1993. Toxicity has been limited to local reactions; adverse reactions filed with Wyeth-Ayerst were all considered not vaccine-related. Analysis of immunogenicity data is limited to T cell proliferative responses, which, although not statistically distinct, suggest a trend to decreased immunogencity in volunteers with CD4 cell counts less than 300.

CONCLUSIONS
This trial is completed. The PI had to extend the trial by amendment pending completion of ongoing clinical efficacy trials using rgp160 vaccine. However, this was not feasible secondary to the limitation of research funds available for therapeutic clinical research. The data documented the immunogenicity of rgp160 in volunteers treated with AZT. However, it suggested limitations related to cellular immunogenicity in volunteeers with advanced disease.

REPORT DATE: 09/13/93 WORK UNIT # 8828

DETAIL SUMMARY SHEET

TITLE: Evaluation of SQ 32,756 (BV-araU) Versus Acyclovir in the Treatment of Localized Herpes Zoster in HIV-Infected Patients (-38/-022) (ACTG 169)

KEYWORDS: SQ 32, 756 (BV-araU), acyclovir, herpes zoster

PRINCIPAL INVESTIGATOR: Hawkes, Clifton LTC MC

SERVICE: HIV Research STATUS: Completed
APPROVAL DATE: Dec 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To compare the efficacy of oral BV-araU (40 mg once daily) and oral acyclovir (800 mg five times daily) for the treatment of localized herpes zoster in HIV-infected adults.

TECHNICAL APPROACH
In this double-blind trial, each patient will be assigned to one of two treatment groups according to a computer-generated randomization scheme, with numbers assigned sequentially. Treatment with study drug must begin within 72 hours of zoster rash.

PRIOR AND CURRENT PROGRESS
Protocol has been terminated. No patients were enrolled.

CONCLUSIONS
Protocol terminated.

REPORT DATE: 09/13/93 WORK UNIT # 8829

DETAIL SUMMARY SHEET

TITLE: A Phase III Comparative Study of Dapsone/Trimethoprim and Clindamycion/Primaquine Versus Trimethoprim/Sulfamethoxazole in the Treatment of Mild-to-Moderate PCP in Patients with AIDs (ACTG 108)

KEYWORDS: treatment, PCP, AIDS

PRINCIPAL INVESTIGATOR: Hawkes, Clifton LTC MC

SERVICE: HIV Research STATUS: Completed
APPROVAL DATE: Dec 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To evaluate the efficiency of two oral regimens in the therapy of mild-to-moderate PCP: dapsone 100 mg/day plus trimethoprim 300 mg every 8 hours and clindamycin 600 mg every 8 hours plus primaquine 30 mg every day, as compared to a standard regimen of trimethoprim/sulfamethoxazole at a dose of 320 mg trimethoprim (two double-strength tablets) every 8 hours.

TECHNICAL APPROACH
This is a prospective, randomized, double-blind, multi-center study in which AIDS patients with a diagnosis of mild-to-moderate PCP will be enrolled and treated. Using a blocked stratification scheme, patients will be evenly distributed among the three treatment groups on the basis of the following two variables: 1) PCP prophylaxis within the 30 days prior to study entry; and 2) ACTU. To minimize bias, primary analyses will be performed using "intention to treat."

PRIOR AND CURRENT PROGRESS
Protocol terminated; no patients were enrolled.

CONCLUSIONS
Protocol terminated.

REPORT DATE: 09/13/93 WORK UNIT # 8830

DETAIL SUMMARY SHEET

TITLE: A Pilot Study Evaluating Penicillin G and Cetriaxone as Therapies for Presumed Neurosyphillis in HIV Seropositive Individuals (ACTG 145)

KEYWORDS: therapy, neurosyphilis, HIV

PRINCIPAL INVESTIGATOR: Hawkes, Clifton LTC MC

SERVICE: HIV Research STATUS: Completed
APPROVAL DATE: Feb 1993

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To assess the response to treatment as measured by resolution, improvement, unchanged status, or failure of CSF VDRL, CSF leukocytosis, CSF protein concentration, and serum RPR; to measure the resolution of signs and symptoms of neurosyphilis; and to assess safety and tolerance of the two treatment regimens.

TECHNICAL APPROACH
This was to be an open-labelled, randomized pilot trial evaluating Penicillin G and Ceftriaxone for 100 HIV-infected patients (50 patients per treatment regimen) with presumed neurosyphilis. Therapy was to be given for 10 days; all patients were to be followed for 50 weeks post-treatment. Patients were to be stratified for prior treatment.

PRIOR AND CURRENT PROGRESS
Protocol has been terminated; no patients were enrolled.

CONCLUSIONS
Protocol terminated.

REPORT DATE: 04/11/94 WORK UNIT # 8831

DETAIL SUMMARY SHEET

TITLE: Active Immunization of Early HIV-Infected Pregnant Women with Recombinant GP160 HIV Protein: A Pilot Study of Toxicity, Dosing, Immunogenicity and Feasibility

KEYWORDS: recombinant GP160, HIV, pregnant women

PRINCIPAL INVESTIGATOR: Redfield, Robert, LTC MC

SERVICE: HIV Research STATUS: Completed
APPROVAL DATE: Apr 1993

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To evaluate the safety and immunogenicity of recombinant envelope-based vaccine in HIV infected pregnant female volunteers.

TECHNICAL APPROACH
Active inoculation will be done of pregnant volunteers in early pregnancy, and they will be monitored for safety and specific, adaptive anti-HIV immune responses.

PRIOR AND CURRENT PROGRESS
This clinical trial was deprogrammed prior to initial enrollment because of changing programmatic priorities within the U.S. Army's HIV research program.

CONCLUSIONS
Trial has been deprogrammed.

REPORT DATE: 06/26/94 WORK UNIT # 8102

DETAIL SUMMARY SHEET

TITLE: Carpal Tunnel Syndrome: An Occupational Hazard ofthe Dental Practice

KEYWORDS: carpal tunnel syndrome

PRINCIPAL INVESTIGATOR: Isaac, Joseph MAJ DC

DEPARTMENT: Army Community Hospitals
SERVICE: Ireland ACH, Fort Knox, KY

STATUS: Completed
APPROVAL DATE: Sep 1993

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To study via videotape the risk factors associated with Carpal Tunnel Syndrome. Occupational risk factors in Dental Health Care Workers (DHCW) with symptoms of Carpal Tunnel Syndrome (CTS) will be observed and compared with DHCW without symptoms of CTS.

TECHNICAL APPROACH

Dental health care workers (DHCW), half with histories or symptoms of CTS and half without, will be videotaped for 5 mintues each while performing their predominant tasks. Pinching force, resisted hand and finger motions, abnormal hand posture, and vibration episodes will be observed on the videotapes and tallied independently by four reviewers.

PRIOR AND CURRENT PROGRESS

Twenty DHCW were videotaped (10 with CTS histories or symptoms and 10 without). The project is completed and ready for submission to the Journal of the American Dental Association.

CONCLUSIONS

All CHCW in this study were exposed to occupational factors that may contribute to CTS.

REPORT DATE: 01/04/94 WORK UNIT # 1504

DETAIL SUMMARY SHEET

TITLE: CALGB 8662 Monitoring Circulating Breast Cancer Associated Antigens with the 15-3 Radioimmunoassay in Metastatic Breast Cancer

KEYWORDS: metastatic breast cancer, CA15-3 antigens

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Cancer & Leukemia Group B APPROVAL DATE: Jan 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine the predictive value of a given change in CA15-3 values related to a known clinical event (response, progression or stability).

TECHNICAL APPROACH
Ten cc of whole blood is drawn at the time of study entry, at each follow-up visit, and at the time of relapse or disease progression. The plasma is mailed on dry ice to the referenced laboratory.

PRIOR AND CURRENT PROGRESS
A total of 23 WRAMC patients have been entered into this study; 2 during this reporting period. Total national accrual is 363; 25 during this reporting period. No patients have withdrawn, and no adverse events have occurred. Blood samples are still being obtained at specified intervals. The study reached its accrual goals in December 1993, and was closed to patient entry. This study is being kept open at WRAMC for follow-up.

CONCLUSIONS
No conclusions have been reached.

REPORT DATE: 02/14/94 WORK UNIT # 1505

DETAIL SUMMARY SHEET

TITLE: CALGB 8963 Psychological Adaptation of Survivors of Acute Leukemia

KEYWORDS: psychosocial adaptation, survivors, leukemia

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD

DEPARTMENT: Department of Medicine
SERVICE: Cancer & Leukemia Group B

STATUS: Completed
APPROVAL DATE: Feb 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To assess the long-term psychological impact of a devastating disease, such as acute leukemia, and the impact of surviving treatment.

TECHNICAL APPROACH
The patient has one phone interview and completes one questionnaire from the Department of Psychiatry at Memorial Sloan-Kettering.

PRIOR AND CURRENT PROGRESS
A total of 26 patients from WRAMC have been entered on this study; 15 of those during this reporting period. The total national accrual is 207; 61 of those during this reporting period. This study closed July 30, 1993 after reaching projected accrual. No adverse events have occurred in this low risk study. No patients have withdrawn after giving consent for the interview.

CONCLUSIONS
Analysis is ongoing.

REPORT DATE: 11/09/93 WORK UNIT # 1509

DETAIL SUMMARY SHEET

TITLE: CALGB 9011 A Study of Fludarabine Vs. Chlorambucil Vs. Both Drugs for Chronic Lymphatic Leukemia

KEYWORDS: fludarabine, chlorambucil, crossover therapy

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Cancer & Leukemia Group B APPROVAL DATE: Nov 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To compare the response rates and progression free survival in previously untreated chronic lymphatic leukemia (CLL) patients using three therapeutic regimens; to determine whether the quality of life is superior in any one of the regimens; to determine whether the two drugs fludarabine and chlorambucil, are non-resistant by a crossover design for patients failing to respond to the initial single agent.

TECHNICAL APPROACH
Randomized study for eligible CLL patients comparing the new drug fludarabine with the standard treatment of chlorambucil, or with the two drugs given in combination. Length of treatment depends on patient's response, with the maximum treatment being 2 years. Fludarabine is given intravenously for 5 days every 28 days. Chlorambucil is given by mouth for 1 day every 28 days.

PRIOR AND CURRENT PROGRESS
One patient from WRAMC has been entered on this study; none this reporting period. The total national accrual is 337; 153 of those during this reporting period. The projected national accrual is for 450 patients. No unexpected or serious adverse events have been reported by the CALGB.

CONCLUSIONS
Analysis is ongoing.

REPORT DATE: 11/09/93 WORK UNIT # 1510

DETAIL SUMMARY SHEET

TITLE: CALGB 9051 A Study of Combination Chemotherapy Plus Irradiation for Early Stage Hodgkin's Disease

KEYWORDS: poor risk Hodgkin's, limited chemotherapy, subtotal nodal radiation

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD

DEPARTMENT: Department of Medicine STATUS: Completed
SERVICE: Cancer & Leukemia Group B APPROVAL DATE: Nov 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To establish the response rate to three cycles of EVA and radiation therapy in untreated patients with early stage, poor risk Hodgkin's disease. To establish the short and long term complications of combined therapy. To assess patterns of failure, relapse rate, disease-free survival and overall survival in patients treated with EVA and subtotal nodal irradiation.

TECHNICAL APPROACH
All eligible patients will receive three cycles of chemotherapy at 28 day intervals consisting of VP-16, vinblastine, and doxorubicin. This will be followed by a total of 39 radiation treatments given with a 4-week break in between.

PRIOR AND CURRENT PROGRESS
This study closed June 26, 1992. A total of 59 patients entered (4 of them from WRAMC). All WRAMC patients have completed therapy; one has had a relapse in disease, and the other three have completely responded and are being followed.

CONCLUSIONS
No conclusions have been reached.

REPORT DATE: 11/09/93 WORK UNIT # 1511

DETAIL SUMMARY SHEET

TITLE: CALGB 9081: An Intergroup Study of Rectal Cancer Adjuvant Therapy

KEYWORDS: adjuvant chemotherapy, post-op radiation, poor prognosis

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD

DEPARTMENT: Department of Medicine STATUS: Completed
SERVICE: Cancer & Leukemia Group B APPROVAL DATE: Nov 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine the efficacy of: (1) 5FU, (2) 5FU and leucovorin, (3) 5FU and levamisole, and (4) 5FU, leucovorin, and levamisole when combined with pelvic radiation therapy in the treatment of Stages B-2 and C rectal cancer.

TECHNICAL APPROACH
This is a four-armed study with the same radiation therapy program in all arms, but with varying drug regimens. All eligible patients will be randomized to receive one of four treatment arms with 5FU and radiation being the control arm of the study. All arms receive two courses of chemotherapy, radiation therapy along with two courses of chemotherapy, and then two additional courses of chemotherapy.

PRIOR AND CURRENT PROGRESS
This study was closed to new patient accrual November 22, 1992. A total of 1,792 patients have been entered nationwide, none this year. Six WRAMC patients have been entered altogether. All WRAMC patients have completed therapy; two were removed from the study due to progressive disease, and four continue to be followed for survival. The study should be closed at WRAMC.

CONCLUSIONS
No conclusions have been reached.

REPORT DATE: 12/13/93 WORK UNIT # 1513

DETAIL SUMMARY SHEET

TITLE: CALGB 8923 Randomized Studies of Induction Therapy Adjuncts and Intensification Therapy Regimens for Older Patients with Acute Myelocytic Leukemia

KEYWORDS: AML, over age 60, growth factor

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD

DEPARTMENT: Department of Medicine STATUS: Completed
SERVICE: Cancer & Leukemia Group B APPROVAL DATE: Dec 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine the effect of GM-CSF on the rates of complete remissions (CR) and hypoplastic deaths in elderly patients treated with daunorubicin and Ara-C induction therapy; to compare the incidence of infections, time to bone marrow recovery with GM-CSF vs. placebo; to determine the incidence and significance of leukemic regrowth using GM-CSF; and to determine the efficacy of two different post-remission intensification therapies in prolonging disease-free survival.

TECHNICAL APPROACH
All eligible patients over age 60 will be randomized to receive standard Ara-C and daunorubicin with blinded study drug of GM-CSF or placebo. Those patients who attain a CR after induction are randomized again to receive an intensification of four additional courses of Ara-C or two courses of Ara-C/mitoxantrone.

PRIOR AND CURRENT PROGRESS
The total national accrual has been 367 patients; 110 during this reporting period. A total of two WRAMC patients have been entered; none during this past year. Both WRAMC patients have died of their disease. The study closed to patient accrual November 30, 1993, and is now closed at WRAMC.

CONCLUSIONS
None.

REPORT DATE: 12/13/93 WORK UNIT # 1514

DETAIL SUMMARY SHEET

TITLE: CALGB 9021 Induction Therapy for Relapsed or Refractory Acute Myelocytic Leukemia or Blast Crisis of Chronic Myelocytic Leukemia

KEYWORDS: AML/CML, induction study, growth factor priming

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Cancer & Leukemia Group B APPROVAL DATE: Dec 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To compare response rates of patients with refractory or relapsed acute myelocytic leukemia (AML) and untreated blast crisis of chronic myelocytic leukemia (CML) treated with GM-CSF plus high dose cytarabine to high dose cytarabine alone; to evaluate the toxicity of high dose cytarabine alone and with GM-CSF added; to evaluate in vivo and in vitro effects of GM-CSF on leukemic blood and bone marrow; and to correlate patient response with in vitro studies of the cells.

TECHNICAL APPROACH

This is a study of induction therapy alone. Eligible patients with relapsed or refractory AML or untreated blast crisis of CML will be randomized to receive IV GM-CSF vs placebo 2-5 days before, during, and 24 hours after high dose Ara-C induction therapy. If a complete remission is not achieved, a second induction will be given. Bone marrow and blood samples will be obtained before and after GM-CSF and at specified intervals thereafter. Responders are monitored until relapse.

PRIOR AND CURRENT PROGRESS

No patients from WRAMC have been entered on this study. A total of 124 patients have been entered nationwide; 40 during this reporting period. No unexpected adverse events have been reported. The projected national accrual is for 380 patients.

CONCLUSIONS

No conclusions have been reached.

REPORT DATE: 10/14/93 WORK UNIT # 1516-84

DETAIL SUMMARY SHEET

TITLE: CALGB 8364: Immunological Diagnostic Studies in Adult ALL

KEYWORDS: immunology, lymphocyte, leukemia

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Cancer & Leukemia Group B APPROVAL DATE: Oct 1983

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine the incidence of various monoclonal antibodies' cytochemical and conventional lymphoid markers in adult acute lymphatic leukemia (ALL). To correlate the presence of the various markers with the initial and subsequent clinical characteristics of the disease, response rate, and response duration. To determine if marker status changes at relapse.

TECHNICAL APPROACH
Non-randomized study in which all eligible patients being entered on the ALL treatment protocol agree to allow prior to the initiation of therapy the submission of six air-dried unstained BM smears for confirmatory cytochemical studies and 2cc of bone marrow aspirate, along with 7 cc of peripheral blood to a designated CALGB reference laboratory. The same set of samples is again obtained at relapse.

PRIOR AND CURRENT PROGRESS
A total of 28 patients from WRAMC have been entered on this study; 3 of those during this reporting period. Sixteen patients have died from their disease, 1 was removed from study due to a revised diagnosis, 3 have relapsed during this reporting period, and 8 patients remain in remission and continue to be followed. All required blood and bone marrow samples have been sent. No adverse events have occurred. The total national accrual is 662 patients; 95 of those were entered during the report period.

CONCLUSIONS
Analysis is ongoing.

REPORT DATE: 02/14/94 WORK UNIT # 1517

DETAIL SUMMARY SHEET

TITLE: CALGB 9013: Alpha Interferon and Cytarabine for Untreated Chronic Myelogenous Leukemia

KEYWORDS: untreated CML, Philadelphia chromosome

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD

DEPARTMENT: Department of Medicine STATUS: Completed
SERVICE: Cancer & Leukemia Group B APPROVAL DATE: Feb 1991

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To determine whether the combination of low dose Ara-C and alpha interferon (IFN) can reduce or eliminate the Ph + cells in previously untreated patients with chronic phase chronic myelogenous leukemia (CML); to assess response rate, duration of response, and survival of patients with CML treated with this regimen; to define safety and toxicities of this treatment; and to investigate concordance of Ph - and Ph + cells between blood and bone marrow as remission is achieved.

TECHNICAL APPROACH

All eligible patients will have blood and bone marrow samples sent for cytogenetic analysis. Only Ph + patients will be eligible. Blood and bone marrow samples will be repeated at 6 month intervals. Eligible patients will be started on subcutaneous injections of Ara-C twice per day, and subcutaneous injections of alpha IFN daily. Blood counts will be obtained weekly and the doses adjusted according to results. Complete or partial responders will be treated for a total of 18 months. Patients with stable disease will receive 12 months of treatment.

PRIOR AND CURRENT PROGRESS

No patients from WRAMC have been entered on this study. Thirty-five patients were entered during the past year nationally. The study reached its accrual goal with a national total of 91 patients, and closed on 10 Aug 93.

CONCLUSIONS

Analysis is ongoing.

REPORT DATE: 02/14/94 WORK UNIT # 1518

DETAIL SUMMARY SHEET

TITLE: CALGB 8761: Prognostic Implications of Chromosomal Abnormalities in Chronic Myelogenous Leukemia

KEYWORDS: companion study, CML

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Cancer & Leukemia Group B APPROVAL DATE: Feb 1991

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To determine the chromosome 22 translocation breakpoint for previously untreated chronic myelogenous leukemia (CML) patients; to determine the correlation between the breakpoint and patient characteristics at presentation, during clinical course, and at time of blast crisis; and to determine by sequential samples whether breakpoint location changes during the course of the disease or at time of progression.

TECHNICAL APPROACH

Bone marrow samples (2 ml) and blood samples (40 ml) are obtained prior to treatment, after second treatment cycle, and every 6 months thereafter. Samples are also obtained during blast crisis. The samples are mailed to the reference lab for analysis. These samples are obtained during regularly scheduled blood and bone marrow sampling required for treatment.

PRIOR AND CURRENT PROGRESS

No patients from WRAMC have been entered on this study. A total of 155 patients have been entered nationally; 34 of those during this reporting period. The projected accrual is for 200 patients. No adverse events have been reported.

CONCLUSIONS

No conclusions have been reached.

REPORT DATE: 03/18/94 WORK UNIT # 1519

DETAIL SUMMARY SHEET

TITLE: CALGB 9142 Comparison of Chemotherapy Vs. Chemohormonotherapy in Premenopausal Women with Stage II Receptor Positive Breast Cancer

KEYWORDS: breast cancer, node positive, receptor positive

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Cancer & Leukemia Group B APPROVAL DATE: Mar 1991

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To compare the recurrence rates, disease-free intervals, and hormone receptor positive survival for premenopausal women with lymph node positive breast cancer given adjuvant therapy with cytoxan, Adriamycin, and 5-fluorouracil (CAF) chemotherapy alone, or chemotherapy followed by zoladex, or chemotherapy followed by zoladex and tamoxifen. To compare the relative toxicities of these three regimens, and to assess their effect on blood hormone levels.

TECHNICAL APPROACH

All eligible patients will receive a 6 month course (six cycles) of standard CAF therapy. Initially, they will be randomized to receive an additional 5 years of zoladex, receive an additional 5 years of zoladex and tamoxifen, or end therapy following CAF.

PRIOR AND CURRENT PROGRESS

The total national accrual is 1,330 patients (13 from WRAMC); 348 of those (6 WRAMC patients) were entered during this reporting period. No unexpected adverse reactions have occurred, and no patients have withdrawn from the study. Patient accrual goals were met (and enrollment ended) in February 1994. The study is being kept open for follow-up of patients still receiving treatment.

CONCLUSIONS

Analysis in progress; no conclusions have been reached.

REPORT DATE: 03/18/94 WORK UNIT # 1520

DETAIL SUMMARY SHEET

TITLE: CALGB 9143 Comparison of Combination Chemotherapy with the CAF Regimen Vs. A 16-week 6-Drug Regimen for Stage II Receptor Negative Breast Cancer

KEYWORDS: breast cancer, adjuvant therapy, node positive

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD

DEPARTMENT: Department of Medicine STATUS: Completed
SERVICE: Cancer & Leukemia Group B APPROVAL DATE: Mar 1991

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To compare disease-free and overall survival in node-positive, receptor-negative breast cancer patients receiving adjuvant cytoxan, Adriamycin, and 5-fluorouracil comcomitantly (CAF) or a 16-week multi-drug regimen. To compare toxicities of adjuvant CAF and a 16 week multi-drug regimen.

TECHNICAL APPROACH
Eligible patients are randomized to receive either six 28-day courses of CAF or the 16-week multi-drug regimen. If randomly assigned to the second treatment, a central venous catheter is inserted prior to treatment.

PRIOR AND CURRENT PROGRESS
The total national accrual is 646 patients (2 from WRAMC); 186 were enrolled during the past year (2 from WRAMC). Both WRAMC patients completed their therapy without unexpected adverse reactions. No patient withdrew from the study. The study met its accrual goals (and was closed to new accrual) April 29, 1993. The study is now being closed at WRAMC because all patients have completed therapy. Follow-up of current patients will be maintained.

CONCLUSIONS
No conclusions have been reached.

REPORT DATE: 04/13/94 WORK UNIT # 1521-91

DETAIL SUMMARY SHEET

TITLE: CALGB 9194: Comparison of Adjuvant Chemotherapy with Concurrent or Delayed Tamoxifen vs. Tamoxifen Alone in Postmenopausal Patients with Receptor Positive Stage II Breast Cancer

KEYWORDS: postmenopausal, lymph node positive, receptor positive

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Cancer & Leukemia Group B APPROVAL DATE: Apr 1991

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To compare disease-free survival and overall survival of postmenopausal primary breast cancer patients with involved axillary nodes and positive estrogen and/or progesterone receptors treated with standard adjuvant therapy with long-term tamoxifen, or with chemoendocrine therapy with combined cytoxan, Adriamycin, and 5-fluorouracil (CAF) followed by long-term tamoxifen, or with concurrent chemoendocrine therapy with tamoxifen and CAF.

TECHNICAL APPROACH
Eligible patients will be randomized to receive one of three treatment arms: tamoxifen alone for 5 years, six courses of CAF followed by tamoxifen for 5 years, or six courses of CAF with concurrent tamoxifen for 5 years.

PRIOR AND CURRENT PROGRESS
A total of two patients from WRAMC have been entered on this study; both during this reporting period. Both patients continue on therapy. No unexpected toxicities have been observed; no patients have withdrawn from the study. This is an intergroup study involving four other national study groups other than CALGB. The projected total accrual is for 1,410 patients. CALGB has accrued 71 patients this reporting period. The total national accrual is unknown at this time. Projected closure is for March 1995.

CONCLUSIONS
Analysis is ongoing.

REPORT DATE: 09/15/94 WORK UNIT # 1522-84

DETAIL SUMMARY SHEET

TITLE: CALGB 8461: Cytogenic Studies in Acute Leukemia: A Companion to CALGB 8011, 8323, 8321, and 8411

KEYWORDS: cytogenetics, acute leukemia

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD

DEPARTMENT: Department of Medicine
SERVICE: Cancer & Leukemia Group B

STATUS: Ongoing
APPROVAL DATE: Sep 1984

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine the incidence of specific chromosome abnormalities in adult acute non-lymphatic leukemia (ANLL) and acute lymphatic leukemia (ALL).

TECHNICAL APPROACH
All eligible patients are registered to this companion to treatment protocols. A specimen of marrow and blood is obtained at diagnosis and again at relapse.

PRIOR AND CURRENT PROGRESS
A total of 78 WRAMC patients have been entered on this study; 3 during this reporting period. The national accrual is 2,620; 343 of those during this year. The projected accrual is for a total of 3,250 patients. This is a blood/bone marrow companion study for leukemia. Samples have been sent as requested. No adverse reactions have occurred; no patients have withdrawn from the study.

CONCLUSIONS
Analysis is ongoing.

REPORT DATE: 01/04/94 WORK UNIT # 1525-92

DETAIL SUMMARY SHEET

TITLE: CALGB 9130: A Trial of Chemotherapy and Radiation with or Without Carboplatin for Inoperable Lung Cancer

KEYWORDS: lung cancer, chemotherapy, radiation therapy

PRINCIPAL INVESTIGATOR: Weiss, Raymond M.D.

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Cancer & Leukemia Group B APPROVAL DATE: Jan 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine if the concurrent addition of carboplatin during radiation therapy for Stage IIIA and IIIB inoperable, non-small cell lung cancer will prolong survival and improve local disease control; to determine if the improvement in survival, if any, is related to disease stage: tumor (T) status and nodal status; and to determine if the improvement in survival, if any, is related to tumor size.

TECHNICAL APPROACH
All eligible patients will be randomized to receive one of two treatments: (1) chemotherapy and vinblastine weekly x5, with cisplatin given on the first and last week (a 3 week rest period will be given, followed by a 6 week course of radiation therapy); or (2) the same treatment as #1, with the addition of the drug carboplatin given on the first treatment day of the week during radiation. The total treatment time for both would be 4-5 months.

PRIOR AND CURRENT PROGRESS
A total of three patients from WRAMC have been entered on this study; two during this reporting period. No unexpected adverse events have occurred, and no patients have withdrawn from the study. The total national accrual is 177 patients; 109 of those during this reporting period. The projected accrual is for 270 patients.

CONCLUSIONS
No conclusions have been reached.

REPORT DATE: 01/04/94 WORK UNIT # 1526-92

DETAIL SUMMARY SHEET

TITLE: CALGB 9140: A Phase III Study of CAF-Leucovorin vs. *CAF for Visceral Crisis Breast Cancer

KEYWORDS: metastatic disease, chemotherapy, leucovorin

PRINCIPAL INVESTIGATOR: Weiss, Raymond M.D.

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Cancer & Leukemia Group B APPROVAL DATE: Jan 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To compare the response rates, duration of response, time to treatment failure, and survival of patients with metastatic breast cancer treated with cytoxan, Adriamycin, and 5-fluorouracil (CAF) versus patients treated with CAF plus leucovorin; and to compare the toxicity experienced by the two treatment groups.

TECHNICAL APPROACH
All eligible patients will be randomized to receive one of two treatment arms: (1) CAF every 3 weeks; or (2) CAF and leucovorin every 21 days. The treatment may continue as long as 1 year.

PRIOR AND CURRENT PROGRESS
A total of three patients from WRAMC have been entered on this study; one during this reporting period. Two patients have died of progressive disease, and the third patient continues to receive therapy. No adverse side effects have been reported, and no patients have withdrawn from the study. The total national accrual is 80 patients; 48 during this reporting period. The projected accrual is for 240 patients.

CONCLUSIONS
No conclusions have been reached.

REPORT DATE: 01/04/94 WORK UNIT # 1527-92

DETAIL SUMMARY SHEET

TITLE: CALGB 9190: A Trial of Postoperative Interferon in Resected High Risk Melanoma

KEYWORDS: high-dose interferon, low-dose interferon, observation

PRINCIPAL INVESTIGATOR: Weiss, Raymond M.D.

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Cancer & Leukemia Group B APPROVAL DATE: Jan 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To establish the efficacy of interferon alfa-2b as an adjuvant in increasing the disease-free survival and overall survival in patients at high risk for recurrence after definitive surgery for deep primary lesions or after regional lymph node recurrence.

TECHNICAL APPROACH

Eligible patients are randomized to receive one of three treatment plans: (1) high dose interferon for approximately 1 year; (2) low-dose interferon for approximately 2 years; or (3) observation only - frequent follow-up for 2 years, then annually. Those patients randomized to receive interferon will be trained to self-administer their subcutaneous injections at home.

PRIOR AND CURRENT PROGRESS

One patient from WRAMC has been enrolled on this study (during this reporting period). This patient was assigned to the observation only arm: therefore, no adverse events have occurred. No patients have withdrawn from the study. The total CALGB accrual is 63 patients; 36 during this reporting period. Two other national study groups, ECOG and SWOG, are also enrolling patients, but their totals are unknown at this time. The projected national accrual is for 498 patients.

CONCLUSIONS

No conclusions have been reached.

REPORT DATE: 01/05/94 WORK UNIT # 1528-92

DETAIL SUMMARY SHEET

TITLE: CALGB 9195: A Trial of Adjuvant Chemoradiation vs. Observation After Gastric Resection of Adenocarcinoma

KEYWORDS: post-gastrectomy, adjuvant therapy, observation

PRINCIPAL INVESTIGATOR: Weiss, Raymond M.D.

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Cancer & Leukemia Group B APPROVAL DATE: Jan 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To compare overall and disease-free survival between patients treated with gastrectomy only and those treated with gastrectomy plus adjuvant therapy; to compare the incidence and patterns of disease failure between these two groups of patients; and to assess patient tolerance of upper abdominal chemoradiation after gastric resection.

TECHNICAL APPROACH
Eligible patients will be randomized to receive either adjuvant chemoradiation, consisting of five courses of 5-fluorouracil and leucovorin plus one course of radiation, or to observation only. This arm would consist of close observation for symptoms of recurrence over a 2-year period, then annual follow-up thereafter.

PRIOR AND CURRENT PROGRESS
No patients from WRAMC have been entered on this study. The total national accrual is 142 patients; 92 of those during this reporting period. The projected accrual is for 350 patients. No unexpected adverse reactions have been reported by CALGB.

CONCLUSIONS
No conclusions have been reached.

REPORT DATE: 04/16/93 WORK UNIT # 1531-92

DETAIL SUMMARY SHEET

TITLE: CALGB 9160: A Phase III Trial of High Dose Cyclophosphamide With G-CSF With or Without Amifostine

KEYWORDS: solid tumor, no standard therapy, chemoprotective agent

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD, DAC

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Cancer & Leukemia Group B APPROVAL DATE: Apr 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine whether the addition of WR-2721 will ameliorate the depth of granulocyte and/or platelet nadirs or the duration of granulocyte and/or platelet nadirs in cancer patients receiving intensive cyclophosphamide combined with granulocyte macrophage colony-stimulating factor (GM-CSF). To determine whether WR-2721 will lessen the clinically significant sequela of intensive cyclophosphamide therapy.

TECHNICAL APPROACH
All eligible patients will receive high dose cyclophosphamide, Mesna, and GM-CSF. They will be randomized to receive or not receive WR-2721 with their treatments. Treatment cycles will be repeated every 15 days. All patients responding with a partial remission or complete remission after four doses can be continued on treatment while they continue to respond. The study was amended in August 1993 to include cyclophosphamide pharmacokinetics. The patient consent form was revised April 1994 to include this change.

PRIOR AND CURRENT PROGRESS
A total of WRAMC patients have been registered on this study; two of those during this reporting period. Of those six patients, three have died of progressive disease, one patient was removed from the study due to hematologic toxicity and subsequently progressed, one patient was removed due to disease progression, and one patient continues therapy and has stable disease after seven cycles. No patients have withdrawn from the study. No unexpected toxicities have been reported. The projected accrual is for 42 patients. Fifteen patients have been entered nationwide, 13 of those during this reporting period.

CONCLUSIONS
Analysis is ongoing.

REPORT DATE: 06/08/94 WORK UNIT # 1532-92

DETAIL SUMMARY SHEET

TITLE: CALGB 9261 A Phase I Study of Topotecan and Cisplatin

KEYWORDS: solid tumor, Phase I, topotecan/cisplatin

PRINCIPAL INVESTIGATOR: Weiss, Raymond M.D.

DEPARTMENT: Department of Medicine STATUS: Completed
SERVICE: Cancer & Leukemia Group B APPROVAL DATE: Jun 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To define the maximum tolerated dose of cisplatin that can be administered with a fixed dose of topotecan, and to determine the toxicities of the combination.

TECHNICAL APPROACH
All eligible patients, when registered, will be assigned a specific dose of cisplatin and topotecan. There will be three patients per dose level. An evaluation of all patients will be done weekly to determine toxicities. The doses of cisplatin will be escalated with each cohort of three patients until the maximum tolerated dose for that level has been determined.

PRIOR AND CURRENT PROGRESS
A total of 17 patients from WRAMC have been entered on this study, one during this reporting period. That patient was subsequently removed from the protocol due to progressive disease. No unexpected toxicities occurred. After their removal from the protocol, 14 of the 17 patients died. The three remaining patients are still being followed for survival. The study closed to new accrual 28 Aug 93. A total of 36 patients were entered nationwide, 12 of those this reporting period. This study is being closed at WRAMC since all patients have now completed therapy.

CONCLUSIONS
Analysis is in progress.

REPORT DATE: 11/09/93 WORK UNIT # 1533-92

DETAIL SUMMARY SHEET

TITLE: CALGB 9134: Combined Modality Therapy for Stage III Non-Small Cell Lung Cancer

KEYWORDS: surgical resection, radiation, chemotherapy

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Cancer & Leukemia Group B APPROVAL DATE: Nov 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To evaluate and compare the disease-free and overall survival of patients with Stage IIIA (N2) non-small cell lung cancer who are treated by radiotherapy and surgical resection with or without chemotherapy, to determine the impact of induction chemotherapy, and to determine the impact of induction chemotherapy and preoperative radiotherapy on rates of operability and resectability.

TECHNICAL APPROACH

All eligible patients will be randomized to receive one of two treatment arms: 1) radiation therapy, surgery, radiation therapy; or 2) chemotherapy, surgery, chemotherapy, radiation therapy. Total treatment time for either arm amounts to 405 months. Patients will then be followed for survival. Growth factors (granulocyte colony stimulating factor) will be used during chemotherapy.

PRIOR AND CURRENT PROGRESS

No patients from WRAMC have been entered on this study. The total national accrual is 27; all were enrolled during this reporting period. The total projected accrual is for 250 patients. No unexpected adverse events have been reported by the Cancer and Leukemia Group B.

CONCLUSIONS

No conclusions have been reached.

REPORT DATE: 11/09/93 WORK UNIT # 1534-92

DETAIL SUMMARY SHEET

TITLE: CALGB 9191: A Randomized Study of All-Trans Retinoic Acid vs Standard Induction Therapy for Acute Promyelocytic Leukemia

KEYWORDS: induction, consolidation, crossover

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Cancer & Leukemia Group B APPROVAL DATE: Nov 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To compare the complete remission rate and disease-free survival of trans retinoic acid (TRA) to that achieved with conventional induction chemotherapy including Cytosine Arabinoside plus daunorubicin in patients with previously untreated acute promyelocytic leukemia; to compare the toxicities of TRA to those of cytosine/daunorubicin as induction therapy; and to determine the value of maintenance therapy with TRA.

TECHNICAL APPROACH
All eligible patients will be intially randomized to receive one of two induction treatments: 1) TRA orally for 45-90 days; or 2) standard chemotherapy with cytosine and daunorubicin for 7 days total. Once a complete response is achieved, consolidation therapy will be given for two courses with cytosine, one course being high dose. If the response remains, the patient is randomized again to receive either maintenance therapy with TRA or observation alone. If the leukemia returns after achieving a response and the patient was randomized to TRA, they will crossover to receive the second therapy.

PRIOR AND CURRENT PROGRESS
The total national accrual is 16 patients, all of them during this reporting year. None of these patients have been from WRAMC. No serious or unexpected adverse reactions have been reported.

CONCLUSIONS
Analysis is ongoing. No conclusions have been reached.

REPORT DATE: 11/09/93 WORK UNIT # 1535-92

DETAIL SUMMARY SHEET

TITLE: CALGB 9222: A Randomized Study of Intensification Therapy for Patients Under Age 60 with Acute Myelogenous Leukemia

KEYWORDS: post-remission, high-dose cytosine, sequential therapy

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Cancer & Leukemia Group B APPROVAL DATE: Nov 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To compare two post-remission chemotherapy regimens: 1) intensification with single agent high dose cytosine arabinoside; and 2) three courses of sequential, potentially non-cross-resistant treatment. To confirm patient tolerance; and to continue to investigate the prognostic significance of cytogenetics and immunophenotyping in patients with acute myelogenous leukemia.

TECHNICAL APPROACH

All eligible patients wil receive the same standard induction, up to two times to achieve a complete response. Responders will then be randomized to receive either: 1) six high doses of cytosine arabinoside repeated at 28-day intervals for a total of three courses; or 2) six sequential doses of high dose cytosine, followed by a second cycle of cyclophosphamide and etoposide, and then a third cycle of diaziquone and mitoxantrone with granulocyte colony stimulating factor. Patients will then be followed for relapse or survival.

PRIOR AND CURRENT PROGRESS

The total national accrual is 137 patients, all during this reporting period. Two WRAMC patients have been enrolled. One WRAMC patient has completed therapy and has achieved a complete remission, and the other one died of progressive disease 10 days into therapy (this death was not attributed to the study regimen). No unexpected or serious adverse reactions were reported. The projected enrollment goal for the study is 270 patients.

CONCLUSIONS

No conclusions have been reached.

REPORT DATE: 11/09/93 WORK UNIT # 1536-92

DETAIL SUMMARY SHEET

TITLE: CALGB 9263: Detection of Trisomy Genetic Change in Chronic Lymphatic Leukemia

KEYWORDS: Trisomy 12, cytogenetics

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Cancer & Leukemia Group B APPROVAL DATE: Nov 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To reassess the prevalence of Trisomy 12 in chronic lymphocytic leukemia (CLL) by employing interphase cytogenetic analysis on peripheral blood cells from consecutive patients with CLL; and to assess the association of Trisomy 12 with response to therapy and overall survival.

TECHNICAL APPROACH
This is a companion study to CALGB 9011, the other treatment study for CLL. Following registration into 9011, patients will be asked to enroll into this blood-drawing study. Three separate blood samples will be obtained and sent to the referenced laboratory; at study entry, at 2 months after complete response to treatment, and at the time of relapse following a complete response.

PRIOR AND CURRENT PROGRESS
No patients from WRAMC have been entered on this study. The total national accrual is 115 patients, 103 of those during this reporting period (another 12 patients were enrolled prior to this study's approval at WRAMC). No unexpected adverse events have occurred as reported by Cancer and Leukemia Group B. The projected accrual is for 400 patients.

CONCLUSIONS
Analysis is ongoing.

REPORT DATE: 12/13/93 WORK UNIT # 1537-92

DETAIL SUMMARY SHEET

TITLE: CALGB 9162 Study of Pharmacokinetic Parameters in the Efficacy and Toxicity of 5-FU

KEYWORDS: drug level, toxicity, colon cancer

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD

DEPARTMENT: Department of Medicine STATUS: Completed
SERVICE: Cancer & Leukemia Group B APPROVAL DATE: Dec 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To explore the relationships between steady-state 5 fluorouracil concentration, toxicity, and response in patients receiving 5-FU alone as a 24-hour weekly infusion and in patients receiving 5-FU plus PALA.

TECHNICAL APPROACH

This study is a companion to treatment study CALGB 9092. All patients registered will have been assigned to one of the treatment arms utilizing 5-FU and PALA. Pharmacokinetic blood samples will be drawn at specified hourly or weekly intervals during their treatment. The samples will be mailed to the referenced lab, and the drug levels obtained will be compared to the toxicity observed and the antitumor effect of 5-FU alone and 5-FU plus PALA.

PRIOR AND CURRENT PROGRESS

No patients from WRAMC have been entered on this study. The study closed to accrual on 18 Mar 93. The total national accrual at the time of closure was two patients. One patient was entered in 1991, and the second was entered in 1992. The frequency of the sampling was decreased in late 1992 to encourage participation; however, there was no additional accrual. The study is being closed at WRAMC.

CONCLUSIONS

No conclusions have been reached.

REPORT DATE: 12/03/93 WORK UNIT # 1538-92

DETAIL SUMMARY SHEET

TITLE: CALGB 9163 A Randomized Study of Vinblastine with Modulators in Metastatic Renal Cancer

KEYWORDS: renal cell, vinblastine, multi-drug resistance

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Cancer & Leukemia Group B APPROVAL DATE: Dec 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine the efficacy (response rate and duration of response) of the combination of continuous infusion vinblastine and either cyclosporin A or tamoxifen as modulators of multi-drug resistance (MDR) in patients with metastastic, recurrent, or unresectable renal cell carcinoma who are refractory to vinblastine chemotherapy.

TECHNICAL APPROACH
All eligible patients will be randomized to receive vinblastine plus a modulator; either cyclosporin A or tamoxifen in conjunction with the vinblastine. All patients will receive a minimum of two cycles of continuous 5 day infusion of vinblastine and then reevaluated. If the cancer does not show a response, the modulator, as randomized, will be added to the treatment.

PRIOR AND CURRENT PROGRESS
Four patients from WRAMC have been entered on this study; three were randomized to receive tamoxifen, and one to receive cyclosporin A. There have been no unexpected or serious adverse reactions. No patients were withdrawn from the study. A total of 98 patients have been entered nationwide since the study opened, all during this reporting period. The projected accrual is for 116 patients.

CONCLUSIONS
No conclusions have been reached.

REPORT DATE: 12/03/93 WORK UNIT # 1539-92

DETAIL SUMMARY SHEET

TITLE: CALGB 9242 Topotecan for Advanced Breast Cancer

KEYWORDS: investigational, single-agent, Stage IV breast cancer

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Cancer & Leukemia Group B APPROVAL DATE: Dec 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To determine the efficacy and safety of Topotecan in the treatment of Stage IV adenocarcinoma of the breast; to evaluate the anti-tumor activity in the treatment of inoperable, recurrent, or metastatic carcinoma of the breast; and to determine the duration of response, survival, and quality of survival balanced against toxicity.

TECHNICAL APPROACH

All eligible patients will be registered to receive Topotecan intravenously over 30 minutes for 5 days every 21 days. A minimum of two cycles will be given, followed by reevaluation. The treatment will be continued as long as the cancer growth is controlled.

PRIOR AND CURRENT PROGRESS

No patients from WRAMC have been entered on this study. A total of nine patients have been entered nationwide since the study opened. The projected accrual is for 40 patients. No serious or unexpected adverse events have been reported.

CONCLUSIONS

No conclusions have been reached.

REPORT DATE: 12/03/93 WORK UNIT # 1540-92

DETAIL SUMMARY SHEET

TITLE: CALGB 9092 A Study of 5-Fluorouracil (5-FU) With or Without Modulators in Advanced Colorectal Cancer

KEYWORDS: adenocarcinoma, unresectable, 5FU control arm

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Cancer & Leukemia Group B APPROVAL DATE: Dec 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To compare: a) PALA vs 5-fluorouracil alone, b) IV leucovorin vs. oral leucovorin, c) IV leucovorin vs. interferon, and d) IV leucovorin vs. 5-fluorouracil alone. In addition, IV leucovorin vs. PALA/5FU will be compared as a secondary objtive. Lastly, response rates and times to progression among the different treatments will be compared.

TECHNICAL APPROACH
All eligible patients will be randomized to receive one of five treatment plans: 1) 5FU alone; 2) PALA and 5FU; 3) oral leucovorin and 5FU, 4) IV leucovorin, or 5) interferon and 5FU. A minimum of 1 month's treatment will be continued as long as the cancer does not progress or toxicities do not become severe.

PRIOR AND CURRENT PROGRESS
One patient from WRAMC has been entered on this study. No unexpected or serious toxicities have occurred. The patient was removed from the study due to progressive disease and has died of disease. The total national accrual is 569 patients, 238 of those during this reporting period. Projected accrual is for 900 patients.

CONCLUSIONS
No conclusions have been reached.

REPORT DATE: 03/18/94 WORK UNIT # 1541-93

DETAIL SUMMARY SHEET

TITLE: CALGB 9153: A Trial of Cladribine in Advance Stage, Low Grade non-Hodgkin's Lymphoma

KEYWORDS: low grade lymphoma, advanced

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Cancer & Leukemia Group B APPROVAL DATE: Mar 1993

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To determine the percentage of patients with advanced, previously untreated, low grade lymphomas who respond with complete or partial remissions to treatment with Cladribine; to estimate the duration of response for patients with partial and complete responses; and to describe the toxicity of Cladribine treatment in this population.

TECHNICAL APPROACH

All eligible patients will be registered and will receive treatment with Cladribine intravenously as a 2-hour infusion for 5 consecutive days, every 28 days. A maximum of six cycles will be given. All patients will be reevaluated every two cycles for response.

PRIOR AND CURRENT PROGRESS

Two patients from WRAMC have been entered on this study, both during this reporting period. No unexpected adverse events have been reported; no patients have withdrawn from the study. The total national accrual is 42 patients, all of those during this reporting period. The study closed to accrual December 15, 1993, but remains open at WRAMC because one patient is still receiving treatment.

CONCLUSIONS

No conclusions have been reached.

REPORT DATE: 04/01/94 WORK UNIT # 1542-93

DETAIL SUMMARY SHEET

TITLE: CALGB 9154: A Comparison of Two Dose Levels of Chope Combination Chemotherapy and G-CSF for Non-Hodgkin's Lymphoma

KEYWORDS: dose comparison, large cell lymphoma

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD

DEPARTMENT: Department of Medicine
SERVICE: Cancer & Leukemia Group B

STATUS: Completed
APPROVAL DATE: Mar 1993

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To further evaluate disease response rates and toxicities associated with two separate doses of CHOPE regimen (cyclophosphamide, doxorubicin, vincristine, prednisone, and etoposide) utilizing recombinant human granulocyte-colony stimulating factor (rhG-CSF).

TECHNICAL APPROACH
All eligible patients will be randomized to receive one of two different dose levels of cyclophosphamide and etoposide in combination with the additional drugs listed. A maximum of eight courses of therapy will be given at 28 day intervals, as long as the disease is responding.

PRIOR AND CURRENT PROGRESS
This study was never activated by CALGB (never opened).

CONCLUSIONS
None.

REPORT DATE: 03/21/94 WORK UNIT # 1543-93

DETAIL SUMMARY SHEET

TITLE: CALGB 9256: A Study of Taxotere in Advanced Stage Non-Hodgkin's Lymphoma

KEYWORDS: relapsed, refractory, lymphoma

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Cancer & Leukemia Group B APPROVAL DATE: Mar 1993

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To evaluate the response rate and response duration of previously treated non-Hodgkin's lymphoma IWF A-H when treated with taxotere. To assess the toxicity at the suggested Phase II solid tumor dose in patients with lymphoma.

TECHNICAL APPROACH

All eligible patients will receive taxotere intravenously in a 2 hour infusion every 3 weeks. After two cycles, the disease will be reevaluated. Patients who are showing tumor response will continue treatment every 3 weeks until a maximum of six cycles are given. After that time, close observation for disease recurrence will be done.

PRIOR AND CURRENT PROGRESS

No patients from WRAMC have been entered to this study so far. A total of 18 patients nationwide have been entered. No unexpected adverse events have been reported.

CONCLUSIONS

No conclusions have been reached.

REPORT DATE: 10/25/93 WORK UNIT # 1544-86

DETAIL SUMMARY SHEET

TITLE: CALGB 8525: A Phase III Comparative Study of Post-Remission Intensive Ara-C in Patients with Acute Nonlymphocytic Leukemia in First Remission (addendum CALGB 8661 Epidemiology of Acute Leukemias in Adults .... Cytogenically Determined Subgroups)

KEYWORDS: epidemiology, myelodysplastic, interview

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Cancer & Leukemia Group B APPROVAL DATE: Oct 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To identify: 1) environmental and genetic risk factors for leukemia in adults; and 2) risk factors for cytogenetically defined subgroups of leukemia. To determine if risk factors such as occupational or medical exposure to chemicals or family history of cancer are more strongly associated with specific cytogenetically defined subgroups.

TECHNICAL APPROACH
This study was a companion study to CALGB 8525, which was closed in 1989. CALGB 8661 was reopened this past year to registration of patients with a diagnosis of myelodysplastic syndrome. A trained medical interviewer will contact eligible patients by phone. After obtaining the patient's permission, a telephone interview will take place, lasting approximately 45 minutes. Questions to be answered are about health, occupation, hobbies, and environmental exposure.

PRIOR AND CURRENT PROGRESS
A total of 49 patients from WRAMC have been entered on this companion study since it originally opened in 1986. Since the study was reopened to patients with myelodysplastic syndrome this past year, two patients have been enrolled from WRAMC. A total of 1,060 patients have been entered nationwide since 1986; 14 patients during this reporting period. This is considered a low risk study; therefore, no adverse events have occurred. No patients have withdrawn from the study.

CONCLUSIONS
Analysis is ongoing. No conclusions have been reached.

REPORT DATE: 05/04/94 WORK UNIT # 1544-93

DETAIL SUMMARY SHEET

TITLE: CALGB 9294. An Intergroup Study of Colon Cancer Adjuvant Therapy

KEYWORDS: chemotherapy, radiation, adjuvant

PRINCIPAL INVESTIGATOR: Weiss, Raymond M.D.

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Cancer & Leukemia Group B APPROVAL DATE: May 1993

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine whether 5-fluorouracil, levamisole, and radiation therapy result in superior overall survival when compared to 5-fluorouracil and levamisole without radiation in patients with completely resected colon cancer. To evaluate disease-free survival, patterns of failure, and toxicity.

TECHNICAL APPROACH
All eligible patients will be randomly assigned to receive one of two treatments; 1) 1 year of chemotherapy with 5-fluorouracil and levamisole, or 2) 1 year of 5-fluorouracil and levamisole plus radiation for 5-5 1/2 weeks. The levamisole will be given as oral medication for 3 consecutive days. The 5-fluorouracil is intravenously given 5 consecutive days in the beginning, followed by once-per-week injections for the remainder of the year.

PRIOR AND CURRENT PROGRESS
No patients from WRAMC have been entered on this study since it opened last March. Fifty-five patients have been entered nationally this past year. The projected accrual is for 700 patients. No unexpected toxicities have been reported. No benefit to the patient has been determined thus far.

CONCLUSIONS
No conclusions have been reached.

REPORT DATE: 06/13/94 WORK UNIT # 1545-93

DETAIL SUMMARY SHEET

TITLE: WRAMC 9302. A WRAMC/NCI Collaborative Phase I Study of Taxol Given as a Continous Infusion

KEYWORDS: solid tumor, taxol

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Cancer & Leukemia Group B APPROVAL DATE: Jun 1993

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine the maximum tolerated doses of taxol by 14 day continuous infusion in patients with advanced metastatic cancer treated on 28 day cycles. To determine the overall and dose-limiting toxicities of 14-day taxol infusion schedule. To study whether Pgp or GST expression in patients' tumors is associated with clinical response to 14-day infusional taxol.

TECHNICAL APPROACH
All eligible patients who consent will be assigned a specified dose of taxol to be administered by continuous infusion for a specific number of days. Cohorts of three patients will be treated at one time, and observed for toxicities from the taxol therapy. If the drug is tolerated, the next three will move up to the next dose level until the maximum tolerated dose is achieved. The maximum treatment time will be 14 days of continuous infusion. Addenda addressing the progression of doses to the next level have been reviewed by the IRB at WRAMC.

PRIOR AND CURRENT PROGRESS
A total of three patients from WRAMC have been entered on this study. No patients have withdrawn. Two of those patients were removed from the study due to disease progression; one patient continues therapy with stable disease. No unexpected toxicities were observed. A total of nine patients have been registered overall during this past year, according to the Research Coordinator at the National Cancer Institute. Side effects have been minimal.

CONCLUSIONS
No conclusions have been reached.

REPORT DATE: 06/14/94 WORK UNIT # 1546-93

DETAIL SUMMARY SHEET

TITLE: CALGB 9362: A Phase I Study of Topotecan and Taxol

KEYWORDS: solid tumor, combination therapy, optimal dose

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Cancer & Leukemia Group B APPROVAL DATE: Jun 1993

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To define the maximum tolerated dose of taxol, given in a 3-hour infusion, that can be administered with a fixed dose of topotecan (without and with G-CSF support). To determine the toxicities of the combination. To define the optimal dose of the combination of drugs for Phase II studies.

TECHNICAL APPROACH

All eligible patients will receive taxol intravenously over 3 hours on day 1 and topotecan intravenously over 30 minutes on day 1. On days 2-5 the topotecan will be repeated (total of 5 days). The current dose level of taxol will be assigned at the time of registration; the dose of topotecan will remain constant. Three patients at a time will be assigned a specific dose level, with close observation for toxicities. When the maximum tolerated dose has been reached, colony-stimulating factors will be added to the treatment. The cycle of treatment will be repeated every 3-4 weeks.

PRIOR AND CURRENT PROGRESS

A total of eight patients from WRAMC have been entered on this study since it opened last year. Five patients have been removed from the study due to progressive disease; three remain on treatment with stable disease. No patients have withdrawn from the study; no unexpected adverse events have occurred. The total national accrual is 34 patients. Six dose combination cohorts have been completed. Growth factors were added to the treatment after the third cohort dose escalation was assigned. The drug combination has been well tolerated; the main dose-limiting toxicity has been hematologic.

CONCLUSIONS

No conclusions have been reached.

REPORT DATE: 06/08/94 WORK UNIT # 1560-87

DETAIL SUMMARY SHEET

TITLE: CALGB 8642: A Master Protocol to Study Single Agent Chemotherapy Vs. Standard Chemotherapy for Advanced Breast Cancer

KEYWORDS: chemotherapy, cancer, breast

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Cancer & Leukemia Group B APPROVAL DATE: Jun 1987

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To evaluate single Phase II agents in achieving responses in previously untreated metastatic breast cancer patients.

TECHNICAL APPROACH
Randomized study in which all eligible patients receive either standard cytoxan, Adriamycin, and 5-fluorouracil (CAF) therapy or a Phase II agent. Those randomized to receive a Phase II agent are treated for two cycles, then reevaluated for response or progression. If progression occurs, they are switched to CAF therapy. The next Phase II drug treatment arm, using alsamitrucin, was approved by the CALGB June 1992 for limited institutions.

PRIOR AND CURRENT PROGRESS
A total of 18 patients from WRAMC have been entered on this study, one during this past year. No unexpected adverse events have been observed; no patients have withdrawn from the study. Ten patients have subsequently died of progressive disease, four have been removed from the study and are receiving other therapy for their progressive disease, and four have achieved a complete response (one of those patients is still on treatment). The patients with complete responses continue to be followed and are on no other therapy. This study closed to new accrual 31 Dec 93. The total national accrual was 365 patients, 29 this past year.

CONCLUSIONS
Analysis is in progress.

REPORT DATE: 10/14/93 WORK UNIT # 1573-87

DETAIL SUMMARY SHEET

TITLE: CALGB 8762: Molecular Subtypes in Acute Lymphatic Leukemia with Philadelphia Chromosome

KEYWORDS: Philadelphia chromosome, ALL

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Cancer & Leukemia Group B APPROVAL DATE: Oct 1987

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine the incidence of pH positivity in patients with previously untreated acute lymphatic leukemia (ALL).

TECHNICAL APPROACH
Non-randomized comparison study in which all eligible patients who consent allow a sample of blood and bone marrow to be sent to a reference laboratory at the time of diagnosis, first intensification, and at relapse.

PRIOR AND CURRENT PROGRESS
A total of nine patients from WRAMC have been entered on this study, three of those during this reporting period. Four of those nine patients have died of their disease, one was removed from study due to revised diagnosis, two have relapsed after achieving a remission, and two remain in follow-up and are in remission. All required blood and bone marrow samples have been obtained. No adverse reactions have occurred.

CONCLUSIONS
Analysis is ongoing.

REPORT DATE: 10/14/93 WORK UNIT # 1574-87

DETAIL SUMMARY SHEET

TITLE: CALGB 8763: Immunoglobulin and T Cell Receptor Gene Rearrangement in Adult Acute Lymphatic Leukemia

KEYWORDS: immunoglobulin, T-cell receptor, ALL

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Cancer & Leukemia Group B APPROVAL DATE: Oct 1987

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine the incidence of Ig and T-cell receptor gene rearrangements from samples of patients with previously untreated adult acute lymphatic leukemia (ALL).

TECHNICAL APPROACH
Non-randomized companion study in which all eligible patients who consent allow a sample of bone marrow and blood to be sent to CALGB reference laboratory at the time of diagnosis, prior to first intensification, and at relapse.

PRIOR AND CURRENT PROGRESS
To date, eight patients have been enrolled from WRAMC; one during this past reporting period. The total national accrual is 250; 55 within the past year. Of the WRAMC patients, four have died of their disease, two have relapsed within the past year, and two remain in remission. All blood and bone marrow samples have been sent at the required intervals. No unexpected adverse reactions have occurred.

CONCLUSIONS
Analysis is ongoing.

REPORT DATE: 12/13/93 WORK UNIT # 1577-80

DETAIL SUMMARY SHEET

TITLE: CALGB 8361: Immunologic Diagnostic Studies in AML (blood drawing phase); previously CALGB 7921): A Comparative Study of 3 Remission Induction Regimens and 2 Maintenance Regimens for AML (treatment phase); previously CALGB 8321

KEYWORDS: immunology, oncology, leukemia

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Cancer & Leukemia Group B APPROVAL DATE: Dec 1981

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

a) To determine the incidence of various markers in acute myelogenous leukemia (AML); b) To correlate the presence of these markers and the surface antigen phenotype they determine with the FAB histological classification; and c) To correlate the presence of the various markers with the initial and subsequent clinical characteristics of the disease.

TECHNICAL APPROACH

All eligible patients are registered prior to the initial therapy. From the diagnostic bone marrow procedure, 2 cc of bone marrow and 7 cc of peripheral blood are collected and sent by express mail to the CALGB reference laboratory for analysis and confirmation of classification. Samples are again obtained at relapse.

PRIOR AND CURRENT PROGRESS

A total of 60 patients from WRAMC have been entered on this study, none during this reporting period. The patients continue to be followed, with blood and bone marrow samples obtained and mailed for analysis at the same interval that their regular samples are taken to monitor disease progress. No unexpected adverse events have occurred. No patients have withdrawn from the study. The total national accrual is 1,981 patients; 217 of those were entered during this reporting period.

CONCLUSIONS

Analysis is ongoing.

REPORT DATE: 01/05/94 WORK UNIT # 1579-88

DETAIL SUMMARY SHEET

TITLE: CALGB 8861: Monitoring Circulating Breast Cancer-Associated 15-3 Antigen in Stage II Breast Cancer

KEYWORDS: antigen, breast cancer, Stage II

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD

DEPARTMENT: Department of Medicine
SERVICE: Cancer & Leukemia Group B

STATUS: Ongoing
APPROVAL DATE: Jan 1988

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To evaluate the predictive value of rising CA15-3 levels in patients who are clinically free of recurring disease.

TECHNICAL APPROACH
Ten cc of whole blood is collected prior to first therapy, at 28 day intervals during therapy, at 4 month intervals for 2 years, and then every 6 months for 4 years. Blood is processed at WRAMC and shipped to CALGB approved reference laboratory for analysis.

PRIOR AND CURRENT PROGRESS
A total of 24 patients from WRAMC have been entered on this study, 10 during this reporting period. The total national accrual is 401 patients, 57 during this reporting period. Blood samples continue to be drawn at the specified follow-up intervals and shipped to the referenced lab. No adverse events have occurred, and no patients have withdrawn. The projected accrual is for 750 patients.

CONCLUSIONS
Analysis is ongoing.

REPORT DATE: 01/05/94 WORK UNIT # 1590-89

DETAIL SUMMARY SHEET

TITLE: CALGB 8852: A Study of CHOPE in Diffuse Lymphomas

KEYWORDS: lymphoma, CHOPE, high-dose

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Cancer & Leukemia Group B APPROVAL DATE: Jan 1989

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To identify the maximum tolerated dose of cyclophosphamide, doxorubicin, vincristine, prednisone, and etoposide (CHOPE) in the treatment of lymphoma, and to assess the safety of giving multiple cycles of high-dose CHOPE therapy.

TECHNICAL APPROACH
Standard doses of CHOPE will be given to the first 20-25 patients enrolled. If tolerated, the doses will be escalated for the next groups sequentially, until the maximum tolerated dose is reached.

PRIOR AND CURRENT PROGRESS
Five WRAMC patients have been entered into this study, two during this reporting period. Three WRAMC patients have died of progressive disease; the remaining two continue to be followed for relapse. Nationally, 227 patients have been enrolled, 43 during this reporting period. The study was closed to patient accrual 24 May 93. No unexpected adverse events have been reported, and no patients have withdrawn. This study remains open for follow-up.

CONCLUSIONS
No conclusions have been reached.

REPORT DATE: 04/13/94 WORK UNIT # 1595-89

DETAIL SUMMARY SHEET

TITLE: CALGB 8961 RAS Mutations in Myelodysplasia

KEYWORDS: Ras gene, oncogenes, myelodysplasia

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD

DEPARTMENT: Department of Medicine
SERVICE: Cancer & Leukemia Group B

STATUS: Ongoing
APPROVAL DATE: Apr 1989

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To determine the prevalance of mutant RAS genes in myelodysplasia. To determine if the presence of such a mutation predicts subsequent leukemic development.

TECHNICAL APPROACH

Non-randomized, non-treatment protocol in which all eligible patients are registered. Blood and bone marrow samples and slides are obtained at entry and again when acute leukemia develops.

PRIOR AND CURRENT PROGRESS

A total of seven WRAMC patients have been entered on this study; one was entered this reporting period. The total national accrual is 148 patients, 32 of those during this reporting period. No patients have withdrawn from the study. No adverse experiences have occurred. No benefit to the patient has yet been determined.

CONCLUSIONS

Analysis is ongoing. No conclusions have been reached.

REPORT DATE: 08/10/94 WORK UNIT # 1598-89

DETAIL SUMMARY SHEET

TITLE: CALGB 8952 Combination Chemotherapy for Advanced Hodgkin's Disease, Phase III

KEYWORDS: chemotherapy, Hodgkin's disease

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Cancer & Leukemia Group B APPROVAL DATE: Aug 1989

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To compare ABVD to the MOPP/ABV hybrid as therapy for patients with Hodgkin's disease in terms of complete response rates, disease-free survival, failure-free survival, and both intermediate and long-term toxicities.

TECHNICAL APPROACH
Randomized study in which eligible patients receive either ABVD or the MOPP/ABV hybrid combination for a minimum of six cycles unless progression is documented.

PRIOR AND CURRENT PROGRESS
A total of nine WRAMC patients have been entered on this study, three of those during this reporting period. The total national accrual is 615 patients, 65 of those during this reporting period. The projected national accrual is for 900 patients. No unexpected adverse events have been reported. No patients have withdrawn from the study.

CONCLUSIONS
No conclusions have been reached.

REPORT DATE: 05/04/94 WORK UNIT # 1685

DETAIL SUMMARY SHEET

TITLE: WRAMC 9301. A WRAMC/NCI Collaborative Phase I Study of Topotecan and Adriamycin

KEYWORDS: drug combination, maximum dose, continous infusion

PRINCIPAL INVESTIGATOR: Weiss, Raymond M.D.

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Cancer & Leukemia Group B APPROVAL DATE: May 1993

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To: 1) determine the maximum tolerated dose of topotecan given as a continous infusion intravenously for 72 hours and doxorubicin given by intravenous injection on day 5 every 3 weeks; 2) define the toxicity of the combination of these drugs; and 3) determine the maximum tolerated dose of these drugs in combination with granulocyte colony stimulating factor to correct the granulocytopenia.

TECHNICAL APPROACH

Eligible patients have advanced stage solid tumors and have failed all potentially curative or life-prolonging therapy. Cohorts of three patients at a time will be treated with 72 hours of continous IV topotecan, and on Day 5 by one IV injfection of doxorubicin. The three patients will be observed closely for toxicities for 21 days. Doses will be escalated for the next cohort of three patients until maximum tolerated dose is reached. If granulo-cytopenia is dose limiting toxicity, colony stimulating factor will be added to therapy by subcutanous injection, and other toxicities noted. Protocol was amended in February 1994 to include two bone marrow exams on future patients.

PRIOR AND CURRENT PROGRESS

A total of 12 patients from WRAMC have been enrolled on this study; 7 of these were removed from the study due to progressive disease and subsequently died. Four were removed due to progressive disease and have started other therapies. One patient continues therapy with stable disease. Two unexpected adverse events with abnormal liver function tests were observed and reported to the IRB and the NCI. A total of 30 patients have been registered with the National Cancer Institute for this study.

CONCLUSIONS

No conclusions have been reached.

REPORT DATE: 04/01/94 WORK UNIT # 1260

DETAIL SUMMARY SHEET

TITLE: Antiarrhythmic Therapy in Congestive Heart Failure, VA Cooperative Study #320

KEYWORDS: heart failure, antiarrhythmic therapy, survival

PRINCIPAL INVESTIGATOR: Hull, Robert MAJ MC

DEPARTMENT: Department of Medicine STATUS: Completed
SERVICE: Cardiology Service APPROVAL DATE: Oct 1989

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine whether the treatment of ventricular arrhythmias with amiodarone prolongs survival by reducing sudden death in patients with congestive heart failure.

TECHNICAL APPROACH
The study is a multicenter, randomized, double-blinded, placebo-controlled trial of the effects of amiodarone on survival in patients with congestive heart failure. Patients qualifying for enrollment must have significant heart failure and ventricular ectopy on ambulatory ECG monitoring. Patients are then randomized to either amiodarone or placebo and then followed for the endpoints of the study. No modifications have been made to the original protocol methods.

PRIOR AND CURRENT PROGRESS
The enrollment period was completed in April 1993. Patient follow-up concluded March 1994. A total of 25 patients have been randomized from WRAMC. During the period of October 1993 to March 1994, one patient has died due to worsening congestive heart failure. There have been no serious adverse reactions with the remaining patients during this time. All surviving patients are to return to Cardiology Clinic for routine follow-up in June 1994.

CONCLUSIONS
Patient follow-up has concluded. No formal study results are available at this time.

REPORT DATE: 10/29/93 WORK UNIT # 1264

DETAIL SUMMARY SHEET

TITLE: The Role of Tumor Necrosis Factor After Balloon Angioplasty in a Pig Model

KEYWORDS: TNF, balloon, angioplasty

PRINCIPAL INVESTIGATOR: Carter, Andrew MAJ MC

DEPARTMENT: Department of Medicine
SERVICE: Cardiology Service

STATUS: Completed
APPROVAL DATE: Oct 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 517 Total: $ 517

STUDY OBJECTIVE
To detect the presence of tumor necrosis factor (TNF) in coronary arteries after local injury with balloon angioplasty utilizing immunohistochemical and molecular biologic techniques in the pig model.

TECHNICAL APPROACH
Hogs will undergo coronary angioplasty procedures. Following euthanasia, their coronary arteries will be examined for presence of TNF.

PRIOR AND CURRENT PROGRESS
Fourteen animals underwent 24 successful coronary balloon angioplasty procedures. Three deaths occurred (anesthetic - 1; and acute procedure - 2) during or within 24 hours of a procedure. Acute procedural complications included: coronary artery rupture (1); and myocardial infarction due to coronary occlusion (1). Animal studies for this project were completed in 1992. Plans are to conduct confirmational studies with a monoclonal anbibody specific for porcine TNF. As stated in prior progress reports, study data indicates that TNF-alpha mRNA is induced at 24 hours. On day 7 after injury, the protein is identified most intensely in regions of the media adjacent to sites of deep arterial wall injury.

CONCLUSIONS
TNF-alpha MRNA expression is induced by arterial injury. Immunolocalization of TNF indicates that the monokine may be produced by proliferating smooth muscle cells within the evolving neointima.

REPORT DATE: 10/07/93 WORK UNIT # 1265

DETAIL SUMMARY SHEET

TITLE: Cardiac Safety of Sexual Intercourse Following Myocardial Infarction as Assessed by High Resolution Holter Monitor

KEYWORDS: sexual intercourse, myocardial infarction, Holter monitor

PRINCIPAL INVESTIGATOR: Prewitt, Kerry CPT MC
ASSOCIATES: Cambier, Patrick MAJ MC; Wortham, Dale COL MC

DEPARTMENT: Department of Medicine
SERVICE: Cardiology Service

STATUS: Ongoing
APPROVAL DATE: Oct 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To determine the cardiac safety of sexual intercourse following myocardial infarction by directly assessing for the presence of ischemia and dysrhythmias using high resolution Holter monitoring.

TECHNICAL APPROACH

Patients who are 1 month post myocardial infarction will undergo a history, physical examination, and exercise. Patients will then wear a Holter monitor for 24 hours during which time they will have sexual intercourse. Holter studies will be analyzed for ST segment depression, dysrhythmias, and symptoms.

PRIOR AND CURRENT PROGRESS

A total of 22 patients have been entered altogether; none during the past year. No progress was made this past reporting period due to the transfer of the original principal investigator and a 9-month temporary duty assignment of the new principal investigator. There has been no incidence of serious or unexpected adverse reactions. No patients withdrew or received recognizable benefit.

CONCLUSIONS

No conclusions can be made based on the present data.

REPORT DATE: 05/20/94 WORK UNIT # 1267

DETAIL SUMMARY SHEET

TITLE: Cholesterol and Recurrent Events

KEYWORDS: cholesterol, pravastatine, therapy

PRINCIPAL INVESTIGATOR: Gorman, Patrick MAJ MC

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Cardiology Service APPROVAL DATE: May 1991

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine whether intensive therapy to lower plasma cholesterol will decrease fatal and nonfatal coronary heart disease and/or cause mortality in patients who have had infarction and do not have "high risk" cholesterol.

TECHNICAL APPROACH
Patients with r/o MI who do not have high risk cholesterol will be randomized to placebo or pravastatine. At least 8 weeks after infarction, patients will be screened by EKG, lab, and MUGA as indicated. Those enrolled will begin "run-in" placebo therapy. Thereafter, the patient will complete randomization with Hx/PE, dietary counseling, lipid profile, and safety lab every 3 months for the 5-year study, and yearly eye exams, and EKG's.

PRIOR AND CURRENT PROGRESS
Enrollment was completed in November 1991. Study is ongoing through 1995. Data collection and processing is in progress in Houston, Texas. Total enrollment at WRAMC is four. No further enrollment is planned. No adverse events have been reported.

CONCLUSIONS
Data collection and analysis is in progress.

REPORT DATE: 07/18/94 WORK UNIT # 1269

DETAIL SUMMARY SHEET

TITLE: The Porcine Restenosis Model: Characterization of the Vascular Proliferative Response to Injury

KEYWORDS: coronary vascular injury, intracoronary stents, smooth muscle cell

PRINCIPAL INVESTIGATOR: Carter, Andrew MAJ MC

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Cardiology Service APPROVAL DATE: Jul 1991

FUNDING: Current FY: $ 7,765 Previous FYs: $ 9,401 Total: $ 17,166

STUDY OBJECTIVE
To induce consistent smooth muscle cell proliferation after coronary vascular injury using metallic stents.

TECHNICAL APPROACH
The study involves placement of metallic intracoronary stents via aseptic carotid cutdown in the porcine model.

PRIOR AND CURRENT PROGRESS
The time course of smooth muscle cell proliferation and the morphologic features of lesion formation after experimental stent placement in normal porcine coronary arteries have been characterized. Smooth muscle cell proliferation is maximal on day 7, and this precedes maximal neointimal formation. By 28 days, intimal smooth muscle cell proliferation declines to low levels similar to stable atheroma. A total of 31 animals have been used, 7 this past year. There have been no adverse reactions.

CONCLUSIONS
Neointimal formation after experimental coronary stent placement is primarily dependent on smooth muscle cell proliferation.

REPORT DATE: 08/03/94 WORK UNIT # 1270

DETAIL SUMMARY SHEET

TITLE: Electrophysiologic Identification of Concealed Accessory Pathway Conduction as a Potential Predisposing Factor in "Lone" Atrial Fibrillation

KEYWORDS: fibrillation, electrocatheters, predisposing factor

PRINCIPAL INVESTIGATOR: Wiley, Thomas MAJ MC
ASSOCIATES: Hull, Robert MAJ MC

DEPARTMENT: Department of Medicine
SERVICE: Cardiology Service

STATUS: Ongoing
APPROVAL DATE: Jul 1991

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine the electrophysiologic substrate in patients with lone atrial fibrillation compared with control patients undergoing electrophysiologic studies for syncope.

TECHNICAL APPROACH
The patients are taken to the Cardiac Catheterization Laboratory in the post-absorptive and sedated state. Multipolar electrocatheters are then placed in the high right atrium, bundle region, right ventricular apex, and coronary sinus. Programmed burst and progressive decremental pacing is then performed from the right ventricular apex and the high right atrium.

PRIOR AND CURRENT PROGRESS
Thus far, 12 patients and 7 controls have been enrolled in the study; 9 patients and 5 controls were enrolled this past year. Four of the 12 patients have demonstrated physiology capable of producing early atrial extrastimuli, while no controls have had this finding. There have been no serious or unexpected adverse reactions.

CONCLUSIONS
Patients with lone paroxysmal atrial fibrillation may have a higher than expected incidence of dual atrioventricular node reentrant physiology or concealed accessory pathways.

REPORT DATE: 10/29/93 WORK UNIT # 1272

DETAIL SUMMARY SHEET

TITLE: Pharmacokinetic Drug Interactions with Terfenadine

KEYWORDS: terfenadine, pharmacokinetics, cardiac repolarization

PRINCIPAL INVESTIGATOR: Cantilena, Louis MD PhD
ASSOCIATES: Wortham, Dale COL MC

DEPARTMENT: Department of Medicine
SERVICE: Cardiology Service

STATUS: Ongoing
APPROVAL DATE: Oct 1991

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine if the biotransformation of terfenadine is altered by several known inhibitors of drug metabolism. To determine if such altered metabolism is found to occur whether there may be associated electrocardiographic changes.

TECHNICAL APPROACH
Volunteer, otherwise healthy, subjects will be given FDA-recommended dose of terfenadine (60 mg BID) for 1 week. Blood will be sampled during dosing interval at end of 1 week. Subjects will then be started on potential inhibitor of interest for second week while continuing terfenadine. Second pharmacokinetic profile will be performed at the end of the second week. Electrocardiograms will be performed at baseline, after 1 week of terfenadine, and daily pre-dose after starting the inhibitors. Subjects wear Holter monitors during blood profiles to allow for concentrations effect analysis. For safety purposes, subjects will be hospitalized on telemetry for first 72 hours of inhibitor.

PRIOR AND CURRENT PROGRESS
A total of 57 subjects (15 this past year) have been enrolled. Studies investigating drug-drug interactions with terfenadine are continuing. Studies investigating the interaction of terfenadine with itraconazole have been completed in six healthy normal volunteers. Relatively "slow metabolizers" of terfenadine have been recently identified, and studies are ongoing using higher, clinically utilized doses in six subjects from this population. A terfenadine-erythromycin interaction has also been started with this poor metabolizer population. To date, three of the anticipated six volunteers have been enrolled.

CONCLUSIONS
These studies have had significant impact with FDA labeling of the popular antihistamine terfenadine (Seldane). For instance, new labels exist on intraconazole and terfenadine warning against the use of these two drugs concomitantly.

REPORT DATE: 02/06/94 WORK UNIT # 1273

DETAIL SUMMARY SHEET

TITLE: A Study Investigating the Safety and Duration of Effect of Isosorbide-5-Mononitrate in a Controlled-Release Formulation in Patients with Stable Effort Angina Pectoris

KEYWORDS: angina pectoris, nitrates, stress testing

PRINCIPAL INVESTIGATOR: Pearson, Clarence LTC MC
ASSOCIATES: Gurczak, Patricia MAJ MC

DEPARTMENT: Department of Medicine STATUS: Completed
SERVICE: Cardiology Service APPROVAL DATE: Jan 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine the chronic antianginal efficacy and safety of isosorbide-5-mononitrate in a controlled-release formulation at 12 and 24 hours after administration in patients with chronic stable angina and objective evidence of ischemia. Also, to demonstrate that patients do not develop tolerance to the nitrate preparation.

TECHNICAL APPROACH
This is an 8-9 week, outpatient, multicenter, double-blind, parallel group study where the efficacy of the agent is determined by serial treadmill testing. The study consists of two parts. Part A is a 2-3 week single-blind safety phase, during which the study patients will be randomly assigned to receive either placebo or isosorbide-5-mononitrate in a controlled release formulation. Part B consists of serial treadmill testing, pre- and post-oral administration of the medicine, and repeat treadmills 12 hours later.

PRIOR AND CURRENT PROGRESS
Total number of patients screened: 23 (none during the past year). Total number of patients found eligible: 7. Total number of eligible patients who completed the entire study: 3. Four patients did not continue to Phase B due to failure meeting eligibility requirements. Patient enrollment has ended. No adverse reactions were reported.

CONCLUSIONS
This double-blinded, placebo-control study is completed. However, it is not certain which patients received the placebo, and which patients received the drug.

REPORT DATE: 01/14/94 WORK UNIT # 1274

DETAIL SUMMARY SHEET

TITLE: Transcoronary Mapping of Accessory Pathways in Patients Undergoing Percutaneous Accessory Pathway Radiofrequency Ablation

KEYWORDS: accessory pathway, radiofrequency ablation, coronary mapping

PRINCIPAL INVESTIGATOR: Hull, Robert MAJ MC

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Cardiology Service APPROVAL DATE: Jan 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To study the safety and efficacy of an intracoronary electrode catheter in the localization of accessory pathways in patients who are to undergo ablative therapy.

TECHNICAL APPROACH
After arrythmia induction, an 8 F arterial sheath will be inserted, and 10,000 U of heparin administered. The over-the-wire catheter will be inserted into the coronary artery through a guiding catheter. The over-the-wire catheter will then be pulled back into the guiding catheter while recording coronary electrograms during ventricular pacing or tachycardia. After localizing the pathway, the catheter will be removed, and the remainder of the patient's procedure will be completed.

PRIOR AND CURRENT PROGRESS
To date, two patients have been enrolled in this protocol, both during the past year. Each of these cases have been without complications. In the first, mapping of the right atrioventricular ring required 4 minutes, including guidewire insertion. In the second, total mapping time was 2 minutes. In the latter case, the patient had already undergone an unsuccessful attempt at accessory pathway ablation at Bethesda Naval without the use of this catheter. With the use of this catheter, surgery was successful. In the former case, intracoronary mapping confirmed that the pathway was anteroseptal, and ablation was performed.

CONCLUSIONS
The use of this catheter has enabled rapid and safe pathway mapping in this very limited number of patients. In one patient, it was vital to a successful procedure as evidenced by the prior unsuccessful attempt at radiofrequency ablation.

REPORT DATE: 07/15/94 WORK UNIT # 1275

DETAIL SUMMARY SHEET

TITLE: Percutaneous Balloon Pericardotomy for the Treatment of Pericardial Effusion/Tamponade

KEYWORDS: balloon, pericardial window

PRINCIPAL INVESTIGATOR: Laird, John MAJ MC
ASSOCIATES: Gorman, Patrick MAJ MC; Prewitt, Kerry MAJ MC

DEPARTMENT: Department of Medicine
SERVICE: Cardiology Service

STATUS: Ongoing
APPROVAL DATE: Jul 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To study the effectiveness of a new percutaneous technique of balloon pericardiotomy for the treatment of pericardial effusion and cardiac tamponade/impending tamponade. This involves the use of large balloons, similar to the balloons used for balloon valvuloplasty, to create a pericardial window.

TECHNICAL APPROACH
The study is being performed as part of a multicenter registry with the goal of evaluating the therapeutic efficacy and risks of percutaneous balloon pericardiotomy. The study will also evaluate and modify technical aspects of percutaneous balloon pericardiotomy for the treatment of pericardial effusion.

PRIOR AND CURRENT PROGRESS
No patients were enrolled in the study. Very few eligible patients presented within the past year, and of those who did, none consented to be in the study.

CONCLUSIONS
None.

REPORT DATE: 08/17/94 WORK UNIT # 1276

DETAIL SUMMARY SHEET

TITLE: CAVEAT II. A Study Investigating the Primary and Long-Term Outcome in Patients with De Novo Vein Graft Lesion Randomly Assigned to Either Balloon Angioplasty or Directional Atherectomy

KEYWORDS: balloon angioplasty, direction atherectomy, restenosis

PRINCIPAL INVESTIGATOR: Pearson, Clarence LTC MC
ASSOCIATES: Gorman, Patrick MAJ MC; Laird, John MAJ MC

DEPARTMENT: Department of Medicine
SERVICE: Cardiology Service

STATUS: Completed
APPROVAL DATE: Aug 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To determine the outcome in patients with de novo vein graft lesions assigned to either balloon angioplasty (PTCA) or directional atherectomy (DCA). The hypothesis being tested in whether 6 month restenosis rates are lower in patients with de novo vein graft lesions.

TECHNICAL APPROACH

Patients who meet the angiographic criteria will be identified and will be randomized to receive either PTCA or DCA. The patients will undergo the procedure and return in 6 months for a repeat stress test and cardiac catherization. All interval cardiovascular events (fatal or non-fatal) will be recorded.

PRIOR AND CURRENT PROGRESS

A total of four WRAMC patients were enrolled; none this past year. Complete, 6-month follow-up, including angiography, was obtained from three subjects who did not have restenosis. One patient had an acute ischemic event at about 2-3 months (Non-Q-Wave). This patient did not receive the 6-month catherization and was treated at another hospital. All WRAMC procedures were successful, and there were no complications. Studywide adverse reaction data is not currently available.

CONCLUSIONS

The WRAMC patient sample in this multicenter study is too small to reach statistically significant conclusions. Conclusions should be reached after results from the other centers are analyzed.

REPORT DATE: 06/16/93 WORK UNIT # 1277

DETAIL SUMMARY SHEET

TITLE: Side Branch Occlusion with Directional Coronary Atherectomy: Incidence and Risk Factors

KEYWORDS: atherectomy

PRINCIPAL INVESTIGATOR: Campos, Miguel MAJ MC
ASSOCIATES: Laird, John MAJ MC; Kufs, William MAJ MC

DEPARTMENT: Department of Medicine
SERVICE: Cardiology Service

STATUS: Completed
APPROVAL DATE: Dec 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine the incidence of and risk factors for side branch occlusion following directional coronary atherectomy.

TECHNICAL APPROACH
Retrospective chart and cine-angiographic review of the first 100 consecutive directional coronary atherectomies performed at WRAMC.

PRIOR AND CURRENT PROGRESS
Study has been completed and submitted for publication.

CONCLUSIONS
Side branch occlusion occurred in 16% of side branches at risk. Take-offs from the target stenosis and ostial side branch narrowing identifies a high risk group. Side branch loss was well tolerated (only 1/12 of patients had a myocardial infarction). Atherectomy does not appear to have a lower risk of myocardial infarction compared to PTCA.

REPORT DATE: 03/14/94 WORK UNIT # 1278

DETAIL SUMMARY SHEET

TITLE: Investigation of Non-Linear Pharmacokinetics and Electrocardiographic Pharmacodynamics of Terfenadine

KEYWORDS: terfenadine, pharmacokinetics, cardiac repolarization

PRINCIPAL INVESTIGATOR: Cantilena, Louis, M.D., Ph.D
ASSOCIATES: Wortham, Dale COL MC

DEPARTMENT: Department of Medicine
SERVICE: Cardiology Service

STATUS: Completed
APPROVAL DATE: Feb 1993

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To investigate the hypothesis that there exists a wide ability in the population at large to metabolize the commonly used antihistamine, terfenadine. Such individuals may be susceptible to cardiac adverse events as a result of a terfenadine interaction with a metabolic inhibitor or the use of greater than recommended does of terfenadine alone.

TECHNICAL APPROACH

Six subjects known to be poor metabolizers of tefenadine (known from previous outpatient studies performed at USUHS) will receive the recommended dose of terfenadine for 1 week. Serial blood sampling and electrocardiograms will then be obtained. The subjects will receive double the recommended dose (120 mg BID) for 1 week with blood and ECG sampling at the end of that period. If the safety parameters (see below) are not exceeded, the subjects will receive three times the recommended dose for the third and final week. Subjects will have daily Am ECGs and will be discontinued from the study if the corrected QT interval increases 25% from baseline or if the patient has QT-U interval morphology changes.

PRIOR AND CURRENT PROGRESS

The study was completed without any adverse events to any of the volunteer subjects. Only one of the six subjects was able to complete the 3 weeks of scheduled terfenadine dosing. Five of the six subjects had to be prematurely discontinued from the study because the QT-U segments on the daily AM ECGs demonstrated morphological changes consistent with the known repolarization abnormalities associated with terfenadine.

CONCLUSIONS

There exists a wide population variability in the ability to metabolize terfenadine. Subjects who are found to be relatively deficient in the hepatic enzyme responsible for terfenadine biotransformation are likely to be more susceptible to adverse cardiac events associated with terfenadine.

REPORT DATE: 07/08/94 WORK UNIT # 1279

DETAIL SUMMARY SHEET

TITLE: Pharmacokinetic and Pharmacodynamic Interactions Between Terfenadine and Erythromycin

KEYWORDS: terfenadine, pharmacokinetics, cardiac repolarization

PRINCIPAL INVESTIGATOR: Cantilena, Louis Jr MD PhD
ASSOCIATES: Wortham, Dale COL MC; Graumlich, James MD

DEPARTMENT: Department of Medicine
SERVICE: Cardiology Service

STATUS: Completed
APPROVAL DATE: Jul 1993

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

1) To determine if the biotransformation of terfenadine is altered by the concomitant administration of erythromycin base in persons (poor metabolizers) known to have measurable unmetabolized terfenadine present in their blood at steady state. 2) To determine whether there may be associated electrocardiographic changes if such altered metabolism occurs.

TECHNICAL APPROACH

Healthy subjects take the FDA recommended dose of terfenadine (60 mg bid) for 1 week. Blood and ECG's are then sampled (pharmacokinetic profile or PK) during dosing interval. Subjects take erythromycin base 500 mg tid for 1 week, followed by a second PK. They are hospitalized on telemetry during the time the potential inhibitor (erythromycin) reaches steady state, and ECG's are given daily pre-dose while the subjects take the potential inhibitor for safety. Following the second PK profile, subjects go off medication for 1 week. After 7 days medication-free, an ECG-only profile is given. Subjects take erythromycin base 500 mg tid for 1 week, after which an ECG profile will be given during dosing interval.

PRIOR AND CURRENT PROGRESS

A total of four subjects were enrolled in the study. Study medications were dispensed by the WRAMC Pharmacy. After enrollment of three subjects, pharmacy personnel notified the PI that they had lost the lot number information. This necessitated use of a different lot of terfenadine, and a change of manufacturers for erythromycin base mid-study. Two subjects were unable to complete the study due to severe nausea and vomiting during the phase of comcomitant erythromycin and terfenadine administration. The other two subjects experienced nausea and fatigue, but were able to complete the study.

CONCLUSIONS

This study will not be completed because: 1) the unexpected frequency of side effects experienced by the volunteers has made it difficult for them to complete the study, and discouraged recruitment of new subjects; 2) the pharmacy error that resulted in changing lot numbers of erythromycin and terfenadine mid-study will confound the analysis of study results. The known variability in erythromycin bioavailability would require repeating three subjects not budgeted for.

REPORT DATE: 10/01/94 WORK UNIT # 1280

DETAIL SUMMARY SHEET

TITLE: Treatment and Outcome of Acute Myocardial Infarction in a Military Medical Center: Participation in the National Registry

KEYWORDS: thrombolytic therapy, myocardial infarction

PRINCIPAL INVESTIGATOR: Collier, Edward MAJ MC

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Cardiology Service APPROVAL DATE: Aug 1993

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To compare demographic and clinical characteristics of military and civilian patients enrolled in this national registry.

TECHNICAL APPROACH
This will be a record review study of patients admitted to WRAMC who have objective evidence of having had an acute myocardial infarction. This also includes patients transferred to WRAMC with a recent infarction. After review of the records, case report forms will be completed.

PRIOR AND CURRENT PROGRESS
Presentation, treatment, and outcome data on 38 patients enrolled in the National Registry of Myocardial Infarction from January 1994 to July 1994 were reviewed. The majority of patients received appropriate concomitant medications; 95% received IV heparin, 42% received IV beta blockers, 90% received aspirin, and 100% were given IV nitroglycerin. Coronary arteriography was undergone by 75% of the patients, and PTCA was undergone by 34%. Nine (26%) of the eligible patients were treated with thrombolytic therapy, and four underwent immediate PTCA. The mortality rate for all patients was 5.2%.

CONCLUSIONS
Study data provide supportive evidence that the treatment of patients with acute myocardial infarction at WRAMC adheres to adopted practice standards. Thus far, it appears that military patients are more likely to undergo cardiac catherization and angioplasty, and have significantly lower mortality than civilian counterparts. Further investigation comparing military and civilian hospital populations with ischemic heart disease may be warranted.

REPORT DATE: 09/06/94 WORK UNIT # 1281

DETAIL SUMMARY SHEET

TITLE: Coumadin-Aspirin Reinfarction Study

KEYWORDS: coumadin, aspirin, myocardial infarction

PRINCIPAL INVESTIGATOR: Gorman, Patrick MAJ MC

DEPARTMENT: Department of Medicine
SERVICE: Cardiology Service

STATUS: Ongoing
APPROVAL DATE: Aug 1993

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To investigate the potential benefit of a combination of low-dose coumadine and aspirin compared to aspirin alone in patients who have sustained a myocardial infarction.

TECHNICAL APPROACH

Patients who have had a documented myocardial infarction are randomized to aspirin or a combination of aspirin and coumadin (1 mg or 3 mg). Following the initiation of double-blind treatment, patients will return to study on weeks 1, 2, 3, 4, 6, and 12 for protime evaluations. They will then be evaluated every 12 weeks. Concomitant medications, adverse clinical experiences, hospitalizations, and study medication compliance will be recorded. Primary endpoints are repeat myocardial infarction, stroke, and cardiovascular death.

PRIOR AND CURRENT PROGRESS

Enrollment will be continued through 1995. Study will remain ongoing through November 1997. Total WRAMC enrollment is three patients. No adverse events have occurred in any study patients.

CONCLUSIONS

Data collection and analysis are in progress. To date, no results have been produced. The Safety Monitoring Committee, which follows the data as it is assembled, has determined that the study may continue.

REPORT DATE: 01/29/94 WORK UNIT # 1815

DETAIL SUMMARY SHEET

TITLE: Investigation of a Viral Etiology in Pityriasis Rosea

KEYWORDS: pityriasis rosea, picornavirus, polymerase chain reaction

PRINCIPAL INVESTIGATOR: James, William COL MC

DEPARTMENT: Department of Medicine STATUS: Completed
SERVICE: Dermatology Service APPROVAL DATE: Jan 1991

FUNDING: Current FY: $ 0 Previous FYs: $ 1,100 Total: $ 1,100

STUDY OBJECTIVE
To attempt to amplify viral DNA fragments using picornavirus primers in skin biopsies from patients with pityriasis rosea using the polymerase chain reaction.

TECHNICAL APPROACH
Punch biopsies from the cutaneous rash of patients with pityriasis rosea will be done. Blood will be drawn at the same time, centrifuged and frozen. A single step method of RNA extraction will be done with the acid guanidinum thiocyanate-phenol-chloroform method. The polymerase chain reaction will be done on the specimen after RNA extraction using reverse transcriptase reaction initially and then the amplification process.

PRIOR AND CURRENT PROGRESS
A total of 5 controls and 14 patients have entered the study, none during the past year. There have been no adverse reactions. All analyses of the completed biopsies have revealed no consistent findings. No further work is being done on this protocol now that Dr. Rowe is transferred.

CONCLUSIONS
This should be considered a negative study as no evidence of the PCR-screened virus was found in the tissue of patients with pityriasis rosea.

REPORT DATE: 12/07/93 WORK UNIT # 1817

DETAIL SUMMARY SHEET

TITLE: 5-Fluorouracil Iontophoretic Therapy for Bowenoid Conditions

KEYWORDS: Bowen's disease, iontophoresis, 5-fluorouracil

PRINCIPAL INVESTIGATOR: Turiansky, George MAJ MC
ASSOCIATES: Welch, Mark MAJ MC; Smith, Kathleen COL MC

DEPARTMENT: Department of Medicine
SERVICE: Dermatology Service

STATUS: Ongoing
APPROVAL DATE: Nov 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To determine if the iontophoresis of 5-fluorouracil (5FU) is an effective treatment for Bowen's disease and/or bowenoid actinic keratoses.

TECHNICAL APPROACH

This study involves one pre-treatment biopsy to demonstrate either Bowen's disease or bowenoid actinic keratosis. A pretreatment photo will be taken for localization. Each treatment will initially involve iontophoresing 1% lidocaine with epinephrine 1:100,000 into the lesion at a dose of 30mA-minutes. Next, 5FU is iontophoresed at a dose of 300mA-minutes. Eight treatments will be given over 4 weeks, and at least 3 months after treatment completion a local excision will beperformed. This specimen will be sectioned through the entire block, and evaluated for histologic evidence of residual bowenoid changes. If present, the changes would indicate a treatment failure.

PRIOR AND CURRENT PROGRESS

Seven patients have been enrolled and completed the protocol to date. There have been no serious or unexpected adverse reactions. No patients have been withdrawn from the study. Six of the seven patients demonstrated no residual bowenoid changes on the post-treatment excisional biopsies. One patient had a small focus of residual bowenoid changes deep in the dermis. The benefit to these patients is that their skin lesions are cured, either by the iontophoresed 5FU or the post-treatment excision.

CONCLUSIONS

Early results of the study are promising as six of seven showed total clearing of their skin lesions after the treatments. The fact that the lone occurrence of residual bowenoid change was found deep in the dermis would indicate a need to measure the depth of the original lesion and plan the number of treatment sessions accordingly (i.e., more treatment sessions for deeper lesions).

REPORT DATE: 11/30/93 WORK UNIT # 1818

DETAIL SUMMARY SHEET

TITLE: Topical Corticosteroid Inhibition of Dermal Delayed Type Hypersensitivity

KEYWORDS: hypersensitivity, corticosteroid, dermis

PRINCIPAL INVESTIGATOR: Beard, Jeffrey CPT MC
ASSOCIATES: James, William COL MC; Engler, Renata COL MC

DEPARTMENT: Department of Medicine
SERVICE: Dermatology Service

STATUS: Ongoing
APPROVAL DATE: Nov 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To examine the mechanisms of dermal delayed type hypersensitivity (DTH) induced by intradermal antigen skin testing by observing the effects of pre-and post-treatment with potent topical corticosteroids.

TECHNICAL APPROACH

Study participatns will be randomized into three groups based upon the timing of topical steroid application: 1) pre-treatment; 2) concurrent treatment; and 3) post-treatment. Three antigen preparations will be injected intradermally on the medical aspect of both upper arms. One arm will be treated with clobetasol ointment; the other arm will serve as control. Erythema and induration will be measured daily for 4 days. One of the antigen sites on each arm will be biopsied. A battery of immunohistologic stains will be performed on the biopsy specimens.

PRIOR AND CURRENT PROGRESS

A total of 14 patients have been enrolled in the study. Preliminary findings suggest substantial reduction of erythema and induration with both pre-treatment and concurrent treatment with topical corticosteroids. Less inhibition has been noted in the post-treatment group. No immunohistologic studies have been performed. There have been no serious or unexpected adverse reactions. No patients have withdrawn from the study.

CONCLUSIONS

Preliminary findings suggest that pre-treatment or concurrent treatment with potent topical corticosteroids can substantially inhibit dermal delayed type hypersensitivity. The immunohistologic studies of the biopsy specimens will hopefully serve to elucidate some of the mechanisms of such inhibition.

REPORT DATE: 12/16/93 WORK UNIT # 1311-88

DETAIL SUMMARY SHEET

TITLE: Incidence of Fractures in Post-Menopausal Women

KEYWORDS: fractures, thyroid hormone, postmenopausal

PRINCIPAL INVESTIGATOR: Solomon, Barbara DNSc
ASSOCIATES: Wartofsky, Leonard COL MC; Burman, Kenneth COL MC

DEPARTMENT: Department of Medicine
SERVICE: Endocrine-Metabolic Service

STATUS: Completed
APPROVAL DATE: Dec 1988

FUNDING: Current FY: $ 300 Previous FYs: $ 658 Total: $ 958

STUDY OBJECTIVE
To determine whether having thyroid disease or taking thyroid hormone is a risk factor for fractures in postmenopausal women.

TECHNICAL APPROACH
Data will be collected via survey.

PRIOR AND CURRENT PROGRESS
Data collection began in September 1989 at Nolwood Retirement Community. Additional subjects were recruited from the patient population of the Thyroid Clinic, WRAMC. Data collection was suspended in December 1990 due to the temporary reassignment of the PI during Desert Storm; with a total of 227 subjects entered by this date. Data collection was reinstituted in August 1991. A total of 300 interviews were completed by November 1991, at which time patient enrollment ended. Of the 300 postmenopausal women, 160 had thyroid disease, and 140 did not have thyroid disease.

CONCLUSIONS
Postmenopausal white women with a history of thyroid disease do not have more hip, vertebral, or forearm fractures than other postmenopausal white women. The dose or duration of thyroid hormone therapy, duration of disease, use of calcium or estrogen did not influence the type or number of fractures. Women with a history of hyperthyroidism are at risk of having a fracture at a younger age than other women.

REPORT DATE: 04/01/94 WORK UNIT # 1312-89

DETAIL SUMMARY SHEET

TITLE: Treatment of Oligospermia with Antiestrogens

KEYWORDS: oligospermia, clomiphene, tamoxifen

PRINCIPAL INVESTIGATOR: Glass, Allan COL MC

DEPARTMENT: Department of Medicine STATUS: Completed
SERVICE: Endocrine-Metabolic Service APPROVAL DATE: Apr 1989

FUNDING: Current FY: $ 0 Previous FYs: $ 737 Total: $ 737

STUDY OBJECTIVE
To compare the effectiveness of tamoxifen and clomiphene in treating oligospermia.

TECHNICAL APPROACH
Randomized, prospective study of clomiphene, 25 mg every other day, and tamoxifen, 10 mg twice daily, for treatment of idiopathic oligospermia.

PRIOR AND CURRENT PROGRESS
A total of 10 patients have been enrolled in this study, none during this past year. No serious adverse reactions have been reported. There were no results in the 10 patients. In accordance with the Army's 5-year time limit on protocols, this study was closed 01 Apr 94.

CONCLUSIONS
None. Protocol not completed.

REPORT DATE: 08/12/94 WORK UNIT # 1316-89

DETAIL SUMMARY SHEET

TITLE: Identification of Unique Nucleotides in the Thyroid Gland of Patients with Various Thyroid Disorders

KEYWORDS: thyroid, gene, RNA

PRINCIPAL INVESTIGATOR: Burman, Kenneth COL MC
ASSOCIATES: Nagy, Endre MD

DEPARTMENT: Department of Medicine
SERVICE: Endocrine-Metabolic Service

STATUS: Terminated
APPROVAL DATE: Jul 1989

FUNDING: Current FY: $10,082 Previous FYs: $ 5,006 Total: $ 15,088

STUDY OBJECTIVE
To identify unique thyroid genes that are expressed in autoimmune thyroid disease and cancer.

TECHNICAL APPROACH
Construct cDNA library from thyroid tissue of patients with autoimmune thyroid disease and cancer. The cDNA library is then screened by labelling RNA or cDNA from the tissue of interest.

PRIOR AND CURRENT PROGRESS
This research protocol has been administratively terminated.

CONCLUSIONS
This research protocol has been administratively terminated.

REPORT DATE: 05/26/94 WORK UNIT # 1324-90

DETAIL SUMMARY SHEET

TITLE: Use of Corticotropin Release Hormone in the Evaluation of Hypercortisolemia and Hypocortisolemia

KEYWORDS: hypercortisolemia, hypocortisolemia, Cushing's syndrome

PRINCIPAL INVESTIGATOR: Schaaf, Marcus MD

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Endocrine-Metabolic Service APPROVAL DATE: May 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To define the source of excessive adrenocarticotropic hormone (ACTH) production in ACTH-dependent Cushing's syndrome (pituitary or ectopic), and to help in differentiating other temporary hypercortisolemic states, such as depression. Additionally, hypocortisolemic patients with low ACTH values will be examined to distinguish hypothalamic versus pituitary cause.

TECHNICAL APPROACH

Corticotropin-releasing hormone (CRH) 1.0 ug/kg will be administered over 1 to 2 minutes into a peripheral vein with peripheral venous blood sampling for ACTH and cortisol at -15, -1, +5, +15, +30, and +60 minutes. When CRH is administered during inferior petrosal sinus (IPS) sampling for localization of pituitary ACTH-secreting tumors, blood from both right and left sinuses and a peripheral vein will be sampled at 3, 5, and 10 minutes after CRH.

PRIOR AND CURRENT PROGRESS

A total of two subjects have been enrolled since the study began. No subjects have been enrolled since the last APR. Patients who meet the entrance criteria are rare. One patient's CRH testing (with and without inferior petrosal sinus sampling) had helped establish a diagnosis of occult ectopic ACH syndrome, source unknown. A Cushing's syndrome patient whose malady had been cured by transphenoidal surgery and adrenalectomy was also evaluated. Neither patient required CRH testing. No patients with hypoadrenalism due to ACTH deficiency required CRH testing.

CONCLUSIONS

CRH testing alone or during IPS sampling remains the most sensitive, reliable, and discriminating means to reveal the source of excessive ACTH production in Cushing's syndrome, i.e., pituitary or ectopic tumor production of ACTH, thereby permitting the proper surgical approach. Since this can be an exceedingly difficult distinction, it is vital to retain protocol approval for CRH testing until FDA approval of CRH is completed, which is expected within the year.

REPORT DATE: 10/13/93 WORK UNIT # 1328-90

DETAIL SUMMARY SHEET

TITLE: Mechanisms of Thyrotropin Releasing Hormone Regulation of Thyrotropin Gene Expression

KEYWORDS: TRH, TSH, gene

PRINCIPAL INVESTIGATOR: Carr, Frances PhD
ASSOCIATES: Smallridge, Robert COL MC; Fisher, Carolyn BS

DEPARTMENT: Department of Medicine
SERVICE: Endocrine-Metabolic Service

STATUS: Completed
APPROVAL DATE: Oct 1990

FUNDING: Current FY: $39,754 Previous FYs: $ 45,637 Total: $ 85,391

STUDY OBJECTIVE

To determine: 1) the DNA sequence(s) essential for mediating TRH stimulation of TSH gene expression, 2) the role of calcium and protein kinase C as intracellular signaling events, and 3) the potential involvement of proto-oncogenes (JUN, FOS) in this system.

TECHNICAL APPROACH

Deletion/mutation analysis of TSHB subunit gene in reporter plasmid vectors monitored in transient expression assays (cell culture). Stimulation and inhibition of intracellular pathways and monitoring these effects on TRHB gene promoter activity. Measurement of JUN/FOS mRNA levels in transiently transfected cells in response to TRH in the presence/absence of intracellular stimulators/inhibitors. Determine the effect of antisense RNA's to JUN/FOS on TRH actions. Determine DNA:protein interactions by gel shift, Southwestern hybridizations.

PRIOR AND CURRENT PROGRESS

TSHB DNA -271/-231 TRH response element contains multiple overlapping response elements to include TRH response element localized to -261/-241. This element also mediates PKC activity. A second region -271/-251 mediates PKC and Ca2+ but not PKC nor TRH activity. Inhibition of cjun and cfos synthesis through antisense expression vectors, blocks TRH stimulation of CJUN and CFOS protein, mRNA, and blocks TRH stimulation of TSHB gene expression. CJUN and CFOS bind to DNA-protein complexes that are formed within the TRH response element of the TSHB subunit gene. TRH stimulates translocation of the early response genes from the cytoplasm to the nucleus.

CONCLUSIONS

TRH stimulation of gene expression occurs, in part, through activation of protein kinase C and mobilization of Ca2+. These intracellular signalling events initiate new synthesis and translocation of the early response genes, CJUN and CFOS, which in turn bind indirectly to the TRH-RE to stimulate TSHB gene expression. Established an antisense expression assay as a means to selectively inhibit gene expression which has therapeutic and experimental implications.

REPORT DATE: 12/15/93 WORK UNIT # 1329-90

DETAIL SUMMARY SHEET

TITLE: Search for p53 Genetic Abnormalities in Tissue obtained from Normal and Pathological Thyroid Glands

KEYWORDS: p53, thyroid, carcinoma

PRINCIPAL INVESTIGATOR: Burch, Henry MAJ MC
ASSOCIATES: Burman, Kenneth COL MC

DEPARTMENT: Department of Medicine
SERVICE: Endocrine-Metabolic Service

STATUS: Ongoing
APPROVAL DATE: Dec 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 236 Total: $ 236

STUDY OBJECTIVE

To investigate the nature of qualitative and quantitative p53 alterations in pathological thyroid tissue.

TECHNICAL APPROACH

The use of immunohistochemical staining of tissue obtained at the time of surgery. Specimens will include thyroid tissue and non-thyroid (controls) tissue. The addition of controls was approved in an addendum to the HUC/IRB in January 1992. Commercially acquired antibodies which recognize both wild-type and mutant human p53 will be utilized. Gene sequencing is carried out via polymerase chain reaction (PCR) amplification of sequences, followed by DNA sequencing.

PRIOR AND CURRENT PROGRESS

A total of 29 thyroid patients, and no non-thyroid patients have been enrolled, none during the past year. Enrollment has now ended. There have been no serious or unexpected adverse reactions. Collaboration has been initiated with Dr. Arlo Clark of UCSF and with Applied Biosystems, and an addendum will be submitted at WRAMC for approval. Comparison of DNA sequencing to identify abnormalities in p53 in cell lines and in thyroid tissue is being done with SSCP electrophoresis. Approximately 10 specific nucleotide defects have been identified, and attempts are being made to characterize them further.

CONCLUSIONS

There are specific defects in thyroid cell lines for the study p53.

REPORT DATE: 12/29/93 WORK UNIT # 1330-90

DETAIL SUMMARY SHEET

TITLE: A 16 Week Double-Blind Placebo Controlled Dose Response Study Using Glipizide GITS Tablets for the Treatment of Noninsulin Dependent Diabetes Mellitus

KEYWORDS: diabetes mellitus, glipizide GITS, treatment

PRINCIPAL INVESTIGATOR: Clement, Stephen MAJ MC

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Endocrine-Metabolic Service APPROVAL DATE: Dec 1990

FUNDING: Current FY: $ 2,888 Previous FYs: $ 0 Total: $ 2,888

STUDY OBJECTIVE
To evaluate the efficacy and safety of glipizide GITS in the treatment of patients with non-insulin-dependent diabetes mellitus (NIDDM); to define the dose-response relationship with glipizide GITS; and to assess the long-term safety and efficacy of glipizide GITS.

TECHNICAL APPROACH
Patients with NIDDM will be enrolled and in a double-blind fashion will be given one of the following doses of glipizide GITS: placebo, 5 mg, 20 mg, or 60 mg per day. Weekly measurements of plasma glucose and intermittent measurements of hemoglobin A1C, insulin, and drug levels will be performed over a period of 16 weeks. After this, the patients will be enrolled in the open-label, long-term treatment phase of the study.

PRIOR AND CURRENT PROGRESS
All 14 original patients have been enrolled in the long-term treatment phase. Since the last annual report, two patients have been discontinued from the study; one due to death from a suspected cardiovascular event, and one due to a reduced need for the medication. The remaining nine patients continue to return for every-3-month visits per the protocol. Pfizer, Inc. continues to monitor their progress for the purpose of determining long-term safety and efficacy of the drug.

CONCLUSIONS
The medication, Glipizide GITS, seems to be safe and efficacious in the treatment of NIDDM.

REPORT DATE: 04/15/94 WORK UNIT # 1331-91

DETAIL SUMMARY SHEET

TITLE: Response of Multinodular Goiters with Substernal Extension to Therapeutic Doses of Iodine-131

KEYWORDS: multinodular goiter, substernal goiter, iodine 131

PRINCIPAL INVESTIGATOR: Burman, Kenneth COL MC

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Endocrine-Metabolic Service APPROVAL DATE: Feb 1991

FUNDING: Current FY: $ 0 Previous FYs: $ 3,221 Total: $ 3,221

STUDY OBJECTIVE
To determine the effect of moderate doses of radioactive iodine on reduction of size and control of symptoms in patients with large multinodular goiters.

TECHNICAL APPROACH
After informed consent, patients will be admitted to the Kyle Metabolic Unit. They will undergo an iodine 131 scan and uptake, as well as computerized tomography (CT) scanning and chemical thyroid function testing. Iodine 131 is administered in an approximate dose to deliver 100-150 uCi/gm of tissue. After observation for 5 to 10 days, patients will be discharged and followed up as outpatients. Outpatient follow-up will include thyroid function testing and CT at 6, 12, and 24 months to determine response to treatment.

PRIOR AND CURRENT PROGRESS
A total of 10 patients have been studied. No new patients were enrolled in the past fiscal year. No adverse reactions were noted. One patient had phrenic nerve paresis, probably related to goiter size rather than iodine 131. The average goiter size of patients in the study has increased by about 50%. This study is being kept open for patient follow-up.

CONCLUSIONS
Radioiodine represents an effective therapy for multinodular glands.

REPORT DATE: 04/15/94 WORK UNIT # 1333-91

DETAIL SUMMARY SHEET

TITLE: Endothelin and Cultured Human Thyroid Cells

KEYWORDS: endothelin, thyroid, human

PRINCIPAL INVESTIGATOR: Lahiri, Sabita MS

DEPARTMENT: Department of Medicine
SERVICE: Endocrine-Metabolic Service

STATUS: Completed
APPROVAL DATE: Apr 1991

FUNDING: Current FY: $ 261 Previous FYs: $ 31,004 Total: $ 31,265

STUDY OBJECTIVE

To determine the interaction of endothelin and cultured human thyroid cells (CHTC) with regard to: the characteristics of endothelin binding and the endothelin receptor, the effect of endothelin binding on CHTC and the mechanism involved, and the interaction of endothelin and other growth factors in CHTC. Also, to determine the significance of abnormal serum endothelin levels in patients with thyroid disease.

TECHNICAL APPROACH

Thyroid tissues obtained at surgery are digested with collagenase, and the isolated follicular cells are cultured. Competitive binding studies are performed using radiolabelled endothelin, and modulation of binding by other growth factors is assessed. Levels of endothelin and other hormones are measured in the culture media, and changes in thymidine incorporation are determined. Serum levels of endothelin in patients with thyroid disorders are also measured by radioimmunoassay.

PRIOR AND CURRENT PROGRESS

A total of 81 subjects were enrolled, none this past year. Endothelin mRNA has been identified within five thyroid glands proving that it is made by thyrocytes. It does not seem to be regulated by TSH or T4. Patient enrollment has ended. There have been no serious or unexpected adverse reactions.

CONCLUSIONS

Endothelin is produced within the thyroid gland.

REPORT DATE: 04/29/94 WORK UNIT # 1334-91

DETAIL SUMMARY SHEET

TITLE: A Search for Glycosylated Insulin in Patients with Non-Insulin Dependent Diabetes Mellitus

KEYWORDS: diabetes, insulin, glycosylated

PRINCIPAL INVESTIGATOR: Clement, Stephen MAJ MC

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Endocrine-Metabolic Service APPROVAL DATE: May 1991

FUNDING: Current FY: $ 2,572 Previous FYs: $ 48,725 Total: $ 51,297

STUDY OBJECTIVE

To determine if patients with non-insulin dependent diabetes mellitus (NIDDM) produce from the beta cells of their pancreas an abnormal insulin variant which is glycosylated prior to release from the beta cell. This posttranslational modification may hinder binding and activation of the insulin receptor in target tissues.

TECHNICAL APPROACH

Insulin will be extracted from 30cc of the patient's blood via affinity chromatography using a polycolonal insulin antibody. The eluated insulin will be further purified with the use of a Sep Pac cartridge and then subjected to polyacrylamide gel electrophoresis using high density gels. After electrophoresis, the gels will be stained with silver stain or immunostained for carbohydrate or insulin using various antibodies. The above will be done before or after deglycoslyation with N-glycosidase.

PRIOR AND CURRENT PROGRESS

Altogether, serum has been drawn from 62 patients and 6 controls. Since May 1993, blood has been drawn from 23 patients; ten were repeats. There have been no serious or unexpected adverse reactions. A technique was developed to isolate low-molecular weight insulin fragments (MW 3-4000) using patient and control samples; the electrophoresed sample is transerred to a specially-prepared diazobenzyloxymethyl paper which covalently bonds the peptide and prevents loss during further analysis, allowing identification of a low-molecular weight insulin fragment (MW about 3500) in two of the diabetic subjects. The peptide was not present in the control samples. Western blot analysis using polyclonal insulin antibody identified the peptide as insulin-like. All previously-studied patients are now being screened for presence of this insulin variant. Once its prevalence is determined, the exact structure of the peptide will be determined.

CONCLUSIONS

A low molecular weight insulin-like peptide has been identified in a subgroup of patients with non-insulin dependent diabetes. This insulin variant may compete with and reduce the binding of normal circulating insulin, thus impairing insulin action. The peptide appears to be prevalent in patients with high circulating insulin levels. Work is underway to determine the prevalence and chemical structure of this new peptide.

REPORT DATE: 07/01/94 WORK UNIT # 1335-91

DETAIL SUMMARY SHEET

TITLE: The Preparation of a Selective Pericentromeric Chromosome 10 YAC (Yeast Artificial Chromosome) DNA Library to Further Define MEN2 Gene Location

KEYWORDS: YAC, MEN II, chromosome 10

PRINCIPAL INVESTIGATOR: Francis, Thomas CPT MC

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Endocrine-Metabolic Service APPROVAL DATE: Jun 1991

FUNDING: Current FY: $15,959 Previous FYs: $ 35,044 Total: $ 51,003

STUDY OBJECTIVE
To develop yeast artificial chromosome cloning techniques; to construct a chromosome 10 specific yeast artificial chromosome library; to identify MEN II marker clones and construct a contiguity; and, to use contiguous YAC clones to study MEN II patient DNA for specific location and characterization of gene defects.

TECHNICAL APPROACH
Genomic DNA will be prepared from a human-hamster hybrid cell line, restriction cut to molecular weight >400,000 base pairs, ligated to yeast artificial chromosome vector pYAC4, and then transformed into yeast. Human chromosome 10 clones will be selected and gridded into a permanent library. The library will be screened with known zero and low recombination markers to identify MEN II contiguous clones. These clones will be characterized and used to screen MEN II patient DNA for the defect gene.

PRIOR AND CURRENT PROGRESS
YAC cloning is the principal technique used in the human genome project, which involves gene mapping and identification of genes responsible for inherited diseases. Significant improvements in YAC cloning technology have resulted in much improved YAC productivity with minimization of YAC chimerism. A human Chromosome 10-specific library has been partially constructed; this library will be a resource to the human genome project community for mapping and gene identification. Ongoing work is focused on expansion of this library and identification of endocrine genes of interest. A second goal is to create a total human genomic library from WBC DNA of MEN I patients which will facilitate identification of the di]eased gene in collaboration with other investigators in this field.

CONCLUSIONS
This has significantly improved YAC cloning techniques in terms of productivity (# YACs produced/day) and quality (less chimerism) which should have a major impact on YAC cloning in general and the human genome project. Our specific gene interest has now switched to the MEN I disease locus, and this technology is being applied towards producing relevant clones.

REPORT DATE: 10/13/93 WORK UNIT # 1336-91

DETAIL SUMMARY SHEET

TITLE: Investigation of Cross-Reactivity in the Immune Response Against the Human Thyrotropin Receptor and the HIV-1 New Protein in Rabbits

KEYWORDS: thyrotropin, Nef, protein

PRINCIPAL INVESTIGATOR: Burch, Henry MAJ MC

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Endocrine-Metabolic Service APPROVAL DATE: Oct 1991

FUNDING: Current FY: $ 672 Previous FYs: $ 17,177 Total: $ 17,849

STUDY OBJECTIVE
To investigate the relevance of an observed amino acid and nucleotide homology between HIV-1 Nef protein and the human TSH receptor (hTSH-R).

TECHNICAL APPROACH
Protein synthesis will be performed on cells taken previously from animals of another study, using expression PCR. Synthetic peptide analysis will be done using ELISA and T-cell epitope mapping techniques. Rabbit immunization will be performed with homologous hTSH-R and Nef peptides.

PRIOR AND CURRENT PROGRESS
Findings to date: 1) Graves' sera and anti-TSH receptor rabbit antisera recognize homologous Nef peptides and proteins (recombinant). 2) T-cell responsiveness against a Nef peptide corresponds to responsiveness against a homologous hTSH-R peptide. Rabbit antisera against TSH-R peptide in the region of homology with Nef recognize immunoreactive species in cultured retroocular fibroblasts. There were no serious or unexpected adverse reactions.

CONCLUSIONS
The region of the TSH-receptor sharing amino acid homology with the HIV-1 Nef protein is becoming increasingly implicated in the pathogenesis of Graves' disease and Graves' ophthalmopathy.

REPORT DATE: 10/06/93 WORK UNIT # 1337-91

DETAIL SUMMARY SHEET

TITLE: Treatment of Graves' Disease with Cholestyramine

KEYWORDS: Graves' disease, cholestyramine

PRINCIPAL INVESTIGATOR: Solomon, Barbara DNSc
ASSOCIATES: Burman, Kenneth COL MC

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Endocrine-Metabolic Service APPROVAL DATE: Oct 1991

FUNDING: Current FY: $ 6,780 Previous FYs: $ 0 Total: $ 6,780

STUDY OBJECTIVE
To determine whether adjunctive use of cholestyramine with anti-thyroid drugs in Graves' disease is better than anti-thyroid drugs alone.

TECHNICAL APPROACH
A two-group repeated measured design with random assignment between groups will be used. Group 1 receives Atenolol 50 mg PO qd and Tapazole 30 mg PO qd as standard medical therapy for Graves' disease. Group 2 receives the same medications plus cholestyramine 4 gms four times per day. Subjects are seen weekly for 4 weeks to determine symptom assessment and to obtain blood samples for hormone levels. The principal investigator is blinded to group placement to avoid bias in assessment.

PRIOR AND CURRENT PROGRESS
Since this study began, 17 of 24 patients have been enrolled at WRAMC (10 during this reporting period), and 2 of 24 patients have been enrolled at Fitzsimons (1 during this reporting period). There are 10 patients in the cholestyramine group (mean age 44.7 years). Two patients did not complete the 4-week study; one developed an allergic reaction to Tapazole, and the other moved from this area. There have been no serious or unexpected adverse reactions.

CONCLUSIONS
None.

REPORT DATE: 11/04/93 WORK UNIT # 1338-91

DETAIL SUMMARY SHEET

TITLE: A Sixteen-Week, Open-Label, Two-Way Cross-Over Switch Study Comparing Glucotrol and Glipizide GITS in the Treatment of Non-Insulin Dependent Diabetes Mellitus and An Open-Label, Long-Tern Evaluation of Glipizide GITS for the Treatment of NIDDM

KEYWORDS: diabetes, psychological import, glipizide

PRINCIPAL INVESTIGATOR: Clement, Stephen MAJ MC

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Endocrine-Metabolic Service APPROVAL DATE: Oct 1991

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To measure the efficacy of a long-acting form of glipizide, glipizide GITS, in the treatment of diabetes. A secondary objective is to measure the impact of participating in an intensive protocol on patients' self-care activities and their attitudes regarding diabetes care.

TECHNICAL APPROACH
This will be a 16 week open-label, cross-over design and open-label, long-term efficacy trial with an every 3 month follow-up. There are no changes in the original protocol or the addendum. Patients randomized to the control group will not participate in the trial. Hemoglobin A1C and data from questionnaires from this group will be compared to the study group. During long-term evaluation, patients randomized to the drug group were seen by the investigators every 3 months. The control patients were seen yearly.

PRIOR AND CURRENT PROGRESS
All subjects (15 controls and 17 patients) have completed the 1 year follow-up phase of the trial. One of the patients randomized to participate in the drug study has died (previously described), and eight have discontinued taking the drug due to hyperglycemia. The nine patients now being treated with the drug are receiving acceptable glycemic control. The results of the 1 year follow-up data are currently being analyzed in collaboration with Dr. Marc Peyrot, a Social Science specialist in Baltimore, Maryland. Preliminary analysis shows that the initial benefit of participating in the drug study is lost during the long-term follow-up phase. This suggests that the patients must be seen in follow-up more frequently than every 3 months in order to sustain the benefit of intensive treatment.

CONCLUSIONS
The participation in an intensive drug trial for non-insulin-dependent diabetes is associated with an initial improvement in glycemic control. This improvement is not sustained during 1-year follow up. Self-care behaviors which are learned with intensive treatment require reinforcement more frequently than every 3 months.

REPORT DATE: 12/02/93 WORK UNIT # 1340-91

DETAIL SUMMARY SHEET

TITLE: The Bone Mineral Density of Women Treated with Thyroid Hormone

KEYWORDS: bone, thyroxine, density

PRINCIPAL INVESTIGATOR: Duncan, William LTC MC
ASSOCIATES: Solomon, Barbara DNSc; Chang, Audrey PhD

DEPARTMENT: Department of Medicine
SERVICE: Endocrine-Metabolic Service

STATUS: Completed
APPROVAL DATE: Dec 1991

FUNDING: Current FY: $ 746 Previous FYs: $ 778 Total: $ 1,524

STUDY OBJECTIVE
To determine the factors influencing the bone mineral density (BMD) in women taking thyroid hormone.

TECHNICAL APPROACH
The medical records of women who are taking thyroid hormone and who are having one or more measurements of their bone mineral density will be reviewed.

PRIOR AND CURRENT PROGRESS
The records of 216 women have been reviewed; 202 women met the inclusion criteria. No new records were reviewed this past year. The data has been collected and analyzed by the generalized estimation of equations method. A manuscript has been submitted, and the data has also been presented at the Annual Meeting of the American Society for Bone and Mineral Research.

CONCLUSIONS
Thyroid hormone therapy was not associated with a significant effect on BMD of the spine or hip, but decreased BMD of the proximal radius was related to both previous thyrotoxicosis and dose of thyroid hormone.

REPORT DATE: 04/15/94 WORK UNIT # 1341-92

DETAIL SUMMARY SHEET

TITLE: Recognition of Hospital Malnutrition by Primary Physicians

KEYWORDS: malnutrition, recognition, primary

PRINCIPAL INVESTIGATOR: Kushner, Jonathan MAJ MC
ASSOCIATES: Martin, Brian LTC MS; Smith, Sandra RD

DEPARTMENT: Department of Medicine
SERVICE: Endocrine-Metabolic Service

STATUS: Completed
APPROVAL DATE: Jan 1992

FUNDING: Current FY: $ 827 Previous FYs: $ 0 Total: $ 827

STUDY OBJECTIVE

To perform a cross-sectional and observational study to quantify physicians' awareness of the nutritional state of their inpatients; to document the degree of nutritional assessment and therapeutics undertaken during typical hospitalizations in a major teaching center; and to compare the nutritional assessment of primary care physicians with the assessment of a nutrition support team.

TECHNICAL APPROACH

Chart review of 100 randomly selected adult inpatients evenly distributed throughout the hospital. The chart review will focus on appearance and use of nutrition-related terms; listing of "nutrition" as a problem in notes or problem lists; available objective data such as weight, weight changes, and labs; and nutrition consultations and interventions. Independent assessment of the same 100 patients for nutritional status will be made by interview and exam.

PRIOR AND CURRENT PROGRESS

The enrollment of 100 subjects was completed in March 1992. Patient chart reviews and interviews were concluded at that time. No adverse events were reported. Benefits included thorough nutrition assessment and notification to primary physicians of any malnourished patients.

CONCLUSIONS

A significant number of admissions lack documentation of weight, weight history, dietary intake, nutritional state, or nutritional diagnosis. While severe malnutrition is recognized, lesser degrees of malnutrition go undocumented by primary providers.

REPORT DATE: 02/16/94 WORK UNIT # 1342-92

DETAIL SUMMARY SHEET

TITLE: The Interaction of Steroids and Atrial Natriuretic Peptide in Cultured Thyroid Cells

KEYWORDS: ANP, glucocorticoids, hydrocortisone

PRINCIPAL INVESTIGATOR: Burman, Kenneth COL MC

DEPARTMENT: Department of Medicine STATUS: Completed
SERVICE: Endocrine-Metabolic Service APPROVAL DATE: Feb 1992

FUNDING: Current FY: $ 4,697 Previous FYs: $ 8,422 Total: $ 13,119

STUDY OBJECTIVE
To determine the effects of steroid hormones on atrial natriuretic peptide (ANP) in thyroid cells, and to measure the physiologic response of thyroid cells co-cultured with steroids.

TECHNICAL APPROACH
Surgically obtained human thyroid tissue will be digested with collagenase and then cultured in 24-well plates at a concentration of 100,000 cells per well. Competitive binding studies will be performed using varying concentrations of glucocorticoids and I-125 labelled ANP. The effects of glucocorticoids on the cell media will be analyzed for thyroglobulin (Tg) using ELISA methodology and on the cell growth by thymidine incorporation.

PRIOR AND CURRENT PROGRESS
A total of 15 patients have been enrolled in this study, 5 during the past year. There have been no serious or unexpected adverse reactions. High affinity binding sites for ANP and endothelin have been shown within the thyroid. The kD is about 10-9 m. Further, the thyroid gland produces each of these cytokines. They also have been produced in the thyroid gland and decrease thyroglobulin production.

CONCLUSIONS
The thyroid gland makes cytokines that regulate thyroid hormone secretion of other hormones.

REPORT DATE: 03/28/94 WORK UNIT # 1343-92

DETAIL SUMMARY SHEET

TITLE: Hormonal Regulation of the Vitamin D Receptor in Human Breast Cancer Cells: A Novel Strategy for Augmenting the Antiproliferative Effectr of Calcitriol

KEYWORDS: vitamin D receptor, breast cancer, antiproliferative

PRINCIPAL INVESTIGATOR: Duncan, William LTC MC
ASSOCIATES: Nicholson, Diarmuid PhD

DEPARTMENT: Department of Medicine
SERVICE: Endocrine-Metabolic Service

STATUS: Ongoing
APPROVAL DATE: Mar 1992

FUNDING: Current FY: $ 30 Previous FYs: $ 70,849 Total: $ 70,879

STUDY OBJECTIVE

To study the hormonal regulation of the vitamin D receptor (VDR) in human breast cancer cells to determine if changes in this receptor augments or decreases the antiproliferative effect of calcitriol.

TECHNICAL APPROACH

Quantitative PCR and hormone binding assays will be used to determine the effects of several hormones, known to regulate the VDR in other tissues, on the concentration of the VDR in human breast cancer cells. The active hormonal treatments will be used to regulate the VDR when testing the antiproliferative effects of calcitriol.

PRIOR AND CURRENT PROGRESS

Dr. Feng was hired in October 1993 to perform the experiments for this protocol. Studies with various hormones have shown that estradiol increases the growth of T47D breast cancer cells, while tamoxifen inhibits their growth. Treatment with testosterone, progesterone, and triiodothyronine does not effect cell growth.

CONCLUSIONS

The effects of the above mentioned hormones need to be further investigated to determine their role in the regulation of the VDR.

REPORT DATE: 03/29/94 WORK UNIT # 1344-92

DETAIL SUMMARY SHEET

TITLE: The Vascular Endothelium: A Critical Site of Toxin Action

KEYWORDS: mammary arteries, nitric oxide

PRINCIPAL INVESTIGATOR: Taylor, Thomas COL MC

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Endocrine-Metabolic Service APPROVAL DATE: Mar 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To study the responses of internal mammary artery rings to nitric oxide before and after exposure to the toxin.

TECHNICAL APPROACH
Rings will be cut from internal mammary tissue. These rings will then be hung in a 37 C tissue bath. Response to physiological stimuli will be studied and recorded.

PRIOR AND CURRENT PROGRESS
Study was interrupted by hospitalization of PI at start. Equipment has been updated for studies and coordination with co-investigators is planned. At start of study, three internal mammary artery segments were studied and compared with animal models; no patients were enrolled during the past year. There were no adverse reactions.

CONCLUSIONS
Segments of mammary artery may not be suitable because of their limited size. Discussion must be started with co-investigators to explore an alternate vessel.

REPORT DATE: 04/29/94 WORK UNIT # 1346-92

DETAIL SUMMARY SHEET

TITLE: Development of a Quantitative Polymerase Chain Reaction for Vitamin D Receptor mRNA

KEYWORDS: mRNA, receptor, cholecalciferol

PRINCIPAL INVESTIGATOR: Nicholson, Diarmuid Ph.D., DAC
ASSOCIATES: Duncan, William LTC MC; Wray, H. Linton COL MC

DEPARTMENT: Department of Medicine
SERVICE: Endocrine-Metabolic Service

STATUS: Ongoing
APPROVAL DATE: Apr 1992

FUNDING: Current FY: $ 5,416 Previous FYs: $ 12,398 Total: $ 17,814

STUDY OBJECTIVE

To develop a quantitative polymerase chain reaction (PCR) technique for measuring vitamin D receptor (VDR) mRNA; and to utilize this technique to investigate the ontogenesis at the transcriptional level of the hepatic and renal VDR in male and female rats.

TECHNICAL APPROACH

Total RNA is isolated from the tissues by extraction in the presence of phenol and denaturants. The VDR is detected by PCR amplification with VDR specific primers. The amplification is quantified by the inclusion of a synthetic DNA with the same VDR primer sites. Two PCR products are made, authentic and synthetic VDR, which differ in size and can be separated and quantified on a sizing gel. The protocol has been modified to include fluorescence as a detection method.

PRIOR AND CURRENT PROGRESS

The synthetic DNA has been constructed and when included in a PCR amplification with VDR specific primers yields a product 254bp in size. Authentic VDR cDNA produces a product of 275bp when included in the same PCR reaction. These two products can be separated on a 6% denaturing polyacrylamide gel. When fluorescent primers are used in the PCR reaction, the product yield can be quantified based on the areas of the respective electrophoretogram peaks. The number of copies of VDR mRNA in as little as 100ng total RNA can be calculated from plots of area versus concentration of initial RNA in the reverse transcription reaction. Twelve of the 15 rats ordered were used; all of them were euthanized. No rats were used this past year.

CONCLUSIONS

Quantitative PCR can be used to measure the initial copy number of specific messenger RNA molecules in the total RNA extracted from a variety of tissues and cultured cell lines. When fluorescent primers are used, automated analysis of PCR product yields can be achieved.

REPORT DATE: 05/12/94 WORK UNIT # 1348-92

DETAIL SUMMARY SHEET

TITLE: Combined Free Thyroxine and Sensitive TSH Testing in a Large Clinical Practice: Comparison with Conventional Thyroid Laboratory Testing in Patients with Various States of Thyroid Function and Acquired Binding Protein Abnormality

KEYWORDS: combined, free, thyroxine

PRINCIPAL INVESTIGATOR: Burch, Henry MAJ MC
ASSOCIATES: Solomon, Barbara DNSc

DEPARTMENT: Department of Medicine
SERVICE: Endocrine-Metabolic Service

STATUS: Completed
APPROVAL DATE: May 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To compare the utility of a new thyroid hormone profile to that of a classic profile.

TECHNICAL APPROACH
Each of four thyroid function tests or derived indices (in the three clinical states of hyperthyroidism, euthyroidism, and hypothyroidism) will be assessed for discordance rates from the remaining three tests.

PRIOR AND CURRENT PROGRESS
A total of 261 patients were enrolled; none since the last APR. Comparison is completed. A very close statistical correlation was found to exist between free thyroxine index and newer laboratory function tests in all states of thyroid hormone economy.

CONCLUSIONS
Both older and newer assays for thyroid function testing provide accurate information in patients without ongoing non-thyroidal illness.

REPORT DATE: 05/12/94 WORK UNIT # 1349-92

DETAIL SUMMARY SHEET

TITLE: Acute Changes in Total and Free Thyroid Hormone Levels Following Radioiodine Ablation Therapy in the Treatment of Graves' Disease

KEYWORDS: ablation, changes, Graves' disease

PRINCIPAL INVESTIGATOR: Burch, Henry MAJ MC
ASSOCIATES: Burman, Kenneth COL MC

DEPARTMENT: Department of Medicine
SERVICE: Endocrine-Metabolic Service

STATUS: Completed
APPROVAL DATE: May 1992

FUNDING: Current FY: $11,747 Previous FYs: $ 7,776 Total: $ 19,523

STUDY OBJECTIVE

To assess for acute changes in free and total thyroid hormones following the discontinuation of antithyroid drugs and administration of radioiodine (I-131) in Graves' disease (GD).

TECHNICAL APPROACH

Patients with GD are admitted to the Kyle Metabolic Unit. Following baseline laboratory testing, antithyroid therapy (ATD) is stopped. Serial blood specimens are obtained for the 6 days preceding and 2 weeks following I-131 ablation.

PRIOR AND CURRENT PROGRESS

A total of 22 patients comleted the protocol, 7 since the last APR. Statistically significant increments in thyroid hormones occurred following discontinuation of antithyroid drugs, without further change. No adverse reactions were noted.

CONCLUSIONS

Exacerbation of hyperthyroidism in association with I-131 ablation occurs as a result of stopping ATD in preparation for I-131, rather than as a result of the I-131 administration per se.

REPORT DATE: 08/09/94 WORK UNIT # 1350-92

DETAIL SUMMARY SHEET

TITLE: The Effect of Etidronate on Bone Mienral Density (BMD) in Patients on Levothyroxine Suppression

KEYWORDS: cyclical etidronate, bone mineral density

PRINCIPAL INVESTIGATOR: Torrens, Javier CPT MC

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Endocrine-Metabolic Service APPROVAL DATE: Aug 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine the effects of short and intermediate term therapy with cyclical etidronate on bone mineral density and bone turnover in patients receiving levothyroxine for suppression of nodular thyroid disease or thyroid cancer.

TECHNICAL APPROACH
Patients will be stratified according to the covariates (1) menopausal status and (2) time on levothyroxine. Patients will be randomized to either etidronate treatment or no etidronate treatment. Randomization will be determined using every WRANDOM program. Patients will be evaluated at baseline and 6 months, for a total of 24 months, by BMD, T3RIA, FT4, TSH, ionized calcium, PTH, osteocalcin, as well as 24 hour hydroxyproline, calcium, Pyridinium cross-links and creatinine.

PRIOR AND CURRENT PROGRESS
A total of 59 patients have been enrolled, two this past year. Enrollment of new patients has ended. This study is being kept open for patient follow-up. Four patients dropped out (one for palpitations with increasing synthroid dose, one for initiation of estrogen therapy, one for initiation of Lasix, and one due to their move out of the area).

CONCLUSIONS
None at present.

REPORT DATE: 10/12/93 WORK UNIT # 1351-92

DETAIL SUMMARY SHEET

TITLE: The Management of Papillary Thyroid Carcinoma in the United States

KEYWORDS: thyroid, cancer, survey

PRINCIPAL INVESTIGATOR: Solomon, Barbara DNSc
ASSOCIATES: Burman, Kenneth COL MC; Wartofsky, Leonard COL MC

DEPARTMENT: Department of Medicine
SERVICE: Endocrine-Metabolic Service

STATUS: Ongoing
APPROVAL DATE: Oct 1992

FUNDING: Current FY: $ 909 Previous FYs: $ 0 Total: $ 909

STUDY OBJECTIVE

To determine whether: 1) new techniques available for the diagnosis and mangement of papillary thyroid carcinoma are being used clinically; and 2) there is a national consensus for management of papillary thyroid cancer given differing options for both surgical and radioiodine therapy; and 3) a national consensus exists for long-term follow-up.

TECHNICAL APPROACH

Survey design with a questionnaire mailed to 408 clinical members of the American Thyroid Association. There is no consent form for this study.

PRIOR AND CURRENT PROGRESS

Of 408 questionnaires mailed, 233 (57.1%) were returned answered, and 68 (16.7%) were returned unanswered for a variety of reasons. The overall response rate was 73.8%. All data has been entered with results of means or frequencies obtained.

CONCLUSIONS

There is a great deal of variation in the approach to diagnosis, treatment, and follow-up of the patient with papillary cancer by thyroidologists. There is more consensus when the patient presents with a 5 cm solitary nodule, blood vessel or thyroid capsule invasion, or lymph node and lung metastasis.

REPORT DATE: 11/11/93 WORK UNIT # 1352-92

DETAIL SUMMARY SHEET

TITLE: Effects of 1,25-Dihydroxyvitamin D on the Growth of Human Breast Carcinoma Cells in Culture

KEYWORDS: 1,25-Dihydroxyvitamin D, breast, carcinoma

PRINCIPAL INVESTIGATOR: Lasswell, William Jr MAJ MC
ASSOCIATES: Duncan, William LTC MC; Wray, H. Linton COL MC

DEPARTMENT: Department of Medicine
SERVICE: Endocrine-Metabolic Service

STATUS: Ongoing
APPROVAL DATE: Nov 1992

FUNDING: Current FY: $15,648 Previous FYs: $ 0 Total: $ 15,648

STUDY OBJECTIVE

To: 1) define the effects of 1,25-dihydroxyvitamin D (calcitriol) on the growth of a large variety of human breast cancer cells in culture; and 2) identify those cell lines which are most responsive to calcitriol in order to further define their responsiveness as a function of dose of calcitriol.

TECHNICAL APPROACH

Breast cancer cells are obtained from the ATCC and grown in culture in defined medium. The growth curves of these cultures are assessed using cell counts and DNA content. Growth curves will be compared when cells are exposed to calcitriol versus an ethanol blank in order to define the response of a given cell line to calcitriol. After the responses of some 22 cell lines are defined, several lines will be selected which represent those which are most inhibited (or most stimulated) by calcitriol. These lines will then be used for future studies.

PRIOR AND CURRENT PROGRESS

Several cell lines have been obtained and successfully grown in culture. Methods of assessing growth have been successfully performed and are being refined. The optimal conditions for achieving useable and reproducible growth curves are now being identified. Systematic, final phase studies on the entire series of 22 cell lines should begin within 2-3 months.

CONCLUSIONS

Results thus far indicate that the methods described above will prove to be effective in assessing the response of cultured breast carcinoma cell lines to calcitriol.

REPORT DATE: 11/11/93 WORK UNIT # 1353-92

DETAIL SUMMARY SHEET

TITLE: Effects of Administration of the Contrast Agent Hexabrix on Thyroid Function Tests and Thyroid Uptake of Iodine

KEYWORDS: Hexabrix, thyroid function, uptake

PRINCIPAL INVESTIGATOR: Lasswell, William Jr MAJ MC
ASSOCIATES: Burman, Kenneth COL MC; Laird, John LTC MC

DEPARTMENT: Department of Medicine
SERVICE: Endocrine-Metabolic Service

STATUS: Ongoing
APPROVAL DATE: Nov 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To determine the duration of time over which a commonly used angiographic contrast agent, Hexabrix, impairs radioactive iodine (RAI) uptake and/or perturbs thyroid hormonal profiles.

TECHNICAL APPROACH

Approximately 30 patients will participate in this study by donating blood and urine samples and by having RAI uptake measurements performed at predetermined time periods; just before, 1 week after, 1 month after, and 2 months after coronary angiography. The results of these studies will be tabulated and analyzed in order to answer the questions posed above.

PRIOR AND CURRENT PROGRESS

Four of the seven patients interviewed have shown interest in participating in this study. The study needed to be discontinued in three cases due to abnormal thyroid function tests, failure of the participant to follow up, or uninterpretable test results. There were no unexpected or serious adverse reactions. Twenty-three more subjects will be needed.

CONCLUSIONS

Based on evidence obtained from study participants thus far, this study will provide useful information regarding the effects of a radiographic contraast agent on the parameters indicated in the section of goals.

REPORT DATE: 11/08/93 WORK UNIT # 1354-92

DETAIL SUMMARY SHEET

TITLE: Analysis of MHC Bound Peptides on the Surface of Epithelial Cells

KEYWORDS: MCH, thyroid

PRINCIPAL INVESTIGATOR: Burman, Kenneth COL MC
ASSOCIATES: Payne, Matthew CPT; Atwa, Mohammed; Lukes, Yvonne

DEPARTMENT: Department of Medicine
SERVICE: Endocrine-Metabolic Service

STATUS: Ongoing
APPROVAL DATE: Nov 1992

FUNDING: Current FY: $25,049 Previous FYs: $ 0 Total: $ 25,049

STUDY OBJECTIVE
To identify the proteins on the thyroid cell surface.

TECHNICAL APPROACH
Cytokines will be used to increase HLA DR/IA expression. HPLC mass spectrometry will be used to analyze peptides being expressed.

PRIOR AND CURRENT PROGRESS
A total of five patients have been enrolled in this study. There have been no serious or unexpected adverse reactions. Work is being done to optimize the system, using human thyrocytes and FRTL cell lines.

CONCLUSIONS
None yet.

REPORT DATE: 06/29/94 WORK UNIT # 1355-92

DETAIL SUMMARY SHEET

TITLE: Longitudinal Study on Bone Metabolism in Patients Receiving Sequentially Increasing Doses of Levothyroxine

KEYWORDS: calcium metabolism, Levothyroxine

PRINCIPAL INVESTIGATOR: Bernet, Victor CPT MC
ASSOCIATES: Burman, Kenneth COL MC

DEPARTMENT: Department of Medicine STATUS: Completed
SERVICE: Endocrine-Metabolic Service APPROVAL DATE: Dec 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To assess the change in calcium metabolism in patients being started on LT4 therapy.

TECHNICAL APPROACH
To measure serum and urine calcium in patients taking L-thyroxine.

PRIOR AND CURRENT PROGRESS
Unfortunately, the PI was able to recruit only one patient.

CONCLUSIONS
Study to be closed due to inability to recruit patients and principal investigator's impending departure due to permanent change of station.

REPORT DATE: 12/15/93 WORK UNIT # 1356-92

DETAIL SUMMARY SHEET

TITLE: L-Tryptophan Eosinophilia Myalgia Syndrome (91-M-12) and Other Autoimmune Disorders

KEYWORDS: L-tryptophan, eosinophilia, myalgia

PRINCIPAL INVESTIGATOR: Burman, Kenneth COL MC

DEPARTMENT: Department of Medicine
SERVICE: Endocrine-Metabolic Service

STATUS: Ongoing
APPROVAL DATE: Dec 1992

FUNDING: Current FY: $16,123 Previous FYs: $ 4,352 Total: $ 20,475

STUDY OBJECTIVE
To determine whether autoimmune thyroid disease is associated with altered ability to secrete cortisol and to response to stress.

TECHNICAL APPROACH
Detailed workup will be performed, especially of the hypothalamic-pituitary axis, including 24-hour blood sampling and measurements after CRH and ACTH stimulation. This will be used to try to determine whether there are stress abnormalities (specifically in cortisol secretion) in patients with autoimmune disorders.

PRIOR AND CURRENT PROGRESS
Patients who have hypothyroidism or autoimmune thyroid disease are actively being sought. At present, no one has volunteered for this protocol.

CONCLUSIONS
None yet.

REPORT DATE: 12/15/93 WORK UNIT # 1357-92

DETAIL SUMMARY SHEET

TITLE: The Effects of Arginine Vasopressin Administration on Neuroendocrine Response and Cognition in Patients with Major Psychiatric Illness

KEYWORDS: Arginine, vasopressin, neuroendocrine

PRINCIPAL INVESTIGATOR: Burman, Kenneth COL MC

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Endocrine-Metabolic Service APPROVAL DATE: Dec 1992

FUNDING: Current FY: $ 2,968 Previous FYs: $ 0 Total: $ 2,968

STUDY OBJECTIVE
To study the role of vasopressin in neuroendocrine response and cognition in autoimmune thyroid disease.

TECHNICAL APPROACH
Up to 1,000,000 international pressor units of synthetic AVP per kilogram of body weight will be administered in each of up to eight separate 1-hour infusions. During and following the infusions, Beta endorphin, ACTH, growth hormone, prolactin, cortisol, oxytosin, and vasopressin responses will be measured. These responses will be correlated with the results obtained from a specially devised battery of cognitive tests before, during, and after each infusion.

PRIOR AND CURRENT PROGRESS
To date, no patient has volunteered for this study.

CONCLUSIONS
None yet.

REPORT DATE: 11/05/93 WORK UNIT # 1358-92

DETAIL SUMMARY SHEET

TITLE: Dose Dependent Effects of Graded Exercise on Hypothalamic-Pituitary Adrenal Function in Patients with Putative Central Adrenal Insufficiency

KEYWORDS: dose, dependent, insufficiency

PRINCIPAL INVESTIGATOR: Burman, Kenneth COL MC
ASSOCIATES: Duester, Pat MD; Gold, Philip MD

DEPARTMENT: Department of Medicine
SERVICE: Endocrine-Metabolic Service

STATUS: Ongoing
APPROVAL DATE: Dec 1992

FUNDING: Current FY: $ 2,075 Previous FYs: $ 0 Total: $ 2,075

STUDY OBJECTIVE
To evaluate the pituitary axis response to graded exercise.

TECHNICAL APPROACH
To administer corticotropin releasing factor (CRF), and to measure adrenocorticotropic hormone (ACTH) and cortical response to exercise.

PRIOR AND CURRENT PROGRESS
No patients have been enrolled yet, partly because the study collaborators needed to improve their assays, which they have since done.

CONCLUSIONS
None yet.

REPORT DATE: 12/27/93 WORK UNIT # 1359-92

DETAIL SUMMARY SHEET

TITLE: Interactions of Cytokines, Thyrotropin, and Iodide in the Thyroid Gland

KEYWORDS: cytokines, thyrotropin, iodide

PRINCIPAL INVESTIGATOR: Lahiri, Sabita MS

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Endocrine-Metabolic Service APPROVAL DATE: Dec 1992

FUNDING: Current FY: $ 645 Previous FYs: $ 68,425 Total: $ 69,070

STUDY OBJECTIVE

To assess the effects and interaction of cytokines (epidermal growth factor, EGF, insulin, transforming growth factor alpha and beta, atrial natriuretic factor, and endothelin) in the maintenance of thyroid cell growth and differentiated functions functions such as iodide uptake, cyclic AMP, cyclic GMP production, and TG synethesis. To assess and quantitate the differential expression of endothelin messages in abnormal thyroid cells.

TECHNICAL APPROACH

Human thyroid cells taken from left-over tissue donated by the pathologist will be cultured and treated with TSH, iodide, and cytokine assays of the binding of EGF, ANP, and ET-1 to receptors on the cells. Assays will also be done of ET, TG, cyclic AMP, and cyclic GMP. mRNA will be isolated from thyroid tissue and cultured thryoid cells. After endothelin cDNA is synthesized, it will be purified, identified, and its molecular size determined. The sequences of the isolated ET-1 probe will be analyzed, and the differential expression of ET-1 will be estimated by Northern Blot techniques.

PRIOR AND CURRENT PROGRESS

Fifteen thyroid tissues were donated for this study, though 50 patients signed consent forms. The patients experienced no serious or unexpected adverse reactions. Cultured thyroid cells were incubated with growth factors, and insulin and responses were studied. Cultured thyroid cells were used for the receptor binding study and for the study of endothelin mRNA. Measurable endothelin (ET-1) was found in serum-free media of cultured thryoid cells. Binding of ET-1 to the receptors of thyroid cells was observed. Prepro-endothelin precursor mRNA in human thyroid cells was identified.

CONCLUSIONS

Study data indicate that endothelin is synthesized in follicular human thyroid cells. Further studies of the ET mRNA of diseased thyroid tissue may elucidate the possible role of ET in controlling the physiology of thyroid cells in humans.

REPORT DATE: 04/15/94 WORK UNIT # 1360-93

DETAIL SUMMARY SHEET

TITLE: Identification of Mutations by Single Stranded Conformational Polymorphisms (SSCP)

KEYWORDS: thyroid, cancer, gene

PRINCIPAL INVESTIGATOR: Burman, Kenneth COL MC
ASSOCIATES: Yin-Ying, Djuh; Keslar, Phyllis

DEPARTMENT: Department of Medicine
SERVICE: Endocrine-Metabolic Service

STATUS: Ongoing
APPROVAL DATE: Mar 1993

FUNDING: Current FY: $16,053 Previous FYs: $ 0 Total: $ 16,053

STUDY OBJECTIVE
To determine if single stranded conformational polymorphisms (SSCP) can detect genetic mutations.

TECHNICAL APPROACH
Compare SSCP to gene sequencing to detect mutations. SSCP involves gel electrophoresis with dye labelled primers. If there is a defect, the DNA will migrate differently than control.

PRIOR AND CURRENT PROGRESS
A total of 12 patients have donated tissue, and 8 have donated blood. A total of 22 mutations have been found by gene sequencing, and, thus far, all have been identified by SSCP. The mutations have been found in codon 273, 248, and 175.

CONCLUSIONS
SSCP is an effective, rapid method of screening for DNA mutation.

REPORT DATE: 03/22/94 WORK UNIT # 1361-93

DETAIL SUMMARY SHEET

TITLE: Development of Graves' Disease and Graves' Ophthalmopathy in Patients with Hodgkin's Disease: Relationship to Prior History of Radiation Therapy

KEYWORDS: Hodgkin's disease, Graves' disease

PRINCIPAL INVESTIGATOR: Burman, Kenneth COL MC
ASSOCIATES: Diehl, Louis COL MC

DEPARTMENT: Department of Medicine
SERVICE: Endocrine-Metabolic Service

STATUS: Ongoing
APPROVAL DATE: Mar 1993

FUNDING: Current FY: $24,799 Previous FYs: $ 0 Total: $ 24,799

STUDY OBJECTIVE

To determine the frequency of thyroid antibodies and thyroid function abnormalities in patients who receive radiation therapy for Hodgkin's disease.

TECHNICAL APPROACH

Serum samples from patients previously treated with XRT are obtained. They are analyzed for thyroid function and the presence of thyroid antibodies by ELISA and Western blot.

PRIOR AND CURRENT PROGRESS

Ten Georgetown and one WRAMC patient have been enrolled in this study. There have been no serious or unexpected adverse reactions. A total of 20-30 patients will be needed for initial analysis to begin. The researchers are currently accumulating more samples.

CONCLUSIONS

None yet.

REPORT DATE: 03/08/94 WORK UNIT # 1362-93

DETAIL SUMMARY SHEET

TITLE: Nyctohemeral Plasma Concentrations of TSH and FT4 in Patients Receiving Suppressive Doses of LT4

KEYWORDS: TSH, levothyroxine, nyctohemeral

PRINCIPAL INVESTIGATOR: Bernet, Victor CPT MC
ASSOCIATES: Solomon, Barbara DNSc; Burman, Kenneth COL MC

DEPARTMENT: Department of Medicine
SERVICE: Endocrine-Metabolic Service

STATUS: Ongoing
APPROVAL DATE: Mar 1993

FUNDING: Current FY: $ 7,887 Previous FYs: $ 0 Total: $ 7,887

STUDY OBJECTIVE

To quantitate the degree and consistency of TSH suppression obtained during a 24 hour period in patients receiving suppressive and replacement doses of LT4.

TECHNICAL APPROACH

Patients from three groups (MNG/benign nodule, thyroidectomy, and hypothyroidism) will be admitted for q20 minutes sampling to evaluate TSH, FT4, and T3RIA levels following their standard dose of LT4.

PRIOR AND CURRENT PROGRESS

The 12 patients approved for the initial pilot study have been completed, and the TSH assays will be run after the assay kits arrive from Nichols Diagnostic Institute. FT4 and T3RIA assays may be run when the TSH data can be reviewed. The patients tolerated the sampling well, except that several needed repeat IV placement to complete the study. Potential benefits cannot be determined until data analysis is complete.

CONCLUSIONS

No conclusions are possible until the assays are completed and the data is reviewed.

REPORT DATE: 11/04/93 WORK UNIT # 1371-86

DETAIL SUMMARY SHEET

TITLE: Transplantation Antigens on Spermatozoa

KEYWORDS: transplantation, HLA, spermatozoa

PRINCIPAL INVESTIGATOR: Glass, Allan COL MC

DEPARTMENT: Department of Medicine STATUS: Completed
SERVICE: Endocrine-Metabolic Service APPROVAL DATE: Nov 1985

FUNDING: Current FY: $ 0 Previous FYs: $ 11,403 Total: $ 11,403

STUDY OBJECTIVE
To determine the nature and amount of transplantation antigens in spermatozoa. To compare transplantation antigens in blood cells and sperm.

TECHNICAL APPROACH
Detection of transplantation antigens in spermatozoa by use of specific antisera and fluorescent detection techniques. Detection of released antigens by means of hemolytic plaque assay.

PRIOR AND CURRENT PROGRESS
No studies were carried out during the past year. This protocol has been concluded.

CONCLUSIONS
No transplantation antigens are detectable on spermatozoa.

REPORT DATE: 10/07/93 WORK UNIT # 1385-87

DETAIL SUMMARY SHEET

TITLE: Molecular Biology of Thyroid Disease

KEYWORDS: molecular, thyroid, biology

PRINCIPAL INVESTIGATOR: Burman, Kenneth COL MC
ASSOCIATES: Wartofsky, Leonard COL MC; Burch, Henry MAJ MC

DEPARTMENT: Department of Medicine
SERVICE: Endocrine-Metabolic Service

STATUS: Completed
APPROVAL DATE: Oct 1986

FUNDING: Current FY: $ 0 Previous FYs: $ 65,494 Total: $ 65,494

STUDY OBJECTIVE
To clone the genes encoding for TSH receptor and TSH receptor antibody, and to characterize the receptor gene product.

TECHNICAL APPROACH
This study will try to clone the TSH receptor and related proteins via two different methods. The first involves setting up a Lambda GT11 cDNA expression library from the thyroid gland and screening expression proteins with TSH receptor antibodies, both polyclonal and monoclonal. The second uses expression PCR with specific primers. SSCE will be used to identify specific abnormal areas, that are then sequenced.

PRIOR AND CURRENT PROGRESS
Techniques described above have been used to screen a library. Observation has shown that thyroblobulin has immunogenic epitopes, and the TSH receptor is immunogenic in aa352-380. Further, the library is being screened for abnormal areas in the oncogenes p53 and PTC in the TSH receptor, and in related relevant DNA coding areas for peroxidase, RAS, and actin. There are no obvious or consistent p53 abnormalities. Areas of the TSH receptor that are immunogenic have also been identified.

CONCLUSIONS
The TSH receptor is composed of different transcripts. Intrathyroidal lymphocytes from patients with autoimmune disease show a polyclonal heterogeneity. A unique area in the TSH receptor that is immunogenic has been identified. Thyroglobulin may have gene abnormalities. The TSH receptor and p53 are normal in these states.

REPORT DATE: 10/05/94 WORK UNIT # 1812

DETAIL SUMMARY SHEET

TITLE: Oncogenes in Basal Cell Nevus Syndrome, Cowden's Disease and Tore's Disease

KEYWORDS: epidermal growth factor, EGF-R

PRINCIPAL INVESTIGATOR: Burman, Kenneth COL MC
ASSOCIATES: James, William COL MC

DEPARTMENT: Department of Medicine STATUS: Terminated
SERVICE: Endocrine-Metabolic Service APPROVAL DATE: Sep 1989

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To assess whether there is a relationship between oncogenes and diseases involving multiple skin neoplasms associated with internal malignancies.

TECHNICAL APPROACH
DNA will be isolated from peripheral white blood cells and/or lesional tissue in study patients as per "Molecular Cloning: A Laboratory Manual" by T. Maniatis, et al. DNA samples will then be electrophoresed on agarose gel and hybridized with p32-labelled EGF-R probe after Southern blotting. Homologous areas will be visually assessed via autoradiograms. RNA samples will also be prepared by standard techniques and examined as above. No modifications noted to original protocol.

PRIOR AND CURRENT PROGRESS
The studies have been completed, and a manuscript has been submitted for publication. This protocol has been administratively terminated due to retirement of the PI.

CONCLUSIONS
No defects were found.

REPORT DATE: 12/14/93 WORK UNIT # 1404

DETAIL SUMMARY SHEET

TITLE: Treatment of the Microscopic Colitis/Collagenous Colitis Syndrome with Sulfasalazine: A Double-Blind Crossover Controlled Trial

KEYWORDS: microscopic/collagenous, colitis, sulfasalazine

PRINCIPAL INVESTIGATOR: Moses, Frank LTC MC

DEPARTMENT: Department of Medicine STATUS: Completed
SERVICE: Gastroenterology Service APPROVAL DATE: Dec 1988

FUNDING: Current FY: $ 0 Previous FYs: $ 100 Total: $ 100

STUDY OBJECTIVE
To determine whether sulfasalazine is effective therapy for the microscopic colitis/collagenous colitis (MC/CC) syndrome.

TECHNICAL APPROACH
A retrospective review and a prospective, double-blind, placebo-controlled crossover study of the efficacy of 12-weeks' treatment with oral sulfasalazine in patients with the MC/CC syndrome.

PRIOR AND CURRENT PROGRESS
Previously, 14 patients suspected to have the MC/CC syndrome were reviewed to better define the population prior to the prospective trial. Patients with inflammation of the lamina propria (4/14) had greater clinical disease and stool weight. Sulfasalazine appeared to be effective in achieving a clinical response in selected patients. Four patients were enrolled to the prospective arm of the study but did not fulfill histologic criteria for randomization to treatment. During the last year, no additional patients were enrolled in the protocol. There were no serious or unexpected adverse reactions.

CONCLUSIONS
The MC/CC syndrome causes chronic diarrhea. Histologic features correlate with clinical disease. Sulfasalazine appears to be effective in selected patients. Due to difficulties recruiting patients and elapsed time, the protocol is closed.

REPORT DATE: 04/20/94 WORK UNIT # 1406

DETAIL SUMMARY SHEET

TITLE: Campylobacter Pylori: Serologic Studies as a Measure of Efficacy of Treatment

KEYWORDS: helicobacter pylori, peptic ulcer, gastritis

PRINCIPAL INVESTIGATOR: Cheney, Christopher LTC MC

DEPARTMENT: Department of Medicine STATUS: Terminated
SERVICE: Gastroenterology Service APPROVAL DATE: Mar 1989

FUNDING: Current FY: $ 1,116 Previous FYs: $ 10,467 Total: $ 11,583

STUDY OBJECTIVE

a) To determine if H. pylori is a chronic infection; b) to determine efficacy of treatment and whether antibody levels fall with successful eradication of H. pylori; and c) to determine if salivary antibodies are present in detectable amounts to predict infection with the organism.

TECHNICAL APPROACH

Patients known or suspected of harboring H. pylori undergo upper endoscopy with gastric biopsy to confirm the presence of the organism. A tube of blood is drawn and saliva is collected for determination of antibody to the organism. If the organism is present, treatment with Pepto Bismol, tetracycline, and metronidazole is given for 3 weeks. Patients return 1 month and 6 months later for reevaluation.

PRIOR AND CURRENT PROGRESS

This research protocol was administratively terminated.

CONCLUSIONS

This research protocol was administratively terminated.

REPORT DATE: 04/20/94 WORK UNIT # 1407

DETAIL SUMMARY SHEET

TITLE: Effectiveness of Pneumatic Dilations in the Treatment of Achalasia

KEYWORDS: achalasia, pneumatic dilation

PRINCIPAL INVESTIGATOR: Wong, Roy COL MC
ASSOCIATES: Maydonovitch, Corinne BS

DEPARTMENT: Department of Medicine
SERVICE: Gastroenterology Service

STATUS: Completed
APPROVAL DATE: Apr 1989

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To study the efficacy of pneumatic dilations performed in patients at WRAMC; and to determine if manometric or esophageal emptying studies can predict success of dilation.

TECHNICAL APPROACH
Review charts of patients evaluated for achalasia in the GI Clinic at WRAMC. Data collection will include patient's symptoms and weight, esophageal manometry studies, and esophageal emptying studies prior to and 1 month after dilation.

PRIOR AND CURRENT PROGRESS
A total of 30 charts from newly diagnosed, untreated patients with achalasia were reviewed for this study; none this past year. Data collection from charts included recording the resting pressure, the length and the residual relaxation pressure of the lower esophageal sphincter (LES), the peak esophageal retention activity during cornflakes-emptying studies, and symptomatic parameters of weight loss and heartburn, chest pain, regurgitation, and dysphagia measured on an analog scale. This data was collected at baseline, before pneumatic dilation, and 1, 6, and 12 months after dilation. This study is completed.

CONCLUSIONS
Although no specific parameters could predict the outcome of dilation for an individual patient, a significant decrease in resting LES pressure and esophageal retention activity was noted in successfully treated patients at 1 and 6 months after dilation. This decrease was not noted in those who failed to successfully respond to treatment.

REPORT DATE: 05/09/94 WORK UNIT # 1408

DETAIL SUMMARY SHEET

TITLE: Nocturnal Gastroesophageal Reflux--Factors Associated with Reflux Events: A Retrospective Review of 24 Hour Esophageal pH Monitoring Data

KEYWORDS: nocturnal, gastroesophageal reflux, 24 hr pH monitoring

PRINCIPAL INVESTIGATOR: Wong, Roy COL MC
ASSOCIATES: Maydonovitch, Corinne BS

DEPARTMENT: Department of Medicine
SERVICE: Gastroenterology Service

STATUS: Completed
APPROVAL DATE: May 1989

FUNDING: Current FY: $ 64 Previous FYs: $ 0 Total: $ 64

STUDY OBJECTIVE

To review 24 hr pH monitoring studies to identify behavioral and physiologic events associated with gastroesophageal reflux (GER) events.

TECHNICAL APPROACH

Review 24 hr pH studies performed in the WRAMC GI Clinic over the past 4 years to select two groups: 1) patients with significant GER, as defined by a monitoring score >20; and 2) a control group, patients evaluated for GER who had a score </=20. Reflux events in each group will be analyzed for time of day they occurred, relationship to meals, patient's posture, and duration of reflux episode.

PRIOR AND CURRENT PROGRESS

A total of 220 charts were reviewed under this study. Based on the inclusion criteria of the study, data was collected from 64 charts of patients with supine GER and 112 charts of patients with upright reflux. Data has been collated and analyzed. One manuscript is completed and submitted for publication; a second manuscript is in progress. The study is completed.

CONCLUSIONS

The results of this study conclude that resting lower esophageal sphincter pressure (LESp) by itself does not predict severe supine GER. In this study, only 25% of patients had a decreased LESp. However, in these patients, a longer intrathoracic LES segment was compared and may play a significant role in the mechanism of GER.

REPORT DATE: 10/14/93 WORK UNIT # 1410

DETAIL SUMMARY SHEET

TITLE: Open Label Trial of Low Dose Oral Pulse Methotrexate Therapy for Primary Sclerosing Cholangitis

KEYWORDS: methotrexate, sclerosing, cholangitis

PRINCIPAL INVESTIGATOR: Moses, Frank LTC MC
ASSOCIATES: Peller, Thomas MAJ MC

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Gastroenterology Service APPROVAL DATE: Oct 1989

FUNDING: Current FY: $ 1,016 Previous FYs: $ 0 Total: $ 1,016

STUDY OBJECTIVE
To determine possible efficacy of low-dose methotrexate in the treatment of primary sclerosing cholangitis (PSC).

TECHNICAL APPROACH
After baseline evaluation to rule out other potential etiologies of liver disease, the patient has an ERCP, liver biopsy, and HIDA scan. They are then placed on gradually increasing doses of methotrexate (up to a maximum dose of 25 mg weekly). The patients are followed on a monthly basis. At the end of 1 year, a total re-evaluation is performed, with treatment continued for an additional year.

PRIOR AND CURRENT PROGRESS
Eleven patients have been enrolled in the study; 2 during the past year. They have been followed for a mean of 11 months (range 3-30 months). Cholestatic enzymes and symptoms have improved while on therapy. Two patients were referred for liver transplant due to progressive disease. One patient withdrew from the protocol at 1 year for nonmedical reasons. None were removed for dose-limiting drug toxicity.

CONCLUSIONS
These data demonstrate a substantial decrease in serum markers of cholestasis while on methotrexate. Liver biopsy material suggests improvement in inflammatory histology. Further evaluation of methotrexate in patients with PSC is warranted.

REPORT DATE: 02/14/94 WORK UNIT # 1411

DETAIL SUMMARY SHEET

TITLE: The Effect of Lithium Carbonate on Gastric Emptying and Gastrointestinal Hormones in Humans: A Double Blind Randomized Study

KEYWORDS: lithium, carbonate, gastric emptying

PRINCIPAL INVESTIGATOR: DeMarkles, Michael CPT MC
ASSOCIATES: Wong, Roy COL MC; Sjogren, Robert COL MC

DEPARTMENT: Department of Medicine
SERVICE: Gastroenterology Service

STATUS: Completed
APPROVAL DATE: Jan 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 1,510 Total: $ 1,510

STUDY OBJECTIVE
To study the effect of lithium carbonate on gastric emptying and gastrointestinal hormones in humans.

TECHNICAL APPROACH
Twenty patients will be given either placebo or lithium carbonate (300 mg PO Q3hrs X 10 doses). A gastric emptying study with a concurrent electrogastrogram will be done after each medication. Gastric hormone and lithium levels will be drawn during the study.

PRIOR AND CURRENT PROGRESS
Seven patients have completed this study; none during the past 2 years. Accrual has been slow due to difficulty scheduling gastric emptying studies in Nuclear Medicine, and the fact that the Nuclear Medicine physician working on this protocol left the Army.

CONCLUSIONS
No significant difference in gastric emptying has been noted in the seven patients on lithium carbonate who have completed the study.

REPORT DATE: 02/14/94 WORK UNIT # 1412

DETAIL SUMMARY SHEET

TITLE: Clinical and Serologic Evaluation of Blood Donors at Walter Reed Army Medical Center

KEYWORDS: hepatitis C antibody, blood donors

PRINCIPAL INVESTIGATOR: Sjogren, Maria COL MC

DEPARTMENT: Department of Medicine STATUS: Completed
SERVICE: Gastroenterology Service APPROVAL DATE: Feb 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
(1) To survey blood donors for the prevalence of hepatitis C antibody, and (2) to determine the prevalence of chronic hepatitis in blood donors who are rejected for donation due to the presence of increased ALT/presence of hepatitis B core antibody.

TECHNICAL APPROACH
To determine the prevalence of hepatitis C antibody, blood donors (at the time of donation) will provide an additional sample of blood to be tested for the presence of hepatitis C antibody. The antibody studies will be performed in Dr. Sjogren's lab at WRAIR. To determine the significance of abnormal ALT or hepatitis B core antibody, blood donors with such an abnormality will be invited via mail to participate in the study.

PRIOR AND CURRENT PROGRESS
Records of 7,921 consecutive blood donors were screened for hepatitis C antibody over a 1 year period, none during the past 2 years. There were no serious or unexpected side effects from this chart review study. A total of 18 civilian and 25 military blood donors were found to have antibody to HCV. Antibody was confirmed with RIBA.

CONCLUSIONS
Military donors were significantly less likely to be positive for HCV compared to civilian donors.

REPORT DATE: 02/18/94 WORK UNIT # 1413

DETAIL SUMMARY SHEET

TITLE: Large Bowel Adenomatous Polyp Dietary Intervention Study-Clinical Centers

KEYWORDS: colon polyps, fat, fiber

PRINCIPAL INVESTIGATOR: Kikendall, J. Walter COL MC
ASSOCIATES: Mateski, Donna MS RD; Murphy, Joseph MAJ MC

DEPARTMENT: Department of Medicine
SERVICE: Gastroenterology Service

STATUS: Ongoing
APPROVAL DATE: Feb 1990

FUNDING: Current FY: $ 5,053 Previous FYs: $ 34,319 Total: $ 39,372

STUDY OBJECTIVE

1) To determine whether a high fiber, low fat diet can reduce the recurrence of colonic adenomas; 2) To determine whether the diet modulates several putative intermediate markers of carcinogenesis (ODC activity, PCN antigen, labeling index); and 3) To determine the degree of correlation between recurrence of adenomas and modulation of markers.

TECHNICAL APPROACH

WRAMC is one of eight centers. Each center enrolls healthy subjects who have recently undergone colonscopic removal of all adenomas. Subjects are randomized to no intervention or to a low fat, high fiber, high fruit and vegetable diet. Subjects randomized to diet are intensively counselled. Colonoscopy is repeated at 1 and 4 years, and all polyps are removed and examined histologically. Unprepped sigmoidoscopy is performed at entry, 1, and 4 years to obtain mucosal samples for analysis for intermediate endpoints. Blood specimens and diet and health questionnaires are collected on an annual basis.

PRIOR AND CURRENT PROGRESS

Since the last APR, 95 more subjects have been enrolled. As of the end of study recruitment on 07 Jan 94, a total of 202 subjects were enrolled at WRAMC. Of these, 181 also consented to participate in the intermediate endpoint sub-study. Another 58 people had 1 or 2 visits but were ineligible, and not enrolled. Nutrition counselling continues at WRAMC, Ft. Myer, Ft. Belvoir, Ft. Meade, Ft. Detrick, Ft. Ritchie, Vint Hill Farms, and Andrews Air Force Base. All subjects receive follow-up for adenomas. Intervention subjects also receive the benefits of a diet compatible with guidelines of major health groups. One subject had post-polypectomy hemorrhage. One subject died of an unrelated causse.

CONCLUSIONS

It is too early to draw any conclusions, as the earliest randomized subjects are only 2 years into their 4-year period of participation.

REPORT DATE: 04/15/94 WORK UNIT # 1415

DETAIL SUMMARY SHEET

TITLE: The Compassionate Use of Cisapride in the Treatment of Patients with Refractory Nonulcer Dyspepsia, Diabetic Gastropareseis with Intolerance to Metoclopramide and Chronic Intestinal Pseudo-obstruction

KEYWORDS: Cisapride, non-ulcer dyspepsia, diabetic gastroparesis

PRINCIPAL INVESTIGATOR: Sjogren, Robert COL MC
ASSOCIATES: Shay, Steven COL MC

DEPARTMENT: Department of Medicine
SERVICE: Gastroenterology Service

STATUS: Completed
APPROVAL DATE: Apr 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To treat patients with refractory non-ulcer dyspepsia, diabetic gastroparesis, and intestinal pseudo-obstruction with Cisapride, a prokinetic agent not yet approved by the FDA.

TECHNICAL APPROACH
Patients are treated with 20 mg PO and tid of Cisapride. Short-term treatment for 6 weeks is initiated. If symptomatic improvement occurs, the medication is continued long-term, as long as improvement continues. Appropriate blood tests and urinalysis are periodically obtained.

PRIOR AND CURRENT PROGRESS
One patient has been enrolled altogether; no new patients were enrolled this past year. The one patient was taking Cisapride for nonulcer dyspepsia and was continued on the medication without side effects and with good effects. With the FDA approval of Cisapride in August 1994, Janssen Pharmaceuticals terminated all protocols for compassionate use of it. Therefore, the lone patient was removed from the protocol in September 1994.

CONCLUSIONS
This protocol is closed. There were insufficient numbers of patients entered to permit conclusions on efficacy of Cisapride.

REPORT DATE: 06/07/94 WORK UNIT # 1417

DETAIL SUMMARY SHEET

TITLE: Incidence of Gastric Mucosal Injury in Patients Ingesting Liquid Versus Solid Ibuprofen

KEYWORDS: gastritis, mucosal injury, ibuprofen

PRINCIPAL INVESTIGATOR: Wong, Roy COL MC
ASSOCIATES: Maydonovitch, Corinne BS

DEPARTMENT: Department of Medicine
SERVICE: Gastroenterology Service

STATUS: Ongoing
APPROVAL DATE: Jun 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 20,014 Total: $ 20,014

STUDY OBJECTIVE
To determine if there is a difference in the incidence of gastric mucosal injury between liquid and solid forms of ibuprofen.

TECHNICAL APPROACH
To examine the gastric mucosa endoscopically before and after 3 days of a randomized course of either liquid or solid ibuprofen.

PRIOR AND CURRENT PROGRESS
A total of 34 subjects have been enrolled in this study with no new patients enrolled over the past year due to personnel transfer. A new co-investigator has been designated to continue recruitment of subjects. Of the subjects enrolled, none have experienced serious or unexpected reactions or complications, and all subjects completed the study.

CONCLUSIONS
Data thus far indicates that ibuprofen impairs prostaglandin E2 production in the atrium but not fundus of the stomach. No differences in endoscopic or histologic injury of the stomach have been noted between liquid vs. solid ingestion.

REPORT DATE: 07/20/94 WORK UNIT # 1418

DETAIL SUMMARY SHEET

TITLE: Prospective Evaluation of 99mTechnetium Sulfur Colloid Liver Spleen Scan and 99mTechnetium Mebrofenin Hepatobiliary Radionuclide Scan for Diagnosis of Diffuse Hepatocellular Disease

KEYWORDS: diffuse liver disease, scintigraphy

PRINCIPAL INVESTIGATOR: Moses, Frank LTC MC

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Gastroenterology Service APPROVAL DATE: Jun 1991

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To compare the utility of quantitative liver-spleen and hepatobiliary scintigraphy to liver biopsy for evaluating severity and etiology of hepatocellular abnormalities.

TECHNICAL APPROACH
Patients between 18 and 70 years old suspected of having diffuse liver disease and in whom a liver biopsy is indicated will be enrolled in the study. To evaluate severity of liver disease a liver-spleen scan, hepatobiliary radionuclide scan, and liver biopsy will be performed and the results will be compared.

PRIOR AND CURRENT PROGRESS
A total of six patients have been enrolled in this study since its inception in June 1991. There have been no serious or unexpected adverse reactions, and no patients have been withdrawn from the study. Over the preceding 12 months, no additional patients were entered. Current Nuclear Medicine shortages preclude further enrollment at this time, but further work will be done as staffing improves.

CONCLUSIONS
Ongoing study.

REPORT DATE: 11/24/93 WORK UNIT # 1420

DETAIL SUMMARY SHEET

TITLE: Household Transmission of Hepatitis C Virus in Military Populations

KEYWORDS: hepatitis C, transmission

PRINCIPAL INVESTIGATOR: Sjogren, Maria COL MC

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Gastroenterology Service APPROVAL DATE: Nov 1991

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine the prevalence of hepatitis C virus (HCV) in household members of patients positive for the anti-hepatitis C antibody.

TECHNICAL APPROACH
All subjects with detectable antibody to hepatitis C, as well as control individuals, will undergo an initial medical history, physical exam, and biochemical testing to obtain evidence of chronic liver disease. All individuals will be followed at 3-month intervals for 1 year. The quarterly tests will consist of liver tests and serum virological markers. Subjects found to have clinical and/or biochemical evidence of liver disease will be followed by a gastroenterologist or a pediatrician.

PRIOR AND CURRENT PROGRESS
Eight index patients were enrolled in the study during this year, bringing the total number to 50. Six of the 50 spouses tested positive for hepatitis C; however, 2 out of 6 had independent risk factors for infection with the hepatitis C virus. Therefore, the rate of finding an infected spouse is 8%. Follow-up is ongoing; no further seroconversions have been observed among the spouses or other household members. All 34 household members (other than spouses) tested negative for hepatitis C infection. The study is observational; no unexpected adverse reactions have been observed.

CONCLUSIONS
Preliminary results show a moderate risk to acquire HCV infection when the subject is married to an infected individual. Whether this represents sexual transmission or exposure to the same risk factor is unknown. Viral genotyping would be pursued.

REPORT DATE: 11/24/93 WORK UNIT # 1421

DETAIL SUMMARY SHEET

TITLE: A Randomized, Controlled Trial of Interferon Alpha and Thymosin Alpha 1 in Patients with Hepatitis C Antibody Positive Chronic Active Hepatitis

KEYWORDS: hepatitis C, interferon alpha, thymosin alpha-1

PRINCIPAL INVESTIGATOR: Sjogren, Maria COL MC

DEPARTMENT: Department of Medicine
SERVICE: Gastroenterology Service

STATUS: Ongoing
APPROVAL DATE: Nov 1991

FUNDING: Current FY: $ 672 Previous FYs: $ 570 Total: $ 1,242

STUDY OBJECTIVE

To demonstrate efficacy of recombinant interferon alpha-2b in the treatment of eligible subjects with chronic hepatitis C, and to investigate the augmentation of response with interferon using thymosin alpha-1 as an immunomodulator.

TECHNICAL APPROACH

Eligible subjects are randomized to one of three study arms: Treatment with IFA, IFA+TMA-1, or control; up to 40 patients in each group. Patients will begin treatment while hospitalized. Outpatient follow-up will be weekly x 2, biweekly x 3, and monthly thereafter. Patients must undergo liver biopsies within 3 months of study enrollment and within 1 month of completion of the initial 6 months of treatment. Each visit will include a record of side effects, general health assessment, specific problems, and lab work. All patients will be offered definitive therapy.

PRIOR AND CURRENT PROGRESS

A total of 12 patients have been randomized (6 during the past year); 7 have completed 6 months of treatment. There have been several mild adverse reactions that have been reported to DCI/IRB. Two of the seven subjects who completed treatment will begin open label Interferon Alpha (IFA) and Thymosin Alpha-1 (TA-1) due to a relapse in their condition. One subject has on two occasions exhibited flu-like symptoms with dehydration, and on the first occasion had a platelet count of 46,000; each incident required 3 liters of intravenous D5RL and confinement to quarters. The independent Medical Monitor from Fitzsimmons AMC was notified. The subject's protocol medications were discontinued for 1 week; his platelet count increased, and the Medical Monitor concluded he should continue on protocol with a reduction of 2/3 dose of "I" medication. Another subject was hospitalized for kidney stones not related to the protocol.

CONCLUSIONS

None to report at the present time.

REPORT DATE: 11/24/93 WORK UNIT # 1422

DETAIL SUMMARY SHEET

TITLE: Significance and Natural History of Detectable Hepatitis C Antibody in Military Populations

KEYWORDS: hepatitis C antibody, natural history

PRINCIPAL INVESTIGATOR: Sjogren, Maria COL MC

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Gastroenterology Service APPROVAL DATE: Nov 1991

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine the prevalence of liver disease in a military population with detectable antibody to hepatitis C in serum, and to determine the clinical, biochemical, and histological extent of the liver disease. To better define the risk factors of hepatitis C virus (HCV) infection.

TECHNICAL APPROACH
The study consists of enrolling anti-HCV-positive individuals and control subjects without detectable anti-HCV. All subjects will undergo two serological screenings for liver disease the first 6 months of the study. Subjects having clinical and/or biochemical evidence of chronic liver disease will be referred for follow-up. During the 3-year follow-up period, all subjects (control and study) will be seen at 6 months for a health exam, liver tests, and serum virological markers. Each subject with chronic liver disease will undergo additional studies during the first year.

PRIOR AND CURRENT PROGRESS
Two additional patients have been enrolled for a total of four. There have been no serious or unexpected adverse reactions experienced by any of the subjects. The study is observational; no direct benefit is expected, and none has been observed.

CONCLUSIONS
None yet to report.

REPORT DATE: 03/29/94 WORK UNIT # 1423

DETAIL SUMMARY SHEET

TITLE: Intermediate Markers of Colonic Neoplasia

KEYWORDS: colonic adenocarcinoma, screening, intermediate markers

PRINCIPAL INVESTIGATOR: Kikendall, James COL MC

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Gastroenterology Service APPROVAL DATE: Mar 1992

FUNDING: Current FY: $ 1,375 Previous FYs: $ 6,763 Total: $ 8,138

STUDY OBJECTIVE
To determine whether colonocyte expression of any of several putative intermediate markers of colonic neoplasia predicts the presence of neoplasia.

TECHNICAL APPROACH
Stool specimens will be collected from patients with colon cancer, patients with colon adenomas, and normal controls. Colonocytes will be harvested from the stool samples and will be tested for several antigens, growth factor receptors, chromosomal and genetic alterations, blood group substances, and lectin binding studies to detect any factors correlating with neoplasia.

PRIOR AND CURRENT PROGRESS
A total of 109 patients have been enrolled; 85 during the past year. Studies of colonocytes (specifically expression of CD and HLA markers, and lectin binding) are ongoing. Approximately 5-10 patients per month are being enrolled in the protocol. Other studies including those for ploidy have been attempted, but techniques need refinement. Since May 1993, data was generated for two abstracts which are under consideration for presentation.

CONCLUSIONS
Colonocyte expression of CD and HLA markers and colonocyte expression of lectin binding may represent markers for colonic neoplasia or identify patients at risk for future colon cancer.

REPORT DATE: 07/08/94 WORK UNIT # 1425

DETAIL SUMMARY SHEET

TITLE: Evaluation of Gastroesophageal Reflux as a Cause of Hoarseness: Evaluation of Pepsin as a Marker of Reflux-Induced Esophageal Injury

KEYWORDS: hoarseness, gastroesophageal reflux

PRINCIPAL INVESTIGATOR: Yavorski, Robert CPT MC
ASSOCIATES: Maydonovitch, Corinne BS; Wong, Roy COL MC

DEPARTMENT: Department of Medicine
SERVICE: Gastroenterology Service

STATUS: Completed
APPROVAL DATE: Jul 1993

FUNDING: Current FY: $ 792 Previous FYs: $ 0 Total: $ 792

STUDY OBJECTIVE

1) To estimate the prevalence of gastroesophageal reflux (GER) in patients with hoarseness; 2) to evaluate the utility of pepsin as a marker for gastric fluid in the posterior pharynx; and 3) to compare differences in reflux parameters generated on 24 hour pH monitor in patients with and without hoarseness.

TECHNICAL APPROACH

Patients presenting to the ENT clinic for evaluation of hoarseness will be evaluated for GERD by 24-hour pH monitor. Those patients having an abnormal reflux score will undergo further studies including voice harmonics, esophageal manometry, endoscopy, and pepsin analysis. GER (+) patients will then be treated with Omeprozole, 20 mg po bid for 6 weeks. After therapy, all tests will be repeated.

PRIOR AND CURRENT PROGRESS

A total of eight patients were enrolled in the study. Three patients had minimal reflux based on 24 hour pH monitor and underwent treatment with Omeprazole. They experienced no adverse effects, and experienced improvement in their hoarseness. None of these patients had severe GER measured by 24-hour pH monitor. Based on this observation, the current study is being terminated and a new protocol is being submitted to treat all hoarseness patients.

CONCLUSIONS

1) Patients with normal physiologic or minimally abnormal GER may experience short episodic acid reflux into the proximal esophagus and hypopharynx causing hoarseness. 2) Hoarseness patients may not have typical GEr symptoms of heartburn and abnormal reflux studies. These patients may benefit from a trial of anti-reflux therapy.

REPORT DATE: 10/07/93 WORK UNIT # 1497

DETAIL SUMMARY SHEET

TITLE: The Effect of Indomethacin on Rectosigmoid Mucosal Blood Flow and Rectosigmoid Mucosal Prostaglandin Levels in Humans

KEYWORDS: indomethacin, blood flow, laser Doppler

PRINCIPAL INVESTIGATOR: Wong, Roy COL MC
ASSOCIATES: Pacicco, Thomas MAJ MC

DEPARTMENT: Department of Medicine
SERVICE: Gastroenterology Service

STATUS: Completed
APPROVAL DATE: Oct 1987

FUNDING: Current FY: $ 0 Previous FYs: $ 1,250 Total: $ 1,250

STUDY OBJECTIVE

To determine the effect of prostaglandin synthesis inhibition with indomethacin treatment on rectosigmoid mucosal blood flow and rectosigmoid mucosal prostaglandin E2 levels.

TECHNICAL APPROACH

In a double-blind, randomized fashion, each subject will receive, on two separate occasions separated by 2 weeks, either placebo TID for 3 days or indomethacin 50mg TID for 3 days. The morning after the final dose of placebo or indomethacin, rectosigmoid mucosal blood flow will be measured with a laser Doppler probe inserted through the biopsy channel of an endoscope. Two rectal mucosal biopsies will be obtained to measure tissue prostaglandin levels, and a blood sample will be taken to measure indomethacin levels.

PRIOR AND CURRENT PROGRESS

A total of 10 control male subjects have been enrolled (none this past year) in this study to test the reproducibility of blood flow measurements by laser doppler technique. No serious or adverse effects were experienced by any of the subjects. Progress has been slow due to technical difficulties and loss of personnel. This study is being closed because of the 5-year limit policy.

CONCLUSIONS

Blood flow measurement with laser Doppler is reproducible from day-to-day ($r=0.9015$), and it did not significantly differ between the two age groups.

REPORT DATE: 04/12/94 WORK UNIT # 1498

DETAIL SUMMARY SHEET

TITLE: Pathophysiology and Treatment for Non-Ulcer Dyspepsia (Using Cisapride)

KEYWORDS: non-ulcer dyspepsia, irritable bowel syndrome, Cisapride

PRINCIPAL INVESTIGATOR: Cremins, James CPT MC
ASSOCIATES: Maydonovitch, Corinne BS

DEPARTMENT: Department of Medicine
SERVICE: Gastroenterology Service

STATUS: Completed
APPROVAL DATE: Dec 1987

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To compare gastric motility and electrophysiology in patients with non-ulcer dyspepsia vs. normal volunteers. To determine the effect of a prokinetic agent, Cisapride, on symptoms and objective tests in patients with non-ulcer dyspepsia in a double-blind, crossover placebo controlled fashion.

TECHNICAL APPROACH
Patients with dyspeptic symptoms, in whom ulcer has been rigorously excluded, will be studied. Three hour electrogastrograms and 24 hour antral motility evaluations will be performed after treatment with placebo and Cisapride. Changes in symptoms will be measured using a questionnaire. A double-blind crossover design will be employed so that each subject receives both placebo and Cisapride.

PRIOR AND CURRENT PROGRESS
A total of six patients have been enrolled; none this past year. There have been no serious or unexpected adverse reactions in any of the patients studied.

CONCLUSIONS
None to state.

REPORT DATE: 01/18/94 WORK UNIT # 1029

DETAIL SUMMARY SHEET

TITLE: Common Symptoms in Ambulatory Medicine: The Effects of Attributions and Expectations on Symptom Outcome and Patient Satisfaction

KEYWORDS: somatization, patient satisfaction, patient expectations

PRINCIPAL INVESTIGATOR: Kroenke, Kurt LTC MC
ASSOCIATES: Marple, Richard MAJ MC(P); Lucey, Catherine MD

DEPARTMENT: Department of Medicine
SERVICE: General Medicine Service

STATUS: Ongoing
APPROVAL DATE: Jan 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To determine the prevalence of various concerns and expectations in patients presenting with common physical complaints; the recognition of these concerns and expectations by the physicians evaluating them; and the predictors of symptom outcome and patient satisfaction at 2-week follow-up.

TECHNICAL APPROACH

Consecutive patients presenting to a general medicine walk-in clinic with a chief complaint of a physical symptom are eligible and are invited to fill out a questionnaire regarding symptom characteristics and their own concerns and expectations regarding evaluation and treatment. After the encounter, physicians also filled out a questionnaire. Two weeks later, patients received a follow-up questionnaire in the mail; those not responding were contacted by telephone. Major outcomes analyzed were prevalence of various patient concerns and expectations, physician recognition of these factors, and symptom outcome and patient satisfaction.

PRIOR AND CURRENT PROGRESS

Accrual goals were met. Analysis was completed of 2-week follow-up date on 328 patients (none enrolled this past year); response rate to mailed questionnaires was 92%. At 2 weeks, 31% of symptoms (SX) had resolved, 47% had improved, and 22% were the same or worse. By logistic regression, independent predictors of improvement were: SX duration of < 2 weeks at initial visit, physician belief that SX cause was either known or not serious, patient not expecting a subspeciality referral, black race, and better patient-perceived health status. At 2 week follow-up, serious illness worry or desire for referral or tests persisted in > 20% of patients; the majority felt their SX had lasted longer than expected, and many didn't recall MD's explanation. Only 56% were fully satisfied with their care, and, next to SX improvement itself, residual concerns and expectations were most powerful correlates of satisfaction.

CONCLUSIONS

The majority of symptoms improved by 2 weeks, and factors that made improvement more likely have been identified. However, better recognition of specific patient concerns and expectations might further enhance patient satisfaction.

REPORT DATE: 01/18/94 WORK UNIT # 1030

DETAIL SUMMARY SHEET

TITLE: Development of a Primary Care Evaluation of Mental Disorders System (PRIME-MD)

KEYWORDS: psychiatry, depression, psychometrics

PRINCIPAL INVESTIGATOR: Kroenke, Kurt LTC MC

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: General Medicine Service APPROVAL DATE: Jan 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To develop a valid psychiatric screening instrument, PRIME-MD, that would allow primary care physicians to efficiently diagnose depressive, anxiety, somatoform, alcohol, and eating disorders in their patients.

TECHNICAL APPROACH
A random sample of patients presenting to primary care clinics at four sites (Walter Reed, New England Medical Center in Boston, University of South Alabama, and Albert Einstein in New York) were invited to fill out a one-page patient questionnaire. For any of the five modules (depression, anxiety, etc.) that were positive, physicians asked structured questions out of a Clinician Evaluation Guide to make DSM-III-R phychiatric diagnoses. Patients also completed validating instruments (Zung Depression and Anxiety Scales, Barsky Somatization Scale, etc.), and a sample was re-interviewed by a mental health professional.

PRIOR AND CURRENT PROGRESS
A total of 100 patients were enrolled during the past year, 23 from WRAMC. Data analysis has been completed on 1,000 patients at 4 sites (303 from WRAMC). PRIME-MD was shown to have criterion validity: telephone reinterview of 431 patients by mental health professionals showed acceptable inter-observer agreements on diagnosis. Physicians also found instrument efficient (average time to administer about 10 minutes), and useful (increased recognition of previously undetected psychiatric disorders, and frequent initiation of new therapy). Eight abstract presentations have been given at national scientific meetings, and four papers have been submitted for publication. Additional abstract presentations are scheduled for this spring, and several additional manuscripts are planned.

CONCLUSIONS
PRIME-MD is an efficient and valid method for the primary care physician to diagnose common psychiatric disorders: depressive, anxiety, somatoform, eating, and alcohol disorders. It should be useful as a clinical, educational, and research instrument.

REPORT DATE: 03/24/94 WORK UNIT # 1031

DETAIL SUMMARY SHEET

TITLE: Advance Directives: Implementation into Clinical Practice

KEYWORDS: advance directives, ethics

PRINCIPAL INVESTIGATOR: Kroenke, Kurt LTC MC
ASSOCIATES: Landry, Francis CPT MC; Lucas, Christine MPH

DEPARTMENT: Department of Medicine STATUS: Terminated
SERVICE: General Medicine Service APPROVAL DATE: Feb 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine if an interactive educational patient seminar increases the number of advance directives formulated by patients, compared to providing written educational materials alone.

TECHNICAL APPROACH
Consecutive patients presenting to the Internal Medicine Clinic on selected half-days will be invited to fill out a questionnaire regarding advance directives (AD), including whether or not they are interested in finding out more about AD. Those potentially interested will be contacted by phone, and if still interested, they will be randomized to receive written information in the mail or to attend a special seminar on AD. Patients will be contacted several months after the intervention to determine if any actions were taken regarding AD.

PRIOR AND CURRENT PROGRESS
This protocol has been administratively terminated.

CONCLUSIONS
This protocol has been administratively terminated.

REPORT DATE: 06/28/94 WORK UNIT # 1032

DETAIL SUMMARY SHEET

TITLE: Value of the PRIME-MD Questionnaire Prior to Upper Endoscopy

KEYWORDS: psychiatric, endoscopy, symptoms

PRINCIPAL INVESTIGATOR: O'Malley, Patrick CPT MC
ASSOCIATES: Wong, Peter CPT MC; Roy, Michael MAJ MC

DEPARTMENT: Department of Medicine
SERVICE: General Medicine Service

STATUS: Completed
APPROVAL DATE: Jan 1993

FUNDING: Current FY: $ 605 Previous FYs: $ 0 Total: $ 605

STUDY OBJECTIVE

To: 1) determine the prevalence of unrecognized psychiatric disorders in patients with gastrointestinal symptoms referred for upper endoscopy; and 2) determine the likelihood of establishing an organic diagnosis in patients with and without psychiatric diagnoses.

TECHNICAL APPROACH

Prospective study of patients >18 years old referred to GI for unexplained GI symptoms. Patients with known organic GI pathology will be excluded; a convenient sample of patients will be enrolled. Patients will be inteviewed prior to endoscopy using PRIME-MD, a validated psychometric qustionnaire. The physician doing the endoscopy was blinded to the results of the PRIME-MD. Patients with and without psychiatric disorders were then compared with respect to the results of endoscopy.

PRIOR AND CURRENT PROGRESS

Of 40 patients, 29 (73%) had 45 psychiatric disorders (some had multiple disorders); somatoform (54%), mood (24%), and generalized anxiety (20%) disorders were the bulk of the diagnoses. Significant GI pathology was found in 7 of the 40 patients. Those patients without significant GI pathology had a much higher prevalence of psychiatric disorders; 85% vs 14% ($p<0.01$). PRIME-MD strongly predicted the likelihood of GI pathology; if positive, the likelihood was 0.17 (3% post test probability); if negative, the likelihood was 5.64 (54% post test probability). No serious or unexpected adverse reactions occurred. No direct benefit to patients was appreciated.

CONCLUSIONS

Three out of four patients with unexplained GI symptoms have at least one psychiatric disorder. Those with psychiatric disorders rarely have significant GI pathology.

REPORT DATE: 05/10/94 WORK UNIT # 1033

DETAIL SUMMARY SHEET

TITLE: Funguria in a Tertiary Care Medical Center

KEYWORDS: funguria, urine cultures, antifungal drugs

PRINCIPAL INVESTIGATOR: Byrd, John CPT MC
ASSOCIATES: Hicks, Charles MD; Byrd, James CPT MC

DEPARTMENT: Department of Medicine
SERVICE: General Medicine Service

STATUS: Ongoing
APPROVAL DATE: May 1993

FUNDING: Current FY: $ 3,231 Previous FYs: $ 0 Total: $ 3,231

STUDY OBJECTIVE

To review the species and prevalence of fungi recovered from urine cultures. To describe known and suspected predisposing factors leading to funguria. To describe newly noted demographic and clinical characteristics of patients with funguria. To review the relationship of funguria and its treatment with clinical outcome. To examine physician response to the recovery of fungi in urine.

TECHNICAL APPROACH

Study is being conducted by obtaining restrospective data from review of outpatient hospital records and via CHCS recorded laboratory and radiographic test results.

PRIOR AND CURRENT PROGRESS

Thus far, the researchers have recovered incidence and prevalence data regarding all urine cultures positive for fungi over the time period August 1990 to December 1993. Inpatient charts from 85 of 111 patients with documented funguria in 1991 have been reviewed, and this data is being introduced in a computerized data base. Presentation of preliminary work examining changing trends of funguria with the introduction of the azole, fluconazole, has been given.

CONCLUSIONS

Chart review of the majority of inpatients with funguria from 1991 is complete. Data basing and analysis of this data is the next step toward the stated objectives. In reaching these objectives, the researchers have examined the diversity and prevalence changes of funguria here at WRAMC using the time point of the introduction of fluconazole for comparison.

REPORT DATE: 11/14/93 WORK UNIT # 1523-91

DETAIL SUMMARY SHEET

TITLE: CALGB 9111. A Trial of G-CSF vs Placebo During Remission Induction and Consolidation Chemotherapy for Adult Acute Lymphatic Leukemia

KEYWORDS: adult acute leukemia, G-CSF

PRINCIPAL INVESTIGATOR: Weiss, Raymond M.D.

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Hematology-Oncology Service APPROVAL DATE: Oct 1991

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To compare time to bone marrow recovery, infection incidence, days of hospitalization, and tolerance of non-hematopoietic organs after intensive chemotherapy for acute lymphatic leukemia (ALL) in patients given either granulocyte colony-stimulating factor (G-CSF) or placebo; to determine G-CSF's effect on CR rate and duration and mortality (during neutropenia) during intensive induction and intensification; and to compare doses that can be given to G-SF vs placebo patients.

TECHNICAL APPROACH

Eligible patients will be randomly assigned to receive daily subcutaneous injections of either G-CSF or placebo starting 3 days after initial chemotherapy. Injections will continue until the WBC count is normal. The pharmacist will be the only one who knows what the patients will be receiving. The study will remain blinded until after the first month. After being unblinded, patients who received G-CSF will continue to receive it during the next course of therapy. Those who did not will not receive any further placebo or G-CSF. Patients will receive a series of five different cancer treatments in sequence; each uses combination chemotherapy, and one involves radiation. Total treatment time is 24 months.

PRIOR AND CURRENT PROGRESS

To date, eight patients have been enrolled from WRAMC; three during this past reporting period. The total national accrual is 225; 97 within the past year. Of the WRAMC patients, eight have died of their disease, three remain in remission and continue to be on maintanance therapy, and two have relapsed within the past year. No unexpected adverse reactions have occurred. The study closed to new patient accrual 30 Jul 93.

CONCLUSIONS

Data is currently under analysis.

REPORT DATE: 11/24/93 WORK UNIT # 1524-91

DETAIL SUMMARY SHEET

TITLE: A NCI/WRAMC Collaborative Phase I Trial of Suramin in Patients with Advanced Solid Tumors

KEYWORDS: metastatic, refractory cancer, suramin

PRINCIPAL INVESTIGATOR: Dawson, Nancy LTC MC

DEPARTMENT: Department of Medicine STATUS: Completed
SERVICE: Hematology-Oncology Service APPROVAL DATE: Nov 1991

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To assess the efficacy and toxicity of the investigational agent suramin in metastatic refractory cancer.

TECHNICAL APPROACH
Suramin is administered intravenously by continuous infusion until the desired blood level is achieved. Therapy is then continued for 8 weeks maintaining this blood level, then discontinued for 8 weeks, and then reinitiated as in cycle one. Therapy continues every 8 weeks until complete remission, progressive disease, or unacceptable toxicity.

PRIOR AND CURRENT PROGRESS
Altogether, 106 of the 112 intended patients have been entered (90 during the past year) into this NCI/WRAMC collaborative study. Four patients have been enrolled from WRAMC; none during the past year. No further patients will be enrolled at WRAMC. Four final patients will be entered at the NIH to obtain additional pharmokinetic data prior to study closure. Response and toxicity data is being analyzed for publication.

CONCLUSIONS
Study is near completion. Results are pending.

REPORT DATE: 03/18/94 WORK UNIT # 1530-92

DETAIL SUMMARY SHEET

TITLE: CALGB 9181. A Comparative Study of Two Doses of Megace in Advanced Prostate Cancer

KEYWORDS: metastatic disease, dose comparison, quality of life

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Hematology-Oncology Service APPROVAL DATE: Mar 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To compare the response rate (complete, as well as partial) of megestrol acetate at a 160 mg daily dose versus a moderately high dose of 640 mg daily in patients with metastatic prostate cancer; to describe overall survival and failure-free survival for each of these treatment groups; to determine the relationship between decrease in prostate specific antigen and objective response; and to assess quality of life issue and symptoms.

TECHNICAL APPROACH

All eligible patients will be randomized to receive one of two treatments: standard dose of megace daily or high dose (4 times higher than standard) on a daily basis. All patients will complete a quality of life questionnaire before treatment and every 8 weeks thereafter until the end of treatment. Treatment is continued as long as cancer growth is controlled.

PRIOR AND CURRENT PROGRESS

A total of seven patients from WRAMC have been entered on this study; none during this reporting period. The total national accrual is 90 patients; 72 of those during this reporting period. The projected accrual is for 144 patients. Five of the seven WRAMC patients have died of progressive disease (one suicide); the other two were removed from the study due to the development of thrombosis. They continue to be followed for their progressive disease.

CONCLUSIONS

Analysis is ongoing. No conclusions have been reached.

REPORT DATE: 08/17/93 WORK UNIT # 1668-89

DETAIL SUMMARY SHEET

TITLE: WRAMC 8904: High Dose Chemotherapy and Autologous Bone Marrow Transplantation for Poor Prognosis Lymphomas, Phase II

KEYWORDS: autologous, bone marrow, chemotherapy

PRINCIPAL INVESTIGATOR: Burrell, Linda MAJ MC

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Hematology-Oncology Service APPROVAL DATE: Aug 1989

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

1) To test the feasibility of autologous bone marrow harvesting after initial tumor debulking with induction chemotherapy. 2) To determine the toxicity, time to marrow reconstitution, response rate, and time to treatment failure after high dose 3-drug consolidation with autologous bone marrow transplantation (ABMT) support.

TECHNICAL APPROACH

Eligible patients with relapsed lymphomas undergo conventional-dose salvage induction therapy. Those who achieve a response can undergo autologous bone marrow harvesting; followed by consolidation high-dose 3-drug chemotherapy using cyclophosphamide, etoposide, and BCNU; followed by infusion of the autologous bone marrow, which had been cryopreserved after harvesting. The patients are hospitalized until marrow engraftment.

PRIOR AND CURRENT PROGRESS

A total of 17 lymphoma patients have been treated with ABMT at WRAMC; 3 during the past year. Four patients were treated with a 4-drug regimen, with two toxic deaths reported. Other institutions found similar toxicities with this regimen. One patient relapsed and died of lymphoma, and one patient still remains in remission. Thirteen patients have been treated with the modified regimen, which eliminated the ARA-C and decreased the BCNU to 600 mg; this was tolerated well, without major toxicities being noted. Six patients are in remission to date, two were in remission but relapsed, one died related to infection, one died late post-transplant related to unknown etiology, one has stable disease, one has progressive disease, and one is waiting for the 60 day evaluation.

CONCLUSIONS

Using the 3-drug regimen with decreased BCNU caused no major toxicities in the 13 patients treated to date. Six patients who have been treated on the 3-drug regimen remain in remission. One patient from the 4-drug regimen has experienced a 4-year remission to date.

REPORT DATE: 09/15/94 WORK UNIT # 1669-89

DETAIL SUMMARY SHEET

TITLE: WRAMC 8905: Chemotherapy with Autologous Bone Marrow Support for Selected Advanced Solid Tumors, Phase II

KEYWORDS: bone marrow, chemotherapy, autologous

PRINCIPAL INVESTIGATOR: Burrell, Linda MAJ MC

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Hematology-Oncology Service APPROVAL DATE: Sep 1989

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine the toxicity, time to marrow reconstitution, response rate, and time to treatment failure for high-dose carboplatin, etoposide, and cyclophosphamide therapy with autologous bone marrow support for selected advanced solid tumors.

TECHNICAL APPROACH
Patients selected per eligibility requirements and presentation to Bone Marrow Transplant Conference. Patients undergo autologous bone marrow harvest with marrow separation and cryopreservation. They then receive 6 days of high-dose chemotherapy, followed by infusion of thawed autologous marrow. They are supported until marrow recovery in-hospital. At 60 days after transplant, they undergo reevaluation to assess response to the therapy and are then followed for clinical progression and/or late complications. An amendment was approved by the HUC/IRB in February 1992 to administer cyclophosphamide on the seventh as well as the sixth day of therapy.

PRIOR AND CURRENT PROGRESS
Over the last 5 years, a total of 29 patients (2 during the past year) have been treated with high dose chemotherapy and autologous bone marrow support for solid tumors. The types of tumors treated include metastatic breast cancer in 22 patients, refractory or recurrent testicular cancinoma in 5 patients, sarcoma in 1, and small cell lung cancer in 1. Study patients have received follow-up for up to 30 or more months. The study regimen has been well tolerated. There have been four toxic deaths (mortality rate of 13%).

CONCLUSIONS
Breast cancer patients enrolled in this study have a complete remission rate of 20% (which is similar to the rate reported by other studies). Particularly interesting is that two patients have remained in complete remission for over 2 years (29 and 34 months). It will be very important to continue to follow those patients for the durability of response.

REPORT DATE: 09/08/94 WORK UNIT # 1676

DETAIL SUMMARY SHEET

TITLE: Detection of Lupus Anticoagulants in Patients with Anticardiolipin Antibodies

KEYWORDS: lupus anticoagulant, cardiolipin antibody

PRINCIPAL INVESTIGATOR: Alving, Barbara COL MC

DEPARTMENT: Department of Medicine STATUS: Completed
SERVICE: Hematology-Oncology Service APPROVAL DATE: Sep 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine if patients with low, medium, or high anticardiolipin antibody titers also have a lupus anticoagulant as determined by two different phospholipid dilution assays.

TECHNICAL APPROACH
Plasma will be obtained from patients known to have anticardiolipin antibodies as determined in the Rheumatology Clinic at WRAMC under the direction of Dr. Joe Tesar. The APTT will be measured in the Coagulation Lab at WRAIR, and tests for lupus anticoagulants will be done utilizing the dilute phospholipid APTT or the RVVT.

PRIOR AND CURRENT PROGRESS
Three patients have been enrolled altogether; none during the past year. There have been no adverse reactions from the blood drawings. The patients received no direct benefit except that they received a profile of their coagulation status in addition to the rheumatologic studies.

CONCLUSIONS
None. Please close this protocol.

REPORT DATE: 04/15/94 WORK UNIT # 1677

DETAIL SUMMARY SHEET

TITLE: Fludarabine Phosphate (FAMP: NSC-312887) in Compassionate Circumstances

KEYWORDS: Fludarabine Phosphate, lymphocytic leukemia, progressive adenopathy

PRINCIPAL INVESTIGATOR: Burrell, Linda MAJ MC

DEPARTMENT: Department of Medicine STATUS: Completed
SERVICE: Hematology-Oncology Service APPROVAL DATE: Apr 1991

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To assess the effectiveness and side effects of Fludarabine Phosphate (FAMP) in a patient with progressive adenopathy from chronic lymphocytic leukemia.

TECHNICAL APPROACH
This is a National Cancer Institute Group C protocol to provide FAMP to physicians in the management of patients with advanced, refractory chronic lymphocytic leukemia who are not candidates for entry onto ongoing clinical trials; and to determine the response rate, response duration, and toxicity of this regimen.

PRIOR AND CURRENT PROGRESS
The sole patient had a good partial response to therapy. In March 1992, therapy was discontinued because of no further response. The patient had stable disease until Spring 1993, and was treated with radiation to the abdominal adenopathy. Because of minimal response to the radiation, this patient was restarted on Fludarabine. Infectious side effects and opportunistic infections have been reported. These side effects have not changed the patient's participation, but prophylactic therapy is being instituted with the chemotherapy agent for pneumocystis pneumonia. Fludarabine is now FDA-approved and is not being obtained by an IND.

CONCLUSIONS
Fludarabine was effective in decreasing tumor burden and is currently being used again for the patient's disease. The patient has experienced no serious adverse side effects from the medication.

REPORT DATE: 11/12/93 WORK UNIT # 1680

DETAIL SUMMARY SHEET

TITLE: An Open Protocol for the Use of Agrelin (Anagrelide) for Patients with Thrombocythemia

KEYWORDS: thrombocythemia

PRINCIPAL INVESTIGATOR: Ward, Frank LTC MC
ASSOCIATES: Burrell, Linda MAJ MC

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Hematology-Oncology Service APPROVAL DATE: Nov 1991

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To assess the effectiveness and side effects of Anagrelide in patients suffering from thrombocythemia of various etiologies.

TECHNICAL APPROACH
Anagrelide at .5 mg by mouth four times a day will be used for the first week. The dose will then be adjusted to control the platelet count. For rapid platelet count reduction, 1 mg by mouth four times a day can be used initially. Platelet counts will be closely monitored to assure thrombocytopenia does not occur. Anagrelide will be given as long as necessary to control platelet counts.

PRIOR AND CURRENT PROGRESS
Two patients are currently enrolled on study, none during the past year. Their platelet counts have been controlled without undue toxicity when the drug is taken as prescribed. One patient has been variably compliant. This patient's course includes a mild asymptomatic anemia attributable to the investigational drug. No patients have withdrawn from the study. Both patients have benefited by the drug's ability to control their platelet counts.

CONCLUSIONS
Anagrelide has controlled the platelet counts in these two patients with thrombocythemia without notable toxicity to date. The only evident toxicity is mild asymptomatic anemia in one patient. These patients should be continued on study.

REPORT DATE: 05/02/94 WORK UNIT # 1681

DETAIL SUMMARY SHEET

TITLE: Characterization of Human Autoantibodies to Neutrophils and to Bone Marrow Myeloid Precursor Cells

KEYWORDS: neutropenia, autoimmunity

PRINCIPAL INVESTIGATOR: Hartman, Kip LTC MC
ASSOCIATES: Ward, Frank LTC MC; Klipple, Gary COL MC

DEPARTMENT: Department of Medicine
SERVICE: Hematology-Oncology Service

STATUS: Ongoing
APPROVAL DATE: Apr 1992

FUNDING: Current FY: $ 1,789 Previous FYs: $ 3,621 Total: $ 5,410

STUDY OBJECTIVE

To characterize the antigenic targets that appear to be involved in the pathogenesis of autoimmune neutropenia.

TECHNICAL APPROACH

This study involves the collection of blood specimens from patients and control subjects. Laboratory evaluation includes flow cytometric measurement of anti-neutrophil antibodies, evaluation of antigenic target proteins using immunoblot and immunoprecipitation techniques, and suppression studies of the growth of myeloid progenitor cells in vitro.

PRIOR AND CURRENT PROGRESS

There have been no adverse reactions to phlebotomy, and there has been no clinical benefit to patients. During this year, two patients have been registered on the study. A total of three patients and three control subjects have been enrolled.

CONCLUSIONS

Autoantibodies to antigens present on myeloid precursor cells may be present in the sera of patients with apparent autoimmune neutropenia. These antibodies may suppress the clonal growth of bone marrow cells in culture.
Characterization of the molecular target antigens of these antibodies and their role in the pathogenesis of disease is the subject of ongoing studies.

REPORT DATE: 10/10/93 WORK UNIT # 1682

DETAIL SUMMARY SHEET

TITLE: Solvent/Detergent Treated Pooled Human Plasma for Patients wtih Coagulopathies Requiring Fresch Frozen Plasma

KEYWORDS: plasma, virus, inactivation

PRINCIPAL INVESTIGATOR: Reid, Thomas, MAJ MC
ASSOCIATES: Alving, Barbara COL MC; Giangeruso, Enrico MC

DEPARTMENT: Department of Medicine
SERVICE: Hematology-Oncology Service

STATUS: Ongoing
APPROVAL DATE: Oct 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To broaden use of S/D-FFP in treatment of patients with deficiencies of: coagulation factors II, V, VII, X, XI, or XIII during bleeding; or multiple factor deficiencies (liver disease, DIC), protein-losing enteropathy (infant), and warfarin toxicity. To determine efficacy of S/D-FFP in bleeding control and as surgical prophylaxis in coagulation factor deficient patients. To evaluate safety of S/D-FFP with respect to any unexpected side effects.

TECHNICAL APPROACH

Bleeding patients will be infused with S/D-FFP, and percent recovery of deficient factor determined. Upon hemostatis, all factor deficient patients will have 3 mL of blood drawn for PT, APTT, and factor level. Bleeding control will be assessed by patient, physician, and blood test results. Surgery patients will have S/D-FFP infused pre-operatively, and percent recovery of deficient factor determined. S/D-FFP will infused, and bleeding control assessed intra-operatively and post-operatively. Infusion rate depends upon comorbid medical problems. Blood pressure, heart rate, and temperature will be recorded before and after (immediate, 5, 20, and 60 minutes) infusion of each unit.

PRIOR AND CURRENT PROGRESS

No patients have been enrolled to date.

CONCLUSIONS

No definitive conclusions can yet be made about the efficacy of this solvent-detergent treated FFP.

REPORT DATE: 11/03/93 WORK UNIT # 1683

DETAIL SUMMARY SHEET

TITLE: Intravenous Anti-Rho(D) [WinRhoSD Preparation] for the Treatment of Immune Thrombocytopenic Purpura

KEYWORDS: anti-D, thrombocytopenia, intravenous

PRINCIPAL INVESTIGATOR: Reid, Thomas MAJ MC
ASSOCIATES: Giangeruso, Enrico MD; Hartman, Kip LTC MC

DEPARTMENT: Department of Medicine
SERVICE: Hematology-Oncology Service

STATUS: Ongoing
APPROVAL DATE: Nov 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To broaden the experience of the WinRhoSD preparation of anti-Rho(D) in treatment of patients with ITP. To determine the efficacy of the WinRhoSD preparation of anti-Rho(D) in treatment of patients with ITP. To evaluate the safety of Win RhoSD with respect to any unexpected side effects.

TECHNICAL APPROACH

Unsplenectomized Rh+ individuals with either acute or chronic ITP will be eligible for entry. An intravenous dose (25-50 ug/kg body weight) is recommended for subjects with ITP. An intravenous dose (25-50 ug/kg body weight) is also recommended as maintenance dosage for subjects with chronic ITP. The frequency and dose used in maintenance therapy will be determined by individual clinical responses of the patients as assessed by measurements of platelet counts, red cell counts, hemoglobin levels, reticulocyte counts, and bilirubin and haptoglobin levels. Patients with Hb </= 7 g/dL are excluded. At the discretion of the PI, a lower initial dose of WinRhoSD (15-25 ug/kg body weight) may be given.

PRIOR AND CURRENT PROGRESS

Seven patients have been entered; six had ITP, and one nonresponder was later found to be ITP-. One patient was HIV+, and five were HIV-. Three were children (ages 12-14), and three were adults (ages 32-83). Initial platelet counts were 23-34x10^9/L. Initial dose of either anti-Rho(D) preparation was given at 25-50 ug/kg; additional doses of 25 ug/kg were given on days 3 and 4 of treatment, if there was no response after previous dose. Five of the six patients responded (83%). Mean platelet rise was 336x10^9/L (range: 183-703); peak responses were observed within 1 week. Mean decrease in hemoglobin (responders and nonresponders) was 28 g/L (20-52); one HIV+ patient who developed fever and hemolysis requiring infusion was DAT+ before therapy began. Increase in platelet count was transitory in all cases (mean response duration: 6 weeks; range: 2-8). All patients (except 1 nonresponder) had had previous therapy with steroids and/or IVIg.

CONCLUSIONS

The overall response rate for WinRhoSD in patients with ITP is 83; similar to that observed for IVIg. Anti-Rho(D) is a reasonable alternative to steroid or IVIg therapy in ITP.

REPORT DATE: 12/14/93 WORK UNIT # 1684

DETAIL SUMMARY SHEET

TITLE: Equilibration of Hemoglobin After Transfusion

KEYWORDS: hemoglobin, transfusion, equilibration

PRINCIPAL INVESTIGATOR: Wiesen, Andrew CPT MC
ASSOCIATES: Hospenthal, Duane CPT MC; Byrd, John CPT MC

DEPARTMENT: Department of Medicine
SERVICE: Hematology-Oncology Service

STATUS: Ongoing
APPROVAL DATE: Dec 1992

FUNDING: Current FY: $ 190 Previous FYs: $ 0 Total: $ 190

STUDY OBJECTIVE

To determine the rise in hemoglobin and the appropriate time to measure this rise following a red cell transfusion; and to determine the effect of transfusion on serum chemistries.

TECHNICAL APPROACH

A prospective, obsevational study in which hemoglobin and chemistry profiles will be measured at 15 minutes, 1 hour, 2 hours, and 24 hours after transfusion of two units of packed red cells. Participants are deemed eligible if they were to receive a 2-unit transfusion of packed red cells, and are older than 18 years. Exclusion criteria include non-availability of completely compatible blood for transfusion, recent active bleeding, and inability to give informed consent.

PRIOR AND CURRENT PROGRESS

A total of 43 participants were enrolled in 1993; 44 two unit transfusions were given to 39 participants. Four men and one woman participated in the study twice. Two participants did not receive a transfusion, and six received other than two unit transfusions. There has been no direct benefit to patients participating in the study. Mean hemoglobin concentration rose 1.9+/= 0.8 g/dl following a two unit transfusion. There was no statistically significant difference in mean hemoglobin concentration measured at 15 minutes, 1 hour, 2 hours, or 24 hours. Mean bilirubin concentration increased from 0.8 +/= 0.6 mg/dl before transfusion to 1.7 +/= 1.0 mg/dl by 15 minutes after transfusion. Bilirubin concentration 24 hours following transfusion was 0.9 +/= 0.5 mg/dl.

CONCLUSIONS

Hemoglobin reaches equilibration rapidly post-transfusion. Measurement of hemoglobin 15 minutes post-transfusion is clinically representative of the 24-hour post-transfusion value. Hemoglobin increases about 1 g/dl/unit transfused for a 2-unit transfusion. Bilirubin increases from it baseline value in >95% of patients by 15 minutes post-transfusion, and returns to baseline by 24 hours post-transfusion. Decisions about success of transfusion therapy can be made rapidly.

REPORT DATE: 10/11/94 WORK UNIT # 1686

DETAIL SUMMARY SHEET

TITLE: Studies of the Prolliferation and Differentiation of Pluripotent Stem Cells and Committed Hematopoietic Precursors from Human Bone Marrow Maintained in Continuouis Long-Term Cultures

KEYWORDS: stem cells, long-term culture

PRINCIPAL INVESTIGATOR: Reid, Thomas MAJ MC

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Hematology-Oncology Service APPROVAL DATE: Sep 1993

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To study the function of hematopoietic cells and stromal cells from human marrow in normal and infected states.

TECHNICAL APPROACH
Human marrow was used in all of the studies. Marrow cells were used either to grow stroma or as a source of CD34+ cells which represent the stem-progenitor cell compartment. Human marrow light density cells were used to develop stromal cell cultures. Human marrow CD34+ cells were purified by immunomagnetic beads and used as a source of stem-progenitor cells. Clonogenic assays were also used to quantitate hematopoietic and stromal progenitor cells as colony forming units (CFU).

PRIOR AND CURRENT PROGRESS
Bone marrow cells were utilzed in the following studies: 1) development of a novel clonogenic assay for CD34+ stromal cell progenitor cells from human marrow, 2) HIV infection of stromal progenitor cells, and function of virus infected stromal cells; 3) development of a SCID mouse model for detecting primitive human CD34+ cells capable of reconstituting both hematopoietic and lymphoid systems; 4) studies of dengue-infected stromal cells; 5) leishmania infection of stromal cells derived from human marrow; and 6) detection of autoimmune antibodies which react with CD34+ myeloid progenitors from human marrow. There were no adverse reactions.

CONCLUSIONS
This study has made significant contributions to the understanding of bone marrow failure syndromes associated with auto-immune mechanisms and virus infections. It helped further characterize the CD34+ stem-progenitor cell pool and mechanisms involved in regulation of hematopoiesis in normal and diseased states; in particular, mechanisms of auto-immune-mediated neutropenia, leishmania parasitic infections of marrow, dengue virus and HIV-mediated marrow suppression in man.

REPORT DATE: 10/25/93 WORK UNIT # 9022-83

DETAIL SUMMARY SHEET

TITLE: Studies of the Proliferation and Differentiation of Pluripotent Stem Cells and Committed Hematopoietic Precursors from Normal Bone Marrow Maintained in Continuous Long-term Cultures

KEYWORDS: stem cells, differentiation

PRINCIPAL INVESTIGATOR: Reid, Thomas MAJ MC
ASSOCIATES: La Russa, Vincent PhD; Salvado, August COL MC

DEPARTMENT: Department of Medicine
SERVICE: Hematology-Oncology Service

STATUS: Completed
APPROVAL DATE: Oct 1982

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To define mechanisms by which progenitor cells in the bone marrow replicate themselves and go on to form mature blood cells.

TECHNICAL APPROACH
The methods involved are: 1) the use of culture tubes and a defined media to study the behavior of stem cells for a period up to 8 weeks in culture; and 2) the use of clonal assays to quantitate the number of stem cells grown in culture.

PRIOR AND CURRENT PROGRESS
Characterization of the cells that make up the hematopoietic microenvironment has begun by immunophenotyping of cells from stromal colonies. Purified CD34+ stromal cell precursors have been studied as targets for infection by HIV and Dengue virus. Bone marrow stromal cultures established with ligh density cells have been studied as an in vitro model for culturing Leishmania, a parasite isolated from U.S. soldiers returning from Operation Desert Storm. The total number of marrow samples obtained for this study is 763; during the past year, 39 marrow samples were obtained from 18 donors. Bone marrow donors have experienced no serious or unexpected adverse reactions.

CONCLUSIONS
These studies provide information on the normal regulation of hematopoiesis and on the mechanism by which certain viral infections cause suppression of hematopoietic function.

REPORT DATE: 07/06/94 WORK UNIT # 1965

DETAIL SUMMARY SHEET

TITLE: Treatment of Cutaneous Leishmaniasis with Pentostam

KEYWORDS: leishmaniasis, Pentostam, IND

PRINCIPAL INVESTIGATOR: Johnson, Steven MAJ MC
ASSOCIATES: Magill, Alan MAJ MC; Gasser, Robert Jr. LTC MC

DEPARTMENT: Department of Medicine
SERVICE: Infectious Disease Service

STATUS: Completed
APPROVAL DATE: Feb 1989

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

1) Provide continuous therapy for cutaneous leishmaniasis; 2) Determine peak and trough serum concentrations, and serum half-life, of Pentostam administered at a dose of 20 mg antimony (Sb)/kg body weight daily for 20 days; 3) Collect additional safety data on this dosing regimen; and 4) Compare 10 days therapy with 20 mg Sb/kg/day to 20 days therapy with 20 mg Sb/kg/day.

TECHNICAL APPROACH

Administration of Pentostam to patients diagnosed as having cutaneous leishmaniasis. Approximately five patients meeting the criteria for receiving Pentostam will be asked to donate blood in order to study the pharmacokinetics of this drug. This protocol will also provide for the randomization of patients to two groups: Group A will receive 20 mg Sb/kg/day for 20 days, and Group B will receive 20 mg Sb/kg/day for 10 days, followed by 50 ml DSW IV qd for 10 additional days. A total of 40 patients will be randomized. Five from each group will be asked to participate in the pharmacokinetic study.

PRIOR AND CURRENT PROGRESS

From 1989 to 1994, 64 patients with leishmaniasis were treated with Pentostam, 14 since the last APR submitted in March 1994. This included 55 patients with cutaneous disease and 9 patients with visceral disease. Only five patients were treated as part of the randomization scheme above; all five did well. The remaining 59 patients received open label Pentostam as allowed by the protocol. As the protocol has reached its 5-year time limit, enrollment stopped on 30 Jun 94. A new protocol, allowing continued access to Pentostam, has been submitted and approved.

CONCLUSIONS

No significant conclusions about the efficacy of different durations of Pentostam can be reached from this study. However, important insights into the presentation and treatment of leishmaniasis have emerged including; 1) the continued importance of cutaneous disease for U.S. troops in Central America; 2) an expanded side effects profile for Pentostam; and 3) the discovery of visceral cases from Operation Desert Storm.

REPORT DATE: 07/11/94 WORK UNIT # 1967

DETAIL SUMMARY SHEET

TITLE: Pharmacokinetics of Polyvalent Hyperimmune Globuin Directed Against Pseudomonas and Klebsiella

KEYWORDS: immunoglobulin, Pseudomonas, Klebsiella

PRINCIPAL INVESTIGATOR: Cross, Alan COL MC
ASSOCIATES: Drabick, Joseph MAJ MC; McClain, J. Bruce COL MC

DEPARTMENT: Department of Medicine
SERVICE: Infectious Disease Service

STATUS: Completed
APPROVAL DATE: Jun 1989

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine the pharmacokinetics of IVIG directed against gram negative germs in patients who are ill and in normal volunteers.

TECHNICAL APPROACH
Volunteers will be given immunoglobulin and have their blood drawn at specified periods of time. The ELISA results will be subjected to pharmacokinetic analysis. In an addendum approved March 1993, a follow-up study will utilize ELISPOT assay of lymphocytes and the measurement of serum IgG, IgA, and IgM against specific bacterial antigens to assess if passively administered IVIG induces new specific antibody formation. Three pairs of volunteers will be enrolled under this addendum.

PRIOR AND CURRENT PROGRESS
A total of 15 patients have been enrolled, 4 during the past year. The hyperimmune globulin product was found to be safe in both normal and ill recipients. The pharmacokinetics was complex and suggestive of active antibody production induced by receipt of the antibody. One individual appeared to be actively immunized by the hyperimmune product whereas none of the controls or the other recipients appeared to be. This individual had an IgM antigen specific response between 10 and 20 days suggestive of primary immunization. The product is currently in use in a large multicenter VA/DOD study.

CONCLUSIONS
The hyperimmune globulin exhibited a complex pharmacokinetics suggestive of active antibody production. This is a phenomenon which has been observed for other products but never commented upon, let alone investigated. Active immunization appeared to take place in one individual; however, the ELISPOT method may not be a sensitive enough test. Further investigation will be required.

REPORT DATE: 09/21/94 WORK UNIT # 1975

DETAIL SUMMARY SHEET

TITLE: A Retrospective Analysis of Corynebacterial Bacteremias at Walter Reed Army Medical Center

KEYWORDS: Corynebacteria, bacteremia

PRINCIPAL INVESTIGATOR: Kester, Kent MAJ MC
ASSOCIATES: Johnson, Steven MAJ MC; McEvoy, Peter LTC MC

DEPARTMENT: Department of Medicine
SERVICE: Infectious Disease Service

STATUS: Ongoing
APPROVAL DATE: Sep 1993

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To retrospectively assess all Corynebacteria cases at WRAMC over the past 5 years to assess whether it is possible to adequately treat IV catheter associated infections without line removal.

TECHNICAL APPROACH
This is a retrospective chart review of inpatient medical records.

PRIOR AND CURRENT PROGRESS
A total of 30 of 35 records of patients with Corynebacterium jeikeium bacteremia have been reviewed. Plans are to review the remaining five records within the next 2 months. After record review is completed, data analysis will be undertaken.

CONCLUSIONS
Pending; data collection is still in progress.

REPORT DATE: 11/12/93 WORK UNIT # 1157

DETAIL SUMMARY SHEET

TITLE: Effects of Thyroid Hormone and Thyrotropin (TSH) on Cultured Kidney Cells: Modulation of ANP Receptors and Epithelial Function

KEYWORDS: 3NP, thyroid hormone, kidney

PRINCIPAL INVESTIGATOR: Moore, Jack LTC MC
ASSOCIATES: Tseng, Yueh-Chu PhD

DEPARTMENT: Department of Medicine
SERVICE: Nephrology Service

STATUS: Completed
APPROVAL DATE: Nov 1988

FUNDING: Current FY: $ 0 Previous FYs: $ 7,796 Total: $ 7,796

STUDY OBJECTIVE
To determine whether the number or binding affinity of ANP receptors on renal cells is affected by incubation of such cells with ranging concentrations of thyroid hormone and thyroid hormone-depleted media; to correlate any changes with post-receptor and functional events.

TECHNICAL APPROACH
Rat papillary collecting duct cells (PCDC) were obtained as a gift from Dr. John Schwartz, Boston University. The ANP receptor in these cells will be indentified and characterized under control conditions, and in cells grown in T3-free media and media enriched with T3. The ANP receptor will be characterized using hot and cold ANP. Guanylate cyclose (cyclic GMP) will be measured using kit.

PRIOR AND CURRENT PROGRESS
ANP was found to cause significant increases in GGMP in the PCDC cell line, but T3 produced no further augmentation. There was no change in specific binding of ANP to its receptor with pre-incubation with T3.

CONCLUSIONS
It was concluded that T3 influence on ANP action in the kidney is not mediated directly via the ANP receptor.

REPORT DATE: 11/12/93 WORK UNIT # 1161

DETAIL SUMMARY SHEET

TITLE: Mechanisms of Action of Thiorphan and Atrial Natriuretic Peptide on Renal Function During Hemorrhagic Shock

KEYWORDS: kidney, shock, ANP

PRINCIPAL INVESTIGATOR: Yuan, Christina CPT MC

DEPARTMENT: Department of Medicine STATUS: Completed
SERVICE: Nephrology Service APPROVAL DATE: Nov 1990

FUNDING: Current FY: $ 709 Previous FYs: $ 3,530 Total: $ 4,239

STUDY OBJECTIVE

To study the effects of atrial natriuretic peptide (ANP) and Thiorphan in renal function during hemorrhagic shock in the rat model. The researchers have previously found that renal function and urine output are acutely improved by this drug, and now wish to study whether renal blood flow is changed by the regimen and whether renal function also is affected 48 hours after hemorrhage.

TECHNICAL APPROACH

Renal artery blood flow will be measured during hemorrhage in animals receiving Thiorphan, ANP, both, or vehicle. In addition, chronic survival studies of GFR, UO, solute excretion, and renal histology are underway. This involves exposing the animal to sublethal hemorrhage while administering ANP/Thiorphan or vehicle, and then measuring UO, Na excretion, and inulin clearance 24 hours later.

PRIOR AND CURRENT PROGRESS

A total of 27 rats have been used for this study; none during the past year. Animal studies are complete. Animals survived surgery and hemorrhage about 75% of the time, and appeared to have a polyuric form of renal injury. Histology is still pending, as is tissue preparation. A paper has been submitted for publication.

CONCLUSIONS

There is no difference in survival between animals receiving ANP and those that served as controls. Renal blood flow did not change significantly between controls and ANP treated animals.

REPORT DATE: 01/12/94 WORK UNIT # 1162

DETAIL SUMMARY SHEET

TITLE: The Regulation of Insulin-like Growth Factor I and Insulin-like Growth Factor Binding Protein Gene Expression in the Mouse Glomerulus

KEYWORDS: TIMP-1, gelatinase, glomerulosclerosis

PRINCIPAL INVESTIGATOR: Carome, Michael CPT MC
ASSOCIATES: Moore, Jack COL MC; Striker, Liliane MD

DEPARTMENT: Department of Medicine
SERVICE: Nephrology Service

STATUS: Completed
APPROVAL DATE: Jan 1991

FUNDING: Current FY: $ 1,725 Previous FYs: $ 13,641 Total: $ 15,366

STUDY OBJECTIVE

To elucidate the molecular and cellular biologic events which lead to the development of glomerulosclerosis. In particular, the effects of the growth hormone (GH)-IGF-I axis on the gene expression of extracellular matrix (ECM) components, matrix metalloproteinases (MMP), and tissue inhibitor of metalloproteinase (TIMP) are being studied.

TECHNICAL APPROACH

Matrix synthesis and degradation display will be displayed in vitro in mesangial cells derived from normal and bGH transgenic mice, and in vivo in glomeruli isolated by microdissection from these same animals. The bGH mice will provide a murine model for non-proliferative glomerulosclerosis. Gene expression of ECM, MMP's, and TIMP will be assessed at the mRNA level by in situ reverse transcription, followed by competitive PCR quantitation of the cDNA's of interest. Gelatinase secretion, TIMP-1 synthesis, and collagen secretion will be measured by standard techniques. Renal histology will be assessed by light and immunofluorescence microscopy.

PRIOR AND CURRENT PROGRESS

A total of 26 mice have been studied; none in the past year. No unexpected adverse reactions or findings occurred. Cultured mesangial cells derived from normal mice and from mice transgenic for bGH synthesized and secreted TIMP-1 and 72 kDa gelatinase, Only the normal mesangial cells secreted significant amounts of 82 kDa gelatinase. Normal murine glomeruli expressed 72 kDa gelatinase mRNA and protein in vivo; the level of expression was significantly increased in glomeruli of bGH mice. This increase in 72 kDa gelatinase gene expression in bGH mice was not due to an increase in glomerular cell number, based upon a morphometric analysis. In contrast to the in vitro findings in cultured mesangial cells, TIMP-1 gene expression was not detectable in glomeruli from normal or bGH mice.

CONCLUSIONS

Significant differences in gelatinase and TIMP-1 expression were found between intact glomeruli and mesangial cells in vitro, and an up-regulation in the expression of 72 kDa gelatinase in bGH glomeruli as compared to controls. Elucidation of the mechanisms underlying these differences may enhance understanding of glomerulosclerosis and the role of the GH-IGF-I axis in this disease process.

REPORT DATE: 03/14/94 WORK UNIT # 1163

DETAIL SUMMARY SHEET

TITLE: Effects of Cyclosporin A on the Production of Vasoactive Hormones by Endothelial Cells in Culture

KEYWORDS: cyclosporin A, endothelin, prostacyclin

PRINCIPAL INVESTIGATOR: Yuan, Christina CPT MC
ASSOCIATES: Kiandoli, Luana BSc(MT); Moore, Jack COL MC

DEPARTMENT: Department of Medicine
SERVICE: Nephrology Service

STATUS: Ongoing
APPROVAL DATE: Mar 1991

FUNDING: Current FY: $ 6,014 Previous FYs: $ 0 Total: $ 6,014

STUDY OBJECTIVE

To determine whether cyclosporin A can directly stimulate endothelin release from cultured endothelial cells; and if so, is the release of other endothelial-derived vasoactive substances perturbed.

TECHNICAL APPROACH

Both human and bovine endothelial cells in culture will be exposed to varying concentrations of cyclosporine. Endothelin and prostacyclin production will be measured at 24 hours, and cell viability will be assessed at 24 hours. Phosphoramidon, an inhibitor of endothelin release, was added also, and the effect on endothelin and prostacyclin production was measured.

PRIOR AND CURRENT PROGRESS

Cyclosporine stimulated endothelin production in a dose-dependent manner and also stimulated prostacyclin production. Cell viability declined in a dose-dependent manner. Phosphoramidon inhibited both endothelin and prostacyclin production, but not cell viability decline. Intracellular endothelin increased phosphoramidon treatment. A paper is being prepared.

CONCLUSIONS

Cyclosporine stimulates endothelin and prostacyclin production in a dose dependent manner. Phosphoramidon inhibits production of both hormones but has no effect on the decline in cell viability produced by increasing concentrations of cyclosporine.

REPORT DATE: 04/15/94 WORK UNIT # 1164

DETAIL SUMMARY SHEET

TITLE: Synthesis and Degradation of Collagen and Modulation of its Biology in Sclerosing Forms of Human Glomerulonephritis: Analysis of Gene Expression

KEYWORDS: glomerulonephritis, collagen, TIMP

PRINCIPAL INVESTIGATOR: Moore, Jack LTC MC
ASSOCIATES: Carome, Michael MAJ MC

DEPARTMENT: Department of Medicine
SERVICE: Nephrology Service

STATUS: Ongoing
APPROVAL DATE: Apr 1991

FUNDING: Current FY: $18,944 Previous FYs: $ 16,810 Total: $ 35,754

STUDY OBJECTIVE

To obtain isolated golmeruli from patients with glomerulonephritis (GN) or patients who are undergoing nephrectomy for renal cancer. To use these glomeruli to explore the balance between collagen synthesis and degradation by (a) analyzing the synthesis of Type I and IV collagen, and (b) analyzing the biodegradation of collagen by measuring the synthesis of tissue inhibitor of metalloproteinase (TIMP) 1 and 2.

TECHNICAL APPROACH

Tissue from patients with GN or normal tissue removed from cancer nephrectomies are microdissected to obtain isolated glomeruli. The glomeruli are solubilized with triton, and messenger RNA (mRNA) is inhibited. Messenger RNA is reverse transcribed into stable cDNA. Then this cDNA is used, with appropriate primers, in a competitive PCR experiment which allows detection of mRNA for both TIMP's. Mutant TIMP's are constructed and run in the competitive PCR, and the mutant product is compared to wild type. This allows quantitation of the different forms of TIMP. Light microscopic analysis of tissue is performed.

PRIOR AND CURRENT PROGRESS

RT-PCR techniques have been used to demonstrate that human glomeruli express the genes for type IV collagen, 72 kDa gelatinase, TIMP-1, and TIMP-2 in vivo, and that the level of expression for collagen and the TIMPs is significantly increased in glomerulosclerosis associated with renal cell carcinoma. To date, 11 patients have been enrolled in this study at WRAMC. None have been enrolled in the past year. There has been no benefit to the subjects. There have been no serious or unexpected adverse reactions, and no subjects have withdrawn from the study.

CONCLUSIONS

Normal glomeruli expressed Type IV collagen, TIMP-1, TIMP-2, and gelatinase mRNA in vivo. Increased expression of Type IV collagen and TIMP's may play a role in the development of some forms of glomerulosclerosis. Application of the above techniques to clinical biopsy specimens may enhance understanding of the molecular events involved in the development of glomerulosclerosis.

REPORT DATE: 09/08/94 WORK UNIT # 1165

DETAIL SUMMARY SHEET

TITLE: The Effects of Cisplatin on the Production of Endothelin and Other Vasoactive Hormones by Endothelial Cells in Culture

KEYWORDS: cisplatin, endothelin, prostacyclin

PRINCIPAL INVESTIGATOR: Bohen, Erin CPT MC
ASSOCIATES: Yuan, Christina CPT MC; Kiandoli, Luana

DEPARTMENT: Department of Medicine
SERVICE: Nephrology Service

STATUS: Completed
APPROVAL DATE: Aug 1991

FUNDING: Current FY: $ 3,185 Previous FYs: $ 7,455 Total: $ 10,640

STUDY OBJECTIVE

To determine whether cisplatin can directly stimulate endothelin release from cultured endothelial cells; and if so, is the release of other endothelial derived vasoactive substances perturbed.

TECHNICAL APPROACH

Endothelial cells in culture will be exposed to varying concentrations of cisplatin. Cell viability will be assessed at 24 hours. Endothelin and prostacyclin production will be measured at 24 hours. The endothelial cells used in this study will be purchased off-shelf.

PRIOR AND CURRENT PROGRESS

All experiments have been completed. An abstract was published during the past year in the Journal of the American Society of Nephrology.

CONCLUSIONS

Although cisplatin was indeed cytotoxic with increasing concentrations, no significant increase in endothelin production was seen 24 hours after exposure to this drug.

REPORT DATE: 11/12/93 WORK UNIT # 1166

DETAIL SUMMARY SHEET

TITLE: The Effects of Gentamicin on the Production of Vasoactive Hormones by Endothelial Cells in Culture

KEYWORDS: endothelin, gentamicin, prostacyclin

PRINCIPAL INVESTIGATOR: Yuan, Christina CPT MC

DEPARTMENT: Department of Medicine STATUS: Completed
SERVICE: Nephrology Service APPROVAL DATE: Nov 1991

FUNDING: Current FY: $ 7,527 Previous FYs: $ 4,582 Total: $ 12,109

STUDY OBJECTIVE
To determine if gentamicin (1) can directly stimulate cultured endothelial cells to secrete endothelin, and (2) affects the production of other endothelial-derived vasocative substances.

TECHNICAL APPROACH
Endothelial cells in culture will be exposed to gentamicin in a dose response experiment. Viability and supernatant levels of endothelin and prostacyclin levels will be measured at 0, 4, 8, and 24 hours.

PRIOR AND CURRENT PROGRESS
The proposed experiments have been completed. Endothelial cells in culture did not increase endothelin production or prostacyclin production in response to a range of gentamicin concentrations, at 4, 8, or 24 hours. An increase was seen at 72 hours. An abstract has been published.

CONCLUSIONS
Gentamicin does not stimulate endothelin production as measured by ELISA in human endothelial cells within 24 hours. Increases in production are seen at 72 hours.

REPORT DATE: 12/01/93 WORK UNIT # 1167

DETAIL SUMMARY SHEET

TITLE: The Effect of Enalapril on Hypertension, Proteinuria, and Renal Function in a New Model of Diabetes Mellitus in Wistar Rats

KEYWORDS: diabetes, hypertension, enalapril

PRINCIPAL INVESTIGATOR: Bohen, Erin CPT MC
ASSOCIATES: Yuan, Christine CPT MC; Moore, Jack COL MC

DEPARTMENT: Department of Medicine
SERVICE: Nephrology Service

STATUS: Ongoing
APPROVAL DATE: Nov 1991

FUNDING: Current FY: $ 5,434 Previous FYs: $ 4,324 Total: $ 9,758

STUDY OBJECTIVE

To determine whether angiotensin converting enzyme inhibitor (CEI) and DuP753 (angiotensin II receptor blocker), when used in this model of diabetes and hypertension, can eliminate or diminish proteinuria, prevent or attenuate the development of renal failure, control the systemic hypertension, and prevent or attenuate renal structural changes.

TECHNICAL APPROACH

The rat model will be used in this study. All animals will undergo 25% reduction in renal mass/streptozotocin injection to create hypertensive, diabetic rats. Animals will then be randomized to receive: (1) enalapril, (2) DuP753, or (3) tap water for 4, 10, or 16 weeks. Blood pressure (BP), renal clearances, proteinuria, and renal pathology will be determined at the three time points.

PRIOR AND CURRENT PROGRESS

During the past year, 30 animals have been used; 150 have been used altogether. There were no unexpected or serious advese reactions. Untreated rats showed increased direct arterial blood pressures at the time of euthanasia. Those treated with enalapril or DuP753 had significantly lower mean arterial pressures than controls at the time of euthanasia. At 4 and 10 weeks after induction of diabetes, inulin clearance (a measure of glomerular filtration rate) was greater in rats treated with enalapril than in controls. At 4 weeks, proteinuria (an indicator of renal injury) is significantly less in enalapril-treated rats than in either controls or DuP753-treated rats. Thirty rats were randomized to receive HOE 140/enalapril vs. an enalapril group to test whether the difference in inulin clearance and proteinuria of enalapril-treated rats vs. DuP753-treated ones was secondary to the bradykinin mediated effects of enalapril.

CONCLUSIONS

Enalapril and DuP753 have antihypertensive effects in this model. At 4 weeks, with equal BP control, enalapril-treated rats have better preserved renal function and less proteinuria than DuP753-treated animals. Data analysis is not complete at this time.

REPORT DATE: 02/01/94 WORK UNIT # 1168

DETAIL SUMMARY SHEET

TITLE: The Acute Effect of Enalapril on Hypertension in a New Model of Hypertension Associated with Diabetes Mellitus in Wistar Rats

KEYWORDS: hypertension, diabetes, angiotensin II

PRINCIPAL INVESTIGATOR: Bohen, Erin CPT MC
ASSOCIATES: Yuan, Christine MAJ MC; Pamnani, Moti MD PhD

DEPARTMENT: Department of Medicine
SERVICE: Nephrology Service

STATUS: Ongoing
APPROVAL DATE: Jan 1992

FUNDING: Current FY: $ 5,017 Previous FYs: $ 5,593 Total: $ 10,610

STUDY OBJECTIVE

To determine the acute effects of angiotensin converting enzyme therapy on the hypertension seen in a new rat model of experimental diabetic nephropathy which results in proteinuria, renal failure, and hypertension.

TECHNICAL APPROACH

Male Wistar rats will undergo 25% reduction in renal mass, and diabetes will be induced with IV streptozotocin. After 4 weeks of diabetes, animals will be anesthetized with Inactin and direct blood pressure measured. Animals will then receive either a) DuP753 (an angiotensin II receptor blocker) followed by enalapril (a converting enzyme inhibitor), b) DuP753 vehicle followed by enalapril, or c) both vehicles. Mean arterial pressure, pulse, and urine output will be measured during these manipulations.

PRIOR AND CURRENT PROGRESS

Thirty-five rats have been used in this protocol, none during the past year. Enalapril and DuP753 when given acutely produce equivalent decrements in mean arterial pressure. Urinary prostanoid excretion and urinary kinin excretion are not influenced by either drug.

CONCLUSIONS

The acute antihypertensive effect of enalapril in this model appears to be due only to inhibition of angiotensin II formation.

REPORT DATE: 02/03/94 WORK UNIT # 1169

DETAIL SUMMARY SHEET

TITLE: Safety and Immunogenicity of Staphylococcus Aureus Capsular Polysaccharide - Pseudomonas Aeruginosa, r-exoprotein A type 5 Conjugate Vaccine Given to Patients with End-Stage Renal Disease (ESRD)

KEYWORDS: Staphylococcus aureus, vaccine, dialysis

PRINCIPAL INVESTIGATOR: Welch, Paul MAJ MC
ASSOCIATES: Moore, Jack COL MC

DEPARTMENT: Department of Medicine
SERVICE: Nephrology Service

STATUS: Completed
APPROVAL DATE: Feb 1992

FUNDING: Current FY: $ 1,923 Previous FYs: $ 150 Total: $ 2,073

STUDY OBJECTIVE

To determine (1) the safety and immunogenicity of Staphylococcus aureus capsular polysaccharide - type 5 conjugate vaccine given to patients on dialysis; (2) if there is a booster response to the second injection of vaccine, given 6 weeks after the first injection; and (3) the nasal carriage rate of Staphylococcus aureus in the patients.

TECHNICAL APPROACH

Patients who meet the inclusion and exclusion criteria will be given the study vaccine, followed 6 weeks later by a booster injection. Safety will be evaluated by monitoring patients' symptoms, temperature, local skin reaction, SGOT, and SGPT. Immunogenicity will be evaluated by measuring the antibody response to the vaccine. Nasal carriage rate will be determined by measuring nasal cultures.

PRIOR AND CURRENT PROGRESS

Seventeen patients have been enrolled and given the study vaccine, none this past year. There were no withdrawals. Transient minor symptoms, i.e., local site reactions, and transaminase elevations, occurred in a minority of patients. There were no serious reactions. Significant immunogenicity was demonstrated after the first injection, but no significant changes occurred after the second injection. Nasal carriage of S. aureus ranged between 17.6% and 29.4%. Patients may be protected from certain strains of S. aureus and P. aeruginosa, but further studies are needed.

CONCLUSIONS

1) This study is both safe and immunogenic. 2) There is no significant booster response to a second injection. 3) Nasal carriage rate of S. aureus was between 17.6-29.4% in this population. Vaccine effects on nasal carriage rates are inconclusive. S. aureus vaccine efficacy trials are currently in progress.

REPORT DATE: 09/08/94 WORK UNIT # 1170

DETAIL SUMMARY SHEET

TITLE: Stress Proteins and Cytoprotection in MDCK Cells in Culture

KEYWORDS: heat shock, cytoprotection, renal tubular cells

PRINCIPAL INVESTIGATOR: Yuan, Christina MAJ MC
ASSOCIATES: Carome, Michael MAJ MC; Bohen, Erin MAJ MC

DEPARTMENT: Department of Medicine
SERVICE: Nephrology Service

STATUS: Ongoing
APPROVAL DATE: Sep 1992

FUNDING: Current FY: $10,640 Previous FYs: $ 21,208 Total: $ 31,848

STUDY OBJECTIVE

To study the effects of several renal toxins on heat shock protein production by the MDCK cells, a renal tubular cell line, and to test whether previous heat shock is protective to the MDCK cell when treated with known cellular toxins (such as cyclosporine, indomethacin, or gentamicin).

TECHNICAL APPROACH

MDCK cells will be heat-shocked, exposed to several toxins in increasing doses, and measured for HSP70 protein levels via ELISA. Cell viability will be assessed with increasing doses of toxin in cells heat-shocked 24 hours prior to toxin exposure and in control cells. An addendum was approved in June 1993 to study the effect of blocking HSP70 production on viability of heat-shocked cyclosporine treated MDCK cells.

PRIOR AND CURRENT PROGRESS

Study results have shown that heat shock is protective against subsequent cyclosporine toxicity in MDCK cells and in LLCPK cells (another renal cell line). The researchers have also shown that heat shock is protective against cisplatinum toxicity in LLCPK cells. In addition, study results have shown that cytoprotection associated with heat shock declines parallel with declining heat shock 70 protein levels, with time post-heat shock. The researchers have not been able to block HSP70 protein expression with anti-sense aligonucleotides to HSP70 mRNA.

CONCLUSIONS

Please see results above.

REPORT DATE: 06/13/94 WORK UNIT # 1171

DETAIL SUMMARY SHEET

TITLE: Analysis of the Distribution of Cellular Uptake of radiolabeled Oligodexoynucleotides Within the Rat kidney

KEYWORDS: oligonucleotides, antisense, kidney

PRINCIPAL INVESTIGATOR: Carome, Michael CPT MC

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Nephrology Service APPROVAL DATE: Jun 1993

FUNDING: Current FY: $ 3,348 Previous FYs: $ 0 Total: $ 3,348

STUDY OBJECTIVE

To determine the distribution of cellular uptake of radiolabeled oligonucleotides (ODN's) within the glomeruli, tubules, interstitium, and blood vessels of the rat kidney following either systemic intravenous infusion or local infusion into the renal artery.

TECHNICAL APPROACH

A 20-mer phoporothioate ODN will be synthesized using H-phosphonate chemistry on an automated oligonucleotide synthesizer. The ODN will then be oxidized with 35S8 and purified by polyacylamide gel electrophoresis. The radiolabeled ODN will then be injected into male Wistar rats under general anesthesia via either the jugular vein or the renal artery. Animals will then be euthanized at either 1 hour or 4 hours post-infusion. Kidneys, and liver, lung, and heart tissue will then be harvested and placed in a fixative. Tissue autoradiography will then be performed.

PRIOR AND CURRENT PROGRESS

A total of eight animals were studied to date. Six animals received the systemic infusion, and two received infusions directly into the left renal artery. Because of renal artery spasm and subsequent renal ischemia in the latter two animals, adequate renal tissue autoradiography could only be obtained on the systemic infusion animals. Tissue autoradiography results were similar for animals euthanized at both 1 hour and 4 hours post-infusion, and were as follows: 1) The proximal tubular cells had the greatest level of ODN uptake in all animals; 2) Weaker levels of ODN uptake were detected in the cells of the glomerulus and in distal tubular cells; and 3) Minimal to no ODN uptake was detected in the renal vasculature or the cells of the loop of Henle and medullary collecting duct. There were no adverse reactions, and all animals were euthanized under general anesthesia at the time of tissue harvest.

CONCLUSIONS

In conclusion, this study has demonstrated that radiolabeled phosphorothioate ODN's were taken up predominantly by proximal renal tubular cells, and to a lesser extent by glomerular cells and distal tubular cells. It may, therefore, be possible to utilize antisense phosphorothioate ODN's to assess the pathogenetic role of specific gene products in rat models of both tubulo-interstitial and glomerular diseases, including renal failure due to acute tubular necrosis.

REPORT DATE: 06/13/94 WORK UNIT # 1172

DETAIL SUMMARY SHEET

TITLE: Analysis of Glomerular Gene Expression in Diabetic Nephropathy

KEYWORDS: diabetes mellitus, nephropathy, gene expression

PRINCIPAL INVESTIGATOR: Carome, Michael MAJ MC
ASSOCIATES: Welch, Paul MAJ MC; Clement, Stephen MAJ M

DEPARTMENT: Department of Medicine
SERVICE: Nephrology Service

STATUS: Ongoing
APPROVAL DATE: Jun 1993

FUNDING: Current FY: $13,866 Previous FYs: $ 0 Total: $ 13,866

STUDY OBJECTIVE

1) To obtain isolated glomeruli from patients with clinical evidence of diabetic nephropathy to analyze in vivo glomerular gene expression of major proteins involved in synthesis and degradation of extracellular matrix, including genes for types I and IV collagen, matrix metalloproteinases and their inhibitors, growth factors, and cytokines. 2) To determine whether the level of any of these mRNAs is altered in glomeruli from diabetic patients compared to normal glomeruli.

TECHNICAL APPROACH

Patients with type I or II diabetes mellitus, age 18-65, with >0.5 grams of urine protein/24 hours, and a serum creatinine </= 2.0 mg/dl are eligible for enrollment. Renal tissue is obtained by percutanous kidney biopsy. Glomeruli are isolated by microdissection from one core of tissue and subjected to in situ reverse transciption. PCR is then performed using specific primers for each of the above mRNA sequences. Renal tissue is also processed for histology, immunofluorescence, and morphometry. Serum is obtained for P4 chemistry profile, lipid profile, and advanced glycosylation end-products (AGEs). Urine is collected for creatinine clearance, 24-hour protein excretion, and AGEs.

PRIOR AND CURRENT PROGRESS

A total of three patients have been enrolled and undergone biopsy in the entire study to date. Adequate tissue for isolation of glomeruli was obtained from two of the patients. There were no complications from the biopsy procedure in any subject. Histology analyis revealed evidence of diabetic nephropathy in all three cases. Samples of cDNA have been stored at -70 degrees C as well as under liquid nitrogen. PCR assays will be performed once a sample size of six subjects is obtained.

CONCLUSIONS

No conclusions can be drawn until a larger sample size is obtained and the quantitative PCR assays are completed.

REPORT DATE: 09/08/94 WORK UNIT # 1173

DETAIL SUMMARY SHEET

TITLE: Relationship of Heat Shock Protein expression to Proliferation in Mesangial Cells

KEYWORDS: heat shock, mesangium, proliferation

PRINCIPAL INVESTIGATOR: Popham, Sandy CPT MC
ASSOCIATES: Yuan, Christina MAJ MC; Carome, Michael MAJ M

DEPARTMENT: Department of Medicine
SERVICE: Nephrology Service

STATUS: Ongoing
APPROVAL DATE: Sep 1993

FUNDING: Current FY: $ 9,844 Previous FYs: $ 0 Total: $ 9,844

STUDY OBJECTIVE
To invetigate the effects of various cytokine growth factors on the expression of heat shock protein 70 (HSP70) in cultured mesangial cells.

TECHNICAL APPROACH
Mesangial cells will be maintained in tissue culture and exposed to heat shock to document their ability to upregulate HSP70 protein. After this is shown, the response of the cells and HSP70 protein levels to cytokine growth factors will be measured.

PRIOR AND CURRENT PROGRESS
Study results have shown that mesangial cells indeed produce HSP70 in response to heat shock. The growth curves of the heat-shocked and non-heat shocked cells have also been measured. PDGF (a proliferative cytokine) does not appear to affect the growth characteristics of either heat-shocked or non-heat-shocked cells.

CONCLUSIONS
Please see results above.

REPORT DATE: 02/28/94 WORK UNIT # 3011

DETAIL SUMMARY SHEET

TITLE: Comparison of Work of Breathing During Mechanical Ventilation Using Assist Control and Intermittent Mandatory Ventilation

KEYWORDS: work of breathing, mechanical ventilation, oxygen consumption (VO2)

PRINCIPAL INVESTIGATOR: Poropatich, Ronald MAJ MC
ASSOCIATES: Stoltzfus, Daniel MAJ MC

DEPARTMENT: Department of Medicine
SERVICE: Pulmonary & Critical Care Medicine Servi

STATUS: Completed
APPROVAL DATE: Feb 1991

FUNDING: Current FY: $ 697 Previous FYs: $ 0 Total: $ 697

STUDY OBJECTIVE

To determine whether the work of breathing is significantly different for patients receiving full ventilatory support with assist control versus intermittent mandatory ventilation.

TECHNICAL APPROACH

The study is a prospective, randomized, double blinded, two-period crossover design. Patients receiving mechanical ventilation will be randomly placed on one of the two modes of ventilation. Their VO2 will be measured by the metabolic cart. They will then be placed on the other mode and again have their VO2 measured. These VO2 values will be compared for the two modes. To ensure that there is no change in VO2 nonrespiratory during the study period, it will be measured at the beginning and end by adjusting the ventilator so that the patient makes no respiratory efforts, thus eliminating any respiratory component of VO2. Assuming these values are consistent, differences will be due to the work of breathing.

PRIOR AND CURRENT PROGRESS

One patient has been enrolled in this study, none during the past year. The study was terminated on 24 Aug 93 due to difficulty enrolling patients, technical errors in data collection, and excessive time necessary to complete a study (about 3 hours).

CONCLUSIONS

The study is technically difficult to perform with too great a range in data to draw any significant conclusions.

REPORT DATE: 03/15/94 WORK UNIT # 1707

DETAIL SUMMARY SHEET

TITLE: Relationship Between Respiratory Control Mechanisms and Nocturnal Desaturation in Diffuse Pulmonary Fibrosis

KEYWORDS: fibrosis, sleep, respiratory control

PRINCIPAL INVESTIGATOR: Rajagopal, Krishnan LTC MC
ASSOCIATES: Derderian, Sarkis LTC MC

DEPARTMENT: Department of Medicine
SERVICE: Pulmonary Disease Service

STATUS: Completed
APPROVAL DATE: Feb 1981

FUNDING: Current FY: $ 0 Previous FYs: $ 11,787 Total: $ 11,787

STUDY OBJECTIVE

To examine the relationship between respiratory control mechanisms and sleep desaturation in patients with pulmonary fibrosis.

TECHNICAL APPROACH

Patients with well-defined diffused pulmonary fibrosis will be included in the study, and their results will be compared to results from similar tests performed in a group of volunteer controls. Nocturnal polysomnography and hypercapnic ventilatory and occlusion pressure (P100) responses will be performed to quantitate respiratory control mechanisms and nocturnal desaturation. The SPSS statistical package will be used for evaluation of correlates and co-correlates.

PRIOR AND CURRENT PROGRESS

A total of 11 patients have been enrolled, none during this past year. This is an important study. Initial data has shown promising results that suggest that nocturnal hypoxemia can be predicted from daytime saturation and age. This study is now closed.

CONCLUSIONS

Nocturnal hypoxemia can be predicted reasonably well from daytime demographic and pulmonary function data.

REPORT DATE: 02/01/94 WORK UNIT # 1724

DETAIL SUMMARY SHEET

TITLE: Mechanisms of Hypoxia During Simulated Air Travel in Patients with Chronic Obstructive Pulmonary Disease

KEYWORDS: hypoxia, COPD, emphysema

PRINCIPAL INVESTIGATOR: Dillard, Thomas LTC MC
ASSOCIATES: Berg, Benjamin MAJ MC

DEPARTMENT: Department of Medicine
SERVICE: Pulmonary Disease Service

STATUS: Completed
APPROVAL DATE: Jan 1988

FUNDING: Current FY: $ 220 Previous FYs: $ 5,058 Total: $ 5,278

STUDY OBJECTIVE
To describe the hypoxic response to altitude simulation in COPD patients, to identify determinants, and to compare treatment modalities.

TECHNICAL APPROACH
The methods use hypobaric hypoxia to produce hypoxemia. Determinant variables are measured using pulmonary function tests at ground level and hypobaric hypoxia. Treatment with oxygen by two modes of delivery is evaluated at altitude conditions.

PRIOR AND CURRENT PROGRESS
A total of 18 COPD patients entered and completed this study, none during this past year. Data collection has been completed. No complications or adverse clinical sequelae were noted. A number of findings have been summarized in publications under this protocol. Other findings have yet to be reported.

CONCLUSIONS
Findings include: 1) arterial oxygen tension at altitude depends on oxygen tension and spirometry values at sea level; 2) pulse oximetry underestimates hypoxemia at altitude; 3) COPD patients travel by commercial jet often and without consulting their physicians; 4) 203 liters/minute of oxygen by nasal cannulae corrects hypoxemia at 8,000 feet; and 5) oxygen supplementation at altitude has beneficial hemodynamic effects in COPD patients.

REPORT DATE: 03/15/99 WORK UNIT # 1725

DETAIL SUMMARY SHEET

TITLE: Evaluation of Inspiratory Parameters in the Response to Inhaled Bronchodilators

KEYWORDS: inspiration, mechanics, bronchodilators

PRINCIPAL INVESTIGATOR: Rajagopal, Krishnan LTC MC

DEPARTMENT: Department of Medicine STATUS: Completed
SERVICE: Pulmonary Disease Service APPROVAL DATE: Feb 1988

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To examine the effects of improvement in inspiratory measures on the relief in symptoms following the use of bronchodilator medication in patients with airflow obstruction.

TECHNICAL APPROACH
Pulmonary function tests will be performed before and after the inhalation of bronchodilator medications in patients with airflow obstruction. Inspiratory parameters will be examined, and changes in these parameters will be correlated with changes in subjective symptoms.

PRIOR AND CURRENT PROGRESS
A total of 35 patients have been enrolled, 5 during the past year. Lack of technical support has been a problem. This project is now closed.

CONCLUSIONS
No conclusions.

REPORT DATE: 03/15/94 WORK UNIT # 1726

DETAIL SUMMARY SHEET

TITLE: Physiologic Assessment of Exercise Limitation in Upper Airway Obstruction

KEYWORDS: exercise, upper airway, lung mechanics

PRINCIPAL INVESTIGATOR: Rajagopal, Krishnan LTC MC
ASSOCIATES: Becker, Gregory CPT MC

DEPARTMENT: Department of Medicine
SERVICE: Pulmonary Disease Service

STATUS: Completed
APPROVAL DATE: Feb 1988

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To examine the role of inspiratory muscle function in the limitation of exercise function.

TECHNICAL APPROACH
Patients with well-defined upper airflow obstruction will have pulmonary function testing to determine resting inspiratory muscle function. Exercise testing will then be performed with monitoring of both inspiratory and expiratory airflow mechanics. The degree of inspiratory airflow reduction will be correlated with the degree of exercise limitation. Resting values will be used to derive predictors of exercise limitation.

PRIOR AND CURRENT PROGRESS
Five patients have completed the protocol, one during the past year. Since the necessary number of patients cannot be studied, the study will be terminated. Lack of technical support has been a major stumbling block.

CONCLUSIONS
None.

REPORT DATE: 01/14/94 WORK UNIT # 1736

DETAIL SUMMARY SHEET

TITLE: Treatment of Pulmonary Sarcoidosis with High Dose Inhaled Triamcinolone Acetonide

KEYWORDS: sarcoidosis, triamcinolone acetonide, therapy

PRINCIPAL INVESTIGATOR: Poropatich, Ronald MAJ MC
ASSOCIATES: Phillips, Yancy LTC MC

DEPARTMENT: Department of Medicine
SERVICE: Pulmonary Disease Service

STATUS: Ongoing
APPROVAL DATE: Jan 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To determine the efficacy of high dose inhaled triamcinolone acetonide compared with oral prednisone in the treatment of biopsy proven, symptomatic, pulmonary sarcoidosis with or without associated pulmonary symptoms.

TECHNICAL APPROACH

A prospective randomized double-blind, placebo-controlled study. Forty-four patients will be enrolled in the study and undergo laboratory evaluation comprised of biochemical testing and pulmonary function analysis, at initiation, and completion of the study period (duration 6 months). Monthly physician visits will be conducted to assess objective and subjective clinical response, monitor untoward side effects, and assess compliance with therapy. Three chest x-rays will be taken during the study period.

PRIOR AND CURRENT PROGRESS

Since January 1993, two additional patients have been enrolled in the study. To date, a total of 11 patients have been enrolled, with 10 completing the study. There have been no untoward side effects noted, and no patient withdrawals.

CONCLUSIONS

Preliminary results are encouraging in that all patients have improved under therapy. Since all results are still blinded, no conclusion can be made regarding the efficacy of high dose inhaled triamcinolone acetonide in the treatment of pulmonary sarcoidosis.

REPORT DATE: 02/15/94 WORK UNIT # 1737

DETAIL SUMMARY SHEET

TITLE: Predicting Exercise Responses in COPD Patients

KEYWORDS: exercise, COPD, emphysema

PRINCIPAL INVESTIGATOR: Dillard, Thomas MAJ MC
ASSOCIATES: Parker, Joseph MAJ MC

DEPARTMENT: Department of Medicine
SERVICE: Pulmonary Disease Service

STATUS: Completed
APPROVAL DATE: Feb 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To evaluate the accuracy of descriptive models for oxygen consumption and exercise ventilation in COPD patients. Descriptive models for these parameters were previously developed at WRAMC. These models use values from resting pulmonary function tests to predict the parameters at maximum exercise.

TECHNICAL APPROACH
Perform exercise testing of patients and measurement of resting lung function tests. Generate predicted values using previous descriptive models and compare to observed values using statistical methods.

PRIOR AND CURRENT PROGRESS
All anticipated collection of exercise and resting data under this protocol has been completed. A total of 66 patients have completed the protocol, none during this past year. Collected data has yet to be analyzed. No complications have resulted from this study. In the future, data analysis will evaluate the accuracy, precision, and bias of previously described descriptive models.

CONCLUSIONS
This study remains active in the data analysis phase after data collection.

REPORT DATE: 07/06/94 WORK UNIT # 1739

DETAIL SUMMARY SHEET

TITLE: VA Cooperative Study No. 316: Efficacy of Passive Immunization in the Prevention of Infection due to Klebsiella Pneumoniae and Pseudomonas Aeruginosa

KEYWORDS: antibody, Klebsiella, Pseudomonas

PRINCIPAL INVESTIGATOR: Eliasson, Arn MAJ MC

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Pulmonary Disease Service APPROVAL DATE: Jul 1990

FUNDING: Current FY: $ 520 Previous FYs: $ 0 Total: $ 520

STUDY OBJECTIVE
To determine the efficacy of a polyclonal antibody preparation in the prevention of bacteremia and sepsis from Klebsiella and Pseudomonas.

TECHNICAL APPROACH
Patients admitted to the intensive care units who are likely to stay longer than 3 days, and who are not felt to be immediately preterminal, will receive the antibody preparation or a placebo in the form of albumin infusion. Endpoints will include blood cultures, other clinical parameters of infection, and death. This is a multicenter study involving 16 medical centers and anticipates an enrollment of 16,000 patients. An addendum was approved in September 1992 for an increased dose of polyclonal antibody. In July 1993 the IND was transferred from OTSG sponsorship to Swiss Serum and Vaccine Institute.

PRIOR AND CURRENT PROGRESS
The focus of current progress is the ongoing enrollment of patients in this double-blinded randomized prevention of sepsis trial. To date, 65 patients have been enrolled at WRAMC, none this past year. Minimal side effects were noted; all have been minor.

CONCLUSIONS
Data analysis is being conducted, and all conclusions are being formulated at the study coordination center in VA Medical Center, West Haven, Connecticut. The next scheduled analysis of data is expected to occur in the summer of 1995.

REPORT DATE: 10/12/93 WORK UNIT # 1743

DETAIL SUMMARY SHEET

TITLE: Maximum Inspiratory Flow Rate as a Determinant of Maximum Voluntary Ventilation in Normal Patients and Patients with Obstructive Lung Disease

KEYWORDS: pulmonary disease, pulmonary function test

PRINCIPAL INVESTIGATOR: Hnatiuk, Oleh CPT MC
ASSOCIATES: Dillard, Thomas LTC MC; Kumke, Kevin CPT MC

DEPARTMENT: Department of Medicine
SERVICE: Pulmonary Disease Service

STATUS: Ongoing
APPROVAL DATE: Oct 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 660 Total: $ 660

STUDY OBJECTIVE

To examine the validity of previously developed methods for prediction of maximum voluntary ventilation (MVV) in normal patients and in patients with stable chronic obstructive pulmonary disease.

TECHNICAL APPROACH

Patients are recruited from the Pulmonary Disease Clinic based on results of prior pulmonary function tests. Testing protocol requires approximately 1 hour on one visit. Usual medications are maintained. Data collected include: height, weight, resting forced expiratory and inspiratory spirometry, maximum voluntary ventilation, peak airway pressures at the mouth, single breath diffusing capacity for carbon monoxide, oxygen saturation, and total lung capacity by dilution method.

PRIOR AND CURRENT PROGRESS

A total of 50 patients have been studied to date, 10 since the last report. Progress has been significantly slowed by staffing problems in the WRAMC PFT Laboratory. There have been no serious or unexpected adverse reactions associated with this study. Identification of eligible patients continues. There is no direct benefit to patients from this study, unless the primary physician requests the results.

CONCLUSIONS

None as yet.

REPORT DATE: 04/13/94 WORK UNIT # 1746

DETAIL SUMMARY SHEET

TITLE: Clinical Utility of Post-Thoracentesis Radiography

KEYWORDS: chest radiography, thoracentesis

PRINCIPAL INVESTIGATOR: Hnatiuk, Oleh MAJ MC
ASSOCIATES: Doyle, James CPT MC; Torrington, Kenneth LTC MC

DEPARTMENT: Department of Medicine
SERVICE: Pulmonary Disease Service

STATUS: Ongoing
APPROVAL DATE: Apr 1991

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To prospectively assess whether the routine use of post-thoracentesis chest radiography in asymptomatic patients without clinically apparent complications is warranted. The diagnostic utility of this practice has never been prospectively evaluated.

TECHNICAL APPROACH

Patients on the Medical Service undergoing thoracentesis are enrolled after thoracentesis is performed, and a procedure note is completed by the patients' ward physicians. A chest x-ray is then obtained and reviewed for evidence of pneumothorax. Once this is completed, the patient's chart is reviewed within 48 hours following thoracentesis to determine whether any complications have occurred. Also, the chart is reviewed to identify whether obtaining the chest x-ray altered clinical management.

PRIOR AND CURRENT PROGRESS

Data collection has stopped at 198 patients; 18 were enrolled during the past year. Analysis of data has begun. There were 10 pneumothoraces during the study, with 7 being suspected clinically and confirmed on immediate post-procedure film. They subsequently had chest tubes placed. In three cases of pneumothorax the complication was not suspected. The post-procedure film showed pneumothorax in two of these.

CONCLUSIONS

It would appear that the post-procedure film is useful in confirming clinical suspicion of PTX and providing grounds for placement of chest tubes. However, whether it changes clinical practice in unsuspected cases and whether it is cost effective overall are still being evaluated. A decision will have to be made whether to add more patients to the study, after consulting statisticians.

REPORT DATE: 09/28/94 WORK UNIT # 1749

DETAIL SUMMARY SHEET

TITLE: Air Transport of Patients with Pulmonary Defects

KEYWORDS: altitude, hypoxia, emphysema

PRINCIPAL INVESTIGATOR: Torrington, Kenneth COL MC
ASSOCIATES: Phillips, Yancy LTC MC; Knutsen, Sara CPT MC

DEPARTMENT: Department of Medicine
SERVICE: Pulmonary Disease Service

STATUS: Ongoing
APPROVAL DATE: Sep 1991

FUNDING: Current FY: $ 1,507 Previous FYs: $ 155 Total: $ 1,662

STUDY OBJECTIVE

Hypotheses: Hypoxic gas inhalation at ground level produces arterial oxygen tension (AOT) comparable to acute altitude exposure in patients with abnormal lung function under conditions isobaric for oxygen partial pressure. AOT during normobaric and hypobaric hypoxia correlates with and may be predicted from pulmonary function tests and blood gases on room air at ground level before exposure. AOT on oxygen supplementation at altitude correlates with ground level values.

TECHNICAL APPROACH

The protocol will follow the following procedures: measurement of barometric pressure; insertion of arterial catheter into the radial artery; monitoring of blood pressure and pulse oximetery continuously; sampling arterial blood for blood gas tensions and co-oximetery; exposure of subjects to 15% oxygen; ascent to simulated altitude conditions of 8000 feet using hypobaric chamber; sampling of arterial blood gases; addition of oxygen supplementation; and sampling of arterial blood gases. One minute of step-test exercise will be performed on four occasions, followed by sampling of arterial blood gases.

PRIOR AND CURRENT PROGRESS

To date, 33 subjects have been enrolled, 0 during the past year. There have been no serious or unexpected adverse reactions. An article was submitted for publication to the Journal of Aviation, Space, and Environmental Medicine. An abstract was published during the past year, dealing with the impact that exercise at altitude has among individuals with pulmonary disease. No previous publications have documented such data within this patient population at altitude conditions.

CONCLUSIONS

Patients often experience profound hypoxemia during minimal exertion while at altitude. This hupoxemia may exceed the recommended levels for supplemental oxygen. It has been also demonstrated that the degree of hypoxemia correlates with a few sea level parameters: PaO2, FEV1, and FVC.

REPORT DATE: 11/08/93 WORK UNIT # 1751

DETAIL SUMMARY SHEET

TITLE: Postoperative Pulmonary Changes Following Laparoscopic vs. Right Subcostal Cholecystectomy

KEYWORDS: postoperative spirometry, cholecystectomy

PRINCIPAL INVESTIGATOR: Torrington, Kenneth LTC MC
ASSOCIATES: Bilello, John MAJ MC; Hopkins, Terry SSG CRTT

DEPARTMENT: Department of Medicine
SERVICE: Pulmonary Disease Service

STATUS: Completed
APPROVAL DATE: Nov 1991

FUNDING: Current FY: $ 1,154 Previous FYs: $ 0 Total: $ 1,154

STUDY OBJECTIVE

To compare postoperative pulmonary changes following cholecystectomy performed with two different surgical methods: laparoscopic cholecystectomy (LC) versus right subcostal cholecystectomy (RSC).

TECHNICAL APPROACH

Volunteers scheduled for cholecystectomy will be enrolled to compare preoperative with postoperative spirometry, chest x-rays, and arterial blood gases. The plan is to compare the traditional surgical method, RSC, with the recently introduced high tech method, LC. The original protocol has not been modified, but in 1992 the investigators found that very few Walter Reed Army Medical Center patients were operated on using RSC.

PRIOR AND CURRENT PROGRESS

The study has bee completed. Of 26 subjects enrolled between 13 Jan and 21 Sep 92, one withdrew because of postoperative pain and nausea. A total of 25 volunteers completed the protocol: 24 undergoing LC and only 1 undergoing RSC. Comparison was therefore impossible. No complications resulted from participation in the protocol. The study was presented in poster format at the 1993 American Lung Association/American Thoracic Society International Conference, May 16-19, 1993, San Francisco, CA, and was published in abstract in the American Review of Respiratory Disease.

CONCLUSIONS

LC causes a variety of postoperative pulmonary changes including abnormalities on pulmonary physical examination (21%), very mild temperature elevation (>90%), chest radiographic changes of atelectasis or right pleural effusion (35%), minimally increased arterial pH, and approximately 20% reduction if FVC and FEV1. The changes are sufficiently small that all but the most severely impaired pulmonary patients should be able to tolerate surgery with low risk.

REPORT DATE: 02/04/94 WORK UNIT # 1752

DETAIL SUMMARY SHEET

TITLE: Eucapnic Voluntary Hyperventilation as a Bronchoprovocation Technique: Comparison with Methacholine Inhalation in Asthmatics

KEYWORDS: bronchoprovocation, airway hyperreactivity, asthma

PRINCIPAL INVESTIGATOR: Hurwitz, Kenneth CPT MC
ASSOCIATES: Phillips, Yancy COL MC

DEPARTMENT: Department of Medicine
SERVICE: Pulmonary Disease Service

STATUS: Ongoing
APPROVAL DATE: Feb 1992

FUNDING: Current FY: $ 673 Previous FYs: $ 1,339 Total: $ 2,012

STUDY OBJECTIVE

To compare the sensitivity of eucapnic voluntary hyperventilation (EVH) to methacholine inhalation challenge (MIC) in asthmatic subjects. In addition, the effect of presenting these tests in sequence will be examined, and the results of these challenges will be correlated with symptoms, serum immunoglobulin E level, and serum eosinophil count.

TECHNICAL APPROACH

This study is a randomized, prospective crossover trial. There have been no modifications to the original protocol. Subjects will complete a pulmonary questionnaire; have blood drawn for serum IgE level, serum eosinophil count, serum caffeine, and serum theophylline level; and then undergo bronchoprovocation challenge testing with either eucapnic voluntary hyperventilation (EVH) followed by methacholine inhalation challenge (MIC) or MIC followed by EVH. They will then return on a subsequent day and undergo the challenges in the reverse order. A protocol addendum was approved 03 Aug 93 to allow a change in test sequence.

PRIOR AND CURRENT PROGRESS

Sixteen subjects were studied in the initial phase, none during the past year. Each underwent both eucapnic voluntary hyperventilation (EVH) and methacholine challenge (MIC) without complication. The data were separated into two components: 1) correlation between initial EVH and MIC; and 2) evaluation of refractory effects between serial challenges. Presentations of both components have been made at regional and national meetings, and manuscripts are in press. The protocol was modified with DCI approval to allow two MIC's on the first day of testing, followed by EVH and MIC on the second day in a subset of subjects highly sensitive to MIC. Further enrollment continues in this phase to further evaluate the refractory effects of serial challenges.

CONCLUSIONS

EVH and MIC have similar sensitivity in asthmatics. EVH correlates better with symptoms, while MIC relates better to serum IgE levels. The degree of response to EVH correlates with the quantitative response to MIC. In addition, a refractory pattern was found, in that MIC blunted the response to a subsequent EVH. THe converse was true only in subjects highly sensitive to MIC.

REPORT DATE: 06/08/94 WORK UNIT # 1753

DETAIL SUMMARY SHEET

TITLE: Accuracy of Predicted Normal Values in Clinical Spirometry

KEYWORDS: spirometry, height, prediction equations

PRINCIPAL INVESTIGATOR: Parker, Joseph MAJ MC
ASSOCIATES: Dillard, Thomas LTC MC; Phillips, Yancy COL MC

DEPARTMENT: Department of Medicine
SERVICE: Pulmonary Disease Service

STATUS: Completed
APPROVAL DATE: Jun 1992

FUNDING: Current FY: $ 136 Previous FYs: $ 1,364 Total: $ 1,500

STUDY OBJECTIVE

To assess the impact of using a subject's stated normal height versus their measured height on the calculation of predicted normal values for spirometry and on the clinical interpretation of spirometry, and to evaluate the current practices of PFT labs in the Washington, D.C. area.

TECHNICAL APPROACH

Patients referred for spirometry will be evaluated by first asking subjects their height and then measuring their height and arm span. Each subject's predicted normal values for FVC and FEV1 will then be calculated using both stated and measured height. A postal survey of local civilian and military PFT labs will be conducted to determine current practices regarding ascertainment of height.

PRIOR AND CURRENT PROGRESS

A total of 210 subjects were enrolled. A survey of local PFT labs (civilian and military) yielded 25 responders. Data collection has been completed. A manuscript has been completed and accepted for publication by the Am J Resp Dis and Crit Care Med.

CONCLUSIONS

A significant proportion of the time (40%), community PFT labs stated height instead of measured height. Stated height is frequently greater than measured height (5.7 cm mean difference in the oldest age group), particularly in an older age range. These differences produce significant differences in predicted normal values which can cause errors in the interpretation of screening spirometry.

REPORT DATE: 06/20/94 WORK UNIT # 1754

DETAIL SUMMARY SHEET

TITLE: The Effects of Buspirone on Respiraton in Asthma Patients

KEYWORDS: buspirone, asthma, respiration

PRINCIPAL INVESTIGATOR: Kumke, Kevin, CPT MC
ASSOCIATES: Derderian, Sarkis LTC MC; Hamm, Carolyn PhD

DEPARTMENT: Department of Medicine
SERVICE: Pulmonary Disease Service

STATUS: Completed
APPROVAL DATE: Jun 1992

FUNDING: Current FY: $ 2,856 Previous FYs: $ 6,931 Total: $ 9,787

STUDY OBJECTIVE
To examine the effect of the antianxiety medication buspirone on respiration.

TECHNICAL APPROACH
The effect of buspirone on respiration in outpatient asthmatics will be evaluated in a double-blind, randomized, crossover fashion. This evaluation will include a series of three overnight polysomnograms and three central respiratory control evaluations. The central respiratory control studies will measure patient response to changes in airway resistance, carbon dioxide, and hypoxia.

PRIOR AND CURRENT PROGRESS
There have been 154 patients enrolled in this study (one during the past year); 14 have completed the study. There have been no serious or unexpected adverse reactions. One patient was withdrawn due to comlaints of dizziness while on buspirone. The dizziness was resolved when the medication was discontinued. Prior studies involving buspirone have reported a 9% incidence of dizziness. Analysis of the overnight polysomnograms has been completed. The central respiratory control data is presently being evaluated. No further data collection is planned.

CONCLUSIONS
Buspirone increases the mean latency to REM sleep but does not significantly alter sleep efficiency or the percent of sleep stages in stable asthmatics with severe chronic air flow obstruction. Buspirone does not precipitate or aggravate sleep disordered respiratory events in stable asthmatics.

REPORT DATE: 12/02/93 WORK UNIT # 1758

DETAIL SUMMARY SHEET

TITLE: Withholding and Withdrawing Life-Sustaining Treatment from Patients in the Intensive Care Unit

KEYWORDS: withdrawal of care, critical care

PRINCIPAL INVESTIGATOR: Parker, Joseph CPT MC

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Pulmonary Disease Service APPROVAL DATE: Dec 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To evaluate current practices regarding withdrawal/withholding of life-support in the intensive care settin.

TECHNICAL APPROACH
This will be a prospective analysis of patients who have life-sustaining care withheld or withdrawn. Questionnaires will be sent to medical teams, and to patients/patients' families to determine attitudes and perspectives of the differing groups during withdrawal of care.

PRIOR AND CURRENT PROGRESS
To date, 31 patients have been enrolled. Data collection is still in progress.

CONCLUSIONS
No conclusions have been reached to date.

REPORT DATE: 01/14/94 WORK UNIT # 1759

DETAIL SUMMARY SHEET

TITLE: Postoperative Pulmonary Changes Following Video Assisted Thoracic Surgery versus Lateral Thoracotomy

KEYWORDS: postoperative, pulmonary changes, VATS

PRINCIPAL INVESTIGATOR: Torrington, Kenneth LTC MC
ASSOCIATES: Adebonojo, Samuel LTC MC; Hall, Edward

DEPARTMENT: Department of Medicine
SERVICE: Pulmonary Disease Service

STATUS: Ongoing
APPROVAL DATE: Jan 1993

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

1) To assess the severity and duration of postoperative pulmonary changes (measured by spirometry, ABG's, and chest x-ray) following video assisted thoracic surgery (VATS); and 2) to compare changes following VATS to changes following lateral thoracotomy (LT).

TECHNICAL APPROACH

All adult patients undergoing thoracic surgical procedures (pleural or lung biopsy, diagnosis of solitary pulmonary nodules, wedge resection of metastatic nodules, resection of blebs and/or pleurodesis for spontaneous pneumothorax, and mediastinal lymph node biopsy) performed either by VATS or LT, will be invited to participate in this study of preoperative, 24-hour postoperative, and 48-hour postoperative testing with spirometry, ABG's, and chest x-rays. The study will not affect patient care.

PRIOR AND CURRENT PROGRESS

Two patients have completed the protocol. A number of others were enrolled, but they were lost from the protocol when cancellation and rescheduling of surgery (caused by operating room limitations) interfered with respiratory therapy follow-up.

CONCLUSIONS

The study remains important and worthwhile. Efforts will be renewed to enroll patients and to ensure that enrolled patients complete the protocol, despite frequent and unannounced changes in the operating room schedule.

REPORT DATE: 03/14/94 WORK UNIT # 1760

DETAIL SUMMARY SHEET

TITLE: The Utility of Capnography and Transcutaneous Capnometry in the Evaluation of Airflow Obstruction and Gas Exchange in Obstructive Lung Disease

KEYWORDS: capnography, spirometry, obstructive lung disease

PRINCIPAL INVESTIGATOR: Lepler, Lawrence CPT MC
ASSOCIATES: Rayburn, Dan PhD

DEPARTMENT: Department of Medicine
SERVICE: Pulmonary Disease Service

STATUS: Ongoing
APPROVAL DATE: Mar 1993

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To correlate capnographic pattern with spirometry in patients with obstructive lung disease.

TECHNICAL APPROACH
Patients breathe through capnometer prior to spirometry. There has been no change in protocol.

PRIOR AND CURRENT PROGRESS
Nine patients have been studied. Preliminary results suggest negative correlation between the slope of Phase III of the capnograph and forced expiratory volume (FEV). There were no adverse reactions, and no patients withdrew. There were no benefits to the patients.

CONCLUSIONS
None as yet.

REPORT DATE: 07/27/94 WORK UNIT # 1761

DETAIL SUMMARY SHEET

TITLE: Adherence to Established Guidelines for Preoperative Pulmonary Function Testing

KEYWORDS: preoperative, pulmonary, function testing

PRINCIPAL INVESTIGATOR: Hnatiuk, Oleh MAJ MC

DEPARTMENT: Department of Medicine
SERVICE: Pulmonary Disease Service

STATUS: Completed
APPROVAL DATE: Jul 1993

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To determine the percentage of preoperative spirometries performed at WRAMC's Pulmonary Function Laboratory that do not meet the American College of Physicians' (ACP) guidelines, and to characterize why these requests are being generated.

TECHNICAL APPROACH

Screening spirometries performed by WRAMC's Pulmonary Function Laboratory will be sampled over a 4-week period.

PRIOR AND CURRENT PROGRESS

A total of 441 screening spirometries were sampled; 138 (31%) of these were done preoperatively (complete data was available in 135 cases). Patients in the analyzed group had a mean age of 59 years. A total of 52 requests (39%) did not meet ACP guidelines; the majority of these requests were associated with either normal spirometry (n=34) or only mild spirometric abnormalities (n=14). Spirometry revealed severe obstruction in only one case when the request was not indicated. Most of the patients had been referred because of age greater than 70, morbid obesity, or a history of smoking. There were no known complications.

CONCLUSIONS

Stricter adherence to the ACP guidelines is recommended as a means of decreasing the number and cost of unnecessary spirometries being performed.

REPORT DATE: 09/18/94 WORK UNIT # 1762

DETAIL SUMMARY SHEET

TITLE: Determination of Bronchoalveolar Lavage Volume Required for Diagnosis of Pneumocystis Carinii Pneumonia in Immunocompromised Patients

KEYWORDS: bronchoalveolar lavage, HIV infection, Pneumocystis carinii

PRINCIPAL INVESTIGATOR: Torrington, Kenneth LTC MC
ASSOCIATES: Finelli, Maria MT

DEPARTMENT: Department of Medicine
SERVICE: Pulmonary Disease Service

STATUS: Completed
APPROVAL DATE: Sep 1993

FUNDING: Current FY: $ 779 Previous FYs: $ 0 Total: $ 779

STUDY OBJECTIVE

To determine whether low volume bronchoalveolar lavage (BAL) can accurately diagnose Pneumocystis carinii pneumonia (PCP) in immunocompromised patients with symptoms and signs of pulmonary infection.

TECHNICAL APPROACH

During diagnostic BAL, samples from the initial lavage specimen will be compared to the final and aggregate specimens. Specimens will be analyzed for Pneumocystis carinii organisms using immunofluorescence and modified Giemsa techniques.

PRIOR AND CURRENT PROGRESS

Samples were used from 25 patients. The data collection phase of the study has been completed since the protocol was written. The data was presented in poster form at the 1994 American Thoracic Society/American Lung Association International Meeting in Boston in May, 1994. An abstract has been published, and a manuscript has been accepted by the journal, "Chest". The PI is waiting for final approval of the revised version.

CONCLUSIONS

Small volume (60 ml) BAL accurately diagnoses PCP in HIV infected patients with acute pulmonary infections. The use of small volume BAL will help avert complications during or after bronchoscopy procedures in this group of ill patients.

REPORT DATE: 09/09/94 WORK UNIT # 1763

DETAIL SUMMARY SHEET

TITLE: Airway Hyperreactivity in Rheumatoid Arthritis

KEYWORDS: rheumatoid arthritis, airway hyperreactivity

PRINCIPAL INVESTIGATOR: Doyle, James CPT MC
ASSOCIATES: Eliasson, Arn LTC MC; Dennis, Gregory COL MC

DEPARTMENT: Department of Medicine
SERVICE: Pulmonary Disease Service

STATUS: Ongoing
APPROVAL DATE: Sep 1993

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To determine whether there is an increased incidence of airway hyperreactivity (AHR) in patients with rheumatoid arthritis. This will be accomplished through evaluation of their responses to eucapnic voluntary hyperventilation (EVH) with room temperature gas and methacholine inhalation challenge (MIC).

TECHNICAL APPROACH

Apprimately 25 volunteers will be enrolled from WRAMC's Rheumatology Clinic with recently diagnosed and untreated rheumatoid arthritis. Patients will be evaluated for the activity of their RA through physical examination, completion of an RA symptom questionnaire, and laboratory testing. They will then complete an asthma symptoms questionnaire and undergo pulmonary evaluation to include chest x-ray, full PFTs with ABG, post bronchodilator PFTs, methacholine challenge, and eucapnic voluntary hyperventilation. A 20% drop in FEV1 during MIC or a 10% drop after EVH will be considered diagnostic of airway hyperreactivity. The incidence of AHR will be compared to that of the general population.

PRIOR AND CURRENT PROGRESS

To date, nine patients have been enrolled and completed the study. Two of the patients exhibited airway hyperreactivity on testing. One had a positive MIC, and the other had both a positive MIC and EVH. Only one patient had previously been symptomatic. There have been no adverse reactions, and no specific benefit for any patients.

CONCLUSIONS

It is too early to meaningfully interpret the data, but so far there is a trend towards increased AHR in patients with asthma. A preliminary review of the data will be performed after 15 patients have been enrolled.

REPORT DATE: 08/31/94 WORK UNIT # 1764

DETAIL SUMMARY SHEET

TITLE: Eucapnic Voluntary Hyperventilation (EVH) as a Bronchoprovocation Technique: An Analysis of the Late Phase Response After EVH in Asthmatics

KEYWORDS: asthma, hyperventilation, late phase response

PRINCIPAL INVESTIGATOR: Argyros, Gregory MAJ MC
ASSOCIATES: Hurwitz, Kenneth CPT MC; Eliasson, Arn LTC MC

DEPARTMENT: Department of Medicine
SERVICE: Pulmonary Disease Service

STATUS: Ongoing
APPROVAL DATE: Sep 1993

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To determine if there is a late phase response (LPF) after eucapnic voluntary hyperventilation challenge in asthmatics, and if the LPR is associated with an increase in nonspecific airway hyperreactivity.

TECHNICAL APPROACH

Subjects will come to the Pumonary Clinic on 5 consecutive days and perform eucapnic voluntary hyperventilation each day. On the first and fifth days of testing, a methacholine challenge will be performed 2 hours after completion of the hyperventilation challenge. The researchers will be looking for a change in the bronchoconstrictive response to hyperventilation challenge throughout the week, as well as a change in airway hyperreactivity as manifested by a change in response to methacholine challenge on Day 5 versus Day 1.

PRIOR AND CURRENT PROGRESS

None, due to the PI's Critical Care fellowship requirements. The study will begin this fiscal year.

CONCLUSIONS

None, thus far.

REPORT DATE: 03/10/94 WORK UNIT # 9280

DETAIL SUMMARY SHEET

TITLE: Sleep and Respiratory Control in Kyphoscoliosis

KEYWORDS: sleep, kyphoscoliosis, nocturnal oxygenation

PRINCIPAL INVESTIGATOR: Derderian, Sarkis LTC MC
ASSOCIATES: Rajagopal, Krishnan LTC MC; Phillips, Yancy LTC MC

DEPARTMENT: Department of Medicine
SERVICE: Pulmonary Disease Service

STATUS: Completed
APPROVAL DATE: Feb 1990

FUNDING: Current FY: $ 2,249 Previous FYs: $ 2,535 Total: $ 4,784

STUDY OBJECTIVE

To describe the hypercapnic and hypoxic rebreathing responses in kyphoscoliosis and to correlate these respiratory changes with the severity of the spinal deformity, as well as the frequency and severity of nocturnal oxygen desaturations as assessed by standard nocturnal polysomnography.

TECHNICAL APPROACH

Patients between 18 and 60 years of age without airflow limitations, or other disorders affecting respiratory function, will be selected using Cobb's Angle to determine the severity of kyphoscoliosis as mild, moderate, or severe. Each participant will be administered tests of full pulmonary function, arterial blood gas analysis, comprehensive rebreathing under hypoxic and hypercapnic conditions, and nocturnal polysomnography. Results will be compared recording the severity of the disease.

PRIOR AND CURRENT PROGRESS

Only one patient has been enrolled in this study; none have been enrolled during the past 2 years. The study was kept open this past year because the new Chief of the Scoliosis Clinic had expressed an interest in collaborating on the protocol, and felt that he would be able to recruit patients through the clinic. However, the PI has decided to close the study.

CONCLUSIONS

None.

REPORT DATE: 05/19/94 WORK UNIT # 3704

DETAIL SUMMARY SHEET

TITLE: Iontophoresis Therapy for Rheumatoid Arthritis

KEYWORDS: iontophoresis, rheumatoid arthritis

PRINCIPAL INVESTIGATOR: Klipple, Gary COL MC
ASSOCIATES: Mewshaw, Betsy RN, MSN

DEPARTMENT: Department of Medicine
SERVICE: Rheumatology Service

STATUS: Terminated
APPROVAL DATE: Apr 1989

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To evaluate the efficacy and safety of an iontophoretic drug delivery system in the treatment with corticosteroids of synovitis of the hand and wrist joints in patients with rheumatoid arthritis.

TECHNICAL APPROACH
Patients with rheumatoid arthritis with active synovitis of the hand joints are randomized to receive corticosteroids into the affected joints with injection of iontophoresis or to receive sham injection of iontophoresis using normal saline.

PRIOR AND CURRENT PROGRESS
This research protocol has been administratively terminated.

CONCLUSIONS
This research protocol has been administratively terminated.

REPORT DATE: 05/19/94 WORK UNIT # 3705

DETAIL SUMMARY SHEET

TITLE: Iontophoresis Therapy for Osteoarthritis

KEYWORDS: iontophoresis, osteoarthritis

PRINCIPAL INVESTIGATOR: Klipple, Gary COL MC
ASSOCIATES: Mewshaw, Betsy RN MSN

DEPARTMENT: Department of Medicine
SERVICE: Rheumatology Service

STATUS: Terminated
APPROVAL DATE: Apr 1989

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To evaluate the efficacy and safety of an iontophoretic drug delivery system in the treatment with corticosteroids of synovitis of the hand and wrist joints in patients with osteoarthritis.

TECHNICAL APPROACH
Patients with osteoarthritis with synovitis of the hand joints are randomized to receive corticosteroids into the affected joints with injection of iontophoresis or to receive sham injection of iontophoresis using normal saline.

PRIOR AND CURRENT PROGRESS
This research protocol has been administratively terminated.

CONCLUSIONS
This research study has been administratively terminated.

REPORT DATE: 05/19/94 WORK UNIT # 3706

DETAIL SUMMARY SHEET

TITLE: Iontophoresis Therapy for Bursitis and Tendinitis

KEYWORDS: iontophoresis, bursitis, tendinitis

PRINCIPAL INVESTIGATOR: Klipple, Gary COL MC
ASSOCIATES: Mewshaw, Betsy RN MSN

DEPARTMENT: Department of Medicine
SERVICE: Rheumatology Service

STATUS: Terminated
APPROVAL DATE: Apr 1989

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To evaluate the efficacy and safety of an iontophoretic drug delivery system in the treatment with corticosteroids of synovitis, bursitis, and tendinitis.

TECHNICAL APPROACH
Patients with bursitis and tendinitis are randomized to receive corticosteroids into the affected musculoskeletal area with injection of iontophoresis or to receive sham injection of iontophoresis using normal saline.

PRIOR AND CURRENT PROGRESS
This research protocol has been administratively terminated.

CONCLUSIONS
This research protocol has been administratively terminated.

REPORT DATE: 09/12/94 WORK UNIT # 3707

DETAIL SUMMARY SHEET

TITLE: A Study of Autoantibiodies to Neutrophil Integrin Proteins in Patients with Rheumatoid Arthritis

KEYWORDS: autoantibodies, rheumatoid arthritis, integrins

PRINCIPAL INVESTIGATOR: Hartman, Kip MAJ MC
ASSOCIATES: Wright, Daniel COL MC; Klipple, Gary COL MC

DEPARTMENT: Department of Medicine
SERVICE: Rheumatology Service

STATUS: Completed
APPROVAL DATE: Aug 1990

FUNDING: Current FY: $10,763 Previous FYs: $ 11,644 Total: $ 22,407

STUDY OBJECTIVE

To determine the incidence of autoantibodies to the neutrophil adhesion glycoproteins CD11b/CD18 in patients with rheumatoid arthritis, and to investigate the correlation of these autoantibodies with the occurrence of infections.

TECHNICAL APPROACH

After consent, patients seen in the Rheumatology Clinic with the diagnosis of rheumatoid arthritis will be given a questionnaire, followed by a physician interview, and a physical examination. Blood will be collected and sera evaluated for anti-neutrophil antibody activity by immunofluorescent flow cytometry; specific anti-CD11b/CD18 reactivity will be studied in an immunobead antigen capture assay. Sera positive for antibodies to these adhesion proteins will be further evaluated for effects on neutrophil adhesion and opsonin receptor functions.

PRIOR AND CURRENT PROGRESS

No new subjects were enrolled in the study during the past year. A total of 22 subjects were enrolled during the entire study. There were no adverse reactions, no patients withdrew from the study, and there has been no benefit to the patients. The study is now closed to new registrants.

CONCLUSIONS

The incidence of positive anti-neutrophil antibody assay results was less than expected in the group of sera studied. None of the sera studied were found to contain antibodies to neutrophil integrin proteins.

REPORT DATE: 11/15/93 WORK UNIT # 3710

DETAIL SUMMARY SHEET

TITLE: Effects of Anti-IgD-dextran Conjugates on Human B Lymphocyte Antibody Production

KEYWORDS: B lymphocyte, antibody, humoral immunity

PRINCIPAL INVESTIGATOR: Dennis, Greg LTC MC
ASSOCIATES: Katona, Ildy CAPT MC

DEPARTMENT: Department of Medicine
SERVICE: Rheumatology Service

STATUS: Ongoing
APPROVAL DATE: Nov 1991

FUNDING: Current FY: $ 7,712 Previous FYs: $ 12,383 Total: $ 20,095

STUDY OBJECTIVE

To examine the effects of anti-IgD-dextran conjugates on human B lymphocyte expression of B cell activation markers and adhesion molecules, and to examine the effects of anti-IgD-dextran conjugates on human B lymphocyte proliferation and antibody production in the presence or absence of lymphokines.

TECHNICAL APPROACH

Elutriated B cell-enriched fraction will be used as a cell source. B or T cells will be further purified by a negative selection method. Cell surface antigens will be determined by a fluorescence activated cell sorter. Antibody production will be measured by ELISA. In vitro lymphokine production by B or T cells will be measured by ELISA.

PRIOR AND CURRENT PROGRESS

In vitro stimulation with anti-delta-dex or anti-u lead to increased expression of LFA1, HLA-DR, CD20, and IL-2R on B cells and enhanced expression of HLA-DR on T cells cocultured with B cells. These changes are maximal at 72 hours. The increased expression of HLA-DR on T cells that follows B cell activation is dependent on cell contact and can be abolished when physical contact between the B and T cells is prevented with a cell culture chamber insert. T cells cultured without B cells but in the presence of anti-delta-dex or anti-u do not exhibit an increase in HLA-DR expression. Currently, the researchers are investigating the ligand-receptor pair responsible for this interaction. Preliminary data indicates that a monoclonal antibody to the B cell surface antigen B7 (BB-1) is able to partially block the observed T cell changes.

CONCLUSIONS

Activated human B cells exhibit increased expression of HLA-DR, LFA1, CD20, and IL-2R. These activated B cells are able to interact with T cells and induce them to express histocompatibility class II molecules. This interaction is contact-dependent, and the B7 antigen seems to play an important role in its manifestation.

REPORT DATE: 09/19/94 WORK UNIT # 3711

DETAIL SUMMARY SHEET

TITLE: Lymphocyte Abnormalities in Patients with Systemic Lupus Erythematosus

KEYWORDS: SLE, lymphocyte

PRINCIPAL INVESTIGATOR: Tsokos, George MAJ MC

DEPARTMENT: Department of Medicine
SERVICE: Rheumatology Service

STATUS: Completed
APPROVAL DATE: Oct 1991

FUNDING: Current FY: $27,420 Previous FYs: $ 47,063 Total: $ 74,483

STUDY OBJECTIVE
To study signal transduction abnormalities in lymphocytes from patients with systemic lupus erythematosus (SLE). Specifically, do T-lymphocytes from patients with SLE have altered mitogen-induced intracellular free calcium responses, and do T-cells from patients with SLE have altered mitogen-induced phosphoinositol metabolism?

TECHNICAL APPROACH
Lymphocytes are obtained from peripheral blood mononuclear cells (MNC) by gradient centrifugation. T-cell clones are established and characterized. Signal transduction studies are performed in both fresh T-lymphocytes and T-cell lines.

PRIOR AND CURRENT PROGRESS
Eight more patients were studied this year; the total number studied is 42. There were no serious or unexpected adverse reactions. The major accomplishments of this protocol are the discoveries that: 1) T lymphocytes from patients with SLE have increased Ca2+ responses after stimulation with an anti-CD3 mAb (CD4+ cells exhibit higher responses); 2) incubation of lymphocytes with fatty acids diminished the heightened Ca2+ responses; and 3) T cell clones from patients with SLE help autologous B cells produce anti-DNA antibodies.

CONCLUSIONS
T cells from patients with SLE have definite signal transduction abnormalities that may contribute to the pathogenesis of the disease.

REPORT DATE: 05/13/94 WORK UNIT # 3712

DETAIL SUMMARY SHEET

TITLE: Autoreactive T Lymphocytes in the Pathogenesis of Systemic Sclerosis

KEYWORDS: systemic sclerosis, T-cell, autoimmunity

PRINCIPAL INVESTIGATOR: Tsokos, George MAJ MC
ASSOCIATES: Sfikakis, Peter MD

DEPARTMENT: Department of Medicine
SERVICE: Rheumatology Service

STATUS: Ongoing
APPROVAL DATE: May 1992

FUNDING: Current FY: $11,855 Previous FYs: $ 35,816 Total: $ 47,671

STUDY OBJECTIVE

To determine the frequency of hypoxanthine phosphoribosyltransferase (HPRT) gene mutated T-cells in the peripheral blood of patients with systemic sclerosis, and to determine whether HPRT gene mutated T-cell clones derived from patients with systemic sclerosis demonstrate reactivity to the presumed scl-70 autoantigen.

TECHNICAL APPROACH

This is a one-time blood drawing study. Isolate T-cells from the peripheral blood of patients with systemic sclerosis. Use a clonal assay to determine the frequency of HPRT gene mutated T-cells. Expand in vitro T-cell clones. Test their ability to proliferate in the presence of the scl-70 antigen.

PRIOR AND CURRENT PROGRESS

HPRT-mutated T-cells occur more frequently in the peripheral blood of patients with systemic sclerosis; this increase correlates with disease activity and duration. HPRT-mutated clones responded to the presumptive autoantigen scl-10, but wild clones did not. These results support the theory that continuous stimulation of T-cells in vivo by an autoantigen may lead to the expansion of pathogenic T-cells. Seven patients were enrolled this past year; 20 patients have been studied so far. There is no benefit to the patients, and no side effects were noted.

CONCLUSIONS

Continuous autoantigenic stimulation may lead to expansion of autoimmune cells and clinical manifestations.

REPORT DATE: 05/21/94 WORK UNIT # 3713

DETAIL SUMMARY SHEET

TITLE: Antiphospholipid Antibody Syndrome (APAS): Role of Antiphospholipid Antibodies (APLA) and B2-glycoprotein (gp)-I in the Clinical Manifestations of APAS

KEYWORDS: antiphospholipid, B2-glycoprotein-I, thrombosis

PRINCIPAL INVESTIGATOR: Tesar, Joseph MD DAC
ASSOCIATES: Klipple, Gary COL MC; Tsokos, George MAJ MC

DEPARTMENT: Department of Medicine
SERVICE: Rheumatology Service

STATUS: Ongoing
APPROVAL DATE: May 1992

FUNDING: Current FY: $ 5,537 Previous FYs: $ 14,220 Total: $ 19,757

STUDY OBJECTIVE

To define the relationship of antiphospholipid antibody (APLA) and B2-glycoprotein-I to clinical manifestations of arterial and venous thrombosis, platelet aggregation, thrombocytopenia, and livedo reticularis in patients with systemia lupus erythematosis (SLE) and other connective tissue disorders.

TECHNICAL APPROACH

The study is a prospective, randomized investigation of patients with SLE, other connective tissue disorders, and control subjects. Each patient's serum will be tested for APLA, ANA, Ds DNA, VDRL, lupus anticoagulant, and complement and immune complexes. All pertinent clinical manifestations will be dated and recorded. The enhancement (if any) of APLA binding to phospholipids by B2-glycoprotein will be determined in the first phase of the study.

PRIOR AND CURRENT PROGRESS

A total of 253 subjects have been enrolled (213 rheumatic disease patients and 40 controls), 109 during the past year. There were no adverse reactions. Classification and diagnosis of rheumatic diseases was established using ACR criteria. Sera of rheumatic disease patients were examined for anticardiolipin antibody (ACLAB) of IgG and IgM isotypes. A total of 88 sera contained high (100 GPL units) or moderately elevated levels (50 GPL units) of ACLAB. All control sera except two (5%) were negative for ACLAB, and these two positive sera contained low levels. To test whether rheumatic disease and thrombogenic ACLAB may be potentiated by B2-glycoprotein-I (B2GP-I), 30 IgG fractions were taken from ACLAB positive sera. All fractions were devoid of B2GP-I when tested by immunodiffusion and immunoblotting. Of the 30 IgG fractions, 20 were potentiated by adding 10 ug/ml B2GP-I using an ELISA method of ACLAB determination.

CONCLUSIONS

Study data indicate that the majority of rheumatic disease patients with ACLAB have IgG antibodies, the titer of which is increased by complementation with Bl-glycoprotein-I. A significant minority (8/39) of rheumatic disease patients have IgG ACLAB, titer of which is not increased significantly by addition of B2-glycoprotein-I. Tests were performed using a micro-ELISA without using fetal calf serum as diluent.

REPORT DATE: 08/02/94 WORK UNIT # 3716

DETAIL SUMMARY SHEET

TITLE: A Prospective Evaluation of Indeterminate Western Blot Patterns in Patients with Autoimmune Disorders

KEYWORDS: autoimmunity, pathogenesis, retrovirus

PRINCIPAL INVESTIGATOR: Dennis, Gregory LTC MC
ASSOCIATES: Brown, Art LTC MC; Burman, Kenneth COL MC

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Rheumatology Service APPROVAL DATE: Jun 1993

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To: 1) determine the incidence of indeterminate WB for HIV patients with autoimmunity; 2) monitor changes in WB patterns in autoimmunity; 3) determine if there is lot-to-lot variation in various kits; 4) perform virus isolation and characterization; and 5) correlate results with IFA-HIV.

TECHNICAL APPROACH
Serum from volunteer subjects with various autoimmune diseases will be subjected to the following tests: ELISA, Western Blot, HTLV-1, HTLV-2 antibodies, reverse transcriptase assay, viral isolation by co-culture method, and HIV DNA ACR.

PRIOR AND CURRENT PROGRESS
A total of 80 patients with various autoimmune diseases have been tested for HIV using Western Blots. No complaints have been observed from the phlebotomy. Approximately 15 patients identified thus far have indeterminate WB patterns. Presently, there is ongoing dialogue among the investigators regarding the economic feasibility of completing the entire project as designed.

CONCLUSIONS
A high prevalence of indeterminate patterns for HIV was seen in patients with autoimmunity. There is also a need to re-design the follow-up phase of the study, and modification of study objectives may be necessary.

REPORT DATE: 08/09/94 WORK UNIT # 3717

DETAIL SUMMARY SHEET

TITLE: Plasma Endothelin-1 Levels After Cold Provocation in Hypothyroidism

KEYWORDS: endothelin-1, hypothyroidism, Raynaud's

PRINCIPAL INVESTIGATOR: Tesar, Joseph MD
ASSOCIATES: Burch, Henry MAJ MC

DEPARTMENT: Department of Medicine
SERVICE: Rheumatology Service

STATUS: Ongoing
APPROVAL DATE: Aug 1993

FUNDING: Current FY: $ 9,090 Previous FYs: $ 0 Total: $ 9,090

STUDY OBJECTIVE

To determine if plasma endothelin-1 (ET-1) levels are elevated in patients who are hypothyroid, as compared to normal controls and disease controls (i.e., scleroderma). This hormone is often elevated in patients with Raynaud's phenomenon, which has been reported to occur in hypothyroidism.

TECHNICAL APPROACH

Ten cc's of blood will be taken from euthyroid patients, before and after 5 minutes of cold water immersion, and again while they are hypothyroid. Digital blood flow decrement will be documented by associated digital plesthysmography following cold water immersion. This procedure will be performed once in each normal control and disease control patient.

PRIOR AND CURRENT PROGRESS

A total of 55 subjects have been enrolled: 15 with hypothyroidism, 10 scleroderma controls, and 30 normal controls. There have been no adverse reactions. Work on this study began in April 1994. It is not completed yet because of difficuties obtaining a clinical lab to perform the highly technical and difficult-to-run RIA for ET-1. However, recently a contract has been made with Dr. Lerman, Mayo Clinic, Rochester, Minnesota, to peform this assay. If DCI approves the monetary requirements ($8,700 is required by the Mayo Clinic, and the original budget for this protocol was $11,100), the frozen blood samples can be sent for assay.

CONCLUSIONS

This project is significant because of the important role ET-1 plays as the most potent vasoconstrictor known to exist. Currently, ET-1 is a primary etiology in many diseases (i.e., pulmonary hypertension, Raynaud's phenomenon), and further understanding is crucial to successful treatment.

REPORT DATE: 03/04/94 WORK UNIT # 7136

DETAIL SUMMARY SHEET

TITLE: An Investigation of Frontal Lobe Mediated Knowledge Representation

KEYWORDS: cognition, frontal lobe

PRINCIPAL INVESTIGATOR: Salazar, Andres COL MC

SERVICE: Neurology Service STATUS: Completed
APPROVAL DATE: Feb 1988

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
1) To develop face valid and psychometrically constrained tests of executive functions guided by a preliminary neuropsychologically derived information processing model; 2) To obtain normal control data; 3) To motivate a more detailed and complete neuropsychological model of executive (frontal lobe) functions based on observed brain-behavior relationships; 4) To develop guidelines for the care of individuals impaired with clinical or "subclinical" executive function deficits.

TECHNICAL APPROACH
Patients will receive neurological and neuropsychological examinations at WRAMC and at NINDS, NIH.

PRIOR AND CURRENT PROGRESS
Twenty patients have been entered in the study, and have received baseline and q6 month evaluations at the NIH. No further patients have been entered during the past year. There have been no adverse reactions.

CONCLUSIONS
Preliminary analysis of data, to date, supports the model of frontal lobe executive function hypothesized in the original protocol.

REPORT DATE: 03/04/94 WORK UNIT # 7141

DETAIL SUMMARY SHEET

TITLE: Recombinant Beta Interferon as Treatment for Multiple Sclerosis: A Multicenter Protocol

KEYWORDS: beta-interferon, multiple sclerosis

PRINCIPAL INVESTIGATOR: Salazar, Andres COL MC

SERVICE: Neurology Service STATUS: Completed
APPROVAL DATE: Feb 1989

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine the therapeutic efficacy of beta-interferon in multiple sclerosis.

TECHNICAL APPROACH
Patients will be administered 6 million units r-human beta-interferon intramuscularly weekly for 2 years and will then be followed for 1-2 years. During FY-93, there were some administrative protocol modifications and changes to the consent form. The changes were approved by the HUC/IRB in October 1992.

PRIOR AND CURRENT PROGRESS
A total of 301 patients have been entered in the entire multicenter study, 56 at WRAMC. There have been no serious adverse events related to the test article. One heart disease patient who had taken ACE inhibitor for 1 week died at Portland. Eventhough the test article was not suspected as being causal in this event, the possibility could not be absolutely ruled out. The study was completed in February 1994, and unblinded in July 1994. The results were announced in the the Fall of 1994. The related drug, Beta-Interferon was approved by the FDA for patients with this type of MS, although it was not readily available. Study patients were given the option of treatment, and 13 are now on Betaseron. All study patients will be offered treatment with B-IFN-1b when a new protocol is approved in the Spring of 1995.

CONCLUSIONS
RB-Interferon is safe and well tolerated when administered at a dose of 6 million units IM for over 2 years to patients with multiple sclerosis. RB-Interferon slows progression of disability in patients with exacerbating MS by 40% (p=.02), increases time to progression by 75%, and decreases exacerbation rate by one-third (p=.03).

REPORT DATE: 03/31/94 WORK UNIT # 7142

DETAIL SUMMARY SHEET

TITLE: Intramuscular Poly-ICLC and CCNU in the Management of Malignant Gliomas: An Open Trial

KEYWORDS: poly-ICLC, CCNU

PRINCIPAL INVESTIGATOR: Salazar, Andres COL MC

SERVICE: Neurology Service STATUS: Completed
APPROVAL DATE: Mar 1989

FUNDING: Current FY: $12,000 Previous FYs: $ 295 Total: $ 12,295

STUDY OBJECTIVE
To determine the toxicity and tolerance of low doses of poly-ICLC and CCNU in patients with malignant gliomas.

TECHNICAL APPROACH
Originally, patients were administered poly-ICLC at 10, 20, 50, and 100 mcgm/kg twice weekly for 1 year. The dosage schedule was changed in August 1992 by addendum and approved by the HUC/IRB. Currently, patients are receiving 15 mcg/kg three times a week (total 45 mcgm/kg/wk) for 36 months.

PRIOR AND CURRENT PROGRESS
To date, 47 patients with malignant glioma have been entered, 10 during the past year. There was minimal or no toxicity. Thirteen patients on intermittent or short-term poly-ICLC died, but 24 of 31 with 4 to 32 months MRI follow-up achieved regression or stabilization of enhancing tumor (median = 58% volume decrease). All anaplastic astrocytoma (AA) patients remain alive and well, and are off steroids a median of 32 months from diagnosis. Median bioblastoma (GBM) survival is 19 months. (Historical median survival is 26 months for AA and 10 months for GBM). Optimum dose appears to be 10-20 mcg/kg IM two to three times weekly, yielding a 77% response rate (24/31). Tumor response appears associated with 2'5' OAS activation, but not with serum interferon, II-2, II-6, TNF, or neopterin. The PI hypothesizes that poly-ICLC activates a basic host tumor suppressor system. Patient accrual will end in April 1994, but follow-up will continue.

CONCLUSIONS
Poly-ICLC can be safely administered to patients with malignant gliomas with virtually no toxicity over 19 months. Prolonged, quality survival with tumor regression on MRI in most patients suggests a more extensive trial is warranted, and a multicenter study is planned. The concept of long-term, broad spectrum stimulation of host defenses with nontoxic, inexpensive double-stranded RNAs such as poly-ICLC may be applicable to treatment of other aggressive malignancies.

REPORT DATE: 07/14/94 WORK UNIT # 7144

DETAIL SUMMARY SHEET

TITLE: A Controlled Efficacy Study of a Brief Multidisciplinary Brain Injury Rehabilitation Program in Moderately Head Injured Service Members

KEYWORDS: traumatic brain injury, moderate head injury

PRINCIPAL INVESTIGATOR: Salazar, Andres COL MC

SERVICE: Neurology Service STATUS: Ongoing
APPROVAL DATE: Jul 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine the effectiveness and cost efficiency of a comprehensive TBI rehabilitation program, compared to one providing only counseling and support; to determine and quantify the short/long-term neurologic and neuropsychologic consequences of moderate head injury in the Army and its impact on some aspects of military performance; and to develop and test a relatively brief neuropsychologic screen that is sensitive to and predictive of effects of minor/moderate head injury.

TECHNICAL APPROACH
Each subject will receive neurological, neuropsychological, psychiatric, and medical rehabilitation; EEG and evoked potential, and neuroophthalmologic testing; physical and occupational therapy; clinical psychiatry interview; and an MRI. Following the comprehensive evaluation, patients will be randomly assigned to one of two treatment groups. Patients will then be returned to duty and followed.

PRIOR AND CURRENT PROGRESS
A total of 56 patients (up from 33 last year) have been radomized into the study to date. An additional 12 patients (no change from last year) have completed treatment as program controls. Accessions are now beginning to approximate the original target of one to two per week. The overall "return to duty" rate for protocol patients is approximately 75%, which is well above historical rates. There have been no serious or unexpected adverse reactions.

CONCLUSIONS
None.

REPORT DATE: 12/20/93

WORK UNIT # 7146

DETAIL SUMMARY SHEET

TITLE: Investigation of Cardiac and Cerebrovascular Effects of the Diving Reflex

KEYWORDS: diving reflex, electrocardiogram, heart rate

PRINCIPAL INVESTIGATOR: Jabbari, Bahman COL MC
ASSOCIATES: Leone, Leonard CPT MC

SERVICE: Neurology Service

STATUS: Completed
APPROVAL DATE: Dec 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To investigate the effect of sudden exposure of head and face to cold water, with or without breath-holding, on heart rate and brain waves.

TECHNICAL APPROACH

Twenty asymptomatic subjects and 20 patients with brain stem lesions will be studied. EEG, EKG and oxygen saturation will be recorded during 30 second epochs, including baseline, cold water applied to forehead, cold water applied to forehead and breath-holding, and Valsalva's maneuver.

PRIOR AND CURRENT PROGRESS

Altogether, six patients with well-circumscribed brain stem tumors and eight age-matched control subjects were enrolled, none during the past year. There have been no serious or unexpected adverse reactions. Patients with upper brain stem tumors and controls experienced either no change or decreased heart rate in response to the stimuli. In contrast, patients with tumors involving the ponto-medullary region experienced an increase in heart rate.

CONCLUSIONS

Study observations indicate that in humans, isolated lesions involving the ponto-medullary region can disrupt pathways mediating the diving reflex and lead to paradoxical tachycardia.

REPORT DATE: 04/15/94 WORK UNIT # 7147

DETAIL SUMMARY SHEET

TITLE: Investigation of the Localizing Value of Clinical Signs Observed During Epileptic Seizures

KEYWORDS: epilepsy, seizure, electroencephalography

PRINCIPAL INVESTIGATOR: Jabbari, Bahman COL MC

SERVICE: Neurology Service STATUS: Ongoing
APPROVAL DATE: Apr 1991

FUNDING: Current FY: $ 1,048 Previous FYs: $ 1,744 Total: $ 2,792

STUDY OBJECTIVE
To identify those clinical signs and symptoms during an epileptic seizure with localizing value; i.e., indicating the region of the brain from which the seizures begin. Such localizing signs are very important in clinical or surgical management of patients with intractable seizures.

TECHNICAL APPROACH
All videotapes of seizure patients admitted to the Neurology Service over the past 5 years will be reviewed. These tapes include both behavioral seizures and concurrent recorded brain waves during seizures. The films will be observed for a number of clinical signs (e.g., head turning, dystonia, etc.) and recorded on a data sheet included in the protocol. The concurrent electrical brain discharges will be studied in relation to the patient's behavioral seizures.

PRIOR AND CURRENT PROGRESS
A total of 50 epileptic seizures have been reviewed in 35 patients (5 since the last APR) with intractable eilepsy focusing on two behavioral seizure patterns: 1) epileptic dystonic involuntary posturing of the limbs; and 2) head and eye movements. Dystonic posturing was noted in 24% of the recordings and was always on the opposite side of th seizure focus in EEG. Head and eye movements were ipsilateral or contralateral to the seizure focus. Two-thirds of the patients showed contralateral head and eye movements during the seizure.

CONCLUSIONS
Epileptic posturing of the limb(s) is a strong lateralizing sign which occurs contralaterally to the seizure focus. Head and eye movements are non-localizing but occur contralaterally in the majority of the patients.

REPORT DATE: 12/13/93 WORK UNIT # 7148

DETAIL SUMMARY SHEET

TITLE: Computer Modelling of Pupillary Light Reflexes

KEYWORDS: computer modeling, pupillary defects

PRINCIPAL INVESTIGATOR: Rosenberg, Michael Col MC

SERVICE: Neurology Service STATUS: Ongoing
APPROVAL DATE: Nov 1991

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To utilize clinical and laboratory data gathered from normal subjects and patients with afferent pupillary defects to train, test, and formulate a neural network model of pupillary function.

TECHNICAL APPROACH
This study will review 50-100 charts of patients who have had infrared television pupillometry (ITP) studies, either normal or abnormal, as part of their evaluation in the Neuro-Ophthalmology Clinic.

PRIOR AND CURRENT PROGRESS
To date, information from the charts of 134 patients has been collated, 65 during the past year. A computer program was written to allow transformation of the raw data into a format compatible with a neural network. This data is currently being reviewed to ensure accuracy. Early attempts to use the neural network program (Neural Wares) purchased for this project were unsuccessful. Methods to set up this network model are currently being examined.

CONCLUSIONS
None at this time.

REPORT DATE: 07/15/94 WORK UNIT # 7149

DETAIL SUMMARY SHEET

TITLE: Investigation of the Yield of Magnetic Motor Evoked Potentials in Neurosurgical Disorders: Spinal Cord and Posterior Fossa Lesions and Hydrocephalus

KEYWORDS: spinal cord, evoked potentials, magnetic stimulation

PRINCIPAL INVESTIGATOR: Jabbari, Bahman COL MC
ASSOCIATES: Osenbach, Richard MAJ MC

SERVICE: Neurology Service STATUS: Ongoing
APPROVAL DATE: Jul 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To evaluate the usefulness of magnetic motor evoked potentials as a diagnostic test in spinal cord disorders, posterior fossa lesions, and hydrocephalus.

TECHNICAL APPROACH
This protocol is approved by FDA for enrollment of patients with spinal cord disorders and control subjects. Fifty patients with spinal cord disorders and 30 control subjects will be recruited. The integrity of the motor system will be evaluated by stimulating the scalp by a magnetic stimulator of 1.5 tesla strength and recording the response from different hand and leg muscles. Further areas of stimulation will include the posterior cervical region at C6, Erb's point and wrist, or popliteal fossa. Presence and absence of motor responses as well as absolute cortical conduction time and central conduction times will be compared with that of controls.

PRIOR AND CURRENT PROGRESS
A total of 35 patients with spinal cord disorders were tested, 15 during the past year. The group consisted of those with both intra-axial and extra-axial pathologies. Magnetic motor evoked potential (MMEP) was abnormal in 33 of 35 patients (85%). In general, MMEP abnormality correlated with the clinical findings and the results of the patient's somatosenaory evoked potential test (SSEP). MMEP was grossly abnormal in two patients with intrinsic cord pathology who complained of neck pain but had abnormal neurological examinations. All patients tolerated the procedure well, and there were no complications. Enrollment of control subjects has ended.

CONCLUSIONS
These findings demonstrate a high yield for MMEP in patients with spinal cord disorders. MMEP can be abnormal, suggesting spinal cord pathology in some patients with normal neurological examination.

REPORT DATE: 09/14/94 WORK UNIT # 7150

DETAIL SUMMARY SHEET

TITLE: Investigation of the Effectiveness of Botulinum Toxin-A Against Increased Muscle Tone

KEYWORDS: botulinum toxin-A, spasticity, rigidity

PRINCIPAL INVESTIGATOR: Jabbari, Bahman COL MC

SERVICE: Neurology Service STATUS: Completed
APPROVAL DATE: Sep 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To evaluate the effectiveness of botulinum toxin-A against spasticity and rigidity.

TECHNICAL APPROACH
This is a double-blind crossover study of botulinum toxin-A versus normal saline. Patients' degree of spasticity or rigidity will be rated prior to the first injection by a neurologist blinded to the order of injections. If the first injection does not produce any improvement after 2 weeks, then the second agent will be administered. If improvements are seen within the first 2 weeks, the second injection will be delayed for 3 months. Improvements by two or more tone grades were considered significant.

PRIOR AND CURRENT PROGRESS
A total of 16 patients (8 each with rigidity and spasticity) were enrolled; 12 during the past year. The spastic patients have multiple sclerosis, stroke, and trauma. The rigid patients had Parkinson's disease, progressive supranuclear palsy, and corticobasal degeneration. Administration of botulinum toxin resulted in significant improvement of tone in all eight spastic patients, and seven of the eight rigid patients. Improvement of muscle tone paralleled functional improvement and facilitated nursing care in six of eight spastic patients, and five of the eight rigid patients. The tone and functional improvement lasted for 2.5 to 4 months. There were no side effects. The effective dose ranged from 25 to 400 units per session for the spasticity group and from 20 to 400 units per session for the rigidity group.

CONCLUSIONS
Botulinum toxin A can improve muscle tone and nursing care in the majority of patients with spasticity and rigidity. It produced no side effects in this study of 16 patients.

REPORT DATE: 04/06/94 WORK UNIT # 7151

DETAIL SUMMARY SHEET

TITLE: Retinal Modulation of Pupil Size

KEYWORDS: photoreceptors, pupillary size

PRINCIPAL INVESTIGATOR: Kobylarz, Erik MAJ MC

SERVICE: Neurology Service STATUS: Ongoing
APPROVAL DATE: Mar 1993

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To characterize the effects of retinal photoreceptor bleach on pupillary size and to attempt to define the role of specific populations of photoreceptors.

TECHNICAL APPROACH
Dark-adapted eyes will be exposed to 60 seconds of direct light stimulation. Pupil diameters will be measured by infrared television pupillometry in the dark-adapted condition, at the end of the stimulus, and once every minute thereafter for at least 30 minutes. Subjects will report on the subjective scotomata.

PRIOR AND CURRENT PROGRESS
A total of 14 subjects were enrolled and tested. Redilation to control values occurred over approximately 25 minutes post-stimulus in two phases. Mean constriction was maximal for the first 6 minutes. Subjects reported small, dense central scotomata that lasted 20-30 minutes in the dark, the intensity of which paralleled pupillary recovery. Duration of miosis and scotomata were significantly more prolonged after exposure to while light compared to that for red light of equal intensity. A manuscript is being submitted for publication to "Neurology."

CONCLUSIONS
Plans are to continue this study with the application of blue light to determine if rods or blue cones mediate the pupillary response to retinal bleaching.

REPORT DATE: 04/06/94 WORK UNIT # 7152

DETAIL SUMMARY SHEET

TITLE: The Role of GABA in the Control of Ventilation in the Cirrhotic Rat Model

KEYWORDS: GABA, ventilatory control, cirrhosis

PRINCIPAL INVESTIGATOR: Kobylarz, Erik CPT MC
ASSOCIATES: Ling, Geoffrey MAJ MC; Verma, Ajay CPT MC

SERVICE: Neurology Service STATUS: Ongoing
APPROVAL DATE: Mar 1993

FUNDING: Current FY: $10,346 Previous FYs: $ 0 Total: $ 10,346

STUDY OBJECTIVE
To determine the relationship of ventilation to the presence and concentration of the neurotransmitter gamma aminobutyric acid (GABA).

TECHNICAL APPROACH
This above objective is being investigated in a rat model of hepatic cirrhosis that will allow simultaneous determination of GABA levels and ventilation.

PRIOR AND CURRENT PROGRESS
Currently, 20 rats are receiving beta-galactosamine intraperitoneally to induce hepatic cirrhosis and encephalopathy within a 72 hours period in the pilot study. Rats will be observed in plethysmography chambers where physiologic parameters will be measured including tidal volume, minute ventilation, and breathing frequency. Chamber gas concentrations will be kept at normal atmospheric contents. Rats will then be euthanized, and their brainstems will be exposed to GABA receptor-binding agents. The portions of the brainstems involved in respiratory control will be analyzed for changes in GABA receptor density in the cirrhotic rats. Dependent upon the pilot study results, a more elaborate study will then ensue. Longer term observation of mechanical and electrical respiratory parameters will be measured as well as the biochemical analysis of central nervous system respiratory GABAergic changes.

CONCLUSIONS
Pending; they will be submitted upon analysis of the data being collected.

REPORT DATE: 01/07/94 WORK UNIT # 7153

DETAIL SUMMARY SHEET

TITLE: Extraocular Muscle Balance in Carnio-Cervical Dystonia and Normal Subjects

KEYWORDS:

PRINCIPAL INVESTIGATOR: Sinoff, Stuart MAJ MC

SERVICE: Neurology Service STATUS: Terminated
APPROVAL DATE: Mar 1993

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
This protocol has been administratively terminated.

TECHNICAL APPROACH
This protocol has been administratively terminated.

PRIOR AND CURRENT PROGRESS
This protocol has been administratively terminated.

CONCLUSIONS
None. This protocol has been administratively terminated.

REPORT DATE: 08/12/94 WORK UNIT # 7154

DETAIL SUMMARY SHEET

TITLE: Defense and Veterans Head Injury Program (DVHIP): WRAMC Core Evaluation Protocol

KEYWORDS: traumatic brain injury, head injury

PRINCIPAL INVESTIGATOR: Salazar, Andres COL MC

SERVICE: Neurology Service STATUS: Ongoing
APPROVAL DATE: Aug 1993

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To ensure that all military and DVA traumatic brain injury (TBI) patients receive TBI-specific evaluation and follow-up, to concurrently collect standardized patient outcome data to evaluate the relative efficacy and cost of various TBI treatment and rehabilitation strategies, and to define optimal care for victims of TBI.

TECHNICAL APPROACH
Each subject will receive standard diagnostic testing, including neurologic, neuropsychologic, speech and language, psychiatric, and rehabilitation examinations, along with magnetic brain scans (MRI), and electroencephalograms (EEG or brain scan test). Patients will then be discharged and followed.

PRIOR AND CURRENT PROGRESS
A total of 26 patients have received initial baseline evaluations to date. There have been no follow-ups at this time. There have been no serious or unexpected adverse reactions.

CONCLUSIONS
None.

REPORT DATE: 08/16/94 WORK UNIT # 7155

DETAIL SUMMARY SHEET

TITLE: Investigation of the Effect of Solitary Brain Stem Lesion on Sleep Architecture

KEYWORDS: brainstem, REM sleep, polysomnography

PRINCIPAL INVESTIGATOR: Maldonado, Janice CPT MC

SERVICE: Neurology Service STATUS: Ongoing
APPROVAL DATE: Aug 1993

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine if discrete brainstem lesions affect sleep, and if such localization influences the sleep patterns differently.

TECHNICAL APPROACH
Twelve patients with well defined MRI lesions in the brainstem will be studies. Each patient will have an all-night polysomnogram including EEG, EMG, EOG, and apnea recordings. Their sleep will be scored according to the Rechtschaffen and Kales criteria. This data will be compared to normal historic values of sleep parameters from Williams and Haracan, and statistically analyzed using the t-test method.

PRIOR AND CURRENT PROGRESS
A total of two patients have been studied to date. Patient #1 is a 74-year-old woman with history and evidence on MRI of a pontine infarct. Her percentage of REM sleep was 18.9, and REM latency was 71.5 minutes; both parameters fall within normal limits when compared to age and sex matched values. Patient #2 is a 28-year-old woman with a cavernous angioma localized to the left posterior pons. Her percentage of REM sleep was 13.8, and REM latency was 210 minutes. These are clearly abnormal; for sex and age matched values, the normal percentage of REM sleep is 22-29, and normal REM latency is 78-122. There has been no incidence of serious or unexpected adverse reactions.

CONCLUSIONS
No conclusions have been formulated yet due to the small sample of patients studied.

REPORT DATE: 01/03/94 WORK UNIT # 7521

DETAIL SUMMARY SHEET

TITLE: Pregnancy Attitudes, Ambivalence and Symptom Distress

KEYWORDS: pregnancy attitudes, ambivalence, symptom distress

PRINCIPAL INVESTIGATOR: Rich, Irene LTC AN

DEPARTMENT: Department of Nursing STATUS: Completed
APPROVAL DATE: Dec 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To develop and test a self-report questionnaire which measures levels of ambivalence and general pregnancy attitudes of women during pregnancy; and to explore the relationships between psychological symptom distress, ambivalence, and general pregnancy attitudes during the trimesters of pregnancy.

TECHNICAL APPROACH
Women in the Obstetric Clinic will be sent study questionnaires in a prepaid mailer.

PRIOR AND CURRENT PROGRESS
A total of 602 questionnaires were sent to 3 data collection locations; 433 were returned giving a response rate of 72%. The number of WRAMC respondents was 104. No questionnaires were sent during the past year. This study was part of the principal investigator's doctoral work, and was completed in May 1993.

CONCLUSIONS
The pregnancy questionnaire was developed, and reliability established. Both internal consistency and test-retest reliability was established. Both internal consistency and test-retest reliability of the measure support its reliability. A preliminary model was developed depicting the relationships between psychological distress, ambivalence, and pregnancy attitudes.

REPORT DATE: 04/11/94 WORK UNIT # 7525

DETAIL SUMMARY SHEET

TITLE: Determinants of Effective Coping and Adaptation Among Army Medical Department Soliders During Operation Desert Storm

KEYWORDS: adaptation, coping, causal models

PRINCIPAL INVESTIGATOR: Gurney, Cynthia LTC AN
ASSOCIATES: Biskey, Valerie COL AN; Sarnecky, Mary LTC MC

DEPARTMENT: Department of Nursing

STATUS: Ongoing
APPROVAL DATE: Apr 1991

FUNDING: Current FY: $ 0 Previous FYs: $ 29 Total: $ 29

STUDY OBJECTIVE

To identify determinants of effective coping and adaptation to the combat environment for Army Medical Department personnel. Through this, the AMEDD may design training, policy, and instructions that will ease the transition to combat in future conflicts.

TECHNICAL APPROACH

A questionnaire will be mailed to survey Army Medical Department soldiers (officer and enlisted, active duty and reserve components) who served in Southwest Asia during the Gulf War. US Army Personnel Information Command (PERSINSCOM) will provide the data base from which to sample this population. Following data collection, statistical analysis will include descriptive statistics, factor analysis, multi-group analysis, and, finally, causal modeling using path analysis. A total of approximately 2800 enlisted and 2500 officer personnel will be sampled.

PRIOR AND CURRENT PROGRESS

Data collection ended in the fall of 1992. There were 1,310 usable surveys. Data analysis completed to date includes descriptive statistics, factor analysis of scales and subscales, preliminary multiple regression, and path analysis.

CONCLUSIONS

Study data indicate symptom distress (B=.25, p</=.001) and environmental stress (B=-24,p</=.001) were the strongest predictors of adaptation. These variables plus social support (B=.10, </=.05), feelings about deployment (B=.18, p</=.001), age (B=.16,p</=.001), and satisfaction (B=.14, p</=.001) combined to explain 35% of the variance in adaptation (R^2=.35) to combat.

REPORT DATE: 07/15/94 WORK UNIT # 7526

DETAIL SUMMARY SHEET

TITLE: The Effect of a Self Learning Module for Cancer Pain Management on Nurses' Knowledge, Interventions, and Pain Relief for Cancer Patients

KEYWORDS: pain, knowledge, intervention

PRINCIPAL INVESTIGATOR: Petrov, Jean RN MS
ASSOCIATES: Reeder, Jean COL AN

DEPARTMENT: Department of Nursing

STATUS: Completed
APPROVAL DATE: Jul 1991

FUNDING: Current FY: $ 946 Previous FYs: $ 0 Total: $ 946

STUDY OBJECTIVE

To test the effectiveness of a nursing self-learning module for cancer pain management on: nurses' knowledge of cancer pain management, nurses' interventions for pain, and patients' pain relief.

TECHNICAL APPROACH

An experimental pretest/posttest design will be used to compare the effect of the self-learning module (SLM) on pain management knowledge of two groups of nurses from six wards. Wards will be matched according to nurse demographic and pretest data, then randomized for nurses to receive the treatment (SLM) or not. The effect of the SLM on nurse interventions and pain relief will be determined by the accrual of two 20 patient sets (pre and post use of SLM). Interventions will be taken from nursing documentation, and pain relief will be recorded from patient use of visual analogue scales to measure pain intensity.

PRIOR AND CURRENT PROGRESS

All data was collected from both nurse and patient subjects by August 1992. This completed data collection. No data has been collected since then. There are 42 nurse subjects (21 each in control and treatment groups), and 40 patient subjects (20 in each group). There were no adverse reactions. Nurses' pain management knowledge increased and patients' mean pain intensity levels decreased. Patients may also have benefited from knowledge gained by participation.

CONCLUSIONS

Nurses who received the SLM showed significantly greater improvement in test scores (15 +/- 8.2) compared to control nurses (-0.4 +/- 5.8), $t=-6.98$, $p=0.00005$. There were no significant differences in number of interventions per patient per day as monitored for each group. Pre- and post-SLM scores were 2.35 +/- 1.41 and 2.79 +/- 1.52, respectively. Pain intensity was significantly lower after PRN medications were given for post-SLM patients.

REPORT DATE: 01/10/94 WORK UNIT # 7527

DETAIL SUMMARY SHEET

TITLE: Use of an Indwelling Peripheral Catheter for 3-5 Days Sequential Chemotherapy Doses in the Outpatient Setting

KEYWORDS: peripheral IV catheters, Heplocks, sequential chemotherapy

PRINCIPAL INVESTIGATOR: Shotkin, Jane RN

DEPARTMENT: Department of Nursing STATUS: Ongoing
APPROVAL DATE: Jan 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To observe the efficacy and safety of placing peripheral intravenous catheters in outpatients for 3-5 days while receiving daily doses of chemotherapy.

TECHNICAL APPROACH
A #22 gauge Insyte catheter will be inserted into either forearm of the patient and Heplocked. This catheter will be used daily to administer chemotherapy for a period of 3-5 days. The condition of the IV site and the ability to use the Heplock are charted daily.

PRIOR AND CURRENT PROGRESS
Approximately 70 of 100 anticipated patients have been entered into the study altogether. As of January 1993, 33 subjects had been enrolled. Data is still being collected. No infections or serious complications have been reported. Patients are generally pleased with this option of chemotherapy delivery.

CONCLUSIONS
None.

REPORT DATE: 06/05/94 WORK UNIT # 7529

DETAIL SUMMARY SHEET

TITLE: The Oncology Patient's Experience in Making a Treatment Decision

KEYWORDS: oncology patients, treatment, decision making

PRINCIPAL INVESTIGATOR: Jones, Kathleen RN MS

DEPARTMENT: Department of Nursing STATUS: Completed
APPROVAL DATE: Dec 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To explore and describe the process of decision making as experienced by oncology patients when making treatment decisions.

TECHNICAL APPROACH
A qualitative approach based on grounded theory methodology will be employed. This will be a multi-site study with WRAMC serving as a data collection site.

PRIOR AND CURRENT PROGRESS
The total program sample size was 21, 3 from WRAMC. Patients were interviewed, and the verbatim data was transcribed and used for analysis.

CONCLUSIONS
The study findings led to hypotheses to be tested for future research in this area.

REPORT DATE: 08/17/94 WORK UNIT # 7532

DETAIL SUMMARY SHEET

TITLE: Psychology of Pregnancy: Peace and War-Time

KEYWORDS: pregnancy, psychology, war-time

PRINCIPAL INVESTIGATOR: Rich, Irene LTC AN

DEPARTMENT: Department of Nursing STATUS: Ongoing
APPROVAL DATE: Aug 1993

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To gather peace-time data to determine the confounding effects of war-time stressors on pregnant women's ambivalence and attitudes toward pregnancy, and psychological distress. This is a replication study; the PI was unable to determine if the alarmingly high psychological distress levels of respondents were the result of pregnancy or of war-time stressors in her 1993 war-time study of psychological variables in military beneficiaries.

TECHNICAL APPROACH
Cross-sectional sampling will be used to recruit 600 women from all trimesters in the sample. Currently, 390 of 600 respondents have returned questionnaires (response rate is 65%). An ex-post factor, two-group design is being used to make peace vs. war-time and soldier vs. family member comparisons. Multivariate analysis of variance will be used for this analysis. Pregnancy attitudes and ambivalence are being measured using the Rich Pregnancy Attitude and Ambivalence Scales. Derogatis' Symptom Checklist-90-Revised is being used to assess psychological distress. Twenty-three women were recruited to partipate in a pilot project designed to assess changes in the key variables over time.

PRIOR AND CURRENT PROGRESS
Data collection is nearly complete. Coding of data and data entry are in progress. It is anticipated that data collection and data entry will be complete by mid-September 1994. It is anticipated that data analysis will be complete by 01 Oct 94. There has been no incidence of serious or unexpected adverse reactions.

CONCLUSIONS
Study progress is consistent with the project time line. Data analyses are anticipated to be available by October 1994.

REPORT DATE: 09/13/94 WORK UNIT # 7533

DETAIL SUMMARY SHEET

TITLE: A History of the Army Nurse Corps

KEYWORDS: history, Army Nurse Corps

PRINCIPAL INVESTIGATOR: Sarnecky, Mary COL AN

DEPARTMENT: Department of Nursing STATUS: Ongoing
APPROVAL DATE: Aug 1993

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To produce an accurate, up-to-date, scholarly history of the Army Nurse Corps suitable for publication.

TECHNICAL APPROACH
The design of the study will follow the historical method of research. Data relating to the history of the ANC will be collected from sites across the country.

PRIOR AND CURRENT PROGRESS
Study questions have been developed and are being amended and augmented as the study unfolds. Collected data was assessed for validity and reliability, and entered into a data base. All data were organized, integrated, and analyzed. The research report is currently being written. To date, approximately 500 manuscript pages have been written. This represents over 50% of the manuscript. No adverse reactions or benefits were experienced by any participants in this study.

CONCLUSIONS
The investigation has not progressed sufficiently to allow for the accurate development of conclusions.

REPORT DATE: 09/12/94 WORK UNIT # 7534

DETAIL SUMMARY SHEET

TITLE: Quality of Life in Soldiers with HIV Infection

KEYWORDS: quality of life, soldiers, HIV infection

PRINCIPAL INVESTIGATOR: Gurney, Cynthia LTC AN
ASSOCIATES: Schempp, Catherine LTC AN

DEPARTMENT: Department of Nursing

STATUS: Ongoing
APPROVAL DATE: Sep 1993

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To examine the relationships among and between health locus of control, social support, sickness impact, life satisfaction, and quality of life in U.S. soldiers at different stages of HIV. The specific hypotheses are: H1 - There will be significant differences between stage of illness and these quantitative measures; and H2 - There are factors to predict quality of life.

TECHNICAL APPROACH

The study uses a cross sectional design. The investigator will use 140 study subjects stratified from Walter Reed Stage 1 to Walter Reed Stage 6. The study will be conducted in a large Army health care facility. Subjects will be a convenience samples of patients attending scheduled appointments at the Infectious Disease Clinic. Subjects will be asked to complete the informed consent and set of six questionnaires. Analyses include the multiple analysis of variance and multiple regression analysis.

PRIOR AND CURRENT PROGRESS

The data collection process was conducted from November 1993 through May 1994. A total of 140 subjects have participated in the study. The data has been entered into data bases, and statistical analyses have been conducted. A dissertation has been developed based on the information obtained in this analysis. Secondary analysis is currently being done.

CONCLUSIONS

Preliminary conclusions show a significant MANOVA ($F = 2.22$, $df=22,254$, $p = .002$). The multivariate test of significance by Wilks' Lambda Criterion partially supported Hypothesis One. Standard discriminant function coefficients showed four large contributors; internal health locus of control, physical sickness impact, health and functioning capability, and socioeconomic class. Multiple regression demonstrated that satisfaction in the military explained 11% of variance.

REPORT DATE: 08/16/94 WORK UNIT # 8302

DETAIL SUMMARY SHEET

TITLE: Army Women's Breast Cancer Risk

KEYWORDS: breast, cancer, Army

PRINCIPAL INVESTIGATOR: DeCesare, Elaine LTC AN

DEPARTMENT: Department of Nursing STATUS: Ongoing
APPROVAL DATE: Aug 1993

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To describe the overall occurrence of risk factors for breast cancer among active duty Army women utilizing an existing military health appraisal data base; to decribe the occurrence of risk factors based on rank; to explore the differences of risk factors based on rank; to describe the occurrence of risk factors based on ethnicity; and to describe the differences of risk factors based on ethnicity.

TECHNICAL APPROACH
The study will use a descriptive epidemiologic approach. Data consisting of 13,500 cases will be cleaned for duplicate cases and outliers. Descriptive statistics will be performed to analyze the representatives of the overall sample, and the sample will be divided into four population groups based on rank and four population groups based on ethnicity. Descriptive statistics will be calculated for the overall occurrence of risk factors for breast cancer for the overall sample, the four rank groups, and the four ethnicity groups. One-way analysis of variance is being conducted.

PRIOR AND CURRENT PROGRESS
Equipment and supplies were ordered and obtained. A computer specialist was hired, and biostatistician hours were contracted. Data were obtained from the U.S. Army Health Risk Appraisal data base at HCSSA, San Antonio, Texas, and cleaned. Data analysis is nearly completed. Methodology to calculate 10-year, 20-year, 30-year, and life-time incidence for breast cancer for the overall sample is being investigated, and calculation should be completed by 30 Sep 94. Manuscripts will be prepared and submitted for publication during FY95.

CONCLUSIONS
Preliminary findings indicate a statistically significant difference in "age at birth of first child" among senior officers when compared to other rank groups. Other findings will follow.

REPORT DATE: 06/05/94 WORK UNIT # 9305

DETAIL SUMMARY SHEET

TITLE: Evaluation of Nutritional Needs Based on Non-Protein Calories Versus Total Calories in Total Parenteral Nutrition (TPN)

KEYWORDS: total parenteral, nutrition, nonprotein calories

PRINCIPAL INVESTIGATOR: Smith, Sandra RD CNSD

SERVICE: Nutrition Care Directorate STATUS: Ongoing
APPROVAL DATE: Jun 1993

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To compare the nutritional response and metabolic tolerance to the calories in total parenteral nutrition (TPN) in adult patients given TPN calculated with nonprotein calories (dextrosse and fat) or TPN calculated with total calories (dextrose, fat, and amino acids).

TECHNICAL APPROACH
Adults hospitalized at WRAMC without enteral calorie intake and who are TPN candidates will be screened by a project investigator to determine if they are appropriate for the study. If consent is obtained, the patient will be randomized to one of two treatment groups: TPN calculated for nonprotein calories, or TPN calculated for total calories. Calorie needs will be determined using indirect calorimetry prior to full TPN and during the first week of TPN. Serum pre-albumin, triglyceride and glucose, and 24 hours UUN will be assessed prior to full TPN, and during week one of TPN. On 23 Nov 93, the protocol was amended to delete $2,644.00 for contract services for TUN analysis.

PRIOR AND CURRENT PROGRESS
Six subjects were enrolled into the study in 1993, and seven in 1994. So far, only six subjects remained in the study long enough for collection of meaningful data. There have been no adverse reactions associated with participation in the study. Withdrawal from the study was secondary to resumption of oral food intake or, in one case, withdrawal of TPN due to extremely poor prognosis for recovery. One patient who completed the study may have benefited from having energy expenditures (EE) measured. Her EE was 37% above the predicted level. By the end of the study, her prealbumin had increased, and she was in nitrogren balance. Soon after, she came off the ventilator and transferred out of the ICU.

CONCLUSIONS
No conclusions yet, except that it is much more difficult to find appropriate subjects for this study than anticipated. Attempts to make this a local multi-center study failed.

REPORT DATE: 01/13/94 WORK UNIT # 4304

DETAIL SUMMARY SHEET

TITLE: Evaluation of Inflammatory Pap Smears

KEYWORDS: pap, inflammation

PRINCIPAL INVESTIGATOR: Farley, John CPT, MC

DEPARTMENT: Department of Obstetrics and Gynecology STATUS: Completed
APPROVAL DATE: Jan 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine whether inflammatory pap smears predict cervical dysplasia and if they can be treated clinically.

TECHNICAL APPROACH
Patients with inflammatory pap smears will be treated expectantly with antibiotics, sulfa cream, or culture. Pap smear will be repeated after treatment. If inflammation persists, colposcopy will be performed. Another pap smear will be obtained 1 year following the original one.

PRIOR AND CURRENT PROGRESS
A total of 65 patients were enrolled in this study, none this past year. The project has been completed and presented at an OB/GYN conference. There were no serious or unexpected adverse reactions during the course of the study.

CONCLUSIONS
Treatment of inflammatory PAP smears is not necessary. They can be followed expectantly.

REPORT DATE: 06/20/94 WORK UNIT # 4307

DETAIL SUMMARY SHEET

TITLE: The Role of the P53 and Rasw Oncogenes in the Development of Malignant and Premalignant Lesions of the Female Genital Tract

KEYWORDS: p53 gene, Ras gene, gynecologic cancers

PRINCIPAL INVESTIGATOR: Teneriello, Michael LCDR MC

DEPARTMENT: Department of Obstetrics and Gynecology STATUS: Terminated
APPROVAL DATE: May 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine the incidence of p53 and Ki-ras gene mutations in a series of gynecologic neoplasms which span a clinicophathologic spectrum ranging from benign to malignant.

TECHNICAL APPROACH
Cases for analysis will be selected after review of clinical records. Paraffin embedded tissues will be obtained. The blocks will then be sectioned and reviewed histologically. DNA will then be extracted from a tissue section and analyzed for the presence of mutation of the p53 and Ki-ras genes using polymerase chain reaction, design RFLP analysis, PCR/SSCP, and DNA sequencing.

PRIOR AND CURRENT PROGRESS
This research protocol has been administratively terminated.

CONCLUSIONS
This research protocol has been administratively terminated.

REPORT DATE: 01/19/94 WORK UNIT # 4113

DETAIL SUMMARY SHEET

TITLE: Cooperative Gynecologic Oncology Group

KEYWORDS: gynecologic, oncology, group

PRINCIPAL INVESTIGATOR: Mayer, Allan COL MC
ASSOCIATES: Park, Robert MD

DEPARTMENT: Department of Obstetrics and Gynecology STATUS: Ongoing
SERVICE: Gynecologic Oncology Group APPROVAL DATE: Jan 1974

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
Walter Reed section of Gynecologic Oncology is involved with the nationally organized Gynecologic Oncology Group, consisting of 40 major medical centers in the country who are interested in the area of gynecologic tumors and the treatment of gynecologic cancer. The GOG is recognized and funded through the National Cancer Institute.

TECHNICAL APPROACH
Walter Reed is active in approximately 40 GOG protocols. Presently, there are 60 protocols that are either active or continue to provide significant data. These protocols involve treatment of ovarian carcinoma, cervical carcinoma, adenocarcinoma of the endometrium, uterine sarcoma, vulvar carcinoma, and gestational trophoblastic disease.

PRIOR AND CURRENT PROGRESS
This is an umbrella protocol. Approximately 944 patients have been entered into GOG protocols from Walter Reed. A total of 23 patients have been entered since the last report.

CONCLUSIONS
Detailed in individual reports.

REPORT DATE: 03/07/94 WORK UNIT # 4163

DETAIL SUMMARY SHEET

TITLE: GOG 26C: A Phase II Trial of Cis-platinum in the Treatment of Advanced Gyn Cancer

KEYWORDS: cis-platinum, diaminedichloroplatinum, gynecologic cancer

PRINCIPAL INVESTIGATOR: Mayer, Allan COL MC
ASSOCIATES: Park, Robert MD

DEPARTMENT: Department of Obstetrics and Gynecology
SERVICE: Gynecologic Oncology Group

STATUS: Ongoing
APPROVAL DATE: Mar 1979

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To determine the efficacy of cis-platinum in the treatment of advanced or recurrent gynecologic cancers. A rejection type design will be used involving the fixed sample size of 25 disease patients per disease site per drug or drug use in the study. The design allows replacement of ineffective regimens by newer agents or combinations.

TECHNICAL APPROACH

Cis-platinum appears to exert its cytotoxic action by cross-linking DNA and thus acting in a manner similar to the bifunctional alkylating agents. It has demonstrated activity in animal studies against transitional cell carcinoma in mice. Toxicity in animals reveals myelosuppression, lymphoid atrophy, hemorrhagic enterocolitis, renal tubular necrosis, and cochlear damage, as well as some degree of immunosuppression.

PRIOR AND CURRENT PROGRESS

The entire GOG has entered 632 patients (37 during the past year); WRAMC has entered 13 (3 during the past year). This protocol is closed to patients with squamous and nonsquamous cell cervical carcinoma, ovarian epithelial cancers except taxol failures, uterine sarcomas, endometrial adenocarcinoma, vaginal cancer, and vulvar and uterine sarcoma. Overall toxicity has been one each of the following: grade 4 renal toxicity, grade 4 neurotoxicity, GU toxicity, GI toxicity, and neutropenia.

CONCLUSIONS

Cisplatinum has marked activity as first-line chemotherapy in squamous cell carcinoma of the cervix, endometrial cancer, and mixed mesodermal sarcomas of the uterus, and is active as second-line therapy for advanced ovarian adenocarcinoma and mixed mesodermal sarcoma of the uterus. It seems to be inactive as first- and second-line therapy for endometrial and vulvar carcinomas, and leiomyosarcoma of the uterus, but may have limited activity treating cervical adenocarcinomas.

REPORT DATE: 04/22/94 WORK UNIT # 4187

DETAIL SUMMARY SHEET

TITLE: GOG 26N: A Phase II Trial of Dihydroxyanthracenedione (DHAD) in Patients with Advanced Pelvic Malignancies

KEYWORDS: dihydroxyanthracenedione, pelvic malignancies

PRINCIPAL INVESTIGATOR: Mayer, Allan COL MC
ASSOCIATES: Park, Robert COL MC

DEPARTMENT: Department of Obstetrics and Gynecology
SERVICE: Gynecologic Oncology Group

STATUS: Ongoing
APPROVAL DATE: Apr 1981

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To determine the efficacy of dihydroxyanthracenedione (DHAD) in treating patients with advanced pelvic malignancies.

TECHNICAL APPROACH

Patients with histologically-confirmed advanced, recurrent, persistent, metastatic, or local gynecologic cancer with documented disease progression are eligible.

PRIOR AND CURRENT PROGRESS

A total of 193 GOG patients have been entered; 2 during the past year. One WRAMC patient has been entered, none this past year. One incidence of grade 4 hematologic toxicity has been reported.

CONCLUSIONS

The data indicates minimal activity of DHAD in patients with ovarian cancer who have previously received doxorubicin. In patients with previously treated advanced carcinoma of the cervix, this drug also shows minimal activity. DHAD has minimal activity in patients with uterine sarcoma, and those with nonsquamous carcinoma of the cervix, endometrium, vulva, and vagina.

REPORT DATE: 06/14/94 WORK UNIT # 4203

DETAIL SUMMARY SHEET

TITLE: GOG 26Q: A Phase II Trial of Aminothiadiazole in Patients with Advanced Pelvic Malignancies

KEYWORDS: aminothiadiazole, pelvic malignancies

PRINCIPAL INVESTIGATOR: Mayer, Allan LTC(P) MC
ASSOCIATES: Park, Robert MD

DEPARTMENT: Department of Obstetrics and Gynecology STATUS: Completed
SERVICE: Gynecologic Oncology Group APPROVAL DATE: Jan 1983

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine the efficacy of aminothiadiazole in treating advanced pelvic malignancies (a Phase II trial).

TECHNICAL APPROACH
Aminothiadiazole (A-TD) will be administered at a dose of 125 mg/m2 IV per week. All patients will continue to receive A-TD until progression of disease is documented or adverse effects prohibit further therapy.

PRIOR AND CURRENT PROGRESS
There have been a total of 159 patients accrued by the entire GOG, none since the last APR. One patient entered by WRAMC has died. The protocol currently is closed for epithelial ovarian cancer, squamous cell cancer of the cervix, non-squamous cell cancer of the cervix, endometrial adenocarcinoma, leiomyosarcomas, and mixed mesodermal tumors of the uterus. There have been two grade 4 hematologic toxicities, one grade 3 cardiac toxicity, and one grade 3 sepsis reported. This protocol was closed on 23 May 94 and can be terminated.

CONCLUSIONS
None.

REPORT DATE: 05/11/94 WORK UNIT # 4212

DETAIL SUMMARY SHEET

TITLE: GOG 72: Ovarian Tumors of Low Malignant Potential: A Study of the Natural History and a Phase II Trial of Melphalan and Secondary Treatment with Cisplatin in Patients with Progressive Disease

KEYWORDS: ovary, malignant ovarian tumors, potential

PRINCIPAL INVESTIGATOR: Mayer, Allan COL MC
ASSOCIATES: Park, Robert MD

DEPARTMENT: Department of Obstetrics and Gynecology
SERVICE: Gynecologic Oncology Group

STATUS: Ongoing
APPROVAL DATE: May 1984

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To evaluate the biologic behavior of ovarian tumors of low malignant potential; to evaluate the effectiveness of chemotherapy against this disease (initially a Phase II study of melphalan); and to evaluate the response rate to cisplatin in melphalan failures.

TECHNICAL APPROACH

All patients with ovarian tumors considered to have a pathologic classification of low malignancy potential by a study reference pathologist will be eligible. Patients must have undergone adequate surgical staging procedures. Patients may have any stage of disease (from I-IV).

PRIOR AND CURRENT PROGRESS

There have been 477 patients entered into this study; 415 of whom are evaluable. Walter Reed has entered 14 patients into this study. No significant toxicites have been reported among the patients treated. This protocol was closed to patient entry on March 7, 1992.

CONCLUSIONS

Stage I ovarian serous tumors of low malignant potential are biologically benign neoplasms that can be treated conservatively in women of the reproductive age group. Other conclusions are pending final data anlaysis.

REPORT DATE: 07/19/94 WORK UNIT # 4225

DETAIL SUMMARY SHEET

TITLE: GOG 71: Treatment of Patients with Suboptimal (Bulky) Stage IB Carcinoma of the Cervix: A Randomized Comparison of Radiation Therapy Vs. Radiation Therapy plus Adjuvant Extrafascial Hysterectomy, Phase III

KEYWORDS: suboptimal, carcinoma, cervix

PRINCIPAL INVESTIGATOR: Mayer, Allan COL MC
ASSOCIATES: Park, Robert MD

DEPARTMENT: Department of Obstetrics and Gynecology
SERVICE: Gynecologic Oncology Group

STATUS: Completed
APPROVAL DATE: Jul 1985

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To evaluate the role of adjunctive extrafascial hysterectomy in the treatment of suboptimal Stage I-B carcinoma of the cervix with negative para-aortic and high common iliac nodes. Evaluation of the survival and pattern of failure in suboptimal Stage I-B cancer.

TECHNICAL APPROACH
Patients with untreated, histologically confirmed Stage I-B barrel carcinoma of the cervix will undergo evaluation of para-aortic or high common iliac nodes by CT, lymphangiogram, or sonogram. If the nodes are suspicious or positive, they will be evaluated by surgery or fine needle aspiration. If surgically or cytologically negative or negative by extrinsic evaluation, the patient will be randomized to receive radiation alone or radiation followed by extrafascial hysterectomy.

PRIOR AND CURRENT PROGRESS
A total of 262 patients have been entered into this protocol by the entire GOG; 10 have been WRAMC patients. This study was closed to patient entry, 18 Nov 91. There have been nine grade 4 toxicities; five have been gastrointestinal, two cardiovascular, one urinary, and one neurologic. This protocol can be closed as no patients are currently being followed.

CONCLUSIONS
Too early.

REPORT DATE: 04/22/94 WORK UNIT # 4229

DETAIL SUMMARY SHEET

TITLE: GOG 86A: Master Protocol for Phase II Drug Studies in Treatment of Advanced or Recurrent Carcinoma of the Endometrium

KEYWORDS: advanced, carcinoma, endometrium

PRINCIPAL INVESTIGATOR: Mayer, Allan COL MC
ASSOCIATES: Park, Robert MD

DEPARTMENT: Department of Obstetrics and Gynecology STATUS: Ongoing
SERVICE: Gynecologic Oncology Group APPROVAL DATE: Apr 1986

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To identify additional active agents for treating advanced or recurrent endometrial adenocarcinoma by studying single new drugs in patients with this disease who have not been previously exposed to chemotherapy.

TECHNICAL APPROACH
Patients must have histologically confirmed advanced, persistent, or recurrent endometrial carcinoma with documented disease progression after local therapy. All patients must have measurable disease. Patients must have failed local therapeutic measures or must be considered incurable with local therapy.

PRIOR AND CURRENT PROGRESS
This is a master protocol. Please see individual protocols for further information.

CONCLUSIONS
See individual protocols for further information.

REPORT DATE: 05/11/94 WORK UNIT # 4231

DETAIL SUMMARY SHEET

TITLE: GOG 87A: Master Protocol for Phase II Drug Studies in the Treatment of Recurrent or Advanced Uterine Sarcomas

KEYWORDS: advanced, uterus, sarcoma

PRINCIPAL INVESTIGATOR: Mayer, Allan COL MC
ASSOCIATES: Park, Robert MD

DEPARTMENT: Department of Obstetrics and Gynecology STATUS: Ongoing
SERVICE: Gynecologic Oncology Group APPROVAL DATE: May 1986

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To allow the best possible chance for a new cytotoxic agent to demonstrate activity, this study constitutes a Phase II design in a population of patients who have had no prior drug therapy.

TECHNICAL APPROACH
To treat an average sample size of 30 patients per drug studied for each of the following cell categories: mixed mesodermal tumor, leiomyosarcoma, and other sarcomas. Patients will have histologically confirmed advanced, persistent, or recurrent uterine sarcoma with documented disease progression after appropriate local therapy. Each patient will receive a chemotherapeutic regimen as outlined in each segment of the protocol.

PRIOR AND CURRENT PROGRESS
This is a master protocol for evaluation of patients with uterine sarcomas using cytotoxic chemotherapy. There are two subprotocols: W.U.# 4232 (GOG 87B) and W.U.# 4315 (GOG 87D).

CONCLUSIONS
See individual protocols.

REPORT DATE: 06/09/94 WORK UNIT # 4232

DETAIL SUMMARY SHEET

TITLE: GOG 87B: A Phase II Trial of Ifosfamide and the Uroprotector, Mesna, in the Treatment of Recurrent or Advanced Uterine Sarcomas

KEYWORDS: ifosfamide, Mesna, sarcoma

PRINCIPAL INVESTIGATOR: Mayer, Allan COL MC
ASSOCIATES: Park, Robert MD

DEPARTMENT: Department of Obstetrics and Gynecology STATUS: Completed
SERVICE: Gynecologic Oncology Group APPROVAL DATE: May 1986

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
This study is designed to allow the best possible chance for a new cytotoxic agent to demonstrate activity, constituting a Phase II design in a population of patients who have had no prior drug therapy. The study design will involve treating an average sample size of 30 evaluable patients with ifosfamide for each of the following cell type categories: mixed mesodermal tumor, leiomyosarcoma, and other sarcomas.

TECHNICAL APPROACH
Patients will have histologically confirmed advanced, persistent, or recurrent uterine sarcoma with documented disease progression after appropriate local therapy. Each patient will receive ifosfamide and Mesna for 5 days every 4 weeks until disease progression or adverse effects prohibit further therapy.

PRIOR AND CURRENT PROGRESS
There have been 102 patients entered into this protocol for the entire GOG; 93 of whom are evaluable. Walter Reed has entered six patients into this study. Of all the patients treated on protocol 87-B, 10 experienced grade III leukopenia, one experienced grade IV thrombocytopenia, 6 experienced grade IV granulocytopenia, 2 experienced grade IV neurotoxic effects, and one experienced grade IV anemia. Protocol was closed to patient accrual on 23 May 94. Protocol can be terminated as Walter Reed has no patients entered on this protocol.

CONCLUSIONS
Ifosfamide/Mesna may be the most active single agent therapy for advanced mixed mesodermal tumors of the uterus.

REPORT DATE: 06/01/94 WORK UNIT # 4234

DETAIL SUMMARY SHEET

TITLE: GOG 26U: A Phase II Trial of Ifosfamide and the Uroprotector, Mesna, in Patients with Advanced Pelvic Malignancies

KEYWORDS: ifosfamide, Mesna, malignancy

PRINCIPAL INVESTIGATOR: Mayer, Allan COL MC
ASSOCIATES: Park, Robert MD

DEPARTMENT: Department of Obstetrics and Gynecology STATUS: Completed
SERVICE: Gynecologic Oncology Group APPROVAL DATE: Aug 1986

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine the efficacy of chemotherapeutic agents in patients whose advanced malignancies have been resistant to higher priority methods of treatment. A "rejection"-type design will be used involving a fixed sample size of 25 patients per disease site per drug or combination of drugs studied.

TECHNICAL APPROACH
Ifosfamide, like cyclophosphamide, requires activation by a hepatic microsomal NADPH-dependent mixed-function oxidase system. A bi-ability to crosslink and fragment DNA is produced. Mesna has been shown to acceptably reduce the urothelial toxicity of ifosfamide in several European studies. All patients must have biopsy proven advanced pelvic malignancy to be eligible.

PRIOR AND CURRENT PROGRESS
The entire GOG has entered 219 patients into this study; Walter Reed has entered 5 patients. There have been 13 grade 4 toxicities for ovarian sarcoma: 5 leukopenia, 5 granulocytopenia, 1 thrombocytopenia, 1 renal, and 1 anemia. For nonsquamous cell carcinoma there have been 9 grade 4 toxicities: 1 thrombocytopenia, 6 granulocytopenia, 1 GU, and 1 alopenia. For carcinoma of the endometrium, there have been 16 grade 4 toxicities: 4 thrombocytopenias, 10 granulocytopenias, 1 neurotoxicity, and 1 bronchospasm. This protocol was closed and terminated on 23 May 94.

CONCLUSIONS
None.

REPORT DATE: 03/07/94 WORK UNIT # 4244

DETAIL SUMMARY SHEET

TITLE: GOG 90: Evaluation of Cisplatin, Etoposide and Bleomycin (BEP) Induction Followed by Vincristine, Dactinomycin and Cyclophosphamide (VAC) Consolidation in Advanced Ovarian Germ Cell Tumors, Phase II

KEYWORDS: ovarian, germ cell, tumors

PRINCIPAL INVESTIGATOR: Mayer, Allan COL MC
ASSOCIATES: Park, Robert MD

DEPARTMENT: Department of Obstetrics and Gynecology STATUS: Ongoing
SERVICE: Gynecologic Oncology Group APPROVAL DATE: Mar 1987

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To evaluate the effect of induction chemotherapy with cisplatin plus etoposide plus bleomycin (BEP), followed by consolidation with vincristine plus dactinomycin plus cyclophosphamide (VAC) in previously untreated patients with advanced ovarian germ cell tumors.

TECHNICAL APPROACH
Eligible patients include those with histologically confirmed malignant germ cell tumors of the ovary who have incompletely resected Stage II, III, or IV disease. Patients who have previously received pelvic radiation therapy will be eligible, but the initial dose of etoposide will be reduced 20%.

PRIOR AND CURRENT PROGRESS
The entire GOG has entered a total of 88 patients, 13 during the past year. The one WRAMC patient has been entered this past year. Overall, there have been 48 grade 4 episodes of granulocytopenia, 28 episodes of grade 4 leukopenia, 9 episodes of grade 4 thrombocytopenia, 1 episode of grade 4 anemia, 3 episodes of grade 4 GI toxicity, and 1 episode of allergic reaction.

CONCLUSIONS
None as yet.

REPORT DATE: 05/11/94 WORK UNIT # 4247

DETAIL SUMMARY SHEET

TITLE: GOG 95: Randomized Clinical Trial for the Treatment of Women with Selected Stage IC and II (A,B,C) and Selected Stage IAi and IBi and IAii and IBii Ovarian Cancer, Phase III

KEYWORDS: randomized, ovarian, cancer

PRINCIPAL INVESTIGATOR: Mayer, Allan COL MC
ASSOCIATES: Park, Robert COL MC

DEPARTMENT: Department of Obstetrics and Gynecology STATUS: Ongoing
SERVICE: Gynecologic Oncology Group APPROVAL DATE: May 1987

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
This study seeks to compare the progression-free interval and overall survival between P32 and a combination of cyclophosphamide and cisplatin for patients with early ovarian cancer and to determine the patterns of relapse for each form of therapy.

TECHNICAL APPROACH
All patients must have a histopathologic diagnosis of epithelial ovarian cancer of each histologic cell type: serous mucinous; others include endometrioid, transitional mesonephroid (clear cell), adenocarcinoma (endometrioid with squamous metaplasia), mixed epithelial, and unclassifiable (undifferentiated).

PRIOR AND CURRENT PROGRESS
The entire GOG has entered 242 patients (19 of them during the past year); 190 of these patients are currently evaluable. Since the protocol was activated, Walter Reed and its affiliates have entered 16 patients (one during the past year). WRAMC has entered a total of five patients (none during the past year). The five WRAMC patients have experienced no adverse reactions; serious toxicities, or deaths. GOG patients (after over 364 treatment cycles of P32 and chemotherapy combined) have experienced 76 grade 4 neutropenic episodes, 3 grade 4 thrombocytopenias, and 1 grade 4 GI toxicity. Two patients experienced small bowel perforation during P32 administration. There have been no treatment-related deaths. This protocol was closed to patient entry 14 Mar 94.

CONCLUSIONS
None as yet.

REPORT DATE: 07/11/94 WORK UNIT # 4254

DETAIL SUMMARY SHEET

TITLE: GOG 93: Evaluation of Intraperitoneal Chromic Phosphate Suspension Therapy Following Negative Second-Look Laparotomy for Epithelial Ovarian Carcinoma, Stage III, Phase III

KEYWORDS: chromic phosphate, ovarian, carcinoma

PRINCIPAL INVESTIGATOR: Mayer, Allan COL MC
ASSOCIATES: Park, Robert MC

DEPARTMENT: Department of Obstetrics and Gynecology STATUS: Ongoing
SERVICE: Gynecologic Oncology Group APPROVAL DATE: Jul 1987

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To evaluate the role of intraperitoneal chromic phosphate suspension therapy in patients with Stage III epithelial ovarian carcinoma who have no detectable evidence of disease at the second-look laparotomy.

TECHNICAL APPROACH
To be eligible, patients must have histologically confirmed primary epithelial carcinoma of the ovary and be in complete clinical remission. Patients must have a diagnosis of FIGO Stage III ovarian carcinoma.

PRIOR AND CURRENT PROGRESS
A total of 195 patients have been enrolled by the entire GOG, none this past year. WRAMC has entered four patients. GOG-wide there have been three grade 4 adverse effects; one hematologic, one GI, and one surgical.

CONCLUSIONS
None as yet.

REPORT DATE: 09/01/94 WORK UNIT # 4255

DETAIL SUMMARY SHEET

TITLE: GOG 78: Evaluation of Adjuvant Vinblastine, Bleomycin and Cisplatin Therapy in Totally Reducing Choriocarcinoma, Endodermal Sinus Tumor or Embryonal Carcinoma of the Ovary, Pure and Mixed with Other Elements, Phase II

KEYWORDS: VP-16, bleomycin, cisplatin

PRINCIPAL INVESTIGATOR: Mayer, Allan COL MC

DEPARTMENT: Department of Obstetrics and Gynecology STATUS: Ongoing
SERVICE: Gynecologic Oncology Group APPROVAL DATE: Sep 1987

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To evaluate the effect of adjuvant VP-16, bleomycin, and cisplatin chemotherapy in patients with endodermal sinus tumor, choriocarcinoma, embryonal carcinoma, and grade 2 and 3 immature teratoma of the ovary after removal of all gross tumors.

TECHNICAL APPROACH
Eligible patients include those with histologically confirmed Stage I choriocarcinoma, endodermal sinus tumor, embryonal carcinoma, and grade 2 and 3 immature teratoma. Patients with Stage II and III disease are also eligible if all gross tumor is removed. Serum AFP and beta-HCG levels should be normal.

PRIOR AND CURRENT PROGRESS
There have been 117 total entries from the entire GOG, none this past year. Walter Reed has entered two patients, none this year. There have been 50 grade 4 mylosuppressive toxities, 2 grade 4 GI toxities, and 1 dermatologic toxicity reported. This protocol was closed to patient entry on 10 Feb 92. WRAMC continues to follow one patient on this protocol.

CONCLUSIONS
BEP is effective in treating ovarian germ cell tumor patients with complete surgical resection. All future patients should be treated with this combination.

REPORT DATE: 10/07/93 WORK UNIT # 4257

DETAIL SUMMARY SHEET

TITLE: GOG 99: A Phase III Randomized Study of Adjunctive Radiation Therapy in Intermediate Risk Endometrial Adenocarcinoma

KEYWORDS: radiation, endometrial, adenocarcinoma

PRINCIPAL INVESTIGATOR: Mayer, Allan COL MC
ASSOCIATES: Park, Robert MD

DEPARTMENT: Department of Obstetrics and Gynecology
SERVICE: Gynecologic Oncology Group

STATUS: Ongoing
APPROVAL DATE: Oct 1987

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

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

TECHNICAL APPROACH

Patients with primary histologically confirmed grades 2 and 3 endometrial adenocarcinoma are eligible. Patients must have had a total abdominal hysterectomy, bilateral salpingo-oophorectomy, pelvic and para-aortic lymph node sampling, pelvic washings, and found to be surgical Stage I. Patients must have myometrial invasion.

PRIOR AND CURRENT PROGRESS

A total of 287 patients have been entered on this protocol from the entire GOG (42 during this past year). To date, Walter Reed has entered 8 patients; Walter Reed and its affiliates have entered a total of 25 patients. Currently, there are two patients with grade 4 GI toxicity, two with GI obstruction, and one with cutaneous grade 4 toxicity.

CONCLUSIONS

Too early.

REPORT DATE: 05/11/94 WORK UNIT # 4262

DETAIL SUMMARY SHEET

TITLE: A Multicenter Randomized Trial of Adjuvant Cisplatin/Bleomycin Plus Whole Pelvis Irradiation Vs. Cisplatin/Bleomycin Alone in High Risk Stage IB and IIA Carcinoma of the Cervix

KEYWORDS: carcinoma, cervix

PRINCIPAL INVESTIGATOR: Mayer, Allan COL MC
ASSOCIATES: Park, Robert MD

DEPARTMENT: Department of Obstetrics and Gynecology STATUS: Ongoing
SERVICE: Gynecologic Oncology Group APPROVAL DATE: May 1988

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
a) To evaluate the effect of adjunctive pelvic irradiation added to adjunctive chemotherapy for high risk Stage IB and IIA cervical cancer as measured by progression-free interval and survival; and b) To compare the relative toxicities of two regimens with respect to serious complications and/or side effects.

TECHNICAL APPROACH
To be eligible, patients must have had a radical hysterectomy with pelvic and para-aortic lymphadenectomy for Stage IB or IIA cervical carcinoma. They must have one or more of the following poor prognostic signs: nodal metastasis, parametrial involvement, positive surgical margin, tumor diameter greater than 4 cm, deep cervical invasion, adenocarcinoma, adenosquamous carcinoma, or small cell histologic type. Patients are randomized to receive postoperative chemotherapy alone or chemotherapy plus pelvic irradiation.

PRIOR AND CURRENT PROGRESS
A total of 72 patients have been entered into this study; none this past year. Walter Reed has entered eight patients. No significant toxicity has been reported thus far. Protocol is closed to patient entry.

CONCLUSIONS
None as yet.

REPORT DATE: 06/09/94 WORK UNIT # 4263

DETAIL SUMMARY SHEET

TITLE: GOG 26X: A Phase II Trial of Gallium Nitrate in Patients with Advanced Pelvic Malignancies

KEYWORDS: gallium nitrate, pelvic malignancies

PRINCIPAL INVESTIGATOR: Mayer, Allan COL MC
ASSOCIATES: Park, Robert MC

DEPARTMENT: Department of Obstetrics and Gynecology
SERVICE: Gynecologic Oncology Group

STATUS: Completed
APPROVAL DATE: Jun 1988

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine the efficacy of gallium nitrate in the treatment of advanced or recurrent gynecologic cancers.

TECHNICAL APPROACH
Patients will have histologically confirmed recurrent or metastatic gynecologic cancer which is refractory to curative therapy of established treatments.

PRIOR AND CURRENT PROGRESS
A total of 56 patients have been entered into this protocol from the entire GOG. No patients have been entered from WRAMC. No grade 4 adverse effects have been reported. This study was closed to patient entry, 8 Jan 93, and was terminated on 23 May 94.

CONCLUSIONS
Gallium nitrate has modest activity in previously treated patients with epithelial ovarian carcinoma.

REPORT DATE: 06/09/94 WORK UNIT # 4265

DETAIL SUMMARY SHEET

TITLE: GOG 102 A (Master Protocol): Intraperitoneal Administration of Cisplatin and 5-FU in Residual Ovarian Carcinoma, Phase II

KEYWORDS: cisplatin, 5-fluorouracil, ovarian carcinoma

PRINCIPAL INVESTIGATOR: Mayer, Allan COL MC

DEPARTMENT: Department of Obstetrics and Gynecology STATUS: Completed
SERVICE: Gynecologic Oncology Group APPROVAL DATE: Jun 1988

FUNDING: Current FY: $ 0 Previous FYs: $ 238 Total: $ 238

STUDY OBJECTIVE
To determine the activity of cisplatin and 5-fluorouracil when used by the intraperitoneal route in patients who have persistent minimal residual disease epithelial ovarian malignancies after standard therapy.

TECHNICAL APPROACH
Patients with primary, histologically documented, epithelial carcinoma of the ovary, and patients who have had partial or incomplete responses to combination chemotherapy and who have documented minimal residual disease (1.0 cm or less maxi tumor diameter) at second look laparotomy following chemotherapy are enrolled. Patients with a history of complete response followed by a recurrence with no residual nodule greater than 1 cm in diameter are also eligible.

PRIOR AND CURRENT PROGRESS
This is a master protocol. No patients have been entered from WRAMC. This protocol was closed 14 Mar 94.

CONCLUSIONS
None as yet.

REPORT DATE: 07/07/94 WORK UNIT # 4266

DETAIL SUMMARY SHEET

TITLE: GOG 76A: Master Protocol for Phase II Drug Studies in the Treatment of Advanced or Recurrent Squamous Cell Carcinoma of the Cervix.

KEYWORDS: advanced, squamous cell carcinoma, cervix

PRINCIPAL INVESTIGATOR: Mayer, Allan COL MC
ASSOCIATES: Park, Robert MD

DEPARTMENT: Department of Obstetrics and Gynecology STATUS: Ongoing
SERVICE: Gynecologic Oncology Group APPROVAL DATE: Jul 1988

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To continue identification of new active drugs in the treatment of advanced or recurrent squamous cell carcinomas of the cervix so that combinations of cytotoxic drugs can be formed which might lead to an improved complete remission rate.

TECHNICAL APPROACH
Patients enrolled in individual protocols under this Master Protocol will have histologically confirmed advanced, persistent, or recurrent squamous cell carcinoma of the cervix with documented disease progression after local therapy.

PRIOR AND CURRENT PROGRESS
GOG 76-A is a master protocol.

CONCLUSIONS
See individual protocols.

REPORT DATE: 11/10/93 WORK UNIT # 4268

DETAIL SUMMARY SHEET

TITLE: GOG 26DD: A Phase II Trial of Amonafide in Patients with Advanced Pelvic Malignancies

KEYWORDS: amonafide, pelvic, malignancy

PRINCIPAL INVESTIGATOR: Mayer, Allan COL MC

DEPARTMENT: Department of Obstetrics and Gynecology STATUS: Ongoing
SERVICE: Gynecologic Oncology Group APPROVAL DATE: Nov 1988

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine the efficacy of amonafide in the treatment of advanced pelvic malignancies.

TECHNICAL APPROACH
Eligible patients must have histologically confirmed recurrent or metastatic gynecologic cancer which is refractory to curative therapy or established treatments. All patients must have measurable disease.

PRIOR AND CURRENT PROGRESS
The entire GOG has entered 126 patients (75 during the past year); 25 with ovarian cancer, 48 with cervical cancer, and 53 with uterine sarcoma. WRAMC has entered four patients (one during the past year). Eighty percent of patients experienced myelosuppression grade 4, and less than 5% of them had GI toxicity.

CONCLUSIONS
Although amonafide has slight activity in epithelial tumors of the ovary and squamous cell cancer of the cervix, further studies in these tumor types are not warranted due to both low activity and severe hematologic toxicity.

REPORT DATE: 01/19/94 WORK UNIT # 4274

DETAIL SUMMARY SHEET

TITLE: GOG 104: Intraperitoneal Cisplatinum/Intravenous Cyclophosphamide Vs. Intravenous Cisplatinum/Intravenous Cyclophosphamide in Patients with Nonmeasurable Disease Stage III Ovarian Cancer, Phase III

KEYWORDS: cis-platinum, cyclophosphamide, ovary

PRINCIPAL INVESTIGATOR: Mayer, Allan COL MC
ASSOCIATES: Park, Robert MD

DEPARTMENT: Department of Obstetrics and Gynecology
SERVICE: Gynecologic Oncology Group

STATUS: Ongoing
APPROVAL DATE: Jan 1989

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To carry out a Phase III randomized trial of intermediate dose intraperitoneal cis-platinum plus intravenous cyclophosphamide versus intermediate dose intravenous cis-platinum plus intravenous cyclophosphamide for optimal Stage III ovarian cancer.

TECHNICAL APPROACH
Patients will be randomized to receive one of the two regimens listed above. Eligible patients must have a histologically confirmed pure epithelial ovarian carcinoma. Those with a borderline tumor will be excluded.

PRIOR AND CURRENT PROGRESS
To date, the entire GOG has entered 649 patients; 34 this past year. Four patients have been entered from WRAMC, none during this reporting year. There have been 41 grade 4 neutropenia episodes, and 9 grade 4 thrombocytopenic episodes reported. There have been 3 grade 4 GU toxicities and 12 grade 4 GI toxicities. There have been no reported deaths. This protocol closed to patient entry on July 14, 1992. WRAMC continues to follow patients on this protocol. orted. There have been 3 grade 4 GU toxicities and 12 grade 4 GI toxicities. There have been no reported deaths. This protocol closed to patient entry on July 14, 1992. WRAMC continues to follow patients on this protocol.

CONCLUSIONS
None as yet.

REPORT DATE: 05/19/94 WORK UNIT # 4277

DETAIL SUMMARY SHEET

TITLE: GOG 108: Ifosfamide and the Uroprotector, Mesna, with or without Cisplatin in Patients with Advanced or Recurrent Mixed Mesodermal Tumors of the Uterus, Phase III

KEYWORDS: ifosfamide, uterine, sarcoma

PRINCIPAL INVESTIGATOR: Mayer, Allan COL MC
ASSOCIATES: Park, Robert MD

DEPARTMENT: Department of Obstetrics and Gynecology
SERVICE: Gynecologic Oncology Group

STATUS: Ongoing
APPROVAL DATE: May 1989

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To confirm reported high response rates of advanced or recurrent mixed mesodermal tumors of the uterus to ifosfamide/Mesna. To determine whether the addition of cisplatin to ifosfamide/Mesna improves response rates or survival in patients with these tumors.

TECHNICAL APPROACH

Eligible patients include those with primary, histologically confirmed, heterologous or homologous (carcinosarcoma) mixed mesodermal tumors of the uterus. All patients must have measurable disease. Patients who have received prior chemotherapy are not eligible.

PRIOR AND CURRENT PROGRESS

The entire GOG has entered 136 patients (15 since the last report) of which 119 patients are currently evaluable. Walter Reed has entered two patients since the protocol was activated (none during the past year). One patient experienced disease progression and died of disease. There were no treatment related complications. The other patient completed therapy with one episode of grade 4 hematologic toxicity (neutropenia) out of eight total chemotherapy treatments. There were no lasting sequelae. In the groupwide GOG experience, over 600 treatment cycles have resulted in 52 grade 4 neutropenic episodes, 21 grade 4 thrombocytopenias, and 2 grade 4 GI toxicities (nausea and vomiting). There have been no treatment-related deaths. This protocol remains open for patient accrual.

CONCLUSIONS

Too early.

REPORT DATE: 01/19/94 WORK UNIT # 4281

DETAIL SUMMARY SHEET

TITLE: GOG 8801 A Phase I Evaluation of Multiple Daily Fraction Radiation and Hydroxyurea in Patients with Stage IIB, III and IVA Carcinoma of the Cervix with Negative Para-aortic Nodes

KEYWORDS: radiation, hydroxyurea, cervix

PRINCIPAL INVESTIGATOR: Mayer, Allan COL MC
ASSOCIATES: Park, Robert MD

DEPARTMENT: Department of Obstetrics and Gynecology
SERVICE: Gynecologic Oncology Group

STATUS: Ongoing
APPROVAL DATE: Jan 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To determine the toxicity of accelerated hyperfractionated radiation plus hydroxyurea in patients with cancer of the cervix. To determine the optimal tolerated dose of hyperfractionated radiation when combined with hydroxyurea and intracavitary radiation.

TECHNICAL APPROACH

Patients must have primary previously untreated histologically confirmed carcinoma of the cervix; squamous cell carcinoma, adenocarcinoma, and adenosquamous carcinoma are eligible. Patients must have FIGO Stage IIB, IIIA, IIIB, or IV disease with negative para-aortic nodes. Patients must have a para-aortic lymphadenectomy and intraperitoneal exploration with cytologic washings as outlined in the protocol.

PRIOR AND CURRENT PROGRESS

To date, 39 patients have been accrued by the entire GOG; 3 during the past year. Walter Reed has entered 5 patients; none during the past year. There have been four grade 3-4 toxicities; otherwise, minimal toxicity.

CONCLUSIONS

All dose levels (including dose level III) appear safe at this time. A fourth dose level may be added. Data are maturing currently.

REPORT DATE: 01/19/94 WORK UNIT # 4282

DETAIL SUMMARY SHEET

TITLE: GOG 8901 A Phase I Evaluation of Multiple Daily Fraction Radiation and 5FU Plus Cisplatin in Stage IIB, III and IVA Carcinoma of the Cervix with Negative Para-aortic Nodes

KEYWORDS: radiation, 5FU, cisplatin

PRINCIPAL INVESTIGATOR: Mayer, Allan COL MC
ASSOCIATES: Park, Robert MD

DEPARTMENT: Department of Obstetrics and Gynecology
SERVICE: Gynecologic Oncology Group

STATUS: Ongoing
APPROVAL DATE: Jan 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To determine the toxicity of accelerated hyperfractionated radiation plus 5-fluorouracil (5-FU) and cisplatin in patients with cancer of the cervix. To determine the optimal tolerated dose of hyperfractionated radiation when combined with 5-FU, cisplatin, and intracavitary radiation.

TECHNICAL APPROACH

Patients must have primary previously untreated histologically confirmed carcinoma of the cervix. Squamous cell carcinoma, adenocarcinoma, and adenosquamous carcinoma are eligible. Patients must have FIGO Stage IIB, IIIB, or IVA disease with negative para-aortic nodes. Patients must have a para-aortic lymphadenectomy and intraperitoneal exploration with cytologic washings as outlined in the protocol.

PRIOR AND CURRENT PROGRESS

To date, 34 patients have been accrued by the entire GOG; Walter Reed has entered 4 patients. No patients have been entered this past year. This protocol was closed to patient entry November 5, 1993. WRAMC continues to follow patients on this protocol. There have been three grade 3-4 toxicities at dose level 3, one vault necrosis, and one recto-vaginal fistula. Dose levels 1 and 2 had no treatment-related complications.

CONCLUSIONS

Chemotherapy chemosensitization with radiation appears less toxic than standard treatment with hydroxyurea. Data are maturing for acute/chronic reactions.

REPORT DATE: 05/19/94 WORK UNIT # 4291

DETAIL SUMMARY SHEET

TITLE: GOG 26GG A Phase II Trial of Fazarabine in Patients with Advanced or Recurrent Pelvic Malignancies

KEYWORDS: Fazarabine, pelvic, malignancy

PRINCIPAL INVESTIGATOR: Mayer, Allan COL MC
ASSOCIATES: Park, Robert MD

DEPARTMENT: Department of Obstetrics and Gynecology
SERVICE: Gynecologic Oncology Group

STATUS: Completed
APPROVAL DATE: May 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine the efficacy of Fazarabine in the treatment of advanced or recurrent gynecologic cancers refractory to curative therapy or established treatments.

TECHNICAL APPROACH
Patients with histologically confirmed gynecologic cancer either recurrent or advanced on initial presentation and refractory to curative therapy or established treatments will be eligible. The patients will be treated with Fazarabine at the dosage of 30 mg/m2/day for 5 days. Cycles of therapy will be repeated every 28 days.

PRIOR AND CURRENT PROGRESS
To date, 46 patients have been accrued by the entire GOG. Walter Reed has entered one patient. Three cases of grade 4 neutropenia (2 grade 4 leukopenias and one grade 4 sepsis) have been reported. No treatment-related deaths have been reported. This protocol was closed to squamous cell carcinoma of the cervix, 12 June 1990, and epithelial tumors of the ovary 1 September 1990. No WRAMC patients remain on this protocol.

CONCLUSIONS
Fazarabine exhibits no significant activity in patients with epithelial tumors of the ovary and squamous cell carcinoma of the cervix at the dose and schedule tested.

REPORT DATE: 06/09/94 WORK UNIT # 4294

DETAIL SUMMARY SHEET

TITLE: GOG 8803 Flow Cytometrically Determined Tumor DNA Content in Advanced Epithelial Ovarian Cancer

KEYWORDS: flow cytometry, DNA, ovarian carcinoma

PRINCIPAL INVESTIGATOR: Mayer, Allan COL MC

DEPARTMENT: Department of Obstetrics and Gynecology STATUS: Completed
SERVICE: Gynecologic Oncology Group APPROVAL DATE: Jun 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine if tumor ploidy and cell proliferation can be correlated to various tumor and host factors, tumor responses, second look laparotomy findings, relapse and patient survival. To determine if tumor ploidy and cell proliferation are consistent between primary and metastatic sites and if they remain stable before and after chemotherapy.

TECHNICAL APPROACH
Patients with advanced (Stage III or IV) epithelial ovarian cancer that were previously entered on GOG Protocols 47, 52, or 60 will be eligible. In addition, patients must have received enough chemotherapy on protocol to be evaluable for response, have a paraffin-embedded ovarian tumor specimen from the pretreatment laparotomy available for use, and have adequate follow-up information available to include second-look laparotomy findings.

PRIOR AND CURRENT PROGRESS
A total of 274 patients have been entered for the entire GOG; WRAMC entered no patients. Protocol was closed to patient accrual 20 July 1992.

CONCLUSIONS
Too early.

REPORT DATE: 06/09/94 WORK UNIT # 4295

DETAIL SUMMARY SHEET

TITLE: GOG 8809 Flow Cytometrically Determined Tumor DNA Content in Ovarian Tumors of Low Malignant Potential

KEYWORDS: flow cytometry, DNA, ovarian tumors

PRINCIPAL INVESTIGATOR: Mayer, Allan COL MC

DEPARTMENT: Department of Obstetrics and Gynecology STATUS: Completed
SERVICE: Gynecologic Oncology Group APPROVAL DATE: Jun 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine whether the DNA content of borderline ovarian tumors can be correlated with extent/stage of the tumor, potential for recurrence, and patient survival.

TECHNICAL APPROACH
Patients previously entered on GOG Protocol 72 with all stages of ovarian tumors of low malignant potential (any histologic type) can be entered. In addition, one paraffin-embedded specimen from pretreatment laparotomy and adequate follow-up information, to include second-look laparotomy findings or time to progression, must be available.

PRIOR AND CURRENT PROGRESS
A total of 151 patients have been entered from the entire GOG; five patients have been entered from Walter Reed. This protocol was closed to patient entry on 15 February 1993.

CONCLUSIONS
None yet.

REPORT DATE: 06/09/94 WORK UNIT # 4296

DETAIL SUMMARY SHEET

TITLE: GOG 8810 Flow Cytometrically Determined DNA Content in Endometrial Carcinoma

KEYWORDS: flow cytometry, DNA, adenocarcinoma

PRINCIPAL INVESTIGATOR: Mayer, Allan COL MC

DEPARTMENT: Department of Obstetrics and Gynecology STATUS: Completed
SERVICE: Gynecologic Oncology Group APPROVAL DATE: Jun 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine the DNA content of primary, recurrent and metastatic endometrial adenocarcinoma, and to identify whether the presence of aneuploid cell populations is related to histologic cell type, or grade or stage of the tumor, lymph node or distant metastasis, progression free interval, or survival. To determine whether tumor ploidy is consistent between primary tumors and their metastasis.

TECHNICAL APPROACH
Patients are eligible if previously entered on GOG Protocol 33, and if a paraffin block sample from the D&C or hysterectomy is available. If metastatic tumor is present, one paraffin block of the metastatic tumor would be highly desirable.

PRIOR AND CURRENT PROGRESS
A total of 293 patients have been entered for the entire GOG; 5 patients were entered from WRAMC. This protocol was closed to accrual on 8 November 1991. Follow-up is no longer required on this protocol.

CONCLUSIONS
Too early.

REPORT DATE: 06/09/94 WORK UNIT # 4298

DETAIL SUMMARY SHEET

TITLE: GOG 111 A Phase III Randomized Study of Cyclophosphamide and Cisplatin Vs. Taxol and Cisplatin in Patients with Suboptimal Stage III and Stage IV Epithelial Ovarian Carcinoma

KEYWORDS: ovarian carcinoma, cisplatin, Taxol

PRINCIPAL INVESTIGATOR: Mayer, Allan COL MC

DEPARTMENT: Department of Obstetrics and Gynecology STATUS: Completed
SERVICE: Gynecologic Oncology Group APPROVAL DATE: Jun 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine rate, response duration, and survival in suboptimal Stage III and Stage IV ovarian cancer treated with two different platinum-based combination chemotherapy regimens. To compare the relative toxicities of the two regimens.

TECHNICAL APPROACH
Patients with established ovarian epithelial cancer, suboptimal (1 cm in diameter) Stage III or Stage IV, are eligible. All patients must have optimal surgery for ovarian cancer. The following histologically confirmed ovarian malignancies are eligible: serous adenocarcinoma, mucinous adenocarcinoma, clear-cell adenocarcinoma, endometrioid adenocarcinoma, undifferentiated carcinoma, and mixed epithelial carcinoma.

PRIOR AND CURRENT PROGRESS
There have been a total of 410 patients entered into this protocol for the entire GOG; five patients have been from WRAMC. There have been 266 grade 4 leukopenias, 1 grade 4 anemia, 5 grade 4 thrombocytopenias, 13 grade 4 GI adverse effects, 1 grade 4 cardiac toxicity, 1 grade 4 renal toxicity, and 3 grade 4 neurologic toxicities. This protocol was closed to patient entry on 2 March 1992. Four of the patients at WRAMC died, and the fifth is lost to follow-up.

CONCLUSIONS
Too early.

REPORT DATE: 10/07/93 WORK UNIT # 4302

DETAIL SUMMARY SHEET

TITLE: GOG 8906 Extended Radiation Therapy With Concomitant 5-FU Infusion and Cisplatin Chemotherapy in Patients with Cervical Carcinoma Metastatic to Para-Aortic Lymph Nodes

KEYWORDS: radiation, cervix, para-aortic

PRINCIPAL INVESTIGATOR: Mayer, Allan COL MC

DEPARTMENT: Department of Obstetrics and Gynecology STATUS: Completed
SERVICE: Gynecologic Oncology Group APPROVAL DATE: Oct 1991

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To assess tolerance dose levels of 5-FU infusion and cisplatin chemotherapy in a prospective, dose escalating fashion with respect to acute toxicity when administered concomitantly with pelvic-para-aortic field radiation therapy. To assess long-term treatment toxicities.

TECHNICAL APPROACH
All patients have primary, previously untreated, histologically confirmed, invasive carcinoma of the uterine cervix (squamous, adenosquamous, and adenocarcinoma). All clinical stages, except clinical Stages IIIA and IVB, with metastasis to the para-aortic lymph nodes proven by cytologic or histologic means are eligible for this study.

PRIOR AND CURRENT PROGRESS
There have been 11 entries GOG-wide (none this past year), with no patients entered from Walter Reed or its affiliates. No severe toxicities have been noted to date. This protocol was closed 12 January 92.

CONCLUSIONS
The interim data analysis shows that extended field radiation with 5-FU and cisplatinum chemotherapy was well tolerated.

REPORT DATE: 11/10/93 WORK UNIT # 4303

DETAIL SUMMARY SHEET

TITLE: GOG 26-11 Phase II Trial of 5-Fluorouracil and High Dose Leucovorin in Advanced or Recurrent Pelvic Malignancies

KEYWORDS: pelvic, malignancy, 5-FU/leucovorin

PRINCIPAL INVESTIGATOR: Mayer, Allan COL MC

DEPARTMENT: Department of Obstetrics and Gynecology STATUS: Ongoing
SERVICE: Gynecologic Oncology Group APPROVAL DATE: Nov 1991

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine the efficacy of leucovorin in advanced metastatic or recurrent pelvic carcinomas.

TECHNICAL APPROACH
Eligible patients must have histologically confirmed recurrent or metastastic gynecologic cancer which is refractory to curative therapy or established treatments. All patients must have measurable disease.

PRIOR AND CURRENT PROGRESS
The entire GOG has entered 115 patients altogether (9 during the past year): 49 with ovarian cancer and 66 with cervical cancer. Walter Reed has entered two patients (one during the past year). Twenty percent of patients had myelosuppression, grade 4, and less than 5% experienced GI toxicity.

CONCLUSIONS
This drug showed modest activity in ovarian and squamous cervical disease. Future trials in primary disease therapy are planned.

REPORT DATE: 03/07/94 WORK UNIT # 4305

DETAIL SUMMARY SHEET

TITLE: GOG 101 A Phase II Evaluation of Preoperative Chemoradiation for Advanced Vulvar Cancer

KEYWORDS: vulva, cancer, chemoradiation

PRINCIPAL INVESTIGATOR: Mayer, Allan COL MC

DEPARTMENT: Department of Obstetrics and Gynecology STATUS: Completed
SERVICE: Gynecologic Oncology Group APPROVAL DATE: Mar 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine the feasibility, effectiveness, and morbidity of using preoperative chemoradiation and surgery in advanced cancer of the vulva.

TECHNICAL APPROACH
Depending on the TNM stage, patients will be treated with split course chemotherapy followed by radiation therapy to the primary lesion and/or pelvic and groin nodes. All patients will then undergo surgical resection of the residual tumor.

PRIOR AND CURRENT PROGRESS
A total of 100 patients were entered by the entire GOG; 17 during the past year. WRAMC entered no patients. There were 2 grade 4 GI toxicities, 28 grade 4 cutaneous toxicities, and 1 cardiovascular toxicity. This protocol was closed to patient entry in February 1994.

CONCLUSIONS
Based on preliminary evaluation of Phase I accrual, the therapy appears to be effective. The second phase of accrual is ongoing.

REPORT DATE: 04/22/94 WORK UNIT # 4306

DETAIL SUMMARY SHEET

TITLE: GOG 132 A Phase III Randomized Study of Cisplatin Versus Taxol Versus Taxol and Cisplantin in Patients with Suboptimal Stage III and Stage IV Epithelial Ovarian Carcinoma

KEYWORDS: cisplatin, Taxol, ovarian

PRINCIPAL INVESTIGATOR: Mayer, Allan COL MC

DEPARTMENT: Department of Obstetrics and Gynecology STATUS: Ongoing
SERVICE: Gynecologic Oncology Group APPROVAL DATE: Apr 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine the relative efficacy, survival, and toxicities of chemotherapeutic regimens consisting of cisplatin versus Taxol versus a combination of both drugs in patients with suboptimally debulked Stage III and IV epithelial ovarian cancer.

TECHNICAL APPROACH
After complete staging surgery, patients are randomized to receive six courses of cisplatin or Taxol or cisplatin and Taxol. Following therapy, if the patient is clinically free of disease, surgical reassessment will be performed.

PRIOR AND CURRENT PROGRESS
There have been 421 total entries for the entire GOG; 169 during the past year. WRAMC has entered 14, 13 this past year. There have been 250 grade 4 neutropenic episodes, 5 grade 4 thrombocytopenic episodes, 1 grade 4 anemia, 33 grade 4 GI complications, and 1 grade 4 GU complication.

CONCLUSIONS
Too early to conclude.

REPORT DATE: 06/14/94 WORK UNIT # 4308

DETAIL SUMMARY SHEET

TITLE: GOG 125: Extended Field Radiation Therapy with Concomitants 5-FU Infusion and Cisplatin Chemotherapy in Patients with Cervical Carcinoma Metastatic to Para-Aortic Lymph Nodes

KEYWORDS: radiation, cervical, lymph nodes

PRINCIPAL INVESTIGATOR: Mayer, Allan COL MC

DEPARTMENT: Department of Obstetrics and Gynecology STATUS: Completed
SERVICE: Gynecologic Oncology Group APPROVAL DATE: May 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
Patients with cervical carcinoma and para-aortic lymph node metastasis will receive extended field radiation and concomitant chemotherapy with 5-FU and cisplatin. The study will assess progression-free survival, overall survival, sites of failure, and morbidity.

TECHNICAL APPROACH
All patients with primary, previously untreated, histologically confirmed invasive carcinoma of the cervix will be eligible. Any clinical stage (except IIIA and IVB) are eligible. Metastasis to para-arotic nodes must be proven histologically or cytologically. Patients will receive pelvic and para-aortic radiation and cisplatin 50 mg/m2 on days 1 and 29, and 5-FU 1000 mg/m2 on days 2, 3, 4, 5 and 30, 31, 32, 33.

PRIOR AND CURRENT PROGRESS
A total of 95 patients have been accrued in the entire GOG. Walter Reed has entered no patients. No new subjects have been enrolled since the last APR. Six cases of grade 4 GI toxicity have been reported. Two cases of grade 4 hematologic toxicity and one grade 4 GU toxicity were reported. Protocol was closed to patient entry in November 1993. This protocol can be terminated.

CONCLUSIONS
Too early.

REPORT DATE: 06/09/94 WORK UNIT # 4309

DETAIL SUMMARY SHEET

TITLE: GOG 102: A Randomized Comparison of hydroxyurea vs. Hydroxyurea, 5-FU Infusion and Cisplatin vs. Weekly Cisplatin as Adjunct to Radiation Therapy in Patients with Stages II-B, III, or IV-A Carcinoma of the Cervix and Negative Para-Aortic Nodes

KEYWORDS: cervix, carcinoma, Phase III

PRINCIPAL INVESTIGATOR: Mayer, Allan COL MC

DEPARTMENT: Department of Obstetrics and Gynecology STATUS: Ongoing
SERVICE: Gynecologic Oncology Group APPROVAL DATE: Jun 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine whether hydroxyurea; hydroxyurea, 5-FU infusion plus bolus cisplatin; or weekly cisplatin is superior as a potentiator of radiation therapy in locally advanced cervical carcinoma.

TECHNICAL APPROACH
Patients with cervical carcinoma (Stages IIB, IIA, IIIB, or IVA) will undergo extraperitoneal staging surgery. Those patients with negative para-aortic nodes will then be randomized to receive radiotherapy plus either: 1) cisplatin; 2) cisplatin, 5FU and hydroxyurea; or 3) hydroxyurea. Following the completion of therapy the patients will be followed clinically.

PRIOR AND CURRENT PROGRESS
To date, the entire GOG has enrolled 186 patients; Walter Reed has enrolled 2 patients. Six patients on this study have experienced grade 4 hematologic toxicity. Five patients have experienced grade 4 GI toxicity, and one has experienced grade 4 GU toxicity. There have been no deaths during treatment.

CONCLUSIONS
None as yet.

REPORT DATE: 08/15/94 WORK UNIT # 4310

DETAIL SUMMARY SHEET

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

KEYWORDS: ovarian, tissue, collection

PRINCIPAL INVESTIGATOR: Mayer, Allan COL MC

DEPARTMENT: Department of Obstetrics and Gynecology STATUS: Ongoing
SERVICE: Gynecologic Oncology Group APPROVAL DATE: Aug 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To accomplish the collection of human ovarian tissue specimens and serum within GOG participating institutions, and to provide a long-term storage repository for ovarian tumors and serum. The material will be used in studies to better understand the molecular biology of ovarian tumors.

TECHNICAL APPROACH
All patients who have had ovarian tumor tissue or extra-ovarian peritoneal serous carcinoma tissue removed are eligible. All patients who have had ovaries removed because of a family history of ovarian cancer are eligible. The tissue, when removed, is shipped along with serum specimens to the GOG repository facility.

PRIOR AND CURRENT PROGRESS
This is an ovarian tissue accrual protocol. A total of 838 specimens studywide have been submitted to the Tissue Bank; 527 during the past year. WRAMC has entered 34 patients altogether; 20 during the past year. There have been no complications or toxicities.

CONCLUSIONS
Ovarian tissues are being accrued at a rapid rate.

REPORT DATE: 09/01/94 WORK UNIT # 4311

DETAIL SUMMARY SHEET

TITLE: GOG 134: A Phase III Trial of Taxol at Thrfee Dose Levels and G-CSFF at Two Dose Levels in Platinyum-Resistant Ovarian Carcinoma

KEYWORDS: taxol, ovarian, G-CSF

PRINCIPAL INVESTIGATOR: Mayer, Allan COL MC

DEPARTMENT: Department of Obstetrics and Gynecology STATUS: Ongoing
SERVICE: Gynecologic Oncology Group APPROVAL DATE: Sep 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine if taxol at different dose levels affects response rate, progression-free interval, or survival in patients with platinum-resistant ovarian cancer; to compare toxicities of the regimens; and to compare the efficacy and toxicity of G-CSF in patients receiving high dose taxol.

TECHNICAL APPROACH
Patients with platinum-resistant ovarian epithelial cancer with clinically measurable disease will be randomized to receive taxol at three different dose levels. Patients at the highest dose level will also receive G-CSF at one of two dose levels. Patients are then followed clinically to assess response.

PRIOR AND CURRENT PROGRESS
There have been 361 total entries for the entire GOG, 179 during the past year. Walter Reed has a total of six patients, two entered during this year. There have been 167 grade 4 neutropenic episodes (55 febrile), 2 grade 4 anemias, 1 grade 4 GI toxicity, and 1 grade 4 neurologic toxicity.

CONCLUSIONS
None as yet.

REPORT DATE: 10/07/93 WORK UNIT # 4312

DETAIL SUMMARY SHEET

TITLE: GOG 122: Whole Abdominal Radiotherapy versus Combination Doxorubicin-Cisplatin Chemotherapy in Advanced Endometrial Carcinoma

KEYWORDS: radiation, endometrial, chemotherapy

PRINCIPAL INVESTIGATOR: Mayer, Allan COL MC

DEPARTMENT: Department of Obstetrics and Gynecology STATUS: Ongoing
SERVICE: Gynecologic Oncology Group APPROVAL DATE: Oct 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To assess treatment outcomes (survival and progression-free interval) and failure patterns for advanced Stages III and IV endometrial adenocarcinoma patients using adjuvant, whole, abdominal radiation therapy versus combination intravenous chemotherapy. Also, to assess treatment toxicities of either therapy.

TECHNICAL APPROACH
All patients with endometrial carcinoma undergo surgical staging (TAH, BSO, LNS) and in advanced stage disease are randomized to adjuvant whole abdominal radiation (tele-therapy) versus combination intravenous doxorubicin-cisplatin chemotherapy every 3 weeks for eight courses.

PRIOR AND CURRENT PROGRESS
A total of 38 patients have been entered on this protocol in the entire GOG. Walter Reed has entered no patients to date. There have been no significant or unexpected toxicities reported to date.

CONCLUSIONS
None as yet.

REPORT DATE: 11/10/93 WORK UNIT # 4313

DETAIL SUMMARY SHEET

TITLE: GOG 114: A Phase III Randomized Study of Intravenous Cisplatin and Cyclophosphamide Versus Intravenous Cisplatin and Taxol Versus High Dose Intravenous Carboplatin Followed by Intravenous Taxol and Intraperitoneal Cisplatin in Patients with Optimal

KEYWORDS: ovarian, malignancy, Taxol

PRINCIPAL INVESTIGATOR: Mayer, Allan COL MC

DEPARTMENT: Department of Obstetrics and Gynecology STATUS: Ongoing
SERVICE: Gynecologic Oncology Group APPROVAL DATE: Nov 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To compare recurrence-free interval, complete pathologic response, and survivals between standard doses of cisplatinum/taxol and higher doses of intraperitoneal cisplatinum with the addition of carboplatinum.

TECHNICAL APPROACH
Patients with Stage III optimal epithelial ovarian cancer will be randomized to one of two arms of chemotherapy: standard IV does of Taxol and cisplatinum for six courses, or IV carboplatinum for two courses followed by IV Taxol with intraperitoneal high dose cisplatinum for six courses.

PRIOR AND CURRENT PROGRESS
A total of 104 patients have been entered in the GOG. Walter Reed has entered one patient. Less than 5% had myelosuppression, grade 4, and less than 5% experienced GI toxicity, grade 4.

CONCLUSIONS
None as yet.

REPORT DATE: 03/17/94 WORK UNIT # 4314

DETAIL SUMMARY SHEET

TITLE: GOG 127B: Evaluation of Isotretinoin and Alpha Interferon in Advanced or Recurrent Squamous Cell Carcinoma of the Cervix

KEYWORDS: interferon, squamous, cervix

PRINCIPAL INVESTIGATOR: Mayer, Allan COL MC

DEPARTMENT: Department of Obstetrics and Gynecology STATUS: Completed
SERVICE: Gynecologic Oncology Group APPROVAL DATE: Mar 1993

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To estimate the antitumor activity of isotretinoin and alpha interferon in patients with advanced, persistent, or recurrent squamous cell carcinoma of the cervix who have failed on higher priority treatment protocols. To determine the nature and degree of toxicity of isotretinoin and alpha interferon in this cohort of patients.

TECHNICAL APPROACH
Eligible patients include all of those with advanced or recurrent squamous cell cervical carcinoma with measureable disease who failed local therapy.

PRIOR AND CURRENT PROGRESS
A total of 22 patients were entered from the GOG. No patients were entered from WRAMC. One grade 4 thrombocytopenic toxicity was reported. This protocol was closed to patient entry July 1993.

CONCLUSIONS
None as yet.

REPORT DATE: 09/16/94 WORK UNIT # 4816

DETAIL SUMMARY SHEET

TITLE: The Effect of Irradiation on Red Blood Cell Antigen Densities: A Flow Cytometric Analysis

KEYWORDS: red cell, flow cytometry, irradiation

PRINCIPAL INVESTIGATOR: Salata, Kalman PhD
ASSOCIATES: Hershey, Joyce BA; Crowell, Mark LT USN

DEPARTMENT: Department of Pathology and Area Laboratories

STATUS: Ongoing
APPROVAL DATE: Sep 1993

FUNDING: Current FY: $ 3,316 Previous FYs: $ 0 Total: $ 3,316

STUDY OBJECTIVE

To measure the effect of 2500 and 4000 rads of gamma irradiation on red cell antigens using flow cytometry.

TECHNICAL APPROACH

Packed red blood cells are irradiated at 2500 and 4000 rads. Direct and indirect immunofluorescent staining with flow cytomery is used to measure changes in red cell surface antigens, Rho(D) and glycophorin A, over time after gamma irradiation. These results are compared to plasma potassium and hemoglobin levels.

PRIOR AND CURRENT PROGRESS

Eight subjects were enrolled in the study. There were no adverse reactions, and no one withdrew from the study. There were no statistical differences in Rho(D) and glycophorin A expression over 28 days in nonirradiated cells compared to irradiated cells. While there was a trend to higher levels of plasma potassium in irradiated blood, the differences were not statistically significant.

CONCLUSIONS

Irradiation of packed whole blood units at 2500 and 4000 rads did not affect surface density of red cell surface of Rho(D) antigen and glycophorin A. Plasma potassium in irradiated packed red blood cell units rose over time in comparison to unirradiated units, but the differences were not statistically significant.

REPORT DATE: 08/04/94 WORK UNIT # 6064

DETAIL SUMMARY SHEET

TITLE: The Effect of Somatomedin C on Androgen Receptor and 5-a-reductase Activities in a Hormonally Responsive Tissue, the Penile Foreskin

KEYWORDS: somatomedin C, androgen, 5-alpha-reductase

PRINCIPAL INVESTIGATOR: Francis, Gary LTC MC
ASSOCIATES: Poth, Merrily MD

DEPARTMENT: Department of Pediatrics

STATUS: Completed
APPROVAL DATE: Aug 1989

FUNDING: Current FY: $ 2,873 Previous FYs: $ 32,931 Total: $ 35,804

STUDY OBJECTIVE
To determine whether or not growth hormone (GH) acting through its effector hormone, somatomedin C (IGF-1), has in vitro effects on androgen receptor activity or 5-alpha-reductase activity in the penile foreskin.

TECHNICAL APPROACH
Primary explant fibroblast cultures will be prepared from five normal infant foreskins at the time of routine circumcision. Confluent monolayer cultures will be used to assay 5-alpha-reductase activity by the conversion 3H-testosterone to H-dihydrotestosterone and metabolites, as well as androgen receptor activity assayed by specific binding of 3H-dihydrotestosterone to whole cell preparations.

PRIOR AND CURRENT PROGRESS
Final experiments have been performed. After final analysis, the last paper in this series will be submitted. It will describe the effect of testosterone on the production of IGF1 and IGF-binding protein by these foreskin fibroblasts. This paper should be forthcoming during calendar year 1994.

CONCLUSIONS
IGF-1, but not growth hormone, has profound effects on foreskin cells which may or may not be related to the action of androgens on this same tissue.

REPORT DATE: 01/04/94 WORK UNIT # 6256

DETAIL SUMMARY SHEET

TITLE: The In Vitro Effect of Tumor Necrosis Factor on the Function of the Pituitary Gonadotrophs of the Rat

KEYWORDS: TNF, pituitary

PRINCIPAL INVESTIGATOR: Francis, Gary LTC MC

DEPARTMENT: Department of Pediatrics STATUS: Ongoing
APPROVAL DATE: Jan 1990

FUNDING: Current FY: $ 1,327 Previous FYs: $ 3,104 Total: $ 4,431

STUDY OBJECTIVE
To determine if tumor necrosis factor affects the secretion of LH from cultured pituitary cells of the rat.

TECHNICAL APPROACH
Pituitary cell cultures will be established from acutely dispersed cells. Fresh cells must be prepared for each experiment. Cells will be stimulated with GnRH, and the LE released will be measured by Rat LH-RIA. TNF will be added in parallel experiments to determine if it blocks GnRH stimulated LH release.

PRIOR AND CURRENT PROGRESS
Pituitary cell lines have been established in culture. Preliminary results have shown that these cells produce LH and FSH.

CONCLUSIONS
Study is feasible. However, data currently in the literature has shown that TNF does decrease the production of LH and FSH.

REPORT DATE: 01/04/94 WORK UNIT # 6257

DETAIL SUMMARY SHEET

TITLE: The In Vitro Effect of Tumor Necrosis Factor on the Function of the Gonadal Axis of the Rat

KEYWORDS: TNF, gonad

PRINCIPAL INVESTIGATOR: Francis, Gary LTC MC

DEPARTMENT: Department of Pediatrics STATUS: Ongoing
APPROVAL DATE: Jan 1990

FUNDING: Current FY: $ 4,033 Previous FYs: $ 37,021 Total: $ 41,054

STUDY OBJECTIVE
To determine if tumor necrosis factor (TNF) has an effect on testosterone (T) production in the testis.

TECHNICAL APPROACH
Leydig cells will be separated and cultured from acutely dispersed testicular cell preparation. Cells will be incubated with hCG and TNF to determine if TNF inhibits T production.

PRIOR AND CURRENT PROGRESS
This study has resulted in the publication of one paper describing the effects of both macrophage-conditioned media and synthetic cytokines on the production of testosterone by Leydig cell cultures derived from rat testes. In addition, another paper describing the role of nitric oxide in the regulation of Leydig cell function has been submitted, and is under review.

CONCLUSIONS
This study has resulted in the generation of interesting data concerning the relationship between cytokines and the function of the gonad, especially with respect to the previously unknown or suspected role of nitric oxide in testosterone synthesis.

REPORT DATE: 04/29/94 WORK UNIT # 6266

DETAIL SUMMARY SHEET

TITLE: High Dose Chemotherapy with Autologous Bone Marrow Rescue in Children with Recurrent or Progressive Solid Tumors or Primary CNS Malignancies, Phase II

KEYWORDS: autologous, marrow transplantation, solid malignancy

PRINCIPAL INVESTIGATOR: Edwards, E. Glenn MAJ MC

DEPARTMENT: Department of Pediatrics STATUS: Ongoing
APPROVAL DATE: Apr 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To define the toxicities of the preparative regimen high dose Cytoxan, etoposide, and carboplatin. To measure response rate in a group of patients with refractory solid tumors and CNS malignancies following this regimen and autologous bone marrow transplantation (ABMT).

TECHNICAL APPROACH
Patients 21 years old or less will be entered in the study. After marrow is harvested and stored, ablative chemotherapy will be given for 5 days, followed by a day without chemotherapy. The next day, stored marrow will be reinfused as a "rescue" for the marrow damaged by the intensive therapy. This protocol accepts registrants who are refractory to other treatments for solid tumors and CNS tumors. Response will be evaluated at 60 days post marrow reinfusion.

PRIOR AND CURRENT PROGRESS
In the past year, 2 registrants were entered on study (total now 14). There have been no unexpected toxicities in any registrants. Response at day 60 post-ABMT was: five in complete remission, four in partial response, one with stable disease, one too early to assess, and three with progressive disease. To date, 7 of the 14 patients remain alive.

CONCLUSIONS
Study should remain open.

REPORT DATE: 04/26/94 WORK UNIT # 6267

DETAIL SUMMARY SHEET

TITLE: The Value of Sequential C-Reactive Protein Levels in Sickle Cell Anemia Patients Presenting with Symptoms of Crisis or Infection

KEYWORDS: sickle cell disease, c-reactive protein

PRINCIPAL INVESTIGATOR: Maybee, David COL MC

DEPARTMENT: Department of Pediatrics STATUS: Ongoing
APPROVAL DATE: Apr 1990

FUNDING: Current FY: $ 372 Previous FYs: $ 0 Total: $ 372

STUDY OBJECTIVE
To study the clinical value of sequential c-reactive protein (CRP) levels in the differential diagnosis of bacterial infection vs. sickle crisis, and to compile data on age-related ranges of CRP values found in children with sickle cell anemia.

TECHNICAL APPROACH
CRP levels for baseline will be taken at time of regular checkups in the Outpatient Hematology Clinic and updated every 6 months. At the time of presentation with symptoms of bacterial infection or sickle crisis, CRP values will be taken at set intervals and compared to the registrant's baseline. After the event is diagnosed by standard methods, differences in CRP values will then be analyzed.

PRIOR AND CURRENT PROGRESS
A total of 35 samples have been taken from 11 patients. Since last progress report there have been no new registrants or samples. However, PI will task the new Hematology-Oncology fellow with this study shortly after he reports for duty (end of May, early June). Evaluation of data is underway.

CONCLUSIONS
Study should remain open.

REPORT DATE: 11/17/93 WORK UNIT # 6275

DETAIL SUMMARY SHEET

TITLE: Modified Immune Serum Globulin in Neonates (1990)

KEYWORDS: IVIG, neonate, RSV

PRINCIPAL INVESTIGATOR: Weisman, Leonard COL MC

DEPARTMENT: Department of Pediatrics STATUS: Terminated
APPROVAL DATE: Oct 1990

FUNDING: Current FY: $ 352 Previous FYs: $ 0 Total: $ 352

STUDY OBJECTIVE
To determine the RSV-specific antibody pharmacokinetics of RSVIG in neonates with suspected infection.

TECHNICAL APPROACH
Twenty neonates with suspected infection will be evaluated for RSV infection and treated with a single infusion of 1000/mg/kg of one of two RSVIG preparations. Serum IgG and RSV neutralization titers will be determined prior to infusion, immediately, 1, 4, 8, 11, 14 and 42 days after infusion.

PRIOR AND CURRENT PROGRESS
This protocol has been administratively terminated.

CONCLUSIONS
This protocol has been administratively terminated.

REPORT DATE: 07/25/94 WORK UNIT # 6290

DETAIL SUMMARY SHEET

TITLE: Utilization of Foot Length as an Estimation of Gestational Age in the Neonate

KEYWORDS: neonate, gestational age, foot length

PRINCIPAL INVESTIGATOR: Moores, Russell MAJ MC

DEPARTMENT: Department of Pediatrics STATUS: Terminated
APPROVAL DATE: Jun 1991

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine the usefulness of neonatal foot length in the assessment of gestational age in the neonate.

TECHNICAL APPROACH
Foot length is determined on neonates less than 24 hours of age. Each infant will have his or her gestational age determined by maternal dates/ultrasound data, as well as by neonatal Ballard and retinal vasculature exams.

PRIOR AND CURRENT PROGRESS
This protocol has been administratively terminated.

CONCLUSIONS
This protocol has been administratively terminated.

REPORT DATE: 10/31/94 WORK UNIT # 6299

DETAIL SUMMARY SHEET

TITLE: The Neonatal Rat Pup as a Model for Staphylococcus Epidermidis Sepsis in the Newborn: The Effects of a Lipid Emulsion on Survival and Neutrophil Function

KEYWORDS: neutrophil, lipid

PRINCIPAL INVESTIGATOR: Pierce, John COL MC

DEPARTMENT: Department of Pediatrics STATUS: Terminated
APPROVAL DATE: Sep 1991

FUNDING: Current FY: $ 1,160 Previous FYs: $ 10,677 Total: $ 11,837

STUDY OBJECTIVE
To establish a suckling rat model for Staphylococcus epidermidis (S epi) sepsis; to determine the pharmacokinetics of two parenterally administered lipid emulsions in the non-infected suckling rat using single and multiple dose regimens; and to determine the effects of parenterally administered lipids in the above animal model and whether these effects are due to changes in neutrophil function.

TECHNICAL APPROACH
One day old suckling rats will be randomly assigned by weight and litter to receive 10^6 - 10^8 cfu of S epi subcutaneously. Serial blood cultures will be taken at 2, 24, and 168 hours to determine rate and clearing of infection. Weights and mortality will be followed for 7 days. Pups will be randomized to receive one of five single or three multiple injections of 10 or 20% intralipid. Blood will be taken at 0, 2, 24, 48, 72, and 168 hours for serum triglyceride levels via direct cardiac puncture after anesthesia. Third stage of this study involves infection of pups receiving intralipid (described above), and measuring growth and survival. Neutrophil assays will be done on rats receiving lipid and S epi.

PRIOR AND CURRENT PROGRESS
This research protocol was administratively terminated.

CONCLUSIONS
This research protocol was administratively terminated.

REPORT DATE: 10/08/93 WORK UNIT # 6300

DETAIL SUMMARY SHEET

TITLE: The Use of Surfactant Therapy During the Early Management of the Meconium Aspiration Synbdrome in a Piglet Model Ventilated with Either High Frequency or Conventional Mechanical Ventilation

KEYWORDS: meconium aspiration, surfactant, ventilation

PRINCIPAL INVESTIGATOR: Moores, Russell MAJ MC

DEPARTMENT: Department of Pediatrics

STATUS: Completed
APPROVAL DATE: Oct 1991

FUNDING: Current FY: $ 269 Previous FYs: $ 25,523 Total: $ 25,792

STUDY OBJECTIVE
To determine if use of surfactant therapy will improve physiologic parameters, result in less severe histologic findings, or reduce surface tension measurements in a piglet model of the meconium aspiration syndrome.

TECHNICAL APPROACH
Meconium will be insufflated into piglet trachea, followed by randomization to either conventional or high frequency ventilation. A standard dose of surfactant will be administered 1 hour later or the piglets are randomized to twice the standard dose. Physiologic parameters will be followed during the 6 hours of ventilation. After euthanasia, histologic evaluation of the lungs will be performed (using a previously published scoring system). Finally, surface tension measurements will be made during the course of the experiment.

PRIOR AND CURRENT PROGRESS
During the past year, this study was completed and has been published. The laboratory portion of this study was performed in the first year, utilizing a total of 70 neonatal piglets.

CONCLUSIONS
Less severe pulmonary pathologic alterations were noted with the HFV treatment of meconium aspirations. Further clinical studies are needed.

REPORT DATE: 10/15/93 WORK UNIT # 6301

DETAIL SUMMARY SHEET

TITLE: High Dose Chemotherapy with Autologus Bone Marrow Support Using Ex-Vivo Marrow Treatment with 4-Hydroxyperoxycyclophosphamide (4-HC) for Relapsed Acute Myelogenous Leukemia

KEYWORDS: ABMT, ex-vivo purge, myelogenous leukemia

PRINCIPAL INVESTIGATOR: Edwards, E. Glenn MAJ MC
ASSOCIATES: Burrell, Linda MAJ MC

DEPARTMENT: Department of Pediatrics

STATUS: Ongoing
APPROVAL DATE: Oct 1991

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To assess the impact of autologous bone marrow support after ex-vivo treatment with 4-Hydroxyperoxycyclophosphamide (4-HC) purging used with a standard preparative (cytotoxic) myeloid regimen for patients with acute myelogenous leukemia who have relapsed.

TECHNICAL APPROACH

Patients diagnosed with acute myelogenous leukemia who are in first or subsequent remission (adults and children) will have bone marrow harvested. One portion of the marrow will be cryopreserved after purging for cancer cells with the drug 4-HC, and the other portion will be cryopreserved without 4-HC purging for use as a backup should anything go wrong with the purged marrow. At the time of relapse (if this occurs), cytotoxic therapy with Cytoxan and busulfan will be given for 1 week, followed by infusion of the purged stored marrow. Patients will be followed for response.

PRIOR AND CURRENT PROGRESS

To date, 10 patients have been enrolled on study (3 during the past year); 3 who were in second remission and 7 who were in first remission. All have had bone marrow harvested and purged with 4-HC, and the marrow has been cryopreserved. All harvests were performed at WRAMC. In all but two, the marrow was purged by the WRAMC Bone Marrow Processing Laboratory. The first two marrows were purged at Children's National Medical Center, Washington, DC, pending WRAMC approval as an investigative site for 4-HC. There have been no unexpected complications due to the marrow harvest procedure. Sufficient marrow cells were obtained for the storage of an unpurged backup for all but one patient, who has since undergone a second harvest to obtain marrow for the backup. As of yet, no patients have gone on to receive myeloablative therapy and transplantation.

CONCLUSIONS

This study should remain open.

REPORT DATE: 01/04/94 WORK UNIT # 6308

DETAIL SUMMARY SHEET

TITLE: The In Vitro Effect of Cytokines on Placental Steroidogenesis

KEYWORDS: cytokines, labor, placenta

PRINCIPAL INVESTIGATOR: Francis, Gary L. LTC MC
ASSOCIATES: Payne, Matthew CPT PhD; Abdel-rahim, Maged MS

DEPARTMENT: Department of Pediatrics

STATUS: Ongoing
APPROVAL DATE: Jan 1992

FUNDING: Current FY: $18,830 Previous FYs: $ 5,772 Total: $ 24,602

STUDY OBJECTIVE
To determine if cytokines directly affect the production of placental steroids, which might then effect the timing of labor.

TECHNICAL APPROACH
Fragments of human placenta will be established in short-term organ culture and demonstrated to synthesize both progesterone and estradiol from precursors added to culture media. Preliminary studies have shown that cytokines (contained in macrophage conditioned media) decrease progesterone and increase estradiol synthesis. There is a suggestion that this might be associated with a change in PGE2 but not PGF2 production.

PRIOR AND CURRENT PROGRESS
Original observations of the effect of macrophage-conditioned media on the synthesis of steroid hormones by placental fragments have been confirmed. In addition, an established cell line of JEG-3 choriocarcinoma cells has been studied and found to synthesize E2, progesterone, and hCG. Using this system, which is devoid of macrophages, has allowed study of the effect of synthetic cytokines and conditioned media on a pure cell line. These studies are currently in progress.

CONCLUSIONS
This study is progressing well, and generating interesting data concerning the interactions between cytokines and the synthetic capabilities of the placenta and cells derived from the placenta. Further study is underway.

REPORT DATE: 03/09/94 WORK UNIT # 6313

DETAIL SUMMARY SHEET

TITLE: Soluble Interleukin-2 Receptor (sIL2R) Levels in New Onset Insulin Dependent Diabetes Mellitus During Biostator Therapy

KEYWORDS: diabetes mellitus, biostator therapy, SIL2R

PRINCIPAL INVESTIGATOR: Francis, Gary LTC MC
ASSOCIATES: Curley, Moira MAJ MC

DEPARTMENT: Department of Pediatrics

STATUS: Ongoing
APPROVAL DATE: Mar 1992

FUNDING: Current FY: $ 1,260 Previous FYs: $ 6,024 Total: $ 7,284

STUDY OBJECTIVE

To determine: (1) if soluble interleukin-2 receptor (sIL2R) levels (an indicator of the level of immune system activation) are elevated in new onset patients with diabetes mellitus and (2) if these levels are suppressed by therapy with the biostator (artificial pancreas), one of the models of intensive insulin therapy currently in use at the University of South Florida (USF), Tampa.

TECHNICAL APPROACH

Serum samples will be obtained from banked (stored) sera, which is under the auspices of a protocol for biostator therapy use at USF and under the custody of Dr. John Malone. These serum samples will be obtained under his protocol and informed consent. No additional blood samples will be obtained, and none will be obtained at WRAMC. sIL2R levels will be determined by enzyme linked immunoassay using commercially available materials.

PRIOR AND CURRENT PROGRESS

Samples have been obtained from 31 patients with IDDM, 22 family members without IDDM, and 20 normal, age-matched controls. sIL2R levels have been determined on all subjects. Additional samples from controls in the 3-8 year age range are in the laboratory to be analyzed. This should allow for statistical analysis of data stratified by age, years of diagnosis, and presence of anti-islet cell antibodies.

CONCLUSIONS

This study is progressing well, and nearing completion. Data has been submitted to two national meetings for presentation in abstract form.

REPORT DATE: 05/12/94 WORK UNIT # 6321

DETAIL SUMMARY SHEET

TITLE: The Effects of Sex Steroids and Vitamin E on Lipid Peroxidation in the Diabetic Rat Model

KEYWORDS: diabetes, sex steroids, lipid peroxidation

PRINCIPAL INVESTIGATOR: Poth, Merrily MD

DEPARTMENT: Department of Pediatrics STATUS: Ongoing
APPROVAL DATE: May 1992

FUNDING: Current FY: $ 60 Previous FYs: $ 7,464 Total: $ 7,524

STUDY OBJECTIVE
To evaluate the effects of gonadal steroids on lipid peroxidation in the diabetic rat model. The potential protective effects of the antioxidant Vitamin E will also be evaluated.

TECHNICAL APPROACH
Initially, castrated 5-week-old Sprague Dawley rats were used, with puberty initiated using testosterone pellets. This proved unsuccessful; levels of testosterone in an RIA were undetectable. Presently, castrated and intact animals are being used. To induce diabetes, 60 mg/kg streptozotocin is being given. Animals are evaluated for evidence of increased free radicals (the original method of evaluation was felt to be unsuccessful due to the difficulty of recovery of the product); thus, an HPLC method and urinary 8-isoprostane are being used. Evidence of neuropathy is being evaluated after 3 months of being diabetic with an assay which measures for microalbumin.

PRIOR AND CURRENT PROGRESS
A total of 77 rats were used altogether; none during the past year. Data collection is complete and is currently being analyzed. The next step will be to write a manuscript for submission for publication, hopefully during the next year.

CONCLUSIONS
Pending anlaysis of data.

REPORT DATE: 06/01/94 WORK UNIT # 6324

DETAIL SUMMARY SHEET

TITLE: Electrogastrogram and Gastric Emptying in Infants with Hypertrophic Pyloric Stenosis and Gastroesophageal Reflux

KEYWORDS: gastroesophageal reflux

PRINCIPAL INVESTIGATOR: Pineiro, Victor MAJ, MC
ASSOCIATES: Latimer, John COL MC; Pearl, Richard LTC MC

DEPARTMENT: Department of Pediatrics

STATUS: Ongoing
APPROVAL DATE: May 1992

FUNDING: Current FY: $ 2,005 Previous FYs: $ 0 Total: $ 2,005

STUDY OBJECTIVE

To assess gastric emptying, gastric acid secretion, and gastric electromyography in patients with hypertrophic pyloric stenosis (HPS) and compare to patients with gastroesophageal reflux (GER). Specifically, to determine if there is a correlation between gastric emptying and cutaneous electrogastrogram (EGG) in patients with HPS or GER. Any differences in the EGG amplitude, area under the curve, and frequency in patients with HPS or GER will be compared to controls.

TECHNICAL APPROACH

Infants with apnea, HPS, or GER will be recruited to participate. All patients will undergo an electrogastrogram (similar to an electrocardiogram) to study the electrical potential variations generated by the stomach. The control subjects will be studied once, while the patients with GER and HPS will be studied three or four times to determine the effect of therapy on the EGG. In addition, patients with HPS and GER will also undergo placement of a nasogastric tube to determine the rate of gastric emptying and gastric acid output.

PRIOR AND CURRENT PROGRESS

A total of five subjects have been enrolled. Since the last APR, four subjects have been enrolled (two patients with GER and two controls with a history of apnea), and were studied once. Both apnea patients were evaluated for the possibility that GER caused their apnea, and their evaluation proved negative for reflux. The two patients with reflux did not return for their follow-up studies due to distance constraints associated with their parents' duty stations. No adverse reactions or benefits were experienced by the subjects. The researchers have not been able to recruit the number of patients initially intended for the study, partly because of the pattern of referrals to WRAMC. Most reflux patients who have been referred have other underlying disorders that disqualify them from participation.

CONCLUSIONS

Good quality studies have been obtained in the few patients recruited. The researchers are attempting to increase enrollment by requesting referrals of appropriate patients from pediatricians in military primary care clinics in the D.C. area. More patients must be enrolled before conclusions can be drawn from the study.

REPORT DATE: 06/30/94 WORK UNIT # 6326

DETAIL SUMMARY SHEET

TITLE: The Status of Adolescent Medicine in the Military Health Service System

KEYWORDS: adolescent medicine, military, health care

PRINCIPAL INVESTIGATOR: Robinson, C. Anita MD

DEPARTMENT: Department of Pediatrics STATUS: Ongoing
APPROVAL DATE: Jun 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To ascertain the quality and level of health care given to adolescents in the Tri-Service System.

TECHNICAL APPROACH
One hundred randomly selected CONUS and non-CONUS military posts were sent a questionnaire to obtain information on adolescent health care. At each site, the questionnaire was sent to departments most likely to service adoloscents -- i.e., Emergency Room, Pediatrics, Family Practice, Acute Care Clinic, and Internal Medicine.

PRIOR AND CURRENT PROGRESS
Altogether, 560 questionnaires were mailed to 108 military facilities. A total of 277 questionnaires were returned in the first mailing. A reminder notice was sent, and 129 more questionnaires were received. A total of 406 questionnaireswere received; all were appropriate for data analysis. Prior and current program data collection has been completed. Data analysis is in the final stages. Manuscript preparation has began.

CONCLUSIONS
Pending.

REPORT DATE: 06/13/94 WORK UNIT # 6327

DETAIL SUMMARY SHEET

TITLE: Effect of Somatostatin on Glomerular PGE2 Production in the Diabetic Rat

KEYWORDS: somatostatin, prostaglandin E2, diabetes mellitus

PRINCIPAL INVESTIGATOR: Poth, Merrily MD

DEPARTMENT: Department of Pediatrics

STATUS: Completed
APPROVAL DATE: Jun 1992

FUNDING: Current FY: $ 7,352 Previous FYs: $ 5,115 Total: $ 12,467

STUDY OBJECTIVE

To study the effects of somatostatin (SRIH), both in-vitro and in-vivo, on the glomerular production of PG E2 as it relates to diabetic nephropathy in the rat model.

TECHNICAL APPROACH

Whole rat glomeruli will be isolated from diabetic and control animals and incubated with either SRIH or captopril. PG E2 in the supernatant will be assayed by RIA. The acute effects of SRIH infusion vs saline on the in-vivo renal production of PG E2, as measured by urine PG E2 concentrations, as well as on several parameters of renal physiology (GFR, RPF, RVR, FF) using standard PAH/inulin clearance measurements will be determined. STZ diabetic rats and controls will be treated with SRIH or saline via osmotic pump for 8 weeks, after which urine albumin excretion, urine PG E2, and relative kidney hypertrophy will be measured to determine the more chronic effects of SRIH on these parameters.

PRIOR AND CURRENT PROGRESS

The researchers found that rat glomeruli incubated with somatostatin (SRIH) at high concentrations (10 -^6 M) produced increased amounts of PGE2 using glomeruli from both control and diabetic rats. However, at lower concentrations of SRIH (10 -^10 M) glomerular PGE2 was increased only in glomeruli from diabetic rats. This has not been previously reported. A total of 78 rats were used, none this past year. There were no serious or unexpected adverse reactions.

CONCLUSIONS

SRIH increases glomerular PGE2 production, and glomeruli from diabetic rats appear more sensitive to this effect of SRIH compared to glomeruli from control rats. It is possible that this effect on PGE2 production may be responsible for the protective effects of SRIH on the glomerulus in diabetes.

REPORT DATE: 06/24/94 WORK UNIT # 6330

DETAIL SUMMARY SHEET

TITLE: Infrared Thermometry in the Evaluation of Localized Infection

KEYWORDS: infrared, thermometry, infection

PRINCIPAL INVESTIGATOR: Miller, James LCDR MC

DEPARTMENT: Department of Pediatrics STATUS: Completed
APPROVAL DATE: Jun 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To ascertain whether clinical infrared thermometers can be used in the diagnosis of localized infectious processes; such as, cellulitis, septic arthritis, and infectious lymphadenitis.

TECHNICAL APPROACH
This is a validation study. The infrared thermometer will be used to measure the surface temperature over the involved site. A surface temperature will also be measured over an analogous area of the contralateral side of the body. As an additional control, whenever possible, a follow-up measurement will be done over the involved site after resolution of the process.

PRIOR AND CURRENT PROGRESS
The study is completed. All 22 patients entered were evaluable; 4 of these were enrolled this past year. No patients withdrew from the study. There were no adverse reactions to temperature measurement. The use of surface thermometry allowed for a more objective assessment of local inflammation in the patients studied.

CONCLUSIONS
The surface skin temperature as measured by infrared thermometry was greater over sites of infection than over corresponding areas on the contralateral side of the body (1.6 degrees C +/- 1.0; P less than 0.001). After resolution of infection, the differential was less than 0.2 degrees C. This validates the use of infrared thermometry. Further studies in other conditions are needed.

REPORT DATE: 08/15/94 WORK UNIT # 6331

DETAIL SUMMARY SHEET

TITLE: In Vivo Dating of the Time Interval from the Initial Presence of Meconium to Birth

KEYWORDS: meconium

PRINCIPAL INVESTIGATOR: Moores, Russell MAJ MC
ASSOCIATES: Wiswell, Thomas LTC MC

DEPARTMENT: Department of Pediatrics

STATUS: Completed
APPROVAL DATE: Jul 1992

FUNDING: Current FY: $ 4,500 Previous FYs: $ 0 Total: $ 4,500

STUDY OBJECTIVE

To assess the effect of meconium on changes of placental membranes in a fetal rabbit model. The in-vitro portion will involve the effect of various parameters in changing the color of meconium-stained amniotic fluid.

TECHNICAL APPROACH

1) Inject fetal uteri with meconium of various concentrations and examine after several periods of times (hours to days). 2) Instill meconium-stained amniotic fluid with other substances (acid, base, vernix) and follow color changes over time.

PRIOR AND CURRENT PROGRESS

A total of 25 rabbits were used, none this past year. There were no serious or unexpected adverse reactions. The study has been completed. The results were presented at the Society for Pediatric Research's Annual Meeting by Dr. Wiswell. He is currently preparing a manuscript.

CONCLUSIONS

The color changes of meconium staining of the amniotic fluid appear to be independently influenced by meconium concentration, the presence of vernix, and the duration of meconium presence.

REPORT DATE: 09/01/94 WORK UNIT # 6332

DETAIL SUMMARY SHEET

TITLE: The Effect of Profound Hypoglycemia on the Release of Excitatory Amino Acids in the Central Nervous System of the Developing Pig

KEYWORDS: hypoglycemia, excitatory amino acids, brain damage

PRINCIPAL INVESTIGATOR: Darling, Bryan LT MC USNR
ASSOCIATES: O'Neill, Timothy PhD; Payne, Matthew CPT PhD

DEPARTMENT: Department of Pediatrics

STATUS: Ongoing
APPROVAL DATE: Jul 1992

FUNDING: Current FY: $16,171 Previous FYs: $ 0 Total: $ 16,171

STUDY OBJECTIVE

To determine if acute severe hypoglycemia is associated with the release of aspartate (ASP) and glutamate (GLU) from the newborn piglet brain, if ASP and GLU release differs in older pigs, and if ASP and GLU release is related to brain activity.

TECHNICAL APPROACH

Newborn piglets and adolescent pigs will be anesthetized and ventilated. Femoral arterial and venous lines will be placed for fluid and medications, blood pressure measurements, and blood samples. A sagittal sinus catheter will be placed for blood sampling. A 3mm loop microdialysis probe will be placed in the hippocampus area using stereotaxic surgery, and perfused at 2.5 ul/min with artificial CSF. Six piglets and six pigs will be injected with 200 IU/kg of regular pork insulin, followed by a continuous infusion of 20 IU/kg/hr. All measurements and samples will be collected at baseline, 30 min, 1 hr, 1.5 hr, and 2 hr of severe hypoglycemia. CSF amino acids will be determined by HPLC.

PRIOR AND CURRENT PROGRESS

Twelve piglets (1-10 days old) and 12 pigs (8-10 weeks old) have been used (six in each group have been normal saline controls). There have been no serious or unexpected adverse reactions. Baseline ASP and GLU levels were significantly higher in treated and control adolescent pigs when compared with the piglets. Levels did not change in the adolescent animals over the observation period. Treated piglets had a significant rise in CSF, ASP, and GLU levels at approximately 3 hours after insulin administration. The largest contribution to this rise was seen in the piglets who developed isoelectric EEG's. No additional animals were used in the past year because of loss of dedicated research time. The PI plans to finish analyzing frozen serum samples, EEG tracings, and preserved tissue samples during the next fiscal year.

CONCLUSIONS

Newborn and adolescent pigs differ in their response to severe hypoglycemia. There is an exaggerated release of ASP and GLU from the brain of the piglet when stressed with severe hypoglycemia, while the pig shows no significant change from baseline. The piglet is particularly prone to have this exaggerated release when hypoglycemia is severe enough to cause loss of brain activity.

REPORT DATE: 08/15/94 WORK UNIT # 6336

DETAIL SUMMARY SHEET

TITLE: The Use of Saline Lavage and Surfactant Therapy for the Management of the Meconium Aspiration Syndrome in Newborn Piglets - A Model for Intrapartum Management

KEYWORDS: meconium aspiration, saline lavage, surfactant therapy

PRINCIPAL INVESTIGATOR: Moores, Russell MAJ MC

DEPARTMENT: Department of Pediatrics STATUS: Ongoing
APPROVAL DATE: Aug 1992

FUNDING: Current FY: $16,601 Previous FYs: $ 0 Total: $ 16,601

STUDY OBJECTIVE
To assess whether saline lavage, surfactant therapy, or combined saline lavage/surfactant therapy offer any advantage in the early management of the meconium aspiration syndrome.

TECHNICAL APPROACH
The piglet groups will be: saline controls, meconium controls, meconium group treated with saline lavage alone, meconium group treated with surfactant alone, and three meconium groups treated with saline lavage and various dosages/types of surfactants. Piglets will be anesthetized, intubated, and meconium placed into their tracheas via the endotracheal tube. After 15 minutes, airways will be suctioned, and the various treatments done. They will be ventilated for a 6 hour study period, monitoring time multiple oxygenation, ventilation, and pulmonary function parameters, then a chest x-ray will be obtained. They will be euthanized, their lungs removed, and specimens prepared for histologic examination.

PRIOR AND CURRENT PROGRESS
A total of 56 piglets were used, none this past year. Two piglets died secondary to equipment malfunction, and one died secondary to pneumothorax. The study is completed except for the final revisions of the manuscript.

CONCLUSIONS
The use of saline lavage and surfactant replacement, either alone or in combination, is of no benefit in the early management of meconium aspiration syndrome.

REPORT DATE: 08/29/94 WORK UNIT # 6337

DETAIL SUMMARY SHEET

TITLE: Oxandrolone to Increase Growth in Turners Syndrome Patients: Treatment Protocol

KEYWORDS: Turner's Syndrome, oxandrolone, growth

PRINCIPAL INVESTIGATOR: Poth, Merrily MD

DEPARTMENT: Department of Pediatrics STATUS: Ongoing
APPROVAL DATE: Aug 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To allow oxandrolone, a drug which is only available on IND, to be available for treatment of patients with Turner's Syndrome. This treatment is reported to increase the growth rate and eventual height of these patients.

TECHNICAL APPROACH
Patients with Turner's Syndrome are to be offered oxandroline therapy which is anticipated to increase growth rate. Growth and development will be followed on therapy.

PRIOR AND CURRENT PROGRESS
A total of two patients have been enrolled and treated under this protocol, one during the past year. One patient remains on therapy, and the other one ended therapy because she had finished growing. There have been no untoward effects of treatment, and both patients continue to do well.

CONCLUSIONS
Oxandrolone remains a viable therapeutic option to increase growth rate in patients with Turner's Syndrome.

REPORT DATE: 10/13/93 WORK UNIT # 6340

DETAIL SUMMARY SHEET

TITLE: The Incidence of Celiac Disease in North American Children with Short Stature

KEYWORDS: celiac disease, short stature

PRINCIPAL INVESTIGATOR: Degnan, Bernie CPT MC
ASSOCIATES: Poth, Merrily MD; Rogers, Philip LTC MC

DEPARTMENT: Department of Pediatrics

STATUS: Ongoing
APPROVAL DATE: Oct 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To assess the incidence of celiac disease in an unscreened population of American children who are referred to a pediatric endocrinology clinic for evaluation of short stature.

TECHNICAL APPROACH
A total of 100 patients referred to Pediatric Endocrine Clinic for short stature will have serum collected for antigliadin IgA and IgG, antiendomysial IgA, and antireticulin IgA antibody. Patients with elevation of any of these will have further lab evaluation, and small bowel biopsy of the duodenum, to document morphologic features of the mucosal absorptive surface.

PRIOR AND CURRENT PROGRESS
A total of 31 patients have been enrolled; 29 have had negative antibody screens. Two patients have had positive screens; one of these patients had a normal small bowel biopsy, while the other is awaiting evaluation by Gastroenterology Service. There have been no serious or unexpected adverse reactions.

CONCLUSIONS
The study is ongoing; it will be another year before enough patients are enrolled to draw conclusions from the data.

REPORT DATE: 10/29/93 WORK UNIT # 6341

DETAIL SUMMARY SHEET

TITLE: Interferon-alfa2a Therapy of Children with Chronic Hepatitis B Infection

KEYWORDS: hepatitis B, interferon, children

PRINCIPAL INVESTIGATOR: Latimer, John COL MC USAF
ASSOCIATES: Rogers, Philip LTC MC; Pineiro, Victor LTC MC

DEPARTMENT: Department of Pediatrics

STATUS: Ongoing
APPROVAL DATE: Oct 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine the safety and effectiveness of interferon-alpha 2b in the treatment of children with chronic active hepatitis B infection.

TECHNICAL APPROACH
Inclusion criteria for treatment include: DEERS eligible patients between 12 months and 17 years of age with documented continued presence of hepatitis B viral infection for greater than 6 months, with transaminase elevation greater than twice the upper limit of normal, and with histopathologic confirmation of chronic active hepatitis. Patients entering the study will be treated in an open label, unpublished, non-randomized, decriptive treatment study, and receive 10 MU/m^2 interferon alpha-2b injected subcutaneously three times weekly for a maximum of 24 weeks or until loss of HBeAg.

PRIOR AND CURRENT PROGRESS
This protocol has not been activated because of difficulty getting FDA approval for a Phase II study using the interferon alpha-2a (Roferon-A) as proposed in the original protocol. Subsequently, interferon alpha-2b (Intron-A) has been approved by the FDA for the treatment of chronic hepatitis B in adults. The protocol has been resubmitted changing the proposed treatment to Intron-A given at one dosage level of established greatest efficacy. An IND number from the FDA will not be required for this revised protocol. Approval is pending human use review.

CONCLUSIONS
Protocol is inactive for above stated reasons.

REPORT DATE: 11/23/93 WORK UNIT # 6342

DETAIL SUMMARY SHEET

TITLE: The Developmental Regulation of Serine Oxidation in the Fetal Hindlimb

KEYWORDS: serine, developmental regulation, fetus

PRINCIPAL INVESTIGATOR: Moores, Russell Jr MAJ MC

DEPARTMENT: Department of Pediatrics

STATUS: Ongoing
APPROVAL DATE: Nov 1992

FUNDING: Current FY: $ 18 Previous FYs: $ 0 Total: $ 18

STUDY OBJECTIVE
To determine the ontogeny of serine aminotransferase and serine dehydratase (two major routes of serine disposal) in the fetal non-visceral carcass, liver, kidney, and placenta.

TECHNICAL APPROACH
Ovine fetal and neonatal tissue will be obtained from the University of Colorado. Enzymes will be assayed spectrophotometrically. Data will be standardized to protein content.

PRIOR AND CURRENT PROGRESS
Serine dehydratase methods were refined and validated for this system. The livers and kidneys of 10 animals were studied at various gestational ages. No adverse reactions or findings were noted.

CONCLUSIONS
Serine dehydratase activity is low during gestation in fetal livers and kidneys. It is unlikely to be a major route of fetal serine disposal in these organs.

REPORT DATE: 06/11/94 WORK UNIT # 6344

DETAIL SUMMARY SHEET

TITLE: Solid Media Determination of MICs of Clinical Isolates of Mycobacterium Avium Complex to Trimethoprim, Sulfamethoxazole, and Sulfisoxazole

KEYWORDS: MAC, trimethoprim, sulfamethoxazole

PRINCIPAL INVESTIGATOR: Raszka, William MAJ MC

DEPARTMENT: Department of Pediatrics

STATUS: Completed
APPROVAL DATE: Dec 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine the susceptibility of clinical isolates of M. avium and M. intracellulare to combinations of folate antagonists.

TECHNICAL APPROACH
Twenty isolates will be grown on 7H11 agar, and then a known inoculum size of each will be placed into a quadrant of a 4-quadrant 7H10 agar plate. Susceptability will be determined by proportion method.

PRIOR AND CURRENT PROGRESS
The data was presented as a poster at the 1993 Annual Meeting of the American Society of Microbiology. The paper is under review.

CONCLUSIONS
The data demonstrates that 45% of isolates are susceptible to sulfamethoxazole at levels achievable in the serum. Isolates were not susceptible to sulfisoxazole or trimethoprim. The addition of trimethoprim to sulfamethoxazole lowered the MIC50 to sulfamethoxazole.

REPORT DATE: 06/27/94 WORK UNIT # 6345

DETAIL SUMMARY SHEET

TITLE: The Evaluation of a Common Household Foodstuff in the Treatment of Nausea and Vomiting in Pregnant Women

KEYWORDS: ginger, nausea, pregnant women

PRINCIPAL INVESTIGATOR: Ashton, W. Scott CPT MC

DEPARTMENT: Department of Pediatrics STATUS: Completed
APPROVAL DATE: Dec 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To investigate the ability of ginger to alleviate nausea and to prevent vomitting in pregnant women.

TECHNICAL APPROACH
There have been no changes to the original protocol.

PRIOR AND CURRENT PROGRESS
A total of two subjects have been enrolled. No new patients have been enrolled in the study since the last progress report was submitted in January 1994. There have been no serious or unexpected adverse reactions.

CONCLUSIONS
No conclusions were possible until 44 patients completed the study.

REPORT DATE: 06/14/93 WORK UNIT # 6350

DETAIL SUMMARY SHEET

TITLE: Comparison of the In Vitro Susceptibility of Clinical Isolates of Non-Tuberculous Mycobacteria in HIV Infected and non-HIV Infected Patients

KEYWORDS: mycobacteria, HIV, susceptibility

PRINCIPAL INVESTIGATOR: Raszka, William MAJ MC

DEPARTMENT: Department of Pediatrics

STATUS: Completed
APPROVAL DATE: Mar 1993

FUNDING: Current FY: $ 576 Previous FYs: $ 0 Total: $ 576

STUDY OBJECTIVE
To determine the susceptibility patterns of non-tuberculous mycobacteria in HIV infected and uninfected populations, and to evaluate the hypothesis that HIV patients have more resistant organisms.

TECHNICAL APPROACH
The mycobacteria culture results from June 1985 to December 1992 will be reviewed.

PRIOR AND CURRENT PROGRESS
Data collection is underway; 89 cases have been collected to date.

CONCLUSIONS
Too early.

REPORT DATE: 09/21/94 WORK UNIT # 6358

DETAIL SUMMARY SHEET

TITLE: Evaluation of the Mechanism of Inhibition of Interleukin-6 Synthesis by Indomethacin

KEYWORDS: interleukin-6, cAMP, prostaglandin

PRINCIPAL INVESTIGATOR: Hinson, Roger CPT MC

DEPARTMENT: Department of Pediatrics STATUS: Ongoing
APPROVAL DATE: Sep 1993

FUNDING: Current FY: $ 3,164 Previous FYs: $ 0 Total: $ 3,164

STUDY OBJECTIVE

To evaluate the regulation of interleukin-6 synthesis by cyclooxygenase and cAMP-associated pathway products: specifically, to understand if and how prostaglandins modulate IL-6; by what second messenger pathways regulation occurs; and at what level of signal transduction synthesis is regulated.

TECHNICAL APPROACH

Chronic experimental peritonitis is induced with pristane in BALB/c mice. Peritoneal macrophases are isolated and cultured in vitro. The macrophages are stimulated to produce IL-6 in the presence and absence of different nonsteroidal anti-inflammatory drugs and cAMP agonists. Prostaglandins were used to stimulate the cells as well. The culture supernatant was harvested and assayed for IL-6 by the B9 hybridoma bioassay.

PRIOR AND CURRENT PROGRESS

A total of 164 mice have been used and euthanized. There have been no adverse reactions. Addition of a variety of nonsteroidal anti-inflammatory drugs, which inhibit cyclooxygenase, inhibited IL-6 production by 42-56%. Addition of exogenous PGE2 induced IL-6 synthesis in a dose-dependent manner. PGI2 was ineffective. The effect of elevating intracellular cAMP on IL-6 production was tested with forskolin (an adenylate cyclase activator), IBMX (a phosphodiesterase inhibitor), and dibutyrl cAMP (a cell permeable cAMP agonist). Each induced IL-6 synthesis in a dose-dependent manner. Simultaneous administration of PGE2 and IBMX led to a synergistic increase in IL-6 release.

CONCLUSIONS

These results provide evidence that indomethacin inhibits macrophase IL-6 production by inhibiting prostaglandin synthesis and that PGE2, in particular, stimulates IL-6 production by increasing intracellular cAMP. Abnormal prostaglandin production may play an important role in diseases in which IL-6 is dysregulated.

REPORT DATE: 09/20/94 WORK UNIT # 6359

DETAIL SUMMARY SHEET

TITLE: Risk and Prevalence of Hepatitis B in Adolescents

KEYWORDS: Hepatitis B, adolescents, prevalence

PRINCIPAL INVESTIGATOR: Robinson, C. Anita MD

DEPARTMENT: Department of Pediatrics STATUS: Ongoing
APPROVAL DATE: Sep 1993

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To assess risk and status of Hepatitis B infection in the adolescent population.

TECHNICAL APPROACH
This is a prospective study design using a questionnaire to assess risk and venipuncture to determine serological status.

PRIOR AND CURRENT PROGRESS
The current number of participants enrolled in the study is 100. There have been no serious or unexpected adverse reactions.

CONCLUSIONS
None determined; study is in progress.

REPORT DATE: 01/06/94 WORK UNIT # 6121

DETAIL SUMMARY SHEET

TITLE: POG 7799 Rare Tumor Registry

KEYWORDS: rare tumors, tumors, pediatric tumors

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Mosijczuk, Askold COL MC; Blaney, Susan MAJ MC

DEPARTMENT: Department of Pediatrics
SERVICE: Pediatric Hematology-Oncology Service

STATUS: Ongoing
APPROVAL DATE: Jan 1980

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To accumulate natural history data on malignancies which occur so rarely that larger series of cases cannot be accumulated at any single institution.

TECHNICAL APPROACH
To build a registry which contains pathology review of patients with rare tumors and annual reporting of status of patients.

PRIOR AND CURRENT PROGRESS
A total of 468 patients have been accrued groupwide (183 in the past year), with 8 from WRAMC (none in the past year).

CONCLUSIONS
Study should remain open.

REPORT DATE: 01/24/94 WORK UNIT # 6144

DETAIL SUMMARY SHEET

TITLE: POG 8158 NWTS Long Term Follow-up Study

KEYWORDS: Wilms' tumor, treatment complications

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Mosijczuk, Askold COL MC; Blaney, Susan MAJ MC

DEPARTMENT: Department of Pediatrics
SERVICE: Pediatric Hematology-Oncology Service

STATUS: Ongoing
APPROVAL DATE: Jan 1982

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To gather epidemiological and late effects data on Wilms' tumor patients.

TECHNICAL APPROACH
Data sent to coordinator to evaluate effects of the cancer and its treatment.

PRIOR AND CURRENT PROGRESS
There have been 3,481 registrants entered on study groupwide (334 during the past year); 32 patients from WRAMC (4 during the past year). Review of data submitted from this cohort to date is significant for reports of 29 second malignant tumors. Further data collection and review is planned to correlate tumor location and radiation therapy fields. Forty-two severe cardiac conditions have been reported. These cases are currently being reviewed to determine their possible relationship to the treatment exposure. Requests for pregnancy reports from cohort have yielded 50 reports to date. Further information about pregnancy outcome is being sought.

CONCLUSIONS
Study should remain open.

REPORT DATE: 05/17/94 WORK UNIT # 6177

DETAIL SUMMARY SHEET

TITLE: POG 8602 Evaluation of Treatment Regimens in Acute Lymphoid Leukemia of Childhood (ALinC14), A POG Phase III Study

KEYWORDS: lymphocytic leukemia, childhood leukemia, methotrexate

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Edwards, E. Glenn MAJ MC; Blaney, Susan MAJ MC

DEPARTMENT: Department of Pediatrics STATUS: Ongoing
SERVICE: Pediatric Hematology-Oncology Service APPROVAL DATE: May 1986

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To treat patients with lymphocytic leukemia in order to provide optimal opportunity for possible cure.

TECHNICAL APPROACH
A comparison of regimens to determine if intermediate dose methotrexate (IDM) and Ara-C in consolidation is superior to IDM + L-asparaginase, and if pulses of IDM/Ara-C at 3 week intervals is superior to pulses at 12 week intervals.

PRIOR AND CURRENT PROGRESS
A total of 1,951 patients have been enrolled. The study was closed to accrual 07 Jan 91. All of the eight WRAMC registrants reported alive and off therapy on the last APR remain off therapy and are doing well, according to last patient contact. Three of the four WRAMC registrants reported on therapy on the last APR are alive and off therapy, and one transferred to Fort Sam Houston for a bone marrow transplant. There have been no unexpected late toxicities. Benefits to subjects include partial or complete remission.

CONCLUSIONS
Study should remain open for WRAMC registrant follow-up.

REPORT DATE: 06/29/94 WORK UNIT # 6181

DETAIL SUMMARY SHEET

TITLE: POG 8625/8626 Combined Therapy and Restaging in the Treatment of Stages I, IIA, IIIA1 Hodgkin's Disease in Pediatric Patients, A Phase II Study

KEYWORDS: Hodgkin's disease, radiation, MOPP/ABVD

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Edwards, E. Glenn MAJ MC; Blaney, Susan MAJ MC

DEPARTMENT: Department of Pediatrics
SERVICE: Pediatric Hematology-Oncology Service

STATUS: Ongoing
APPROVAL DATE: Jun 1986

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To treat Hodgkin's disease in patients staged as I, IIA, and IIIA.

TECHNICAL APPROACH
Effectiveness and toxicities of three cycles of MOPP/ABVD are compared with two cycles of MOPP/ABVD plus radiation.

PRIOR AND CURRENT PROGRESS
This study was closed to accrual in September 1992. For treatment 1, 5-year event-free survival is 92%. For treatment 2, 5-year survival is 88%. So far, there is no evidence of a difference between the two randomized arms. Toxicity has been as expected for this patient population and this therapy. Response: The CR rate at the time of randomization was 67%. The overall CR rate at the end of all therapy for the group as a whole was 94%. Benefits to subjects include the possibility of remission of disease. The WRAMC registrants are off therapy and continue to do well.

CONCLUSIONS
Study should remain open to follow WRAMC registrants.

REPORT DATE: 10/14/93 WORK UNIT # 6188

DETAIL SUMMARY SHEET

TITLE: POG 8650 National Wilm's Tumor Study - 4; A POG Phase III Study

KEYWORDS: Wilms' tumor, renal tumor, nephroblastoma

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Blaney, Susan MAJ MC; Mosijczuk, Askold COL MC

DEPARTMENT: Department of Pediatrics
SERVICE: Pediatric Hematology-Oncology Service

STATUS: Ongoing
APPROVAL DATE: Oct 1986

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

a) To gather data on morphology and correlate it with treatment and clinical outcome; and b) To refine clinical trials to reduce therapy to simpler and shorter regimens.

TECHNICAL APPROACH

To attempt to give the usual 5-day course on one day (has been done with other tumors) and to examine in randomized trial with current therapies.

PRIOR AND CURRENT PROGRESS

A total of 3,426 patients have been entered POG-wide, 1,413 since the last APR. The total number of WRAMC patients entered is 14; 4 since the last APR. Treatment results remain blinded. A revised classification system for analyzing anaplasia has been developed and is being applied to regimens DD and J for advanced stage disease. The randomization for anaplasia has been closed, with specific recommendations for those patients to receive one or the other regimen. Toxicity has remained acceptable; an analysis between actinomycin D and doxorubicin was greater on the pulse-intensive regimens, but there was no associated increase in toxicity.

CONCLUSIONS

Study should remain open.

REPORT DATE: 01/06/94 WORK UNIT # 6192

DETAIL SUMMARY SHEET

TITLE: POG 8651 Osteosarcoma Study 2: A Randomized Trial of Pre-Surgical Chemotherapy Vs. Immediate Surgery and Adjuvant Chemotherapy in the Treatment of Non-Metastatic Osteosarcoma, A POG Phase III Study

KEYWORDS: osteosarcoma

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Blaney, Susan MAJ MC; Edwards, E. Glenn MAJ MC

DEPARTMENT: Department of Pediatrics
SERVICE: Pediatric Hematology-Oncology Service

STATUS: Ongoing
APPROVAL DATE: Jan 1987

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

a) To determine whether pre-surgical chemotherapy will improve survival of subjects with non-metastatic osteosarcoma of the extremity or resectable bone compared to up-front surgery; b) To determine the impact of this approach on limb-sparing procedures; c) To evaluate the relationship of pre-surgery response with prognosis; and d) To study the tumor DNA content as a prognostic factor.

TECHNICAL APPROACH

Eligibility includes age less than 30 years, time less than 3 weeks from diagnosis, no prior history of cancer, and no prior therapy. The tumor must be biopsy-proven high-grade, resectable, and non-metastatic. Chemotherapy includes high-dose methotrexate, Adriamycin, cis-platinum, bleomycin, Cytoxan, and actinomycin D. Pre-surgical chemotherapy randomization lasts 7 weeks.

PRIOR AND CURRENT PROGRESS

There are a total of 101 patients accrued on study groupwide; 2 from WRAMC (corrected from last APR). One WRAMC registrant is still alive and with no evidence of disease. Of the 101, 47 are assigned to presurgery chemotherapy. Accrual has not been as expected, and this study will be closing to further accrual when the intergroup osteosarcoma study opens. Treatment specific results are masked. Overall, 3 year disease-free survival rate is 72.3% of toxicities grade 3 or more; the most common involve ANC, WBC, platelets, stomatitis/mucositis, and transaminases, with no toxicity-related deaths. Nine registrants were accrued in POG in the past year; WRAMC registered no registrants in the past year.

CONCLUSIONS

Study should remain open.

REPORT DATE: 03/11/94 WORK UNIT # 6193

DETAIL SUMMARY SHEET

TITLE: POG 8615 A Phase III Study of Large Cell Lymphomas in Children and Adolescents, A Comparison of Two Treatment Regimens, ACOP+ Vs. APO

KEYWORDS: lymphoma, large cell

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Blaney, Susan MAJ MC; Edwards, E. Glenn MAJ MC

DEPARTMENT: Department of Pediatrics
SERVICE: Pediatric Hematology-Oncology Service

STATUS: Completed
APPROVAL DATE: Feb 1987

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

a) To determine the influence of Cytoxan therapy in advanced-stage large cell lymphomas in children and adolescents by comparing in a randomized prospective study the efficacy and toxicity of the above two modified regimens; b) To study these two regimens without adjuvant XRT and with only 12 months of therapy; and c) To study the clinical and biological characteristics of these large cell lymphomas.

TECHNICAL APPROACH

Registrants less than 21 years old with histologically confirmed large cell lymphomas of Murphy Stage III and IV are eligible. Randomization is at the start of therapy. Modified ACOP+ uses a vincristine/Cytoxan/Adriamycin/ prednisone induction, followed by 1 year of multiagent maintenance therapy. Modified APO has a similar induction minus Cytoxan and a similar 12 month maintenance. Both arms are given IT MTX. In December 1991, ACOP+ regimen was closed. Since then, all patients have been assigned to the APO regimen using Adriamycin, vincristine, and prednisone with intrathecal medications given three times.

PRIOR AND CURRENT PROGRESS

Total accrual at time of study closure in December 1992 was 161 with additional non-randomized accrual to the APO registry showing a 96% response rate (comparable with 95% randomized response rate for the ACOP+ arm). Disease-free survival on the two arms is preliminarily 66% for the ACOP arms, and 74% for the APO arms. This is not yet statistically significant. The single WRAMC registrant is alive and disease-free.

CONCLUSIONS

As only one WRAMC registrant is being followed, and is 4 years from start of treatment, recommend closure of study at WRAMC.

REPORT DATE: 04/04/94 WORK UNIT # 6195

DETAIL SUMMARY SHEET

TITLE: POG 8633/8634 The Treatment of Children Less Than Three Years of Age with Malignant Brain Tumors Using Postoperative Chemotherapy and Delayed Irradiation, A POG Phase II Study

KEYWORDS: medulloblastoma, brain irradiation, infant brain tumor

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Edwards, E. Glenn MAJ MC; Blaney, Susan MAJ MC

DEPARTMENT: Department of Pediatrics
SERVICE: Pediatric Hematology-Oncology Service

STATUS: Ongoing
APPROVAL DATE: Apr 1987

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
a) To determine if postoperative chemotherapy in children less than 3 years old with brain tumors will allow delay of cranial irradiation; and b) To assess the response and toxicity rates.

TECHNICAL APPROACH
After surgery, infants are given four drugs over 2 months. If a good response occurs, this is continued for 2 years, and then radiation is given. If there is not a complete response, radiation is given earlier.

PRIOR AND CURRENT PROGRESS
As stated in last year's APR, POG #8633 has closed to accrual; 206 subjects were enrolled altogether. Study coordinators will keep the radiation study (POG #8634) open until early 1995 to allow current registrants to be treated with radiation therapy. The two remaining WRAMC registrants continue to do well.

CONCLUSIONS
Study should remain open to follow the two WRAMC registrants. POG #8633 was closed to accrual 09 Apr 90.

REPORT DATE: 06/29/94 WORK UNIT # 6199

DETAIL SUMMARY SHEET

TITLE: POG 8704: T-Cell #3 Protocol, A POG Phase III Study

KEYWORDS: leukemia, T-cell

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Blaney, Susan MAJ MC; Mosijczuk, Askold COL MC

DEPARTMENT: Department of Pediatrics
SERVICE: Pediatric Hematology-Oncology Service

STATUS: Ongoing
APPROVAL DATE: Jun 1987

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To determine: a) the efficacy of a multi-agent regimen against childhood T-cell leukemia and advanced T-cell lymphoma, b) the advantage gained with addition of high-dose asparaginase to the regimen, and c) the biology of these diseases.

TECHNICAL APPROACH

Children aged 12 months to 21 years are eligible. Simultaneous registration occurs on POG 8600 (leukemia classification protocol). No prior therapy is allowed. The lymphoma must be advanced stage. Pathology review required. Treatment was randomized to yes or no L-asp during maintenance, which lasts 90 weeks. CNS irradiation occurs for high white counts and CNS disease.

PRIOR AND CURRENT PROGRESS

This study has been closed to accrual since January 1992. A total of 563 patients (4 from WRAMC) were enrolled. The 4-year event-free survival (EFS) of high white count patients on L-ASP+XRT is 67%. Of the 373 T-All patients achieving a CR, 363 were randomized. Of the 190 NHL patients achieving a CR, 188 were randomized. Conclusion: L-ASP has efficacy. Note, however, that L-ASP demonstrated a conclusive advantage only in the T-cell group with WBC over 50; this is the subgroup that was irradiated. The one WRAMC registrant still being followed is off therapy and continues to do well. Benefits to subjects include possibility of remission of disease. There have been no reports of serious or unexpected adverse reactions.

CONCLUSIONS

Study should remain open to follow WRAMC registrant.

REPORT DATE: 07/22/94 WORK UNIT # 6204

DETAIL SUMMARY SHEET

TITLE: POG 8751: Low Dose Methotrexate in the Treatment of Rhabdomyosarcoma, A POG Phase II Study

KEYWORDS: methotrexate, rhabdomyosarcoma, POG

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Blaney, Susan MAJ MC; Edwards, E. Glenn MAJ MC

DEPARTMENT: Department of Pediatrics
SERVICE: Pediatric Hematology-Oncology Service

STATUS: Completed
APPROVAL DATE: Jul 1987

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine: a) the response rate and duration of response in children with rhabdomyosarcoma treated with low-dose methotrexate (LD MTX) given every 6 hours for 6 doses, and b) the type and duration of toxicity of low dose sustained oral methotrexate.

TECHNICAL APPROACH
This is a single armed Phase II study of children with biopsy-proven rhabdomyosarcoma unresponsive to standard therapy. Patients cannot have had previous exposure to MTX. MTX is given orally every 6 hours for six to eight doses per course and is designed to sustain MTX levels of 0.5 micromolar for more than 36 hours per pulse.

PRIOR AND CURRENT PROGRESS
This study closed to accrual in March 1993. Thirty-three patients were entered on study prior to closure. There has been no accrual since the last APR. There are no WRAMC registrants. Only four patients are still alive. Of these, three have been followed for less than a year, and one has been followed for about 5 years. Toxicity in this study was as expected for this chemotherapy in this patient population. Benefits to subjects include the possibility of remission of disease.

CONCLUSIONS
Recommend closure since there are no WRAMC registrants to follow.

REPORT DATE: 09/22/94 WORK UNIT # 6210

DETAIL SUMMARY SHEET

TITLE: POG 8761: A Phase II Study of Homoharringtonine for the Treatment of Children with Refractory Nonlymphoblastic Leukemia

KEYWORDS: non-lymphoblastic, leukemia, homoharringtonine

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Blaney, Susan MAJ MC; Edwards, E. Glenn MAJ MC

DEPARTMENT: Department of Pediatrics
SERVICE: Pediatric Hematology-Oncology Service

STATUS: Completed
APPROVAL DATE: Sep 1987

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To evaluate the efficacy of homoharringtonine (HHT) for the therapy of refractory acute non-lymphoblastic leukemia (ANLL) in children, and further assess the toxicity of HHT.

TECHNICAL APPROACH

Registrants must be: a) less than 21 years old, b) in relapse, with recovery from prior therapy, c) with no current therapy, and d) with no CNS disease. Treatment is 10-day continuous IV courses, given every 21 days. This study was amended to allow post-bone marrow transplant patients who have relapsed to receive this drug.

PRIOR AND CURRENT PROGRESS

This study closed 15 Dec 93. Five patients were accrued since the last APR, bringing the groupwide total to 37. There have been no registrants at WRAMC. Toxicity: six adverse reactions were reported. Response data is preliminary pending final data submission. Preliminary results: complete response - 4 (11%), partial response - 1 (3%), mixed response/improved - 1 (3%), no response - 4 (11%), progressive disease - 15 (40%), not evaluable - 9 (24%), early death - 1 (3%), and too early/unknown - 2 (5%). Benefits to patients include the possibility of remission of disease.

CONCLUSIONS

Study should be closed; there are no WRAMC registrants to follow.

REPORT DATE: 12/13/93 WORK UNIT # 6213

DETAIL SUMMARY SHEET

TITLE: POG 8823/24: Recombinant Alpha Interferon in Childhood Chronic Myelogenous Leukemia, Phase II

KEYWORDS: leukemia, chronic myloid, interferon

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Blaney, Susan MAJ MC; Edwards, E. Glenn MAJ MC

DEPARTMENT: Department of Pediatrics
SERVICE: Pediatric Hematology-Oncology Service

STATUS: Ongoing
APPROVAL DATE: Dec 1987

FUNDING: Current FY: $17,502 Previous FYs: $ 14,835 Total: $ 32,337

STUDY OBJECTIVE

To determine toxicity, rate and duration of response to therapy with recombinant alpha-interferon (<-IFN) for newly diagnosed "adult" CML and for "juvenile" CML occurring within the first two decades of life; and to obtain prospective clinical, laboratory, and genetic data on cases of ACML and JCML treated with recombinant <-IFN.

TECHNICAL APPROACH

Qualified registrants must be 21 years of age or less, with no previous treatment, except for emergency lowering of tumor burden. All subjects must meet appropriate specific physical and laboratory eligibility criteria for ACML or JMCL. Monitoring of biologic markers will be performed at several reference labs, including WRAMC Department of Pediatrics lab (serum IFN, B12, LAP, fetal Hb, and muramidase). Patient cells will be separated and cryopreserved at WRAMC and marrow morphology reviewed. IFN will be given as IV daily for 14-day induction, followed by a subcutaneous IFN injection three times a week for maintenance therapy for a minimum of 18 months, according to response.

PRIOR AND CURRENT PROGRESS

Groupwide, a total of 45 patients have been entered on Stratum I (ACML); 1 of these patients is from WRAMC. During the past reporting year, accrual has been adequate with six new registrants; one from WRAMC. Toxicity continues to be acceptable and manageable with IFN dosage manipulation. One registrant had a seizure attributed to IFN (on day 34, appoximately 6 hours post-IFN dose). Otherwise, there are no significant new toxicities or changes. Stratum II (JCML) was closed in FY92 due to completion of accrual goals; 12 patients were enrolled (none from WRAMC).

CONCLUSIONS

Study should remain open pending closure this winter by POG.

REPORT DATE: 05/17/94 WORK UNIT # 6217

DETAIL SUMMARY SHEET

TITLE: POG 8725: Randomized Study of Intensive Chemotherapy (MOPP/ABVD Plus/Minus Low Dose Total Nodal Radiation Therapy in the Treatment of Stages IIB, IIIA2, IIIB, IV Hodgkin's Disease in Pediataric Patients, Phase III

KEYWORDS: Hodgkin's disease, nodal radiation, MOPP/ABVD

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Blaney, Susan MAJ MC; Edwards, E. Glenn MAJ MC

DEPARTMENT: Department of Pediatrics
SERVICE: Pediatric Hematology-Oncology Service

STATUS: Ongoing
APPROVAL DATE: May 1988

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To determine in a randomized study whether the addition of low dose total nodal irradiation to four courses of MOPP/ABVD combination chemotherapy will improve the duration of complete remission and survival when compared with patients who have had chemotherapy only.

TECHNICAL APPROACH

Patients are 21 years old and younger who have previously untreated, histologically proven Hodgkin's disease (Stage IIB, III2A, IIIB, and IV).

PRIOR AND CURRENT PROGRESS

Study was closed to patient accrual in March 1992. A total of 183 patients registered groupwide were fully evaluable. Evaluation of survival at 6 years indicates that the addition of radiotherapy to eight cycles of alternating MOPP/ABVD offers no significant advantage for patients treated for advanced-stage Hodgkin's disease. Two patients had toxic deaths during chemotherapy. The five WRAMC registrants are off therapy and doing well.

CONCLUSIONS

Study should remain open to follow WRAMC registrants.

REPORT DATE: 09/22/94 WORK UNIT # 6221

DETAIL SUMMARY SHEET

TITLE: POG 8821: Intensive Multiagent Therapy Vs. Autologous Bone Marrow Transplant Early in First CR for Children with Acute Myelocytic Leukemia - A Phase III Study

KEYWORDS: autologous bone marrow, transplant, acute myelocytic leukemia

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Blaney, Susan MAJ MC; Edwards, E. Glenn MAJ MC

DEPARTMENT: Department of Pediatrics
SERVICE: Pediatric Hematology-Oncology Service

STATUS: Ongoing
APPROVAL DATE: Sep 1988

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

a) To determine DFS with intensive chemotherapy using non-cross resistant drug pairs; b) To determine if short-term intensive therapy with autologous bone marrow transplant (with 4-Hydroperoxycyclophosphamide purge) is effective therapy; and c) To compare the two regimens' results and to correlate outcome with clinical and laboratory features.

TECHNICAL APPROACH

Registrants are 21 years of age and younger with previously untreated acute myelocytic leukemia (AML). Induction for both arms uses intrathecal Ara-C, daunomycin, Ara-C, 6-TG, followed by high dose Ara-C. Patients are then randomized to receive either IT Ara-C, VP-16/5-AZA plus ABMT with 4-HC purge, or to receive IT Ara-C, HDAC/daunomycin, Ara-C/6-TG, and VP-16/5-AZA.

PRIOR AND CURRENT PROGRESS

This study was closed to accrual on 11 Mar 93. Since the last APR, 51 patients were accrued bringing the groupwide total to 666. In the past year, there were no WRAMC registrants. Three of the six WRAMC registrants previously reported are alive, two have died, and one was transferred to Brooke AMC. While there was an early difference favoring chemotherapy maintenance, the continuing trend in failures in that arm (and the lack of failures in the ABMT arm) have brought the two arms together so that they are not significantly different statistically. Toxicity: A total of 22 episodes of cerebellar toxicity were reported; 17 occurred after HDA6 during induction. Of the 648 evaluable for response: complete reponse + partial response - 555; no response - 67; and early death - 26. Benefits to patients included the possibility of remission of disease.

CONCLUSIONS

Study should remain open to follow WRAMC registrants.

REPORT DATE: 01/06/94 WORK UNIT # 6227

DETAIL SUMMARY SHEET

TITLE: POG 8862: Treatment of First Marrow and/or Extramedullary Relapse of Childhood Acute T-Lymphoblastic Leukemia and T-Non-Hodgkin's Lymphoma with Combination Chemotherapy Including 2'-Deoxycoformycin

KEYWORDS: first relapse, T-lymphoblastic leukemia, T-non-Hodgkin's lymphoma

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Blaney, Susan MAJ MC; Edwards, E. Glenn MAJ MC

DEPARTMENT: Department of Pediatrics
SERVICE: Pediatric Hematology-Oncology Service

STATUS: Ongoing
APPROVAL DATE: Jan 1989

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To assess toxicity and efficacy of low dose 2'-deoxycoformycin (DCF) in prolonging the duration of second remission of T-ALL/T-NHL. To correlate clinical response and toxicities with plasma levels of the metabolized forms of DCF and the in vitro sensitivity of leukemia cells to the drug.

TECHNICAL APPROACH

Patients 21 years old and less in first relapse of T-ALL/T-NHL are treated with an induction regimen of daunorubicin, vincristine, prednisone, and L-asparaginase. Continuation therapy is IV methotrexate and 6-MP, and registrants are randomized to arms receiving this continuation therapy with or without IV push DCF. Triple intrathecal drugs are given throughout the entire regimen.

PRIOR AND CURRENT PROGRESS

A total of 113 patients have been accrued groupwide; 13 during the past year (none from WRAMC). Ninety-three were marrow involved T-ALL, 7 were EMD (non-CNS) T-ALL, and 13 were T-NHL. Analysis has been restricted to T-ALL marrow patients, where actual accrual has been 18.3 per year versus projected accrual rate of 30. Registration of all eligible T-ALL patients is encouraged. Preliminary analysis indicates a 77% complete remission/partial remission rate for that group, but a disappointing 6.9% event-free survival rate. Study remains open pending sufficient accrual to the two arms. There have been no reported adverse reactions. Toxicity has been in the range predicted for this therapy.

CONCLUSIONS

Study should remain open.

REPORT DATE: 01/06/94 WORK UNIT # 6229

DETAIL SUMMARY SHEET

TITLE: POG 8850: Evaluation of Vincristine, Adriamycin, Cyclophosphamide and Dactinomycin with or without the Addition of Ifosfamide and Etoposide in the Rx of Patients with Newly Diagnosed Ewing's Sarcoma of Primitive Neuroectodermal Tumor or Bone, Phase III

KEYWORDS: Ewing's sarcoma, primitive neuroectodermal, childhood tumor

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Blaney, Susan MAJ MC; Edwards, E. Glenn MAJ MC

DEPARTMENT: Department of Pediatrics
SERVICE: Pediatric Hematology-Oncology Service

STATUS: Completed
APPROVAL DATE: Jan 1989

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To compare treatment effectiveness of etoposide and ifosfamide added to the standard treatment regimen. To assess toxicity and adverse orthopedic outcome associated with disease and therapies employed. To assess potential significance of tumor characteristics in prognosis.

TECHNICAL APPROACH

Patients aged 30 years old or less will be randomized to receive the standard chemotherapy (vincristine, Adriamycin, and cyclophosphamide) or the standard along with ifosfamide and etoposide. In August 1992, the study was amended to pilot a potential treatment for the next study on patients with metastatic disease called regimen C. Patients with metastatic disease will be treated wtih a drug regimen containing the drugs ifosfamide, etoposide, vincristine, Adriamycin, actinomycin-D, and cyclophosphamide.

PRIOR AND CURRENT PROGRESS

A total of 248 patients have been accrued, 50 since the last APR. One WRAMC patient has been accrued, none since the last APR. This one WRAMC patients was transferred to Tripler Army Medical Center in 1993. The original accrual goals have been met. The arms for non-metastatic disease were closed December 1992, and only metastatic patients have been accrued since then. Response is masked. Toxicity remains as expected.

CONCLUSIONS

Study should remain open.

REPORT DATE: 02/14/94 WORK UNIT # 6233

DETAIL SUMMARY SHEET

TITLE: POG 8820 VP-16, AMS, and 5-Azacytidine in Refractory ANLL, Phase II-III Study

KEYWORDS: ANLL, refractory disease, chemotherapy

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Blaney, Susan MAJ MC; Edwards, E. Glenn MAJ MC

DEPARTMENT: Department of Pediatrics
SERVICE: Pediatric Hematology-Oncology Service

STATUS: Completed
APPROVAL DATE: Feb 1989

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To compare, in a randomized trial, remission rates of VP-16/AMSA vs. VP-16/AMSA and Az in refractory or recurrent acute nonlymphocytic leukemia (ANLL); to determine duration of remission using pulses of induction regimen as continuation therapy; and to study the relative toxicities of the two regimens.

TECHNICAL APPROACH

Pediatric patients who have failed induction or relapsed on frontline therapy are eligible. Induction is 5 days of AMSA, with 3 days of VP-16 (concurrent). Induction is two cycles; a third may be given if patient responds. Maintenance therapy repeated at 4 week intervals. Az regimen includes this drug for 2 days of the cycle.

PRIOR AND CURRENT PROGRESS

A total of 175 patients have been enrolled (18 during the past year), one from WRAMC (who died of progressive disease). No WRAMC patients have been enrolled since the FY90 reporting year. The study was closed in March 1993 with adequate patient accrual. One death occurred during the reporting year due to sepsis; otherwise toxicity was as expected.

CONCLUSIONS

Study should be terminated (single WRAMC registrant is deceased).

REPORT DATE: 04/18/94 WORK UNIT # 6236

DETAIL SUMMARY SHEET

TITLE: POG 8829 A Protocol for a Case Control Study of Hodgkin's Disease in Childhood

KEYWORDS: childhood, Hodgkin's disease, epidemiology

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: McFarland, Janetta MAJ AN; Blaney, Susan MAJ MC

DEPARTMENT: Department of Pediatrics
SERVICE: Pediatric Hematology-Oncology Service

STATUS: Ongoing
APPROVAL DATE: Apr 1989

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

a) To collect specific data on the epidemiology of childhood Hodgkin's disease (HD). Parameters to be examined are: possible variance between adult and chilhood forms of HD, patterns of previous infectious disease exposure, socioeconomic patterns, familial aggregation, and risk for other diseases. b) To evaluate the parameters listed above according to histologic subtype, stage, and age at diagnosis.

TECHNICAL APPROACH

Newly diagnosed HD patients, ages 15 years and less, seen at POG institutions will complete (the parents will complete) a questionnaire by phone, donate serum for future evaluation, and have clinical study data evaluated. Matched controls will be identified and interviewed over the telephone.

PRIOR AND CURRENT PROGRESS

A total of 43 POG registrants have been accrued in the past year. The total number of WRAMC registrants on this study remains seven. There are 272 POG registrants. Studywide (POG, Children's Cancer Study Group, and the University of Pittsburgh School of Medicine), total registration stands at 570. To date, 420 control interviews have been completed. It is too early to report results. This is a non-therapeutic study. There have been no serious or unexpected adverse reactions.

CONCLUSIONS

Study should remain open.

REPORT DATE: 05/17/94 WORK UNIT # 6242

DETAIL SUMMARY SHEET

TITLE: POG 8828 Late Effects of Treatment of Hodgkin's Disease: A POG Nontherapeutic Study

KEYWORDS: childhood, Hodgkin's disease, long-term effects

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Edwards, E. Glenn MAJ MC; Mosijczuk, Askold COL MC

DEPARTMENT: Department of Pediatrics STATUS: Ongoing
SERVICE: Pediatric Hematology-Oncology Service APPROVAL DATE: May 1989

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To estimate incidence of late effects following treatment for Hodgkin's disease on current frontline POG studies (8625, 8725) and to attempt to identify pre-treatment and/or on-treatment factors which predict high risk of specific late effects.

TECHNICAL APPROACH
Registrants are patients on POG 8625 or 8725 and are followed through completion of late effects study forms every 3 years.

PRIOR AND CURRENT PROGRESS
A total of 366 patients were registered on this non-therapeutic study as of the cutoff date of 29 Oct 93 (7 from WRAMC); 87 have been accrued since the last APR (none from WRAMC). Registrations were received from 67 POG institutions. The breakdown of POG registrants registered on therapeutic studies is: 51% on POG 8625 are registered on POG 8828 (126 registrants), 69% on POG 8725 are registered on POG 8828 (128 registrants), 90% on POG 9225 are registered on POG 8828 (69 registrants), and 79% on POG 9226 are registered on POG 8828 (43 registrants). Data collection begins 3 years from date of registration. Preliminary results are expected to be reported in the Fall Agenda Report. There have been no reported adverse reactions in the examination process of patients, and there are no quantifiable benefits to the subjects.

CONCLUSIONS
Study should remain open to follow WRAMC registrants.

REPORT DATE: 07/21/94 WORK UNIT # 6250

DETAIL SUMMARY SHEET

TITLE: POG 8935 A Study of Biological Behavior of Optic Pathway Tumors

KEYWORDS: optic pathway tumors, children, biology

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Edwards, E. Glenn MAJ MC; Mosijczuk, Askold COL MC

DEPARTMENT: Department of Pediatrics STATUS: Completed
SERVICE: Pediatric Hematology-Oncology Service APPROVAL DATE: Jul 1989

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
a) To assess time to progression in patients with optic pathway tumors (OPT) and with or without neurofibromatosis; b) To estimate response at 2 years post-radiation therapy; c) To estimate incidence of progression in patients with neurofibromatosis; d) To assess long-term effects of being treated for OPT under the age of 21; and e) To assess the value of neurophysiologic techniques in the assessment of disease progression and response.

TECHNICAL APPROACH
Patients 21 years old and less with previously untreated OPT will be enrolled. If disease progresses when registrant is over 5 years old, either radiation therapy for 6 weeks or surgery with or without radiation therapy will be given. If registrant is 5 years old or less, carboplatin will be given on POG protocol 8936 (WU# 6251).

PRIOR AND CURRENT PROGRESS
This study closed to patient accrual 01 Mar 94. Nineteen patients have been accrued groupwide since the last APR, bringing the total to 101. There have been no registrants at WRAMC. Response is masked. There have been no reports of adverse reactions resulting from the radiation therapy or surgery involved in this study. Benefits to patients include the possibility of remission of disease.

CONCLUSIONS
Recommend closure, since there are no WRAMC registrants to follow.

REPORT DATE: 07/21/94 WORK UNIT # 6251

DETAIL SUMMARY SHEET

TITLE: POG 8936 Carboplatin in Progressive Optic Pathway Tumors: Phase II

KEYWORDS: carboplatin, optic pathway tumors, children

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Blaney, Susan MAJ MC; Edwards, E. Glenn MAJ MC

DEPARTMENT: Department of Pediatrics STATUS: Completed
SERVICE: Pediatric Hematology-Oncology Service APPROVAL DATE: Jul 1989

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To assess the response rate to carboplatin (CBDCA) in children with optic pathway tumors, and to assess the efficacy of CBDCA in delaying the progression of disease.

TECHNICAL APPROACH
Registrants on POG 8935 who are 5 years old or less, who have evidence of optic pathway tumor progression, are given IV CBDCA over 1 hour every 4 weeks for 18 months.

PRIOR AND CURRENT PROGRESS
This study closed to patient accrual, effective 01 Mar 94. There have been 10 registrants groupwide since the last APR, bringing the total to 48. There have been no WRAMC registrants. Response is masked. Of the 39 patients evaluable for toxicity, the worst cases were two patients with grade 4 absolute neutrophil count toxicity. Benefits to patients include the possibility of remission of disease.

CONCLUSIONS
Recommend closure since there are no WRAMC registrants to follow.

REPORT DATE: 10/14/93 WORK UNIT # 6252

DETAIL SUMMARY SHEET

TITLE: POG 8945: An Intergroup Protocol for the Treatment of Hepatoblastoma and Hepatocellular Carcinoma, Phase III

KEYWORDS: hepatoblastoma, hepatocellular carcinoma, children

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Edwards, E. Glenn MAJ MC; Blaney, Susan MAJ MC

DEPARTMENT: Department of Pediatrics
SERVICE: Pediatric Hematology-Oncology Service

STATUS: Completed
APPROVAL DATE: Oct 1989

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To compare response rates of hepatocellular carcinoma and hepatoblastoma in patients less than 21 years of age when treated with either Adriamycin and cisplatin or cisplatin/5FU/vincristine. Also, to compare the event-free survival rate and toxicity of the two regimens. Serum alpha-fetoprotein levels will also be studied to determine their value as a relapse predictor. Pure fetal histology tumors are also to be studied.

TECHNICAL APPROACH

Patients less than 21 years old with hepatocellular carcinoma or incompletely resected, unfavorable histology hepatoblastoma are randomized to receive either cisplatin and Adriamycin or cisplatin/5FU/vincristine. Response is evaluated and resection performed as indicated. Serial serum levels of alphafetoprotein and ferritin will be drawn, and their relationship to relapse will be analyzed. Favorable histology hepatoblastoma will be treated with Adriamycin and response evaluated.

PRIOR AND CURRENT PROGRESS

Altogether, 99 patients have been accrued (25 during the past year); none from WRAMC. The study met accrual goals and was closed in November 1992; POG patient accrual exceeded projection. Childrens' Cancer Study Group (CCG) patient accrual exceeded projection; patient accrual and data analyses are pending. The complete response/partial response (CR/PR) rate for the Adriamycin regimen was 62%; the other regimen was 56%. POG disease-free survival rate estimates were 62% and 45%, respectively, for these regimens. Toxicities were acceptable on both regimens. The significance of these findings is pending CCG data input and evaluation.

CONCLUSIONS

This study should be closed as there have been no WRAMC registrants, and POG accrual has been completed.

REPORT DATE: 12/13/93 WORK UNIT # 6253

DETAIL SUMMARY SHEET

TITLE: POG 8930 Comprehensive Genetic Analysis of Brain Tumors

KEYWORDS: brain tumors, children, genetics

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Edwards, E. Glenn MAJ MC; Mosijczuk, Askold COL MC

DEPARTMENT: Department of Pediatrics
SERVICE: Pediatric Hematology-Oncology Service

STATUS: Ongoing
APPROVAL DATE: Dec 1989

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To determine the clinical significance of cellular DNA content, the clinical implications of cytogenetic abnormalities at diagnosis, and of amplification or re-arrangement of proto-oncogenes or allelic loss. To attempt to derive tumor cell lines and a bank of frozen tissue for further studies.

TECHNICAL APPROACH

As pediatric brain tumor patients are registered on POG front-line therapeutic studies, fresh tissue will be submitted for flow cytometry, cytogenetic studies, molecular studies, and cryopreservation, along with peripheral blood specimens.

PRIOR AND CURRENT PROGRESS

There have been 129 registrants accured; 93 since the last APR. Two patients have been accrued from WRAMC; one in the past year. Both WRAMC patients are alive and off treatment; one has progressive disease. Data is too preliminary to report.

CONCLUSIONS

Study should remain open.

REPORT DATE: 02/14/94 WORK UNIT # 6260

DETAIL SUMMARY SHEET

TITLE: POG 9046 A Molecular Genetic Analysis of Wilms' Tumors and Nephrogenic Rests

KEYWORDS: Wilms' tumor, cytogenetics

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Blaney, Susan MAJ MC; Edwards, E. Glenn MAJ MC

DEPARTMENT: Department of Pediatrics
SERVICE: Pediatric Hematology-Oncology Service

STATUS: Ongoing
APPROVAL DATE: Feb 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To define patterns of cytogenetic changes in Wilms' tumor and associated nephrogenic rest tissue and to correlate these patterns with clinicopathologic findings. To establish a bank of molecularly and cytogenetically characterized Wilms' tumors with matched constitutional tissue (lymphoid cells from serum samples).

TECHNICAL APPROACH

Patients 16 years old or less with a previously untreated histologically proven Wilms' tumor of any histological subtype will submit fresh tumor tissue and blood samples for genetic analysis and banking.

PRIOR AND CURRENT PROGRESS

A total of 217 patients have been registered on this study, with 6 from WRAMC (one since the last APR). Patient accrual of 250 on last year's APR is the target accrual for this study and was not the actual total. The objective of correlating changes on tumor cytogenetics and treatment outcome will be completed in the ensuing year. There have been no serious or unexpected adverse reactions.

CONCLUSIONS

Study should remain open.

REPORT DATE: 02/14/94 WORK UNIT # 6261

DETAIL SUMMARY SHEET

TITLE: POG 9047 Neuroblastoma Biology Protocol

KEYWORDS: cytogenetics, neuroblastoma

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Blaney, Susan MAJ MC; Edwards, E. Glenn MAJ MC

DEPARTMENT: Department of Pediatrics STATUS: Ongoing
SERVICE: Pediatric Hematology-Oncology Service APPROVAL DATE: Feb 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To analyze cytogenetics of neuroblastoma cells and determine the clinical significance of genetic variations found, compared to conventional clinical, histologic, and biologic variables in predicting response to treatment or outcome. To develop a neuroblastoma serum and tissue bank for future studies, and to collect natural history and lab data on patients with untreated disease (stages A and DS).

TECHNICAL APPROACH

All newly-diagnosed patients 21 years old or less who are registered on POG neuroblastoma treatment protocols, or stage A or DS (favorable risk), will submit discarded biopsy material and serum for cytogenetic studies and banking.

PRIOR AND CURRENT PROGRESS

A total of 250 patients registered on POG therapeutic protocols have been enrolled on this study (six from WRAMC, four in the past year). In addition, 367 patients for whom no therapeutic study was available have been registered, which makes a group total of 617 (234 since last APR). Much of the data required is missing (forms or material not yet received), but DNA index has been obtained on 86%, LDH on 77%, and N-myc on 82%. There have been no serious or unexpected adverse reactions.

CONCLUSIONS

Study should remain open.

REPORT DATE: 03/17/94 WORK UNIT # 6263

DETAIL SUMMARY SHEET

TITLE: POG 9049 A Study of High Risk Malignant Germ Cell Tumors in Children: A Phase III Treatment Study

KEYWORDS: malignant germ cell tumor, children

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Blaney, Susan MAJ MC; Edwards, E. Glenn MAJ MC

DEPARTMENT: Department of Pediatrics
SERVICE: Pediatric Hematology-Oncology Service

STATUS: Ongoing
APPROVAL DATE: Mar 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To compare the efficacy of two regimens: high-dose cisplatin or standard dose cisplatin used with the drugs etoposide and bleomycin. Data will also be gathered on the response at 12 weeks; organ toxicity (acute and long term), prognostic significance of tumor and mestastatic tumor charateristics, significance of several tumor markers at different points in the course of treatment, and tumor and constitutional cytogenetics will be analyzed.

TECHNICAL APPROACH

Pediatric germ cell tumor patients ages 21 years or less with histologically verified disease will be randomized to receive chemotherapy following their surgery with either a regimen of high or standard dose cisplatin, plus etoposide and bleomycin.

PRIOR AND CURRENT PROGRESS

This study has accrued 24 patients in the past year bringing the total POG registration to 87. This is an intergroup study with Children's Cancer Study Group (CCG). CCG reports 112 registrants. Of six deaths reported to date, two occurred in small children who had recurrences from neonatal sacrococcygeal teratomas; three occurred in patients taken off study after one or two cycles of chemotherapy; and one death occurred from ANLL as a second malignancy in a patient whose germ cell tumor was mediastinal. Reports of significant toxicity have been greater in Arm 1; this includes ototoxicity requiring hearing aids, nephrotoxicity either as renal insufficiency or Fanconi syndrome during therapy, and significantly decreased GFR at completion of therapy. Reports of significant toxicity among patients receiving Arm 2 are much less frequent. The one WRAMC registrant (registered in FY91) continues to do well.

CONCLUSIONS

Study should remain open.

REPORT DATE: 04/18/94 WORK UNIT # 6265

DETAIL SUMMARY SHEET

TITLE: POG 9082 Development of Intervention Strategies to Reduce the Time between Symptom Onset and Diagnosis of Childhood Cancer

KEYWORDS: symptom onset, childhood cancer, diagnosis

PRINCIPAL INVESTIGATOR: Maybee, David COL MC

DEPARTMENT: Department of Pediatrics STATUS: Ongoing
SERVICE: Pediatric Hematology-Oncology Service APPROVAL DATE: Apr 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To describe constellation of symptoms that occur prior to definitive diagnosis of childhood cancer and to evaluate factors that may be associated with the length of time between symptom onset and diagnosis. To determine if these symptoms or time period until diagnosis influence prognosis independent of treatment and disease stage. To provide data that may be used to develop intervention strategies.

TECHNICAL APPROACH
All previously untreated pediatric oncology patients registered on POG treatment studies are registered on this protocol. Questionnaire is given to parents within 7 days of registration on treatment protocol.

PRIOR AND CURRENT PROGRESS
A total of 1,720 patients have been accrued to date; 448 during the past year. WRAMC registered 4 patients in the past year; the WRAMC total is now 24. It is too early to report results. This is a non-therapeutic study. There have been no serious or unexpected adverse reactions.

CONCLUSIONS
Study should remain open.

REPORT DATE: 06/20/94 WORK UNIT # 6270

DETAIL SUMMARY SHEET

TITLE: POG 9048 The Treatment of Children with Localized Germ Cell Tumors, Phase II

KEYWORDS: localized, malignant germ cell tumor, children

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Edwards, E. Glenn MAJ MC; Blaney, Susan MAJ MC

DEPARTMENT: Department of Pediatrics
SERVICE: Pediatric Hematology-Oncology Service

STATUS: Ongoing
APPROVAL DATE: Jun 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To determine long-term, event-free survival for better risk patients treated with surgery alone; to determine long-term, event-free survival for poorer risk patients treated with cisplatin, etoposide, and bleomycin; and to determine prognostic significance of tumor histology, site, size, tumor cytogenetics, and constitutional sex chromosomes.

TECHNICAL APPROACH

Pediatric patients 21 years old and less with good risk malignant germ cell tumors are treated with surgery alone and observed for increase in tumor marker levels. If tumor markers rise, good risk patients are treated, as are the other tumor histologies eligible for this protocol, with four cycles of cisplatin, etoposide, and bleomycin. Tumor tissue cytogenetic studies are also done on all registrants.

PRIOR AND CURRENT PROGRESS

Since the last report, 91 patients have been accrued groupwide (POG and CCG) bringing the total registration to 159. There have been no WRAMC registrants. Response and disease-free survival are both masked. The most noteworthy toxicity concerned the report of a grade 4 absolute neutrophil count (ANC) toxicity in 20 patients. Benefits to patients include the possibility of remission of disease.

CONCLUSIONS

Study should remain open.

REPORT DATE: 06/29/94 WORK UNIT # 6271

DETAIL SUMMARY SHEET

TITLE: POG 9061 The Treatment of Isolated Central Nervous System Leukemia

KEYWORDS: infant leukemia, CNS relapse

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Edwards, E. Glenn MAJ MC; Blaney, Susan MAJ MC

DEPARTMENT: Department of Pediatrics STATUS: Ongoing
SERVICE: Pediatric Hematology-Oncology Service APPROVAL DATE: Jun 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To determine the feasibility and toxicity of intensified systemic treatment with delayed craniospinal radiation for children with acute lymphoblastic leukemia (ALL) and isolated central nervous system (CNS) disease. To study the pharmacokinetics and cytotoxic effect within the cerebrospinal fluid (CSF) of intravenous 6-MP given as a single agent in an up-front treatment window.

TECHNICAL APPROACH

Children less than 1 year old and with ALL in first marrow remission with isolated CNS relapse are given intravenous 6-MP for 2 weeks before a second induction, consolidation, and intensification chemotherapy regimen, followed by craniospinal irradiation and a 76 week maintenance period.

PRIOR AND CURRENT PROGRESS

The study was closed to patient accrual in June 1993. Twenty-two registrants were accrued groupwide in the past year, bringing the total to 84. No registrants have been accrued at WRAMC during the past year. Of the previously reported WRAMC registrants, one is undergoing therapy and is being followed at Portsmouth. The other registrant completed therapy, but has recently relapsed and is being treated at Tripler Army Medical Center. Toxicity, groupwide, remains tolerable. Seventeen patients have completed the planned 2 years of therapy with the longest follow-up 16 months off treatment. As of this report, all patients should have completed craniospinal irradiation. Benefits to subjects include the possibility of remission of disease.

CONCLUSIONS

Study should remain open to follow WRAMC registrants.

REPORT DATE: 07/21/94 WORK UNIT # 6272

DETAIL SUMMARY SHEET

TITLE: POG 9031 The Treatment of Children with High Stage Medulloblastoma: Cisplatin/VP-16 Pre Vs. Post Irradiation, Phase III

KEYWORDS: cisplatin, radiotherapy, medulloblastoma

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Blaney, Susan MAJ MC; Mosijczuk, Askold COL MC

DEPARTMENT: Department of Pediatrics
SERVICE: Pediatric Hematology-Oncology Service

STATUS: Ongoing
APPROVAL DATE: Jul 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To compare survival of children treated with and without pre-irradiation chemotherapy. To determine if c-myc gene amplification in medulloblastoma is associated with an adverse prognosis.

TECHNICAL APPROACH
Children between the ages of 3 and 21 years are randomized to receive either pre-irradiation chemotherapy with cisplatin and VP-16, followed by more cycles of chemotherapy or a second treatment; which is irradiation followed by chemotherapy with cisplatin and VP-16. Specimens are sent to a central office to determine c-myc amplification. An addendum was approved 01 Jun 94 which increased the study accrual from a planned 126 patients to 220 patients. In addition, the power calculation was modified to p=.002 because the original monitoring was too liberal.

PRIOR AND CURRENT PROGRESS
There have been 29 registrants groupwide since the last APR, bringing the total to 129. No registrants have been accrued at WRAMC since the last APR. The one previously reported WRAMC registrant remains stable and off therapy. Worst toxicity: 83 patients were reported with grade 4 ANC toxicity; 20 patients were reported with grade 4 platelet toxicity; and 18 patients were reported with grade 3 platelet toxicity. Response is masked. Benefits to patients include the possibility of remission of disease.

CONCLUSIONS
Study should remain open.

REPORT DATE: 12/13/93 WORK UNIT # 6278

DETAIL SUMMARY SHEET

TITLE: POG 9000 Acute Lymphocytic Leukemia in Childhood #15 Classification Protocol: A Non-therapeutic Study

KEYWORDS: ALL, children, laboratory analysis

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Blaney, Susan MAJ MC; Edwards, E. Glenn MAJ MC

DEPARTMENT: Department of Pediatrics STATUS: Ongoing
SERVICE: Pediatric Hematology-Oncology Service APPROVAL DATE: Dec 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To standardize classification procedures of acute lymphocytic leukemia (ALL) in children with either good risk or poor risk of relapse. To study various features of diagnostic bone marrow and peripheral blood samples and relate these features to treatment outcome.

TECHNICAL APPROACH

Samples of peripheral blood and bone marrow obtained at diagnosis from patients ages 21 years and less are sent to several reference labs at other institutions. Results are obtained after several days to ensure that the patient has been categorized correctly as either good risk or poor risk by the local hospital (WRAMC), and that the patient has been offered the appropriate treatment protocol. Data compiled on laboratory features of registrants on this protocol will be related to their treatment response.

PRIOR AND CURRENT PROGRESS

There have been 1,812 (822 since the last APR) registrants groupwide to date; 14 from WRAMC (3 in the past year). Of these, 1,597 have been placed on a POG therapeutic acute lymphoblastic leukemia (ALL) protocol. Of the 215 on this study, only major reasons for not enrolling on a treatment protocol included in-house protocol (60), no open protocol (27), and refused therapy (28).

CONCLUSIONS

Study should remain open.

REPORT DATE: 12/13/93 WORK UNIT # 6279

DETAIL SUMMARY SHEET

TITLE: POG 9005 Dose Intensification of Methotrexate and 6-Mercaptopurine for ALL in Childhood, Phase III

KEYWORDS: ALL, childhood

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Blaney, Susan MAJ MC; Edwards, E. Glenn MAJ MC

DEPARTMENT: Department of Pediatrics
SERVICE: Pediatric Hematology-Oncology Service

STATUS: Ongoing
APPROVAL DATE: Dec 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine in a randomized trial the most effective way to give methotrexate and 6-mercaptopurine to maintain remission in children with acute lymphocytic leukemia (ALL) at low risk for relapse. Also, to determine the relevance of methotrexate levels to treatment success.

TECHNICAL APPROACH
Newly diagnosed patients, ages 1-21 years, with ALL in first remission will be randomized to receive one of three regimens using the drugs 6-mercaptopurine and methotrexate. All regimens last about 2.5 years. Results will be compared between treatment regimens, stratifying registrants for various possible prognostic factors. During 1992, therapy on study was revised so that methotrexate alone will no longer be given as CNS antileukemia therapy; all intrathecal therapy will use hydrocortisone, methotrexate, and Ara-C. WRAMC registrants were told of this change.

PRIOR AND CURRENT PROGRESS
Groupwide, there have been 715 (252 since the last APR) registrants to date; 8 from WRAMC (2 in the past year). Estimated completion date for patient accrual is July 1994. In May 1993, regimen B closed due to sufficient patient accrual. The present complete remission rate for good prognosis patients is 99% and is close to that for higher risk patients. Event- free survival preliminarily also looks promising. Toxicity remains tolerable.

CONCLUSIONS
Study should remain open.

REPORT DATE: 12/13/93 WORK UNIT # 6280

DETAIL SUMMARY SHEET

TITLE: POG 9006: Acute Lymphocytic Leukemia in Children Study #15: Up Front Alternating 6-MP and Methotrexate Vs. Up Front Alternating Chemotherapy

KEYWORDS: ALL, poor risk, chemotherapy

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Mosijczuk, Askold COL MC; Blaney, Susan MAJ MC

DEPARTMENT: Department of Pediatrics
SERVICE: Pediatric Hematology-Oncology Service

STATUS: Ongoing
APPROVAL DATE: Dec 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To compare in a randomized trial the efficacy and toxicity of 12 courses of IV methotrexate/6-mercaptopurine vs. 12 alternating courses of methotrexate/ 6-mercaptopurine, VM-26/Ara-C, and daunomycin/Ara-C in children with acute lymphocytic leukemia (ALL) who are high risk for relapse.

TECHNICAL APPROACH

Newly-diagnosed non-T, non-B ALL patients, 1-21 years of age, with poor prognostic features will be randomized to receive one of two treatments, both lasting about 2.5 years. Registrant response will be analyzed by stratum (registrants are grouped by disease prognostic factors, such as disease in the central nervous system, cytogenetic factors, etc.).

PRIOR AND CURRENT PROGRESS

There have been 420 (231 since the last APR) registrants groupwide to date; 6 from WRAMC (2 in the past year). Since the last report, one of the six surviving WRAMC registrants has relapsed. Preliminary review of data indicates a 97% CR rate for 304 registrants. Toxicity is as expected.

CONCLUSIONS

Study should remain open.

REPORT DATE: 01/06/94 WORK UNIT # 6281

DETAIL SUMMARY SHEET

TITLE: POG 9140 Treatment for Recurrent or Refractory Neuroblastoma

KEYWORDS: neuroblastoma, recurrent, pediatric

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Mosijczuk, Askold COL MC; Edwards, E. Glenn MAJ MC

DEPARTMENT: Department of Pediatrics
SERVICE: Pediatric Hematology-Oncology Service

STATUS: Ongoing
APPROVAL DATE: Jan 1991

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To determine the response rate and toxicity of three chemotherapy regimens used to treat neuroblastoma that has not responded to initial treatment, and to determine the effectiveness of using retinoic acid to prolong the time to relapse in patients who respond to the chemotherapy regimens on this study. Also, to measure retinoic acid receptors and determine their role in predicting response and toxicity.

TECHNICAL APPROACH

Patients 21 years old and less who have neuroblastoma and have not responded to initial therapy efforts will be randomized among three arms of chemotherapy: 1) cisplatin/sodium thiosulfate/VP-16, 2) CBDCA/VP-16, and 3) ifosfamide/CBDCA. Those who achieve a response will be maintained on retinoic acid. Randomization will be done in a sequential fashion; the first group of patients to present will be treated with Arm 1, and so on. The consent form was revised and approved by the IRB in July 1991 for amendments (addition of the drug G-CSF as supportive therapy and the closure of regimen 1). In April 1993, an amendment was approved that monitors renal function and serum triglycerides more closely.

PRIOR AND CURRENT PROGRESS

Groupwide, 45 patients have been registered; 12 during the past year. A total of two WRAMC patients have been enrolled; none during the past year. The two WRAMC patients died of progressive disease. Response is masked, except for regimen 1 which was closed in July 1991. All five patients on regimen 1 had an objective or subjective response. Toxicity has been as expected for these drugs.

CONCLUSIONS

Study should remain open.

REPORT DATE: 03/17/94 WORK UNIT # 6285

DETAIL SUMMARY SHEET

TITLE: POG 9107 The Treatment of Acute Lymphocytic Leukemia in Infants: Phase III

KEYWORDS: infant, leukemia, chemotherapy

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Blaney, Susan MAJ MC; Edwards, E. Glenn MAJ MC

DEPARTMENT: Department of Pediatrics STATUS: Completed
SERVICE: Pediatric Hematology-Oncology Service APPROVAL DATE: Mar 1991

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To determine toxicity of 1 year of intensive post-induction chemotherapy with a combination of the drugs Ara-C, DNR, 6-MP, methotrexate, vincristine, VP-16, prednisone, and Cytoxan, and to determine the feasibility of this regimen for use in a groupwide Phase III pilot. After this regimen is piloted in 20 patients, the drug GM-CSF will be added to the drug regimen.

TECHNICAL APPROACH

The drugs listed above are given over a 2 year period to children who are less than 1 year old with the diagnosis of acute lymphocytic leukemia. After 20 registrants receive this therapy, the role of GM-CSF in this age group will be addressed by its addition to the study, providing that Phase I data supports that this drug is safe and effective in infants for the lessening of severity and duration of neutropenia associated with chemotherapy. G-CSF proved to be acceptable therapy in this age group and was added to the study (IRB approval September 1992).

PRIOR AND CURRENT PROGRESS

This protocol has achieved its accrual objectives, and has been closed to accrual as of 28 Apr 93, with a final total of 50 patients (12 enrolled during the past year); none from WRAMC. Prelimary results suggest that the duration of neutropenia is shorter and there are fewer episodes of infections with the use of G-CSF. Toxicity has been as expected.

CONCLUSIONS

As there are no WRAMC registrants, closure is recommended.

REPORT DATE: 04/26/94 WORK UNIT # 6287

DETAIL SUMMARY SHEET

TITLE: NPC-1: A Phase II Study of Pre-Irradiation Chemotherapy for Pediaric and Adolescent Patients with Nasopharyngeal Carcinoma

KEYWORDS: nasopharyngeal, carcinoma, pediatric

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Mosijczuk, Askold COL MC; Blaney, Susan MAJ MC

DEPARTMENT: Department of Pediatrics
SERVICE: Pediatric Hematology-Oncology Service

STATUS: Ongoing
APPROVAL DATE: Apr 1991

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To estimate response to methotrexate/cisplatin/5 FU chemotherapy for children with nasopharyngeal carcinoma, to establish local control rates and patterns of failure with radiation therapy for low stage disease or for chemotherapy plus radiation for high stage disease, and to study the genetic features of this tumor.

TECHNICAL APPROACH

Patients 21 years old and less with nasopharyngeal carcinoma will be treated with radiation alone (low stage disease), or radiation plus the chemotherapy (high stage disease). Tumor tissue removed at diagnostic surgery will also be analyzed at St. Jude for cytogenetic features. (Note: This is a St. Jude study that was extended to other medical centers for participation.)

PRIOR AND CURRENT PROGRESS

Twenty-five patients have been registered on the study to date (none from WRAMC); 8 patients have been accrued since the last progress report. The Principal Investigator reports that patients have tolerated the planned treatment well. No neutropenia or kidney toxicity has been observed. No unexpected adverse reactions have been reported.

CONCLUSIONS

Study should remain open.

REPORT DATE: 07/21/94 WORK UNIT # 6292

DETAIL SUMMARY SHEET

TITLE: POG 9135: Pre-Radiation Chemotherapy for Children with Supratentorial Malignant Gliomas and Poorly Differentiated Embryonal Tumors of Childhood

KEYWORDS: malignant glioma, embryonal tumor, childhood

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Mosijczuk, Askold COL MC; Edwards, E. Glenn MAJ MC

DEPARTMENT: Department of Pediatrics STATUS: Ongoing
SERVICE: Pediatric Hematology-Oncology Service APPROVAL DATE: Jul 1991

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To estimate the response of children with supratentorial malignant glioma or poorly differentiated embryonal tumor to three cycles of either BCNU plus continuous-infusion cisplatin or cytoxan plus continuous infusion VP-16; to determine the acute and subacute toxicities; and to estimate the incidence of neuraxis tumor dissemination at diagnosis.

TECHNICAL APPROACH

Following surgical removal or biopsy, children between the ages of 3 and 21 years will be randomized to receive either BCNU plus continuous infusion cisplatin or cytoxan plus continuous infusion VP-16. Treatment is given over approximately 3 months and is designed to be given before radiation therapy (not offered on this study). In July 1992, an addendum was approved requiring the addition of an adverse reaction statement for VP-16 (secondary carcinoma).

PRIOR AND CURRENT PROGRESS

Thirty-three patients have been accrued in the past year, brining the groupwide total to 63. There have been no registrants at WRAMC in the past year. The previously reported WRAMC registrant remains off therapy in hospice care with progressive disease. Worst degree of toxicity reported: Treatment 01 (BCNU/cisplatin) - among 25 patients evaluable for toxicity, 12 reported with grade 4 ANC toxicity, 9 with grade 4 platelet toxicity, and 10 with grade 3 WBC toxicity; and Treatment 02 (cyclophosphamide/VP-16) - among 27 patients evaluable for toxicity, 24 had grade 4 WBC toxicity, 27 had grade 4 ANC toxicity, and 18 had grade 3 NOS/UNK toxicity. Response is masked. Benefits to patients include the possibility of remission of disease.

CONCLUSIONS

Study should remain open.

REPORT DATE: 07/22/94 WORK UNIT # 6293

DETAIL SUMMARY SHEET

TITLE: POG 9136: Phase I/II Dose Escalating Trial of Hyperfractionated Irradiation in the Treatment of Supratentorial Malignant Tumors of Childhood

KEYWORDS: supratentorial tumor, radiation therapy, childhood

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Blaney, Susan MAJ MC; Edwards, E. Glenn MAJ MC

DEPARTMENT: Department of Pediatrics
SERVICE: Pediatric Hematology-Oncology Service

STATUS: Ongoing
APPROVAL DATE: Jul 1991

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To determine whether radiation therapy can be given at a lower dose than previously used in the treatment of this disease by giving therapy twice a day rather than once a day (doses will be increased in steps, starting with the first group of 20 patients, evaluated for 6 months after therapy) in an attempt to reduce toxicity.

TECHNICAL APPROACH

Twenty patients ages 3 to 21 years with supratentorial malignant neoplasms will be given twice daily radiation therapy over 6 weeks. The dose to be used in this first group will be lower than the dose used in conventional schedule (once daily) radiation therapy for this disease, and will not be increased until toxicity for the first group is evaluated for 6 months. Registrants may have been registered for treatment or biological studies on the POG 9135, the pre-radiation chemotherapy protocol.

PRIOR AND CURRENT PROGRESS

Eleven registrants have been accrued groupwide since the last APR, bringing the total to 29. There have been no WRAMC registrants accrued in the past year. The previously reported WRAMC registrant remains off therapy in hospice care with progressive disease. Toxicity has been as expected for this chemotherapy used in this patient population. Response is masked. Benefits to subjects include the possibility of remission of disease.

CONCLUSIONS

Study should remain open.

REPORT DATE: 07/22/94 WORK UNIT # 6294

DETAIL SUMMARY SHEET

TITLE: POG: 9170: Etoposide and Ifosfamide Plus G-CSF in Children with Recurrent Sarcomas: Including Soft Tissue Sarcoma, Ewing's Sarcoma, Rhabdomyosarcoma, and Osteosarcoma: A Pediatric Oncology Group Pilot Study

KEYWORDS: recurrent sarcoma, childhood

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Edwards, E. Glenn MAJ MC; Mosijczuk, Askold COL MC

DEPARTMENT: Department of Pediatrics
SERVICE: Pediatric Hematology-Oncology Service

STATUS: Completed
APPROVAL DATE: Jul 1991

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To establish toxicity of VP-16, ifosfamide, and G-CSF when used in children with recurrent sarcomas; to establish a dose level of ifosfamide used with VP-16 and G-CSF; and to establish the acute and chronic dose-limiting toxicities of this drug combination in children after three cycles.

TECHNICAL APPROACH

Children less than 21 years of age are given the drug combination VP-16, ifosfamide, and G-CSF for a maximum of three cycles on study. Ifosfamide dose will be increased in a step-wise fashion after the first group of three patients has received ifosfamide at that dose. Five steps are planned. Study was amended in January 1993 to allow a higher dose of G-CSF to be used, which will result in twice daily rather than once daily administration of the drug. Another amendment was made in March 1993 to better define dose-limiting toxicity as non-hematologic side effects.

PRIOR AND CURRENT PROGRESS

This study closed 22 Oct 93, with the study objectives met. Fifteen patients were accured groupwide since the last APR, bringing the total to 52. There have been no registrants since the last APR at WRAMC. Responses were seen at dose levels 2, 3, and 4 (MTD). For patients with refractory osteosarcoma, the response rate of 6/13 (46%) was much higher than expected. The maximum tolerated dose for patients on Stratum 1 is dose level 4 (17.55 gms/m^2/course of ifosfamide and 500 mg/m^2/course VP with 5 mcg/kg/day of G-CSF). A total of seven patients developed Fanconi's syndrome. One patient at level 4 developed sepsis and died of congestive heart failure. Overall, toxicity is considered acceptable. Data is still being tabulated for Stratum 2. Benefits to subjects include the possibility of remission of disease. The one WRAMC registrant previously reported, died off protocol of progressive disease June 1994.

CONCLUSIONS

Recommend closure since there are no WRAMC registrants to follow.

REPORT DATE: 08/09/94 WORK UNIT # 6296

DETAIL SUMMARY SHEET

TITLE: POG 9150 Intergroup Rhabdomyosarcoma Study IV: STAGE I Disease: A POG Phase III Study

KEYWORDS: rhabdomyosarcoma, chemotherapy, children

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Mosijczuk, Askold COL MC; Edwards, E. Glenn MAJ MC

DEPARTMENT: Department of Pediatrics
SERVICE: Pediatric Hematology-Oncology Service

STATUS: Ongoing
APPROVAL DATE: Aug 1991

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To compare survival rates after therapy with one of three drug regimens using the drugs vincristine, actinomycin-D, ifosfamide, cyclophosphamide, VP-16; to evaluate Neupogen as an ameliorating agent during chemotherapy; to evaluate the role of either hyperfractionated or conventional schedule radiation therapy; and to correlate tumor cell biology with clinical course.

TECHNICAL APPROACH

Patients meeting the diagnostic criteria for Stage I disease are given about 13 months of chemotherapy with vincristine and are randomized to receive the drug combinations: actinomycin-D+cyclophosphamide, ifosfamide+VP-16, or actinomycin-D+ifosfamide. Some patients may receive radiation therapy, depending on features of their disease. Clinical group 3 disease requiring radiation therapy will be randomized to receive either hyperfractionated or standard schedule radiation. Total dose of ifosfamide is now limited to 72 g/M2. Patients with pre-existing renal abnormality will be assigned to the arm containing cyclophosphamide. G-CSF will be given after each cycle of combination chemotherapy.

PRIOR AND CURRENT PROGRESS

There have been 49 patients accrued in this study groupwide since the last APR. Groupwide total is now 101. There have been no WRAMC registrants. Data from POG does not sort out Stage I registrants from Stage II-IV, but toxicity has been acceptable for this chemotherapy in this total patient population. There have been no reported fatalities. It is too soon to report on response data. Benefits to subjects include the possibility of remission of disease.

CONCLUSIONS

Study should remain open.

REPORT DATE: 08/09/94 WORK UNIT # 6297

DETAIL SUMMARY SHEET

TITLE: POG 9152: Intergroup Rhabdomyosarcoma Study IV: Stage IV, Clinical Group IV, and All Patients with Metastatic Disease: A POG Phase III Study

KEYWORDS: rhabdomyosarcoma, chemotherapy, children

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Blaney, Susan MAJ MC; Mosijczuk, Askold COL MC

DEPARTMENT: Department of Pediatrics
SERVICE: Pediatric Hematology-Oncology Service

STATUS: Ongoing
APPROVAL DATE: Aug 1991

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To compare the efficacy of vincristine/melphalan and ifosfamide/VP-16 in a randomized fashion before therapy with standard drugs for this disease (vincristine/Cytoxan/actinomycin-D plus XRT); to evaluate the efficacy of Neupogen in ameliorating neutropenia with this therapy; and to correlate clinical features with tumor cell biology and genetics.

TECHNICAL APPROACH

Patients with Stage IV or with metastatic disease will be randomized to receive combination chemotherapy with melphalan or with ifosfamide/VP-16 before therapy with vincristine/Cytoxan/actinomycin-D plus XRT. Neupogen will be used during periods of neutropenia. Several amendments are currently being submitted to the IRB that were made in October 1992. They also applied to other POG studies (9150, 9151, 9152) and were submitted at the time to the IRB; however, they were inadvertently not submitted for this study. All of the amendments mentioned in the previous APR were "editorial, administrative"; therefore, they did not require IRB approval.

PRIOR AND CURRENT PROGRESS

There have been 44 patients accrued on this study groupwide since the last APR. Groupwide total is now 83. There have been no WRAMC registrants. There was one toxicity-associated death in the vincristine-melphalan arm of the study. This represents 1/27 eligible, evaluated patients with toxicity data in this arm. It is still too early to compile response data. Other toxicity data has been acceptable for this patient population undergoing this chemotherapy. Benefits to patients include the possibility of remission of disease.

CONCLUSIONS

Study should remain open.

REPORT DATE: 11/02/93 WORK UNIT # 6302

DETAIL SUMMARY SHEET

TITLE: POG: 9151 Intergroup Rhabdomyosarcoma Study IV: Treatment for Stage 2 and 3 Diseases: A Phase III Trial

KEYWORDS: rhabdomyosarcoma, children, chemotherapy

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Blaney, Susan MAJ MC; Mosijczuk, Askold COL MC

DEPARTMENT: Department of Pediatrics
SERVICE: Pediatric Hematology-Oncology Service

STATUS: Ongoing
APPROVAL DATE: Nov 1991

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To compare progression-free survival of children with rhabdomyosarcoma treated with chemotherapy, radiation, and surgery per protocol; to collect data on the toxicity of these treatments; to correlate disease features (cell biology, tumor size and location, and cytogenetic features) with treatment outcome and survival. Study will also collect material for a tumor tissue bank to use in future tumor biology studies.

TECHNICAL APPROACH

Subjects ages 21 years and less with rhabdomyosarcoma or undifferentiated soft tissue sarcoma will be randomized to receive one of three chemotherapy regimens: vincristine/actinomycin-D/cyclophosphamide, vincristine/actinomycin-D/etoposide, or vincristine/etoposide/ifosfamide. Registrants will also be randomized to receive radiation on a once daily or twice daily schedule. Supportive care with G-CSF will be given. Tumor cytogenetics will be evaluated at a central POG laboratory for future correlations with response data. Patients will be followed for relapse.

PRIOR AND CURRENT PROGRESS

In the past year, there have been 81 patients accrued on the study (a total of 136). Since the last report, there has been one WRAMC patient placed on the study (a total of 2). At this time, data, including toxicity information, is too preliminary to report.

CONCLUSIONS

Study should remain open.

REPORT DATE: 11/02/93 WORK UNIT # 6303

DETAIL SUMMARY SHEET

TITLE: POG 9160: Idarubicin Cytosine Arabinoside, for Multiply Recurrent or Refractory ALL: A POG Phase II Study

KEYWORDS: idarubicin, recurrent leukemia, children

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Blaney, Susan MAJ MC; Edwards, E. Glenn MAJ MC

DEPARTMENT: Department of Pediatrics
SERVICE: Pediatric Hematology-Oncology Service

STATUS: Ongoing
APPROVAL DATE: Nov 1991

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To estimate the re-induction rate with Ara-C and idarubicin for children with acute lymphoblastic leukemia (ALL) in first marrow relapse who failed re-induction on other POG studies. For patients who achieve a complete remission, a uniform maintenance therapy will be used with alternating cycles of VP-16, ifosfamide, idarubicin, and Ara-C. Duration of central nervous system remission will also be estimated.

TECHNICAL APPROACH

Children with ALL in relapse will receive induction therapy with the drugs Ara-C and idarubicin. If there is a response, maintenance therapy with Ara-C, idarubicin, ifosfamide, and VP-16 will be given in alternating cycles. Response data and toxicity data will be collected for use in future studies. The study was amended in May 1993 to shorten the duration of induction due to excessive myelotoxicity. This amendment is currently being submitted to the HUC/IRB for review in November.

PRIOR AND CURRENT PROGRESS

There have been 21 patients entered on study since the last APR (total of 46). The one WRAMC patient was reported last APR. Study coordinators report that response remains masked, and that other than the myelosuppression problem, toxicity has been acceptable and as expected for this regimen.

CONCLUSIONS

Study should remain open.

REPORT DATE: 01/12/94 WORK UNIT # 6307

DETAIL SUMMARY SHEET

TITLE: POG 9130: Treatment of Newly Diagnosed Astrocytomas A Pediatric Oncology Group Phase III Study

KEYWORDS: astrocytoma, children

PRINCIPAL INVESTIGATOR: Maybee, David COL MC

DEPARTMENT: Department of Pediatrics STATUS: Ongoing
SERVICE: Pediatric Hematology-Oncology Service APPROVAL DATE: Jan 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 2,371 Total: $ 2,371

STUDY OBJECTIVE
To determine the role of radiation therapy in the treatment of newly diagnosed patients with astrocytoma; to determine the role of surgical resection; to compare the neuropsychological sequelae of surgery and of radiation therapy; to determine the incidence of malignant transformation of low grade astrocytomas (partially or not resected disease) following radiation therapy; and to study long-term neuroendocrine effects.

TECHNICAL APPROACH
Patients 0-21 years of age with newly diagnosed astrocytoma with radical resection will be followed for neuropsychological effects of surgery and neuroendocrine changes. Patients between the ages of 5 and 21 years with incomplete resection who are neurologically stable will be randomized to receive XRT or no further treatment (but still followed). Patients between the ages of 5 and 21 years who are neurologically unstable or whose physicians refuse randomization will be studied as a separate stratum. No formal amendments to the IRB have occurred.

PRIOR AND CURRENT PROGRESS
Groupwide, there are 236 (229 in past year) patients accrued on the study (POG total is 109, and CCG total is 127, with 2 randomized); none from WRAMC. Because accrual rate objectives cannot be met, closure of randomization to treatment has been recommended by the Low Grade Astrocytoma Committee. This study should remain open to natural history for those with totally resected tumors. There are no reports of adverse reactions.

CONCLUSIONS
Study should remain open to accrue registrants as stated above.

REPORT DATE: 01/12/94 WORK UNIT # 6309

DETAIL SUMMARY SHEET

TITLE: POG 9132: Hyperfractionated Irradiation for Posterior Fossa Ependymoma: A Phase II/III Study

KEYWORDS: brain tumor, childhood, radiotherapy (XRT)

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Mosijczuk, Askold COL MC; Blaney, Susan MAJ MC

DEPARTMENT: Department of Pediatrics
SERVICE: Pediatric Hematology-Oncology Service

STATUS: Ongoing
APPROVAL DATE: Jan 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To study the feasibility and toxicity of twice daily radiation therapy; to study disease control and interval and pattern of failure; and to study the relationship between degree of surgical resection and progression-free survival. Toxicity data to be included in study are neuroendocrine and intellect changes.

TECHNICAL APPROACH

Patients between the ages of 36 months and 21 years with posterior fossa ependymoma will be treated with XRT (1.2 Gy in 58 fractions over 6 weeks; total dose is 69.6 Gy) following biopsy and/or surgical resection. Patients will be followed for disease progression, neuroendocrine changes, and intellectual changes.

PRIOR AND CURRENT PROGRESS

Groupwide, 27 patients have been accrued (10 this past year); one from WRAMC (enrolled this past year). Toxicity has been as expected for this therapy. It is too early to report response data.

CONCLUSIONS

Study should remain open.

REPORT DATE: 01/12/94 WORK UNIT # 6310

DETAIL SUMMARY SHEET

TITLE: POG 9259: Carboplatin in the Treatment of Newly Diagnosed Metastatic Osteosarcocma or Unresectble Osteosarcoma: A Phase III Study

KEYWORDS: osteosarcoma, chemotherapy, carboplatin

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Mosijczuk, Askold COL MC; Blaney, Susan MAJ MC

DEPARTMENT: Department of Pediatrics
SERVICE: Pediatric Hematology-Oncology Service

STATUS: Ongoing
APPROVAL DATE: Jan 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To estimate response rate to two cycles of carboplatin given before multi-agent chemotherapy; to estimate survival following this therapy; to study the myelosuppressive effects of carboplatin when renal function and body area (rather than body surface area alone) are used in dose calculations; to relate treatment response to the presence of the multi-drug resistance gene in tumor tissue.

TECHNICAL APPROACH
Patients 30 years old and less with metastatic or unresectable disease at diagnosis will be treated with two cycles of carboplatin chemotherapy, 3 weeks apart, followed by surgical evaluation and resection (if possible). Forty weeks of multiagent chemotherapy will follow the surgery (this multiagent regimen is a proven regimen in the treatment of osteosarcoma), using the drugs methotrexate, ifosfamide, Adriamycin, and cisplatin.

PRIOR AND CURRENT PROGRESS
Thirteen patients have been entered on the study groupwide; none this past year, and none from WRAMC. Toxicity is as expected. It is too early to report on response or overall disease free survival. Investigators are strongly encouraging data collection and flow sheets from enrollees for further analysis.

CONCLUSIONS
Study should remain open.

REPORT DATE: 01/12/94 WORK UNIT # 6311

DETAIL SUMMARY SHEET

TITLE: POG 9182: HIV/Malignancy Biology Study: A Pediatric Oncology Group Aids/Malignancy Network Study

KEYWORDS: AIDS, children, malignancy

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Mosijczuk, Askold COL MC; Edwards, E. Glenn MAJ MC

DEPARTMENT: Department of Pediatrics
SERVICE: Pediatric Hematology-Oncology Service

STATUS: Ongoing
APPROVAL DATE: Jan 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To establish a national registry of HIV-related malignancies in children; to conduct therapeutic trials on these malignancies; and to determine incidence and viral burden of HIV and several other viruses (EBV, CMV, HHV6, HCV) in tumors and body fluids to correlate with other disease and/or treatment information. To study the difference between tumor tissue in HIV positive and HIV negative children.

TECHNICAL APPROACH

Patients 21 years of age or less will be enrolled from three groups: HIV(+) but cancer (-), HIV (-) but cancer (+), and HIV (+) and cancer (+). They will be asked to donate specimens (tumor tissue and body fluids) for the national registry. Cases of HIV-related malignancy will be matched with cases of the same malignancy in a child who does not have HIV. These control cases will be sought from POG registrants in therapeutic trials. So far, studies on viral burden, tumor cytogenetics, and viral incidence are planned for specimens gathered from all three groups. If other factors related to tumor development become uncovered, specimens may be requested from this registry. Chart data will also be collected.

PRIOR AND CURRENT PROGRESS

A total of 27 patients are now on the study (15 since the last APR); 11 malignancies, 10 malignancy controls, and 6 non-malignancy controls. Accrual is as expected to date. More stratum 3 patients are being accrued. No WRAMC registrants have been enrolled to date. There have been no serious or unexpected adverse reactions.

CONCLUSIONS

Study should remain open.

REPORT DATE: 04/08/94 WORK UNIT # 6314

DETAIL SUMMARY SHEET

TITLE: POG 9284/85: Barriers to Enrollment on POG Frontline Therapeutic Clinical Trials and Development of Intervention Strategies: A POG Non-therapeutic Study

KEYWORDS: accrual, oncology treatment

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Mosijczuk, Askold COL MC; Edwards, E. Glenn MAJ MC

DEPARTMENT: Department of Pediatrics
SERVICE: Pediatric Hematology-Oncology Service

STATUS: Ongoing
APPROVAL DATE: Mar 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To prospectively identify factors leading to non-accrual of eligible patients on POG frontline therapeutic studies; and to develop intervention strategies designed to decrease barriers to patient enrollment on POG studies, thus increasing future accrual rates in the POG.

TECHNICAL APPROACH
Patients diagnosed with cancer at POG institutions and their physicians are surveyed within 7 days of their decision whether to participate on POG treatment studies. Survey results from those who decide not to participate (not register on frontline POG study) will be analyzed and compared to the results of those who do register.

PRIOR AND CURRENT PROGRESS
There have been three WRAMC registrants since the study opened; one during the past year. Groupwide, there are 55 registrants; 145 have been enrolled during the past year. It is too early to report study results including adverse reaction data. This is a non-therapeutic study.

CONCLUSIONS
Study should remain open.

REPORT DATE: 03/16/94 WORK UNIT # 6315

DETAIL SUMMARY SHEET

TITLE: POG 9280: Neuroblastoma Epidemiology Protocol: A Non-Therapeutic Study

KEYWORDS: neuroblastoma, childhood, epidemiology

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Blaney, Susan MAJ MC; Mosijczuk, Askold COL MC

DEPARTMENT: Department of Pediatrics
SERVICE: Pediatric Hematology-Oncology Service

STATUS: Ongoing
APPROVAL DATE: Mar 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To evaluate the relationship between environmental exposures and the occurrence of neuroblastoma. Environmental factors that will be studied include maternal drug exposures, parental employment in electronic field, and parental radiation exposure. Also to be analyzed are maternal age at birth, length of gestation of patient, and birth weight of patient.

TECHNICAL APPROACH

Mothers of newly diagnosed, histologically confirmed neuroblastoma patients less than 19 years old will be interviewed once over the telephone by trained interviewers. Clinical data will also be provided by the patient's physician. Data will be analyzed to assess risk factors.

PRIOR AND CURRENT PROGRESS

There have been 74 additional registrants in the past year. The total number of registrants is now 84. No registrants are from WRAMC. It is too early to report results including adverse reaction data.

CONCLUSIONS

Study should remain open.

REPORT DATE: 03/16/94 WORK UNIT # 6316

DETAIL SUMMARY SHEET

TITLE: POG 9225: Study for Advanced Stage Hodgkin's Disease: A Phase II Study

KEYWORDS: Hodgkin's disease, advanced stage, chemotherapy

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Mosijczuk, Askold COL MC; Blaney, Susan MAJ MC

DEPARTMENT: Department of Pediatrics STATUS: Completed
SERVICE: Pediatric Hematology-Oncology Service APPROVAL DATE: Mar 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To evaluate the activity of a new combined modality therapy (irradiation plus the drugs Ara-C/cisplatin/VP-16 and oncovin/procarbazine/prednisone/Adriamycin) and toxicities of this therapy; and to evaluate tumor tissue cytogenetics.

TECHNICAL APPROACH
Patients 21 years of age or less with newly diagnosed advanced-stage Hodgkin's disease will be treated with alternating cycles of the drugs listed above, with irradiation. Therapy is given over 6-7 months. Initial biopsy material will be submitted to a central lab for cytogenetic analysis. Modifications to this study have been submitted to the Department of Clinical Investigation and will be reviewed by committee this month.

PRIOR AND CURRENT PROGRESS
Study was closed to accrual in June 1993 with sufficient accrual (73 patients altogether, 62 during the past year), but no WRAMC registrants. Response and survival data (including toxicity information) is pending.

CONCLUSIONS
Since there were no WRAMC registrants, this study should be closed.

REPORT DATE: 04/18/94 WORK UNIT # 6317

DETAIL SUMMARY SHEET

TITLE: Salvage Therapy for Recurrent Medulloblastoma, Ependymoma, Cerebral Pnet, and Cerebral Low Grade Astrocytoma

KEYWORDS: recurrent brain tumor, childhood, chemotherapy

PRINCIPAL INVESTIGATOR: Mosijczuk, Askold COL MC

DEPARTMENT: Department of Pediatrics STATUS: Completed
SERVICE: Pediatric Hematology-Oncology Service APPROVAL DATE: Mar 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine if the chemotherapy regimen described below is effective in children with recurrent/refractory brain tumors who have not had prior chemotherapy; and to measure disease-free survival, response rate, and toxicity of this therapy.

TECHNICAL APPROACH
Patients 21 years of age and less with central nervous system malignancies, who have not had prior chemotherapy, will be treated with cisplatin/VP-16 and vincristine/cytoxan, both in combination with G-CSF. These drugs are given in alternating cycles every 3 weeks for a maximum of 9 months. Response to therapy will be measured throughout the study and at regular follow-up. Several hospitals, in addition to Walter Reed, will be using this therapy and will be submitting data to the PI.

PRIOR AND CURRENT PROGRESS
Because of competing studies, patient accrual has been difficult. There have been no registrants.

CONCLUSIONS
Recommend closure of study.

REPORT DATE: 04/18/94 WORK UNIT # 6318

DETAIL SUMMARY SHEET

TITLE: POG 9264: Chemotherapy Regimen for Initial Induction Failures in Childhood ALL: A Phase II Study

KEYWORDS: relapse, childhood, ALL

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Blaney, Susan MAJ MC; Mosijczuk, Askold COL MC

DEPARTMENT: Department of Pediatrics
SERVICE: Pediatric Hematology-Oncology Service

STATUS: Ongoing
APPROVAL DATE: Apr 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To estimate response rate, 1 year disease-free survival rate, and toxicity of using the drugs 6-MP and methotrexate for induction; and to use cDNA probes on tissue samples from patients to look for multi-drug resistant genes and to obtain an oncogene profile.

TECHNICAL APPROACH
Patients, ages 21 years and less, who have failed induction therapy for acute lymphocytic leukemia (ALL) will be given a 3-week induction course of intrathecal chemotherapy and the drugs 6-MP and methotrexate. Consolidation therapy will also be given.

PRIOR AND CURRENT PROGRESS
Four patients have been accrued studywide in the past year, bringing the total to eight. There have been no WRAMC registrants. All eight patients are evaluated for toxicity during induction. Response is masked. Toxicity is within the range predicted for this therapy.

CONCLUSIONS
Study should remain open.

REPORT DATE: 04/18/94 WORK UNIT # 6319

DETAIL SUMMARY SHEET

TITLE: POG 9243: Treatment for Children with Intermediate-Risk Neuroblastoma: A Phase III Study

KEYWORDS: neuroblastoma, chemotherapy, surgery

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Blaney, Susan MAJ MC; Mosijczuk, Askold COL MC

DEPARTMENT: Department of Pediatrics
SERVICE: Pediatric Hematology-Oncology Service

STATUS: Ongoing
APPROVAL DATE: Apr 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To estimate response, disease-free survival, and toxicity of therapy (chemotherapy and surgery), and (for patients receiving intensive chemotherapy) to study the effectiveness of G-CSF in emeliorating neutropenia.

TECHNICAL APPROACH

Infants with stage B, C, or D neuroblastoma or patients ages 1-21 years with stages B, DS, or recurrent stage A neuroblastoma will be treated with chemotherapy and surgery, according to risk factors identified by clinical staging and by tumor cytogenetics. Patients who receive the more intensive chemotherapy will also receive G-CSF therapy in an attempt to ameliorate neutropenia that may result from chemotherapy.

PRIOR AND CURRENT PROGRESS

This study has accrued 83 patients in the past year; the total is 118. No WRAMC subjects have been enrolled. It is too early to report on response/disease-free survival. Toxicity has been as follows: 46 patients had grade 4 absolute neutrophil counts, 22 had grade 3 infections not otherwise specific/unknown, 14 had grade 3 sepsis bacteria, and 12 had grade 3 "other bacteria" toxicities.

CONCLUSIONS

Study should remain open.

REPORT DATE: 05/17/94 WORK UNIT # 6322

DETAIL SUMMARY SHEET

TITLE: POG 9222: Mitoxantrone, Etoposide and Cyclosporine Therapy in Pediatric Patients with Relapsed or Refractory Acute Myeloid Leukemia: A Phase II Study

KEYWORDS: relapsed, leukemia, children

PRINCIPAL INVESTIGATOR: Maybee, David A COL MC
ASSOCIATES: Blaney, Susan MAJ MC; Edwards, E. Glenn MAJ MC

DEPARTMENT: Department of Pediatrics STATUS: Ongoing
SERVICE: Pediatric Hematology-Oncology Service APPROVAL DATE: May 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To study the genetics of leukemia blast cells in registrants; to look for expression of two genetic mechanisms for drug resistance; and to measure efficacy and toxicity of the drugs mitoxantrone, etoposide, and cyclosporine in children with relapsed or refractory myeloid leukemia.

TECHNICAL APPROACH
Before therapy begins, blood samples will be drawn for genetic studies. Therapy with the drugs listed above will be given for up to 4 months. If relapse occurs after response to these drugs, additional genetic studies will be run on the registrant.

PRIOR AND CURRENT PROGRESS
As of 28 Oct 93, 47 patients have been entered on the study groupwide; 36 have been accrued since the last APR. No patients have been registered at WRAMC. Accrual is proceeding as planned. It is too early to report on results. Toxicity has been in the range expected for this patient population and these drugs. Possible benefits to patients include achieving partial or complete remission.

CONCLUSIONS
Study should remain open.

REPORT DATE: 05/17/94 WORK UNIT # 6323

DETAIL SUMMARY SHEET

TITLE: POG 9233/34: A Phase III Randomized Trial of Standard vs. Dose-Intensified Chemotherapy <3 Years of Age with a CNS Malignancy Treated With or Without Radiation Therapy

KEYWORDS: brain tumor, child, pre-school, chemotherapy

PRINCIPAL INVESTIGATOR: Maybee, David A COL MC
ASSOCIATES: Mosijczuk, Askold COL MC; Blaney, Susan MAJ MC

DEPARTMENT: Department of Pediatrics
SERVICE: Pediatric Hematology-Oncology Service

STATUS: Ongoing
APPROVAL DATE: May 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To study efficacy and toxicity of dose intensified chemotherapy in children less than 3 years old with selected types of brain tumors by means of a randomized comparison; to relate response to DNA index of tumor; and to attempt to observe for disease progression over 1 year, with the option of giving irradiation if tumor relapses during this year.

TECHNICAL APPROACH

Children less than 3 years of age with selected types of brain tumors will be randomized to receive either intensive or standard chemotherapy (POG 9233). If response is adequate, there will be 1 year of close observation, during which time radiation therapy on POG 9234 will be available if the tumor relapses. Patients who have less than adequate response on 9233 will receive irradiation on POG 9234 as soon as possible. The DNA index of diagnostic tumor tissue will be related to the treatment outcome.

PRIOR AND CURRENT PROGRESS

Since the last APR, 54 patients have been accrued groupwide for a total of 91. There have been no registrants at WRAMC. Accrual is proceeding satisfactorily. It is too early in this protocol to report results. Response is masked. Toxicity has been within the range predicted for this study. Possible benefits to patients include complete or partial remission.

CONCLUSIONS

Study should remain open.

REPORT DATE: 06/29/94 WORK UNIT # 6328

DETAIL SUMMARY SHEET

TITLE: POG 9239: Treatment of Children with Newly Diagnosed Brainstem Glioma Using Cisplatin as a Radiosensitizer with Either Conventional or Hyperfractionated Radiotherapy: A Pediatric Oncology Group Phase III Study

KEYWORDS: children, brain tumor, radiation therapy

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Mosijczuk, Askold COL MC; Edwards, E. Glenn MAJ MC

DEPARTMENT: Department of Pediatrics
SERVICE: Pediatric Hematology-Oncology Service

STATUS: Ongoing
APPROVAL DATE: Jun 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine the efficacy of and to gather data on the toxicity of cisplatin given with cranial irradiation.

TECHNICAL APPROACH
Patients aged 3-21 years will be randomized to receive 6 weeks of cranial radiation with cisplatin given during weeks 1, 3, and 5; with radiation therapy delivered on either a once daily or a twice daily (hyperfractionated) schedule.

PRIOR AND CURRENT PROGRESS
Eleven registrants were accrued in the past year (one from WRAMC), bringing the groupwide total to 42. The one previously reported WRAMC registrant who had completed therapy died of progressive disease. The new WRAMC registrant has undergone radiation therapy. It is too early to report on toxicity or response. Benefits to subjects include the possibility of remission of disease.

CONCLUSIONS
Study should remain open.

REPORT DATE: 06/29/94 WORK UNIT # 6329

DETAIL SUMMARY SHEET

TITLE: POG 9296: T-Cell Leukemia Pilot Study #4 (with IV MTX/IV6-MP) A Pediatric Oncology Group Limited Institution Pilot Study (Phase III)

KEYWORDS: T-cell, leukemia, children

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Blaney, Susan MAJ MC; Edwards, E. Glenn MAJ MC

DEPARTMENT: Department of Pediatrics
SERVICE: Pediatric Hematology-Oncology Service

STATUS: Ongoing
APPROVAL DATE: Jun 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To determine the efficacy of and to gather further toxicity data on this therapy which substitutes intermediate dose methotrexate and high dose IV 6-mercaptopurine (6-MP) for two drugs on the standard multi-drug regimen for this disease. To study this newer regimen for the feasibility of including it in a two-arm randomized comparison study.

TECHNICAL APPROACH

Patients 1 through 21 years old with T-cell disease (leukemia/lymphoma) will be treated with this 2-year multi-drug regimen. Patients will be followed after completing therapy for late adverse reactions or relapse.

PRIOR AND CURRENT PROGRESS

Sixteen registrants have been accrued in the past year, bringing the groupwide total to 46. There have been no WRAMC registrants in the past year. The one WRAMC registrant previously reported continues on therapy. Sufficient data exists to evaluate toxicity on 44 of the 46 patients. Forty-three of the 44 patients reported at least one episode of grade 4 neutropenia, and 31 of the 44 reported grade 3 or 4 thrombocytopenia. In general, patients who have progressed beyond the first year of therapy appear to be tolerating the regimen quite well, with the expected marrow suppression and incidence of infections which result from the neutropenia and immunosuppression. Survival data are quite acceptable at this point. Benefits to patients include possibility of remission.

CONCLUSIONS

Study should remain open.

REPORT DATE: 06/29/94 WORK UNIT # 6333

DETAIL SUMMARY SHEET

TITLE: POG 9237: Idarubicin in Recurrent and Progressive Childhood Brain Tumor Patients: A Pediatric Oncology Group Phase II Study

KEYWORDS: recurrent brain tumor, children, idarubicin

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Blaney, Susan MAJ MC; Mosijczuk, Askold COL MC

DEPARTMENT: Department of Pediatrics
SERVICE: Pediatric Hematology-Oncology Service

STATUS: Ongoing
APPROVAL DATE: Jun 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine the efficacy and toxicity of idarubicin given with granulocyte-colony stimulating factor (G-CSF).

TECHNICAL APPROACH
Eligible patients 21 years of age and less will be given idarubicin as a 4-hour IV infusion every 3 weeks, followed by G-CSF support until neutropenia resolves. Patients may receive up to six doses of idarubicin on this study. Response will be determined by a review of films at a central office.

PRIOR AND CURRENT PROGRESS
Twenty-seven patients have been accrued in the past year, bringing the groupwide total to 56. Of the three WRAMC registrants, two have died off study from progressive disease; the remaining registrant, accrued in the past year, is on therapy and doing well. Toxicity is within the range expected for these patients on this therapy. It is too early to report on response. There have been no reports of adverse reactions. Benefits to subjects include the possibility of remission.

CONCLUSIONS
Study should remain open.

REPORT DATE: 07/22/94 WORK UNIT # 6334

DETAIL SUMMARY SHEET

TITLE: POG 9265: Evaluation of 13 Cis-Retinoic Acid in Children with Juvenile Chronic Myelogenous Leukemia: A Phase II Study

KEYWORDS: JCML, cis-retinoic acid, children

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Blaney, Susan MAJ MC; Mosijczuk, Askold COL MC

DEPARTMENT: Department of Pediatrics
SERVICE: Pediatric Hematology-Oncology Service

STATUS: Ongoing
APPROVAL DATE: Jul 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To determine the efficacy and toxicity of cis-retinoic acid in patients with juvenile chronic myelogenous leukemia (JCML), and to determine the relationship between response to treatment and in vitro cell growth patterns.

TECHNICAL APPROACH

Patients, ages 21 years and less with newly diagnosed JCML who are not immediately eligible for bone marrow transplantation, will receive therapy with oral cis-retinoic acid for a minimum of 2 months or until the patient becomes eligible for bone marrow transplantation.

PRIOR AND CURRENT PROGRESS

Thirteen patients have been accrued groupwide (nine this past year), none from WRAMC. This is a rare type of leukemia, so accrual is expected to be slow. There have been no reports of adverse reactions. It is too early to report on response. Benefits to subjects include the possibility of remission of disease.

CONCLUSIONS

Study should remain open.

REPORT DATE: 09/22/94 WORK UNIT # 6338

DETAIL SUMMARY SHEET

TITLE: POG 9219: The Treatment of localized Non-Hodgkin's Lymphoma in Children: A POG Phase IV Study

KEYWORDS: children, lymphoma, localized

PRINCIPAL INVESTIGATOR: Maybee, David COL MC

DEPARTMENT: Department of Pediatrics STATUS: Ongoing
SERVICE: Pediatric Hematology-Oncology Service APPROVAL DATE: Sep 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To maintain a high cure rate with minimum toxicity in children with localized non-Hodgkin's lymphoma (NHL) in favorable sites, and to analyze prognostic factors which may predict subgroups of patients with a poorer prognosis within patients with localized NHL.

TECHNICAL APPROACH
Chemotherapy will be given for 3-9 months (depending on stage and location of disease). Patients will be followed for relapse.

PRIOR AND CURRENT PROGRESS
Since the last APR, 51 patients have been accrued to this study, bringing the groupwide total to 65. There have been no registrants at WRAMC. Response of the 32 eligible patients: 30 had a complete response; one had a partial response; and one has an unknown response. The current report has no data on toxicity. Benefits to patients include the possibility of remission of disease.

CONCLUSIONS
Study should remain open.

REPORT DATE: 09/22/94 WORK UNIT # 6339

DETAIL SUMMARY SHEET

TITLE: POG 9227: Treatment of Recurrent or Refracttory Hodgkin's Disease with Cyclosporine-A, Actinomycin-D, and Vincristine: A POG Phase II Study

KEYWORDS: soft tissue sarcoma, P-glycoprotein, cyclosporin A

PRINCIPAL INVESTIGATOR: Maybee, David COL MC

DEPARTMENT: Department of Pediatrics STATUS: Ongoing
SERVICE: Pediatric Hematology-Oncology Service APPROVAL DATE: Sep 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To study the toxicity and efficacy of cyclosporin A (CSA), actinomycin-D (ACT), and vincristine (VCR) in the treatment of recurrent or refractory Hodgkin's disease, Wilms' tumor, Ewing's sarcoma, rhabdomyosarcoma, or other soft tissue sarcomas; to assess the prevalence of P-glycoprotein (P-gp) in tumor specimens from patients with these diseases, and to correlate this with clinical response to CSA; and to study the pharmacokinetics of high-dose CSA.

TECHNICAL APPROACH
Patients 21 years old or less, with relapsed disease as listed above, will be treated with chemotherapy between 9 weeks and 1 year depending upon response. An amendment to bar registrants with significant pleural effusions was approved by the WRAMC Department of Clinical Investigation on 22 Apr 94.

PRIOR AND CURRENT PROGRESS
Since the last APR, 10 patients have been accured on this study, bringing the groupwide total to 11. There have been no registrants at WRAMC. The worst degreee of toxicity reported for the seven evaluable patients: five had grade 4 ANC toxicity; and two had grade 4 platelet toxicity. It is too early to report on response or disease-free survival. Benefits to patients include the possiblity of remission of disease.

CONCLUSIONS
Study should remain open.

REPORT DATE: 11/08/93 WORK UNIT # 6343

DETAIL SUMMARY SHEET

TITLE: POG 9220: Treatment for Previously Untreated Acute Promyelocytic Leukemia: A Phase III Intergroup Study

KEYWORDS: childhood, leukemia, chemotherapy

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Mosijczuk, Askold COL MC; Blaney, Sussan MAJ MC

DEPARTMENT: Department of Pediatrics
SERVICE: Pediatric Hematology-Oncology Service

STATUS: Ongoing
APPROVAL DATE: Nov 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To compare the response rate of transretinoic acid to that achieved with conventional induction chemotherapy using cytosine arabinoside plus daunomycin in children with previously untreated acute promyclocytic leukemia; to compare toxicities in each group; and to determine the value of maintenance chemotherapy with transretinoic acid.

TECHNICAL APPROACH

Registrants will be randomized to receive a standard induction therapy or 90 days of transretinoic acid. Both groups will then be given standard consolidation chemotherapy, followed by a second randomization to either transretinoic acid maintenance therapy or no additional therapy.

PRIOR AND CURRENT PROGRESS

In this first year of the study, there have been four patients entered; none from WRAMC. Toxicities are as expected for these agents used in this population. Response data is masked.

CONCLUSIONS

Study should remain open.

REPORT DATE: 01/24/94 WORK UNIT # 6347

DETAIL SUMMARY SHEET

TITLE: POG 9262: The Treatment of Children with Recurrent/Refractory Solid Malignancies with Taxol: A Phase II Study

KEYWORDS: solid malignancy, taxol

PRINCIPAL INVESTIGATOR: Maybee, David COL MC

DEPARTMENT: Department of Pediatrics STATUS: Ongoing
SERVICE: Pediatric Hematology-Oncology Service APPROVAL DATE: Jan 1993

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine the response rate of recurrent/refractory solid tumor malignancies to taxol in a Phase II trial; and to further define the spectrum of taxol's toxicity in children.

TECHNICAL APPROACH
Eligible patients must be less than 21 years old at time of diagnosis with measurable, histologically proven, recurrent/refractory disease. Eligible patients must also have a life expectancy greater than 6 weeks, normal hepatic and renal functions, and a weight at least equal to the 3rd percentile based on height. Registrants will be pre-medicated with dexamethasone IV at 7 and 14 hours prior to taxol infusion and with Diphenhydramine IV at 30 minutes prior to infusion. Three cycles (6 weeks) of taxol will be administered IV over 24 hours.

PRIOR AND CURRENT PROGRESS
A total of 43 patients have been accrued groupwide (none from WRAMC) on the study. It is too early to report any toxicity or response analysis.

CONCLUSIONS
Study should remain open.

REPORT DATE: 02/14/94 WORK UNIT # 6348

DETAIL SUMMARY SHEET

TITLE: POG 9244: Treatment for Children with Newly Diagnosed Stages 2B and 3 Neuroblastoma Older than One Year of Age: A Phase II Pilot Study

KEYWORDS: neuroblastoma, children

PRINCIPAL INVESTIGATOR: Maybee, David COL MC

DEPARTMENT: Department of Pediatrics STATUS: Ongoing
SERVICE: Pediatric Hematology-Oncology Service APPROVAL DATE: Feb 1993

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To estimate response rate/local control/survival in eligible patients given OPEC/OJEC), and response to radiotherapy in patients not achieving complete remission (CR) with chemotherapy and surgery. To evaluate toxicities associated with OPEC/OJEC regimen. To compare degree of surgical resectability to rate of CR, duration of remission/survival, and to determine the value of lab or neuroblastoma (POG 9047) studies in relation to clinical presentation/response/survival.

TECHNICAL APPROACH
Eligible patients must be >/= 365 days old and >/= 21 years old with newly diagnosed neuroblastoma, INSS Stage 2B, or Stage 3, with no previous chemotherapy or radiation therapy. Patients must also register on POG 9047 and must have specimen sent for N-myc copy number determination. Patients must have adquate hematologic, kidney, and liver functions. Patients will be treated with vincristine/etoposide/cyclophosphamide with alternating ciplatin/carboplatin chemotherapy (OPEC/OJEC) and second-look surgery.

PRIOR AND CURRENT PROGRESS
Total patient accrual on study to date is six (none from WRAMC). It's too early to report any toxicity or response date.

CONCLUSIONS
Study should remain open.

REPORT DATE: 02/14/94 WORK UNIT # 6349

DETAIL SUMMARY SHEET

TITLE: POG 9226: Treatment of Stage I, IIA and IIIA1 Hodgkin's Disease with ABVE and Low Dose Irradiation

KEYWORDS: Hodgkin's disease, ABVE, irradiation

PRINCIPAL INVESTIGATOR: Maybee, David COL MC

DEPARTMENT: Department of Pediatrics STATUS: Ongoing
SERVICE: Pediatric Hematology-Oncology Service APPROVAL DATE: Feb 1993

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To study the activity of four cycles of Adriamycin, bleomycin, vincristine, and etoposide (ABVE) followed by irradiation in Stages I, II, and IIIA Hodgkin's disease; to establish response rate (complete and partial remission) and determine therapy-related effects of ABVE; to reduce morbidity without decreasing efficacy of treatment in early stage Hodgkin's disease; and to correlate results to findings in those receiving a laparotomy.

TECHNICAL APPROACH
Newly-diagnosed patients </= 21 years of age with proven Stage I, II, or IIIA Hodgkin's disease will be enrolled. Patients will be given four cycles of ABVE IV. Patients must not have had prior staging laparotomy.

PRIOR AND CURRENT PROGRESS
Twenty-two patients have been accrued groupwide (one from WRAMC) on the study. Accrual on this study has been excellent. Of the 22 patients, 13 have completed four courses of chemotherapy, two have completed two courses, and four are too early to report. Response is masked. It is too early to evaluate disease-free survival.

CONCLUSIONS
Study should remain open.

REPORT DATE: 03/16/94 WORK UNIT # 6351

DETAIL SUMMARY SHEET

TITLE: POG 9317: Chemotherapy for Children with Advanced-Stage (III/IV) Diffuse Undifferentiated Burkitt's Lymphoma and B-Cell ALL: A Phase IIII Study

KEYWORDS: Burkitt's lymphoma, Cytoxan, Ara-C

PRINCIPAL INVESTIGATOR: Maybee, David COL MC

DEPARTMENT: Department of Pediatrics STATUS: Ongoing
SERVICE: Pediatric Hematology-Oncology Service APPROVAL DATE: Mar 1993

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To evaluate the efficacy of adding VP-16/ifosfamide (VP/IFOS) intensification to the treatment of patients with advanced-stage B-cell malignancies (Stages III and IV DU NHL and B-cell ALL), and to compare the toxicity of high doses of Ara-C given by intermittent bolus vs. bolus/continuous infusion.

TECHNICAL APPROACH
Registrants must be 21 years old or younger and have had no previous chemotherapy. Concomitant registration on POG 9000 (biology study) is required. Children with diagnosed advanced-stage (III-IV) diffuse undifferentiated Burkitt's lymphoma and B-cell ALL will receive randomized induction therapy to compare the toxicity of high-dose Ara-C given by intermittent bolus (q 12 hours x 4) vs. bolus/continuous infusion over 48 hours, followed by randomization to receive or not receive VP/IFOS for intensification.

PRIOR AND CURRENT PROGRESS
Fourteen patients have been accrued since March 1993. There are no registrants from WRAMC. It is too early to report results including toxicity data.

CONCLUSIONS
Study should remain open.

REPORT DATE: 04/04/94 WORK UNIT # 6352

DETAIL SUMMARY SHEET

TITLE: POG 9340/41/42: Treatment of Patients One Year and Older at Diagnosis with Stages 2/B3 or 4 High-Risk Neuroblastoma: A Phase II Study

KEYWORDS: neuroblastoma, chemotherapy, toxicity

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Herden, Mary LT CMDR, MC; Edwards, E. Glenn MAJ MC

DEPARTMENT: Department of Pediatrics
SERVICE: Pediatric Hematology-Oncology Service

STATUS: Ongoing
APPROVAL DATE: Apr 1993

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

9340 Stage 4 (only): To evaluate response rate to and toxicity of Phase II single-agent chemotherapy (Taxol and then Topotecan) given prior to Phase III therapy for children >/= 365 days of age with INSS stage 4 neuroblastoma. 9341/2 stage 4 and N-myc amplified stage 2B or 3 (stage C): To measure response rates and patterns of failure of patients treated with six courses of induction therapy prior to ABMT/radiotherapy to the tumor bed.

TECHNICAL APPROACH

POG 9340 (Phase II): Taxol mg/m^2 via 24 hour continuous IV; and Topotecan 1.7 mg/m^2/dx5+ G-CSF given IV twice (at days 0 and 21). Upon recovery, POG 9341/2 multi-agent chemotherapy begins; high dose platinum/VP-16 (HDP/VP), cyclophosphamide/Adriamycin/vincristine (CAV), ifosfamide/VP (IFOS/VP), CBDCA/VP, HDP/VP, and CAV plus G-CSF, followed by local radiotherapy and ABMT. POG 9341/9342: To measure response rates, toxicity, EFS, survival, and patterns of failure of patients who receive five additional therapy courses (IFOS/VP, CAV, HDP/VP, CAV, CBDCA/VP) plus G-CSF followed by local radiotherapy to the tumor bed. To evaluate ABMT toxicity using cyclophosphamide/VP/CBDCA ablation plus local radiotherapy.

PRIOR AND CURRENT PROGRESS

POG 9340: Treatment #1 (Taxol) closed to accrual, 04 Mar 94, after meeting accrual goal of 29 patients (none from WRAMC). Treatment #2 (Topotecan) is open for accrual to the next 30 patients. POG 9341: 15 registrants have been enrolled (none from WRAMC), effective 03 Feb 94. POG 9342: Two registrants have been enrolled (none from WRAMC), effective 03 Feb 94. Samples from marrow aspirate are sent at week 16 for evaluation of efficiency of purging.

CONCLUSIONS

It is too early to report results. Study should remain open.

REPORT DATE: 06/27/94 WORK UNIT # 6353

DETAIL SUMMARY SHEET

TITLE: POG 9310: SIMAL 7: Escalating Rotational Drug Therapy After 1st Marrow Relapse of Non-T, Non-B ALL: A Phase II Pilot Study

KEYWORDS: Burkitt's lymphoma, chemotherapy, B-cell ALL

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Mosijczuk, Askold COL MC; Herden, Mary LCDR MC

DEPARTMENT: Department of Pediatrics
SERVICE: Pediatric Hematology-Oncology Service

STATUS: Ongoing
APPROVAL DATE: Jun 1993

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To: 1) increase event-free survival in children with ALL after first marrow relapse or non-primary CNS extramedullary relapse; 2) determine feasibility of giving G-CSF to those with recurrent ALL and whether administration of G-CSF in continuation will allow escalation of myelotoxic agent active in ALL; 3) compare, via randomized trial, efficacy/toxicity of weekly vs. every-other-week PEG-L-asp; and 4) study pharmacokinetics/dosage of PEG-L-asp for those with ALL in relapse.

TECHNICAL APPROACH

The study will measure the acceptability of toxicity due to continuation therapy. The standard error of the 1-year survival will be less than 6.5%. To guide the development of a successor protocol, this study will descriptively assess the toxicities and their relationship to each of the pairs of rotationally-administered agents.

PRIOR AND CURRENT PROGRESS

Groupwide, a total of 77 patients have been accrued since the study was activated, 28 May 93. WRAMC has had five registrants: two have died; one from an ALL relapse, and the other during a bone marrow transplant at the University of Minnesota Hospital. Two of the five transferred to San Antonio for bone marrow transplants. The remaining WRAMC registrant transferred to Brook Army Medical Center and is continuing treatment. Statistics are only available for the 34 patients accrued as of 29 Oct 93; 18 had complete remission, and 2 had no response. Of 19 patients evaluable for toxicity, 14 had grade 4 platelet toxicity, and 8 had grade 3 infection "not otherwise specified/unknown" toxicity. Study is expected to close in the next 4 months. Benefits to the subject include possibility of remission of disease.

CONCLUSIONS

Study should remain open for follow-up.

REPORT DATE: 06/27/94 WORK UNIT # 6354

DETAIL SUMMARY SHEET

TITLE: POG 9357: The Use of Cyclosporfin A To Overcome Multiple Drug Resistance in Osteogenic Sarcoma: A POG Phase II Study

KEYWORDS: cyclosporin A, osteogenic, sarcoma

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Edwards, E. Glenn LTC MC; Blaney, Susan MAJ MC

DEPARTMENT: Department of Pediatrics
SERVICE: Pediatric Hematology-Oncology Service

STATUS: Ongoing
APPROVAL DATE: Jun 1993

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To: 1) determine the clinical response to cyclosporin A (CDDP) and doxorubicin (DOX) in patients with osteogenic sarcoma that initially progresses or recurs within 4 months of CDDP/DOX therapy; 2) determine the freqeuncy of expression of P-glycoprotein (P-gp) in patients with recurrent/progressive osteogenic sarcoma; and 3) study the effect of CSA on the pharmacokinetics of doxorubicin.

TECHNICAL APPROACH

Treatment plan: two courses (6 weeks) of CSA, doxorubicin, and cisplatin will be administered. CSA will be given by continuous infusion x38 hours. Doxorubicin 45 mg/M^2 IV will be given over 1 hour at hour 24. Eligiblity: age < 21 years old at diagnosis. Patients must have measurable, recurrent, or progressive osteosarcoma with initial presentation with 4 months of CDDP/DOX therapy. Accrual of 28 patients per year is anticipated. Registration goal should be achieved in 1.2 years. Response data will not be printed in POG agendas until study is closed to accrual and all accrued patients have compared protocol therapy.

PRIOR AND CURRENT PROGRESS

POG 9357 opened to accrual 28 Jun 93. As of 03 Feb 94, registration stands at three patients. It is too early to report any results. There have been no WRAMC registrations. There are no reports of toxicity or adverse reactions. Benefits to subjects could include remission of disease.

CONCLUSIONS

Study should remain open.

REPORT DATE: 07/21/94 WORK UNIT # 6355

DETAIL SUMMARY SHEET

TITLE: POG 9330: Taxol in Progressive or Recurrent Childhood Brain Tumorsw: A Phase II Study

KEYWORDS: taxol, brain tumor, recurrent

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Mosijczuk, Askold COL MC; Edwards, E. Glenn LTC MC

DEPARTMENT: Department of Pediatrics
SERVICE: Pediatric Hematology-Oncology Service

STATUS: Ongoing
APPROVAL DATE: Jul 1993

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To estimate the response rate of pediatric central nervous system neoplasms to taxol in a Phase II trial, and to further define the toxicities of taxol in children with brain tumors.

TECHNICAL APPROACH
Taxol will be adminstered at a dose of 350/M^2 IV, over 24 hours, every 21 days. In the absence of clinically progressive disease, patients should receive two cycles of therapy prior to evaluation for response. In the absence of radiographic progression, patients will continue to receive taxol every 3 weeks. Evaluations should be repeated every 6 weeks (prior to alternate doses), and the response noted on the flow sheets, preferably with actual measurements. Patients with PR, CR, or stable disease will continue on taxol for a maximum of 18 cycles (1 year). Patients with progressive disease or unacceptable toxicity (cardiotoxicity, unremitting neurotoxicity) will be taken off-study.

PRIOR AND CURRENT PROGRESS
Latest available data indicate two patients have been accrued groupwide. One patient has been accrued at WRAMC. It is too early to report any results. Benefits to patients include the possibility of remission of disease.

CONCLUSIONS
Study should remain open.

REPORT DATE: 07/21/94 WORK UNIT # 6356

DETAIL SUMMARY SHEET

TITLE: POG 9345: Treatment of unresetable/Metastatic Hepatoblastoma with Chemotherapy and Surgery: A Phase II Study

KEYWORDS: metastatic, hepatoblastoma, chemotherapy

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Herden, Mary LCDR MC; Blaney, Susan MAJ MC

DEPARTMENT: Department of Pediatrics
SERVICE: Pediatric Hematology-Oncology Service

STATUS: Ongoing
APPROVAL DATE: Jul 1993

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To determine toxicity/estimate tumor response rate in hepatoblastoma patients given: 1) single carboplatin (carbo) course initial therapy to those with unresectable disease (Stage III/IV); 2) three courses of carbo, 5-fluorouracil, and weekly vincristine (VCR), and response rate/proportion of those made resectable after initial carbo; and 3) two courses of high-dose cisplatin (HDP/VP16), and response rate/proportion of those made resectable after first two regimes fail.

TECHNICAL APPROACH

One course of carbo will be given and its response evaluated. Three courses of carbo/VCR/FU will follow. Patients will be re-evaluated for surgical resectability. If tumor is completely resected, patients will be given two more courses of carbo/VCR/FU, and stop therapy. If their tumor remains unresectable, the patient will be switched to HDP/VP16 for two courses, and re-evaluated for surgery. If the tumor is completed resected, therapy will be stopped. If the tumor remains unresectable, the patient will be taken off the study.

PRIOR AND CURRENT PROGRESS

During the first 5 months of the study, 11 patients have been accrued groupwide. No patients have been accrued at WRAMC. Two patients have had grade 4 ANC toxicity, and four have had grade 4 platelet toxicity. Benefits to patients include the possibility of remission of disease.

CONCLUSIONS

Study should remain open.

REPORT DATE: 07/21/94 WORK UNIT # 6357

DETAIL SUMMARY SHEET

TITLE: POG 9360: GM-CSF Randomization + High-Dose ICE in the Treatment of Recurrent/Resistant Malignant Solid Tumors of Childhood: Phase II Study

KEYWORDS: ICE, recurrent, tumors

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Mosijczuk, Askold COL MC; Edwards, E. Glenn LTC MC

DEPARTMENT: Department of Pediatrics STATUS: Ongoing
SERVICE: Pediatric Hematology-Oncology Service APPROVAL DATE: Jul 1993

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To: 1) determine the anticarcinogenic activity and toxicity of the maximally-tolerated dose of ifosfamide and carboplatin plus etoposide (high-dose ICE) against childhood malignant solid tumors resistant to conventional chemotherapy; and 2) define the most effective but least toxic dose of GM-CSF for amelioration of the myelosuppression that accompanies ICE therapy.

TECHNICAL APPROACH
Patients will receive VP-16 + MESNA, ifosfamide, and CBDCA q 21-28 days, with GM-CSF on days 4-19 or until >500/ul after the expected nadir. Patients will be evaluated for response after every other course of therapy. Therapy may continue as long as the patient continues to show response and experiences no unacceptable toxicity.

PRIOR AND CURRENT PROGRESS
Thirteen patients have been entered in the study groupwide, none at WRAMC. Five patients were randomized to receive GM-CSF ug/m^2, and six were randomized to receive 500 ug/m^2. No information is available on two patients. Patient accrual is steady. Patients have received one to three courses of therapy and have tolerated it well. Eventhough 3-4+ myelosuppression was universal, recovery was seen in all patients by 4 weeks. It is too early to report on response or disease-free survival. Benefits to patients include the possibility of remission of disease.

CONCLUSIONS
Study should remain open.

REPORT DATE: 11/04/93 WORK UNIT # 3600

DETAIL SUMMARY SHEET

TITLE: Determination of Noncompliance in Prescription Pickup

KEYWORDS: non-compliance, prescription

PRINCIPAL INVESTIGATOR: Nelson, Bruce COL MS

SERVICE: Pharmacy Service STATUS: Completed
APPROVAL DATE: Oct 1989

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine the most common reasons why patients fail to pick up new and refill prescriptions from the Pharmacy. Secondarily, to identify demographically, any significant differences between patients who pick up their prescriptions versus patients who fail to claim their prescriptions.

TECHNICAL APPROACH
Collect an unselected convenience sample of 100 patients with unclaimed, new prescriptions and 100 patients with unclaimed, refill prescriptions. After identifying patients, they will be contacted by phone, asked to participate in the study, and given a short telephone questionnaire. The second part of the study will attempt to identify significant demographic differences between patients who fail to pick up their medication and those who pick up their prescriptions. A random sample of 186 patients in each group (total 372 patients) will be reviewed for differences. Data will be analyzed using logistic regression.

PRIOR AND CURRENT PROGRESS
During the first year of this study, some progress was made on part one. However, the original principal investigator left WRAMC, and there has been no progress during the past 2 years.

CONCLUSIONS
No conclusions; study should be closed.

REPORT DATE: 11/12/93 WORK UNIT # 3604

DETAIL SUMMARY SHEET

TITLE: Pharmacodynamic Analysis of Morphine and Its Metabolites in the Treatment of Chronic Cancer Pain

KEYWORDS: morphine, pain, pharmacodynamics

PRINCIPAL INVESTIGATOR: Solimando, Dominic Jr MAJ MC

SERVICE: Pharmacy Service STATUS: Ongoing
APPROVAL DATE: Oct 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine if there is a correlation between the dose of morphine and plasma, or urine levels of morphine, or the 3- or 6-glucuronide metabolites. To determine if the measured plasma/urine levels of morphine or its metabolites correlate with analgesic efficacy.

TECHNICAL APPROACH
Plasma/urine levels will be measured via high-performance liquid chromatography (HPLC). Analgesic efficacy will be assessed using standard pain assessment instruments.

PRIOR AND CURRENT PROGRESS
To date, two patients have been enrolled. Neither completed the full study of four blood samples and two urine samples. Patient accrual has been hampered by the need for multiple visits to the clinic for blood samples, and by the requirement that morphine be the sole analgesic. An amendement to the original study, modifying the blood/urine sampling plan and limiting the scope of the study, is in preparation. It is hoped the modified study will be more feasible, and will provide useful data.

CONCLUSIONS
No conclusions can be made at this time. No useful data has been derived so far from this study.

REPORT DATE: 02/09/94 WORK UNIT # 9614

DETAIL SUMMARY SHEET

TITLE: A Descriptive Analysis of Patient Referrals to Army Physical Medicine Services During Armed Conflict

KEYWORDS: war, rehabilitation, military

PRINCIPAL INVESTIGATOR: Dillingham, Timothy NAJ MC

SERVICE: Physical Medicine and Rehabilitation Service STATUS: Completed
APPROVAL DATE: Feb 1991

FUNDING: Current FY: $ 1,853 Previous FYs: $ 0 Total: $ 1,853

STUDY OBJECTIVE
To describe the patient characteristics of casualties referred to Army physical medicine services during armed conflict. This includes the quantification of functional deficits in these casualties.

TECHNICAL APPROACH
Survey data will be collected at the time of initial contact when a casualty is referred to Physical Medicine. This data will include patient demographics and details regarding the injuries. It will also include functional limitations. There are no modifications to the original protocol.

PRIOR AND CURRENT PROGRESS
Charts from 222 patients have been reviewed, none during the past year. Injuries seen in active-duty soldiers from the Persian Gulf War included musculoskeletal - 57%, peripheral nerve - 44%, penetrating wounds - 32%, fractures - 28%, amputations - 7%, and burns - 6%. Spinal cord injuries occurred in 3%, with the primary referral service being Orthopaedics (64%). Electrodiagnostic evaluations wee performed for 41% of all referrals. Limb contractures occurred in approximately 10% of patients. Ambulatory impairments were often seen. Data has been analyzed and published. One more publication is planned.

CONCLUSIONS
Study results highlight the need for multidisciplinary rehabilitation to address the needs of injured soldiers.

REPORT DATE: 03/18/94 WORK UNIT # 9615

DETAIL SUMMARY SHEET

TITLE: An Analysis of the Extensor Digitorium Brevis Deep Tendon Reflex in Normals and in Patients with L5 Radicular Compression Syndromes

KEYWORDS: L5, radiculopathy, reflexes

PRINCIPAL INVESTIGATOR: Dillingham, Timothy MAJ MC
ASSOCIATES: Chang, Audrey PhD

SERVICE: Physical Medicine and Rehabilitation Service

STATUS: Completed
APPROVAL DATE: Mar 1991

FUNDING: Current FY: $ 995 Previous FYs: $ 0 Total: $ 995

STUDY OBJECTIVE

To assess the extensor digitorium brevis (EDB) deep tendon reflex in patients with L5 radiculopathy and in normals.

TECHNICAL APPROACH

In order to study the EDB reflex and to define its sensitivity along with its latency characteristics, two populations of subjects (normals and patients) between ages 20-60 will be studied. Normals are those without radicular disease. Patients are those with H&P findings compatible with L5 radiculopathy imaging evidence of root compression. The requirement of no back pain within 6 months prior to testing has been eliminated in normals. The EDB reflex will be tested both physically and electrodiagnostically. The EDB response on the patients will be recorded in a blind fashion.

PRIOR AND CURRENT PROGRESS

A total of 88 enrolled patients have been included in statistical analysis (50 normals, 20 L5 patients, and 18 S1 patients). Nine more S1 subjects were recruited this past year as requested by the editors. The data is currently being analyzed.

CONCLUSIONS

Plans are to assess whether this reflex is useful in identifying radiculopathies, and whether it distinguishes L5 from S1.

REPORT DATE: 06/21/94 WORK UNIT # 9616

DETAIL SUMMARY SHEET

TITLE: Intern Perceptions of Physical Medicine and Rehabilitation

KEYWORDS: physical medicine, perceptions, GME

PRINCIPAL INVESTIGATOR: Braverman, Steven CPT MC
ASSOCIATES: Belandres, Praxedes COL MC

SERVICE: Physical Medicine and Rehabilitation Service STATUS: Completed
APPROVAL DATE: Jun 1991

FUNDING: Current FY: $ 1,154 Previous FYs: $ 0 Total: $ 1,154

STUDY OBJECTIVE
To determine 1991-92 WRAMC Internship Class perceptions of and attitudes toward Physical Medicine and Rehabilitation (PM&R); to explore demographic factors associated with changes in attitude toward PM&R; to determine if perceptions are altered by orientation or routine interactions with the PM&R Service; and to determine the validity of the Leschner 11-item questionnaire used in this study.

TECHNICAL APPROACH
Questionnaires will be given out to the 1991-92 Intern Class at the following four intervals: before and after orientation, 6 months into internship, and at the end of the internship. Questionnaires include the 11-item, 7-point scale originated by Leschner. Statistical analysis will be performed on completed questionnaires as per protocol. Additional questionnaires were distributed to the WRAMC 1992-93 Intern Class before and after their orientation to assess the validity of the questionnaire.

PRIOR AND CURRENT PROGRESS
Data collection was completed July 1992. Fifty-seven of 58 Class of 1991-92 interns completed questionnaires 1 and 2, with about a 25% response rate for questionnaires 3 and 4. Thirty-five of 45 interns in the 1992-93 class returned usab

CONCLUSIONS
The questionnaire was reliable with an alpha reliability of .76. Interns' perceptions of Physical Medicine and Rehabilitation are initially favorable and improve after an orientation.

REPORT DATE: 03/18/94 WORK UNIT # 9617

DETAIL SUMMARY SHEET

TITLE: Use of Topical Capsaicin in Myofascial Pain Syndromes and Primary Fibromyalgia Syndrome

KEYWORDS: substance P, capsaicin, fibromyalgia

PRINCIPAL INVESTIGATOR: Dillingham, Timothy MAJ MC
ASSOCIATES: Zeigler, Daryl LTC MC

SERVICE: Physical Medicine and Rehabilitation Service STATUS: Completed
APPROVAL DATE: Mar 1992

FUNDING: Current FY: $ 995 Previous FYs: $ 0 Total: $ 995

STUDY OBJECTIVE
To show supporting evidence that topical capsaicin decreases subjective pain intensity when applied over trigger points and tender points in patients with myofascial pain syndrome and fibromyalgia.

TECHNICAL APPROACH
Patients will participate in a 6 week open-labeled pilot study to test the use of 0.025% capsaicin cream on tender and trigger points in the neck and shoulder girdle. Baseline pain measurements will be obtained during the first week of the study with use of the McGill Pain Questionnaire and the visual analogue scale. The cream will then be applied for a 5 week treatment period. The same pain measurement questionnaire and pain relief scale will be used to document changes in subjective pain intensity.

PRIOR AND CURRENT PROGRESS
A total of 37 subjects entered this study (ten this past year); 25 were recruited to use capsaicin topically. Only one person dropped out due to intolerable burning. No other significant side effects were noted. Compliance with the medication was good. Significant improvement was noted over the 6-week trial on both the visual analog and pain release scales, but none was noted on the McGill Pain Questionnaire.

CONCLUSIONS
Capsaicin may be of benefit for chronic neck pain, and a double-blind placebo control trial is now necessary.

REPORT DATE: 06/30/94 WORK UNIT # 9620

DETAIL SUMMARY SHEET

TITLE: Radiculopathy Screen: Choosing the Most Sensitive Muscles

KEYWORDS: radiculopathy, electromyography

PRINCIPAL INVESTIGATOR: Lauder, Tamara CPT MC

SERVICE: Physical Medicine and Rehabilitation Service STATUS: Completed
APPROVAL DATE: Aug 1992

FUNDING: Current FY: $ 1,732 Previous FYs: $ 0 Total: $ 1,732

STUDY OBJECTIVE
To determine the sensitivity of selected groups of muscles to allow quantitative insight into the number of muscles required to identify a radiculopathy of the lumbosacral spine.

TECHNICAL APPROACH
This study is a retrospective chart review of lumbosacral radiculopathy patients diagnosed electrodiagnostically over a 3 year period. All studies fulfilling the inclusion criteria for a radiculopathy will be categorized into specific radiculopathy levels based on review of the literature. Once the studies are categorized, data analysis will be performed utilizing dBase III+ and SPSS/PC+ 3.1 software. The sensitivity of each muscle will be described by the percentage of the presence of abnormal spontaneous activity of each muscle. Sensitivity for each muscle group will be calculated by the percentage of positive radiculopathy screens with a 95% confidence interval.

PRIOR AND CURRENT PROGRESS
Approximately 1,000 charts have been reviewed (202 of them during the first year of the study); 201 charts met the inclusion criteria for a total of 247 radioculopathies. The study is complete, and publications have been submitted. Data analysis revealed that the paraspinal muscles alone yielded >75% sensitivity. Three muscle screens yielded 85-94% sensitivity; four yielded 91-97% sensitivity; five yielded 93-98.4% sensitivity; and six yielded 95-98.4% sensitivity. Seven to ten muscle screens did not yield >99% sensitivity.

CONCLUSIONS
A five muscle screen, including paraspinal muscles, provides acceptable sensitivity for preforming electrodiagnostic radiculopathy screens (lumbrosacral). This is important in optimizing patient care and minimizing patient discomfort.

REPORT DATE: 06/21/94 WORK UNIT # 9622

DETAIL SUMMARY SHEET

TITLE: A Description of Soldiers with Amputation: Implications for Return to Active Duty

KEYWORDS: amputees, trauma, vocational rehabilitation

PRINCIPAL INVESTIGATOR: Dillingham, Timothy MAJ MC
ASSOCIATES: Howard, Robin; Kishbaugh, David MAJ MC

SERVICE: Physical Medicine and Rehabilitation Service

STATUS: Completed
APPROVAL DATE: Dec 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine the percentage of active-duty amputees who remain on active duty.

TECHNICAL APPROACH
This will be a retrospective review of cases boarded through the Forest Glen Disability Section over a 10 year period (1981 to 1991) in order to determine the percentage remaining on active duty.

PRIOR AND CURRENT PROGRESS
The records of 464 subjects were reviewed; 2.4% returned to active duty. Those who returned were all hand, foot, or below-knee amputees.

CONCLUSIONS
Return to active duty is a rare event for amputees. Future studies are necessary to determine the impact of amputation on active duty.

REPORT DATE: 05/10/94 WORK UNIT # 9623

DETAIL SUMMARY SHEET

TITLE: Descriptive Analysis of a Collaborative Practice Model Developed by the Physical Therapy and Occupational Therapy Sections at Walter Reed Army Medical Center in Response to Desert Shield/Storm Contingencies

KEYWORDS: organizational model, contingency, Desert Shield/Storm

PRINCIPAL INVESTIGATOR: Beattie, Bonita LTC SP

SERVICE: Physical Medicine and Rehabilitation Service STATUS: Ongoing
APPROVAL DATE: May 1993

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To describe a unique, collaborative training and treatment model designed and implemented by the Physical Therapy (PT) and Occupational Therapy (OT) Sections, WRAMC, to meet the anticipated contingencies of Desert Shield/Storm.

TECHNICAL APPROACH
The researchers are using clinic records and documented organizational data to profile the processes of planning, design, and implementation of this collaborative model. The intent is to describe the flexible functions built into the model that fostered an appropriate response to anticipated variations in patient workload. Additionally, this review is intended to profile this patient population through descriptive statistics, such as means and standard deviations for numerical data, and percentages for categorical data.

PRIOR AND CURRENT PROGRESS
A total of 48 clinic records have been reviewed. To date, the literature review, clinical records review, and descriptive statistical analysis have been completed. A draft manuscript is underway.

CONCLUSIONS
Tentative conclusion: The collaborative practice model developed by Occupational and Physical Therapy, WRAMC, in response to Desert Shield/Storm contingency is a viable medical center response to mobilization activities.

REPORT DATE: 06/21/94 WORK UNIT # 9624

DETAIL SUMMARY SHEET

TITLE: Motor Nerve Conduction in the Deep Temporal and Mylohyoid Nerves

KEYWORDS: temporal nerves, mylohyoid nerves, motor nerve conduction

PRINCIPAL INVESTIGATOR: Dillingham, Timothy MAJ MC

SERVICE: Physical Medicine and Rehabilitation Service STATUS: Completed
APPROVAL DATE: Aug 1993

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To sutdy motor nerve conduction in the deep temporal (DTN) and mylohyoid nerves. This will be a normative study.

TECHNICAL APPROACH
Deep temporal and mylohyoid nerves will be stimulated intraorally. Amplitudes, latencies, and side-to-side differences will be recorded and studied.

PRIOR AND CURRENT PROGRESS
A total of 44 subjects were recruited. There were no signifiant adverse effects. Two sujects did not complete testing due to inability to tolerate stimulae. The mylohyoid nerves provide an excellent diagnostic tool; it is much easier to elicit responses from them than from the DTN's.

CONCLUSIONS
The data will be analyzed, and a paper will be written.

REPORT DATE: 05/03/94 WORK UNIT # 7245

DETAIL SUMMARY SHEET

TITLE: Investigation of Ultradian Rhythms of Mood in Depression

KEYWORDS: ultradian rhythms, depression, mood variance

PRINCIPAL INVESTIGATOR: Hall, Donald CPT MC
ASSOCIATES: Benedek, David CPT MC; Chang, Audrey PhD

DEPARTMENT: Department of Psychiatry

STATUS: Completed
APPROVAL DATE: May 1991

FUNDING: Current FY: $ 1,092 Previous FYs: $ 163 Total: $ 1,255

STUDY OBJECTIVE
To investigate mood changes within the day.

TECHNICAL APPROACH
Patients will complete a simple questionnaire each hour of the day. Mood scores will be graphed versus time of day, and then the graphs will be analyzed for cycles. The study is unchanged from the original protocol.

PRIOR AND CURRENT PROGRESS
A total of 43 subjects were entered into this study (none this past year); 38 of these subjects were tested.

CONCLUSIONS
None.

REPORT DATE: 08/21/94 WORK UNIT # 7246

DETAIL SUMMARY SHEET

TITLE: A Randomized Concentration-Controlled Trial of Fluoxetine in the Treatment of Major Despressive Disorder

KEYWORDS: fluoxetine, concentration-controlled, depression

PRINCIPAL INVESTIGATOR: Oleshansky, Marvin LTC MC

DEPARTMENT: Department of Psychiatry STATUS: Ongoing
APPROVAL DATE: Aug 1991

FUNDING: Current FY: $ 0 Previous FYs: $ 7,854 Total: $ 7,854

STUDY OBJECTIVE

To demonstrate the relationship between steady-state serum concentrations of the antidepressant fluoxetine (Prozac) and the efficacy of its use in the treatment of outpatients with Major Depressive Disorder (MDD).

TECHNICAL APPROACH

This study is a randomized concentration-controlled clinical trial of Prozac in which dosing is adjusted weekly to achieve a targeted serum fluoxetine concentration. After maintenance of steady-state concentrations of fluoxetine at target levels for 3 weeks, the relationship between the serum concentrations and clinical outcome measures of antidepressant efficacy will be examined.

PRIOR AND CURRENT PROGRESS

To date, five patients have been enrolled in the study (none this past year). Only one patient has completed the protocol. One subject did not meet initial entry criteria, one subject was dropped for a positive urine drug screen, and two subjects did not meet entry criteria because they had signs of improvement in the 1 week placebo lead-in. No subjects experienced untoward effects due to the study.

CONCLUSIONS

The one subject who finished the protocol demonstrated the feasibility of predicting a patient's steady-state fluoxetine concentration by assaying serum concentrations after 1 and 2 weeks of treatment and adjusting the dosage based on Bayesian forecasting. The major problem facing this study has been accrual of clinical support.

REPORT DATE: 05/15/94 WORK UNIT # 7248

DETAIL SUMMARY SHEET

TITLE: Psychiatric Diagnoses Included in Medical Discharge Summaries

KEYWORDS: medical discharge, psychiatric diagnoses

PRINCIPAL INVESTIGATOR: Esposito, Maria COL MC

DEPARTMENT: Department of Psychiatry

STATUS: Completed
APPROVAL DATE: Apr 1992

FUNDING: Current FY: $ 650 Previous FYs: $ 0 Total: $ 650

STUDY OBJECTIVE

To determine: 1) the percentage of inpatient narrative summaries in which consultations and psychiatric diagnoses are recorded, and 2) whether a specific method of preparing psychiatric consults will result in a higher percentage of inclusion in the narrative summary.

TECHNICAL APPROACH

Charts will be reviewed after the patient is discharged, the narrative summary will be prepared, and the chart will be finalized by the Patient Administration Directorate (PAD). Charts will be requested from the Medical Records Section of AD. Psychiatric consultations to be included in the study will be referred via the usual channels. Included/excluded charts will be determined per original protocol.

PRIOR AND CURRENT PROGRESS

The project, according to prior investigators, is completed. A total of 181 charts have been reviewed; none during the past year.

CONCLUSIONS

Certain demographic factors may describe patient groups whose diagnoses are or are not documented in narrative summaries. Descriptive statistics would be helpful in designing future studies to investigate miscommunication and stigma in the documentation process.

REPORT DATE: 04/07/94 WORK UNIT # 7249

DETAIL SUMMARY SHEET

TITLE: The Art Therapy Assessment of a Criminally Insane Population

KEYWORDS: art, assessment, insane

PRINCIPAL INVESTIGATOR: Lande, Raymond LTC MC
ASSOCIATES: Howie, Paula MA; Chang, Audrey PhD

DEPARTMENT: Department of Psychiatry

STATUS: Ongoing
APPROVAL DATE: Apr 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To test an art diagnostic assessment tool for potential inclusion as part of the routine forensic psychiatric evaluation of a criminally accused person; and to determine if such an assessment can sufficiently discriminate between two populations matched for psychiatric diagnoses, age, sex, and race. The group variable studies will be the influence, if any, of criminal misconduct.

TECHNICAL APPROACH

The plan is to enroll a minimum of 30 psychiatric patients from Clifton T. Perkins State Hospital Center and the same number of psychiatric patients from Walter Reed Medical Center. The primary focus of this study is to explain the impact of criminal behavior. The primary inclusion factor for enrollment at Clifton T. Perkins would be that the patient has been charged with a crime. The primary exclusion factor for the WRAMC population will be history of arrest. Patients must have AXIS I diagnosis and cannot have only AXIS II diagnosis. Those patients with a diagnosis of substance dependence will be included.

PRIOR AND CURRENT PROGRESS

A total of 80 subjects have been enrolled, none during the past year. This completes enrollment. Of these, 75 have been rated per the protocol. There have been no adverse reactions. There have been no benefits to the subjects. Statistical analysis of the data is being conducted.

CONCLUSIONS

Data analysis is proceeding, and results should be available in 2-4 weeks. Preliminary data suggests good inter-rater reliability of the instrument.

REPORT DATE: 04/09/94 WORK UNIT # 7250

DETAIL SUMMARY SHEET

TITLE: Proto-oncogene Expression in Peripheral Blood Mononuclear Cells in Schizophrenia: A Pilot Study

KEYWORDS: proto-oncogenes, schizophrenia, mononuclear cells

PRINCIPAL INVESTIGATOR: Brown, James CPT MC
ASSOCIATES: Nicholson, Diarmuid PhD; Kapur, Janet BA

DEPARTMENT: Department of Psychiatry

STATUS: Completed
APPROVAL DATE: Apr 1992

FUNDING: Current FY: $ 229 Previous FYs: $ 0 Total: $ 229

STUDY OBJECTIVE
To determine if proto-oncogenes are expressed in peripheral blood mononuclear cells of schizophrenics during acute phases of illness.

TECHNICAL APPROACH
Peripheral blood mononuclear cells will be obtained from 30 schizophrenic patients and 2 normal controls. The controls will be used to verify proper experimental method. The DNA isolated from these cells will be probed for altered proto-oncogene expression. A comparison between normal and schizophrenic expression will be performed. These results will be used to test the autoimmune theory of schizophrenia. The assay will be initiated by drawing 30cc of blood from the subject. Mononuclear cells and their genetic material will be isolated by standard procedures. Probes for numerous proto-oncogenes will then be applied. Hybridization will be measured by densitometer.

PRIOR AND CURRENT PROGRESS
Two normal controls (the primary investigator and his asociate) donated blood from which white blood cells and their genetic material were separated. Admissions of schizophrenics to WRAMC during 1993 and 1994 were dramatically less than previous years. The two available patients refused participation. Consequently, no patients were enrolled in the study this past year; one was enrolled altogether.

CONCLUSIONS
The reduced admission of first-break schizophrenics probably reflects the Army's downsizing in Germany and elsewhere. The principal investigator is being reassigned elsewhere, and a new principal investigator is not available. Consequently, the study will be closed.

REPORT DATE: 10/21/94 WORK UNIT # 7251

DETAIL SUMMARY SHEET

TITLE: An Outcome Study of Schizophreniform Disorder Diagnosed at Walter Reed Army Medical Center

KEYWORDS: schizopreniform

PRINCIPAL INVESTIGATOR: Joslin, Scott CPT MC

DEPARTMENT: Department of Psychiatry STATUS: Terminated
APPROVAL DATE: Sep 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To review the diagnostic outcomes of service members medically retired with the diagnosis of Schizophreniform Disorder at Walter Reed Army Medical Center between 1986-1991.

TECHNICAL APPROACH
Questionnaires with cover letters will be mailed to each former service member with consent to study and for collateral contact with their current physician. Data will be collated in PC Plus computer database.

PRIOR AND CURRENT PROGRESS
This research protocol has been administratively terminated.

CONCLUSIONS
This research protocol has been administratively terminated.

REPORT DATE: 06/06/93 WORK UNIT # 7252

DETAIL SUMMARY SHEET

TITLE: A Referral Coordinator: Implication with Compliance

KEYWORDS: compliance, psychiatry

PRINCIPAL INVESTIGATOR: Belliveau, Paul CPT MC

DEPARTMENT: Department of Psychiatry STATUS: Completed
APPROVAL DATE: Nov 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To describe baseline compliance and to reevaluate compliance after the introduction of a referral coordinator to the treatment team to coordinate after care.

TECHNICAL APPROACH
Baseline compliance will be determined by telephone contact 30 days after referral from the Outpatient Psychiatry Clinic for both populations. The first population of patients (Group A) will be referred following the current SOP. The second population of patients (Group B) will be followed-up by telephone 2 weeks and again 1 month after referral, and thus will be more involved with a referral coordinator who will be determining after-care plans.

PRIOR AND CURRENT PROGRESS
A total of 31 patients were enrolled in group A and 26 patients in Group B. The study has gone to completion, and no further research will be done. A total of 57 patient charts were reviewed. The baseline compliance with referrals by SOP was 27% and with the introduction of coordinated after-care was 73%.

CONCLUSIONS
A referral coordinator should be a routine member of the Outpatient Psychiatry Service treatment team to improve compliance.

REPORT DATE: 06/22/94 WORK UNIT # 7253

DETAIL SUMMARY SHEET

TITLE: Greater Referral Specificity and Its Effect on the Rate of Compliance

KEYWORDS: referral, outpatient, ambulatory

PRINCIPAL INVESTIGATOR: Erbe, Edward CPT MC

DEPARTMENT: Department of Psychiatry STATUS: Completed
APPROVAL DATE: Jul 1993

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine if information about CHAMPUS providers (professional certification, types of patients seen, and types of treatment offered) given to outpatients referred from the outpatient psychiatry clinic has a positive effect on the rate of compliance.

TECHNICAL APPROACH
After stratification based on selected clinical and demographic factors, all CHAMPUS eligible outpatients who did not meet study exclusion criteria were randomly assigned to one of two groups. One group received the CHAMPUS providers' names and telephone numbers (the Basic Group). A second group (the Extra Group) received an identical list with the addition of the above information. Compliance was determined 3 weeks after referral by telephone interview. The possible association between clinical and demographic factors and compliance was examined.

PRIOR AND CURRENT PROGRESS
A total of 24 patients were enrolled in the study. Three patients were excluded: two for not being CHAMPUS beneficiaries, and one for living outside the referral list zip code area. Ten patients were assigned to the Basic Group, and 11 patients were assigned to the Extra Group. There was no statistically significant difference between rate of compliance in the Basic and the Extra Groups. 80% of the patients in the Basic Group had supplemental CHAMPUS insurance versus 9% of patients in the Extra Group. 83% of compliant patients had supplemental CHAMPUS insurance versus 36% of non-compliant patients. This may account for the lack of distinction of compliance in the two study groups. If this study is continued, supplemental CHAMPUS insurance must be included in the stratification.

CONCLUSIONS
1) Compliance was not increased in psychiatric outpatients receiving information about CHAMPUS providers' professional certification, treatment modalities offered, or types of patients seen. The study was limited by low enrollment. 2) Of 16 clinical and demographic factors, the only statistically significant association (positive, in this case) with compliance was with supplemental CHAMPUS insurance.

REPORT DATE: 07/15/94 WORK UNIT # 7254

DETAIL SUMMARY SHEET

TITLE: Effectiveness of Rapid Biofeedback-Assisted Relaxation Training

KEYWORDS: biofeedback, relaxation

PRINCIPAL INVESTIGATOR: Stewart, Frances, CDR, MC

DEPARTMENT: Department of Psychiatry STATUS: Completed
APPROVAL DATE: Jul 1993

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine if normal subjects can learn hand warning by a rapid biofeedback protocol.

TECHNICAL APPROACH
Subjects will be randomly assigned to a control or treatment group. Control subjects will be given an audiotape with relaxation instructions. Treatment subjects will participate in 10 biofeedback training sessions over 2 weeks. The relaxation skills of both groups will be measured again physiologically.

PRIOR AND CURRENT PROGRESS
The principal investigator was unexpectedly moved to another facility 1 week after the protocol was approved. The associate investigator decided he could no longer participate. No subjects were enrolled in this protocol.

CONCLUSIONS
The principal investigator is working on initiating a modified version of this protocol at Malcolm Grow.

REPORT DATE: 09/19/94 WORK UNIT # 7255

DETAIL SUMMARY SHEET

TITLE: Differences in Hypnotic Capacity Between Patients Referred to a Psychiatric Consultation Liaison Service and Patients Referred to a Psychiatric Outpatient Clinic

KEYWORDS: hypnotic capacity

PRINCIPAL INVESTIGATOR: Wain, Harold Ph.D.

DEPARTMENT: Department of Psychiatry STATUS: Ongoing
APPROVAL DATE: Aug 1993

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To ascertain the difference between the hypnotic capacity of patients referred to the Psychiatry Consultation Liaison Service and those referred to the Psychiatry Outpatient Clinic.

TECHNICAL APPROACH
All subjects will be given screening tests. A t test will be used to compare the means of both samples.

PRIOR AND CURRENT PROGRESS
A total of 100 subjects (50 in each group) have been contrasted. There have been no unexpected or serious adverse reactions.

CONCLUSIONS
The mean profile HIP score of the Psychiatry Consultation Liaison Service patients was significantly higher than the respective score of the Psychiatry Outpatient Clinic patients.

REPORT DATE: 09/07/94 WORK UNIT # 7256

DETAIL SUMMARY SHEET

TITLE: The Association of Caffeine Blood Level With Diagnosis in an Outpatient Psychiatric Population

KEYWORDS: caffeine, blood, level

PRINCIPAL INVESTIGATOR: Lande, R. Gregory LTC MC

DEPARTMENT: Department of Psychiatry STATUS: Ongoing
APPROVAL DATE: Sep 1993

FUNDING: Current FY: $ 276 Previous FYs: $ 0 Total: $ 276

STUDY OBJECTIVE
To study the relationship between caffeine consumption and mental state, specifically depression and anxiety.

TECHNICAL APPROACH
All new patients to Outpatient Psychiatry will be offered the opportunity to participate. After agreement, each patient will complete caffeine use questionnaire, BDI, and STAI. Their caffeine blood levels will then be drawn in the lab.

PRIOR AND CURRENT PROGRESS
To date, about 80 patients are enrolled. All have completed written tests and had their blood drawn. There have been no adverse reactions.

CONCLUSIONS
The PI will continue the study with possible protocol modification seeking to speed up the process without affecting the study's integrity.

REPORT DATE: 01/05/94 WORK UNIT # 9106

DETAIL SUMMARY SHEET

TITLE: Differences in Proportions of Diagnosis Between Ethnic Groups: The Case of Puerto Rican Psychiatric Patients in the Military

KEYWORDS: Hispanic, diagnosis, Puerto Rican

PRINCIPAL INVESTIGATOR: Jones, Franklin MD
ASSOCIATES: Febo, Manuel COL MC; Rothberg, Joseph PhD

DEPARTMENT: Department of Psychiatry

STATUS: Completed
APPROVAL DATE: Dec 1984

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To determine whether Hispanic and other minority patients are diagnosed and managed differently from non-minority patients at WRAMC; and to determine whether certain diagnoses are made more commonly in Hispanic patients than other ethnic groups.

TECHNICAL APPROACH

Psychiatric records were reviewed for 2 years with sorting of all Hispanic surnamed patients compared with 100 randomly selected non-Hispanic Caucasian and 100 non-Hispanic Black patients. Demographic and symptom variables will be collected and compared. This study will review all Hispanic surnamed charts, and a random selection of Black and Caucasian patients, for diagnosis and clinical features.

PRIOR AND CURRENT PROGRESS

Study is completed except for analysis. Delay was due to overseas assignment of Dr. Febo. No serious and/or unexpected adverse reactions occurred, amd there were no new developments.

CONCLUSIONS

Island and New York Puerto Ricans appear similar to each other and distinct from non-Hispanic Black and Caucasian populations in demographic and clinical features.

REPORT DATE: 11/03/93 WORK UNIT # 4525

DETAIL SUMMARY SHEET

TITLE: Intravenous Administration of I-131-6-B Iodomethylnorcholesterol for Adrenal Evaluation and Imaging

KEYWORDS: adrenal imaging, I-131 NP-59

PRINCIPAL INVESTIGATOR: Anderson, Jay COL MC

DEPARTMENT: Department of Radiology STATUS: Completed
APPROVAL DATE: Nov 1980

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To clinically evaluate NP-59 as a diagnostic agent for the detection of cortical disorders. (This radiopharmaceutical is in the category of a Phase III IND). Although these radiopharmaceuticals have been valuable in the evaluation of patients with Cushing's syndrome, primary aldosteronism, and hypoandrogenism, radiopharmaceutical companies do not find it commercially profitable to seek a New Drug Application.

TECHNICAL APPROACH

The technical approach is unchanged. The radiopharmaceutical is obtained from the University of Michigan from Dr. Beierwaltes. The exam is only performed on those patients for whom the primary clinical physician believes potential information could be obtained which outweighs the potential risks. (In order to offer this diagnostic modality to patients, this protocol has been submitted and approved.)

PRIOR AND CURRENT PROGRESS

This radiopharmaceutical remains a valuable diagnostic tool. During the report period, no studies were performed, for a total of 28 patients studied. There were no adverse reactions, and no patient has withdrawn. All studies during this period have been clinically useful.

CONCLUSIONS

No conclusion can be made, nor are any conclusions anticipated. This is a standard IND to offer a diagnostic exam for patient benefit. In addition, this study saves WRAMC money because the patient is not referred to a civilian hospital to obtain the same exam.

REPORT DATE: 05/24/94 WORK UNIT # 4539

DETAIL SUMMARY SHEET

TITLE: Evaluation of Breast Masses Using Technetium-99m-Sestamibi Scintigraphy

KEYWORDS: Tc-99m-Sestamibi, breast masses

PRINCIPAL INVESTIGATOR: Williams, Scott CPT MC

DEPARTMENT: Department of Radiology STATUS: Completed
APPROVAL DATE: Apr 1993

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine if Tc-99m-Sestamibi can be used to differentiate benign from malignant breast masses.

TECHNICAL APPROACH
Multiple scintigraphic images of the breasts will be obtained from female patients referred for evaluation of mammographically detected or palpable breast masses. All images will be reviewed on CRT screen.

PRIOR AND CURRENT PROGRESS
Study terminated. A total of 17 patients were studied. One patient was excluded from final evaluation because she did not undergo biopsy. Five patients were found to have breast cancer on biopsy, but only two had positive exams (three false negatives). Eleven patients were found to have benign lesions on biopsy, and 10 of these had negative exams (1 false positive).

CONCLUSIONS
Although the study size was limited, Tc-99m-Sestamibi is probably not useful for differentiating benign from malignant breast masses.

REPORT DATE: 04/21/94 WORK UNIT # 4700

DETAIL SUMMARY SHEET

TITLE: CT Evaluation of Postoperatie Pneumoperitoneum

KEYWORDS: pneumoperitoneum, computed tomography

PRINCIPAL INVESTIGATOR: Earls, James CPT MC
ASSOCIATES: Colon, Edgar MD; Garrett, Meredith CPT MC

DEPARTMENT: Department of Radiology

STATUS: Completed
APPROVAL DATE: Apr 1992

FUNDING: Current FY: $ 251 Previous FYs: $ 0 Total: $ 251

STUDY OBJECTIVE
To evaluate the rate of resorption of pneumoperitoneum in postoperative patients, comparing the sensitivity of computed tomography (CT) to the left lateral decubitus film.

TECHNICAL APPROACH
CT scans and left lateral decubitus films will be performed on patients following uncomplicated abdominal surgery, postoperative days 3 and 6. The studies will be evaluated in a blinded fashion for the presence, location, and volume of free air.

PRIOR AND CURRENT PROGRESS
A total of 27 patients have been enrolled, none since the last APR. Results: Pneumoperitoneum was identified in 87% of CT scans and 53% of plain films on postoperative day 3, and in 50% of CT scans and 8.4% of plain films on postoperative day 6. Only 47% of patients with free air identified on CT demonstrated pneumoperitoneum on the left lateral decubitus exam. Radiographs were false negative in 87% of obese patients in whom pneumoperitoneum was identified on CT scans.

CONCLUSIONS
The left lateral decubitus exam is less sensitive than generally thought. In this study, CT was significantly more sensitive (p=.004) than the plain film in detecting small amounts of free intraperitoneal air. The incidence of pneumoperitoneum in the postoperative period as detected by CT is greater than that previously reported. This study describes two new preferential spaces; the pararectus and midrectus recesses, for collection of small amounts of free air on CT.

REPORT DATE: 06/14/94 WORK UNIT # 4701

DETAIL SUMMARY SHEET

TITLE: CT Directed Needle Localization of Peripheral Pulmonary Nodules Prior to Thoracoscopic Resection

KEYWORDS: computed tomography, pulmonary nodule, biopsy

PRINCIPAL INVESTIGATOR: Earls, James CPT MC
ASSOCIATES: McAdams, H. Page CPT MC; Colon, Edgar MD

DEPARTMENT: Department of Radiology

STATUS: Completed
APPROVAL DATE: Jun 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To develop a new technique to enable resection of peripherally based pulmonary nodules by thoracoscopy.

TECHNICAL APPROACH
On occasion, a patient will require open thoracotomy for pathologic diagnosis of a pulmonary nodule if prior attempts at endoscopic or transthoracic needle biopsy are unsuccessful. By placing a localization needle into or near the nodule, it can then be removed by thoracoscopy, a much less invasive procedure, with less morbidity and mortality than open thoracotomy.

PRIOR AND CURRENT PROGRESS
Transthoracic needle localization was performed on eight patients (five men and three women, mean age 52.4 years) prior to thoracoscopy. No subjects have been enrolled this past year. The procedure was successful in six patients, but in two patients the hookwire was removed prior to resection. One patient was converted to open thoracotomy, and one was still able to be resected via thoracoscopy because of pleural changes marking the location of the lesion.

CONCLUSIONS
Researchers believe that transthoracic CT-directed needle localization of peripheral pulmonary nodules prior to thoracoscopic resection is a useful procedure. Several large series have recently been published in both the radiology and thoracic surgery literature describing this technique. In these series, this procedure has been shown to be a useful, safe technique that can benefit patients by averting the need for open thoracotomy.

REPORT DATE: 10/22/93 WORK UNIT # 2045A

DETAIL SUMMARY SHEET

TITLE: Multicenter Study of the Davol Intraspinal Port

KEYWORDS: epidural, narcotics, cancer pain

PRINCIPAL INVESTIGATOR: Stamatos, John CPT MC

DEPARTMENT: Department of Surgery STATUS: Completed
SERVICE: Anesthesia-Operative Service APPROVAL DATE: Oct 1989

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
Epidural catheters are being used with more frequency to relieve cancer pain in the terminally ill patient. Thus, this protocol will study the placement of permanent epidural catheters with intraspinal ports for the relief of cancer pain.

TECHNICAL APPROACH
A videotape, "The Placement of Davol Permanent Epidural Catheters," has been created, which is 15 minutes long and describes the technique of placement of the catheter. FDA trials are being conducted for these intraspinal ports.

PRIOR AND CURRENT PROGRESS
During the first year of this study, 11 WRAMC patients were enrolled. There has been no further accrual since that time. All 11 patients died secondary to their primary disease. During the past 2 years, the company worked to modify the catheter; however, accrual has never resumed. The study should be closed.

CONCLUSIONS
None.

REPORT DATE: 04/26/94 WORK UNIT # 2051A

DETAIL SUMMARY SHEET

TITLE: Perioperative Myocardial Ischemia or Infarction During and Following Noncardiac Surgery in Patients who have Undergone Previous Coronary Artery Bypass Graft or Percutaneous Transluminal Coronary Artery Surgery

KEYWORDS: myocardial ischemia, myocardial infarction, hemodynamic responses

PRINCIPAL INVESTIGATOR: Guzzi, Louis MAJ MC

DEPARTMENT: Department of Surgery STATUS: Ongoing
SERVICE: Anesthesia-Operative Service APPROVAL DATE: Apr 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To record and compare the hemodynamic responses and the incidence of myocardial ischemia or infarction during and following non-cardiac surgery in patients who have undergone previous percutaneous transluminal coronary artery (PTCA) surgery with those in whom previous coronary artery bypass grafting (CABG) has been performed.

TECHNICAL APPROACH
Essentially, intraoperative hemodynamic responses will be compared, as well as postoperative ischemia episodes, as documented by Holter monitoring, EKG recordings, and cardioenzymes drawn each postoperative day for a maximum of 3 days.

PRIOR AND CURRENT PROGRESS
Only four patients were enrolled in the past 12 months. This was secondary to the PI's recent completion of a Critical Care Fellowship. The study now includes 42 of a planned 50 patients. There has been no benefit noted, and no adverse ractions.

CONCLUSIONS
Ongoing review continues. Data suggests that PTCA may not be as protective as CABG for reducing post-operative ischemia.

REPORT DATE: 07/14/94 WORK UNIT # 2054A

DETAIL SUMMARY SHEET

TITLE: The Effect of theh Sprotte Atraumatic 24 Gauge Spinal Needle on the Incidence of Postdural Puncture Headache

KEYWORDS: Sprotte needle, post dural puncture, headache

PRINCIPAL INVESTIGATOR: Carvill, Kathleen LTC NC

DEPARTMENT: Department of Surgery STATUS: Completed
SERVICE: Anesthesia-Operative Service APPROVAL DATE: Jan 1991

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine the incidence of post dural puncture headache with the 24 gauge Sprotte needle as compared with 25 gauge conventional spinal needles in surgical patients.

TECHNICAL APPROACH
A convenient sample of 100 patients will be randomly assigned to either the Sprotte needle experimental group or to the 25 gauge needle control group. Patients will be assessed postoperatively for the occurrence of postdural puncture headache.

PRIOR AND CURRENT PROGRESS
A total of 60 patients were enrolled. No additional patients were added to the study this past year. While this protocol was in the data collection phase, new data has been published that answers the questions this protocol was designed to address.

CONCLUSIONS
This protocol's status is changed to "completed" for the reason listed in the Prior and Current Progress section above.

REPORT DATE: 10/15/93 WORK UNIT # 2056A

DETAIL SUMMARY SHEET

TITLE: Development of Ultra Long Duration Local Anesthetic Agents in a Rat Model

KEYWORDS: local anesthetic, ultra long, rat

PRINCIPAL INVESTIGATOR: Kline, Mark MAJ MC
ASSOCIATES: Lojeski, Edwin CPT MC

DEPARTMENT: Department of Surgery
SERVICE: Anesthesia-Operative Service

STATUS: Ongoing
APPROVAL DATE: Oct 1991

FUNDING: Current FY: $ 520 Previous FYs: $ 23,113 Total: $ 23,633

STUDY OBJECTIVE

To develop and evaluate ultra-long duration local anesthetics in a rat model. A wide variety of local anesthetics are to be prepared as lecithin-coated microcrystals in an attempt to prolong their duration of action. Agents will be tested for their ability to provide both peripheral neural blockade and major conduction blockade. This study also attempts to evaluate the tissue toxicity of the agents tested.

TECHNICAL APPROACH

The primary screening test for local anesthetic duration will involve performing an intradermal tail block in the rat and monitoring response to a tail clamp assay. Response to major conduction blockade will also be monitored with the tail clamp assay. Tissue toxicity of the test agents will be evaluated by placing the test agent intradermally (next to the sciatic nerve) or in the subarachnoid space. Tissues from euthanized rats will then be evaluated by light and electron microscopy for evidence of toxic effects.

PRIOR AND CURRENT PROGRESS

A total of 211 rats have been used; 68 of them during the past year. There were no serious or unexpected adverse reactions. This study has demonstrated that lecithin-coated tetracaine microcrystals provided an ultra-long duration anesthetic effect of 44 hours in the rat tail. It has also been demonstrated that this forumulation is not toxic to skin tissues when placed intradermally. This year it was demonstrated that lecithin-coated tetracaine microcrystals do not cause peripheral neurotoxicity when placed directly on the sciatic nerve. In addition, initial data indicate that this formulation is not toxic to the spinal cord. Initial trials with lecithin-coated bupivacaine microcrystals indicate that this preparation also has an ultra long duration local anesthetic effect, producing a 43-hour block in the rat tail.

CONCLUSIONS

Lecithin-coated tetracaine microcrystals provide a local anesthetic effect of ultra long duration without causing toxicity to surrounding tissues or nerves. Lecithin-coated bupivacaine microcrystals also appear to anesthetise for ultra-long duration, although tissue toxicity remains to be evaluated.

REPORT DATE: 10/22/93 WORK UNIT # 2058A

DETAIL SUMMARY SHEET

TITLE: The Effect of Anesthesia and Surgery on Patients with Mildly Elevated Liver Enzymes

KEYWORDS: liver enzymes, anesthesia

PRINCIPAL INVESTIGATOR: Stamatos, John CPT MC

DEPARTMENT: Department of Surgery STATUS: Completed
SERVICE: Anesthesia-Operative Service APPROVAL DATE: Oct 1991

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To study patients with mildly elevated liver enzymes to see what effect, if any, anesthesia and surgery have on these patients.

TECHNICAL APPROACH
After baseline enzymes are obtained, liver enzymes will be obtained at the time of surgery, and at 3 days, 1 week, and 3 months after surgery.

PRIOR AND CURRENT PROGRESS
No progress was made on this protocol since its approval due to lack of personnel to conduct the study. The study should be closed.

CONCLUSIONS
None.

REPORT DATE: 01/04/94 WORK UNIT # 2061A

DETAIL SUMMARY SHEET

TITLE: Medtronic Model 3885 PISCES-Delta Lead for Spinal Cord Stimulation

KEYWORDS: spinal, cord, stimulation

PRINCIPAL INVESTIGATOR: Kline, Mark CPT MC

DEPARTMENT: Department of Surgery STATUS: Ongoing
SERVICE: Anesthesia-Operative Service APPROVAL DATE: Jan 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To study the stability of the Pisces-Delta lead in the epidural space. The stimulation pattern of the electrode will be monitored over time.

TECHNICAL APPROACH
The Pisces-Delta will be placed in the epidural space, and placement will be confirmed with flat plate radiographs. Patients will be followed over the course of the next 2 years with serial examination and radiographs to determine if there is any migration of the lead.

PRIOR AND CURRENT PROGRESS
Two patients have been enrolled, both during this past year. There have been no serious or unexpected adverse reactions. However, both patients were withdrawn from the study before the final implant procedure because neither were receiving good relief from the temporary implant. Thus, no data has been obtained yet on long-term lead migration.

CONCLUSIONS
No conclusions can be drawn at this time due to absence of collected data. This year plans are to enroll several patients since referrals for this procedure have been increasing.

REPORT DATE: 04/07/94 WORK UNIT # 2063A

DETAIL SUMMARY SHEET

TITLE: Normothermic vs. Hypothermic Cardiopulmonary Bypass: The Stress Response with Varying Sufentanil Doses

KEYWORDS: stress hormone production, cardiopulmonary bypass

PRINCIPAL INVESTIGATOR: Karan, Steven MAJ MC
ASSOCIATES: Phillips, William MAJ MC; Edwards, Fred COL MC

DEPARTMENT: Department of Surgery
SERVICE: Anesthesia-Operative Service

STATUS: Ongoing
APPROVAL DATE: Jan 1992

FUNDING: Current FY: $31,313 Previous FYs: $ 0 Total: $ 31,313

STUDY OBJECTIVE

To determine if stress hormone production varies during two different types of cardiopulmonary bypass, when a standardized dose of narcotic anesthesia is administered to each patient.

TECHNICAL APPROACH

This study is a non-blinded, prospective, randomized trial. Each patient undergoes preoperative and postoperative neuropsychological testing. During the surgery, six blood samples of 10 cc each are obtained at specified times. Various physiologic parameters are recorded at each sample time. The blood is analyzed for sufentanil, epinephrine, norepinephrine, and cortisol levels. Statistical analysis is performed via ANOVA.

PRIOR AND CURRENT PROGRESS

Currently, 57 patients have been entered into the study. There are no plans to enter more patients. The majority of the last year has been spent waiting for the laboratory results to be completed by the DCI laboratory (approximately 75% of this work is now complete). Once the results are received and analyzed, the study will be closed.

CONCLUSIONS

N/A.

REPORT DATE: 03/15/94 WORK UNIT # 2064A

DETAIL SUMMARY SHEET

TITLE: A Study of the Effect of Acadesine on Adverse Cardiac Outcomes in Patients Undergoing Coronary Artery Bypass Graft (CABG) Surgery

KEYWORDS: Acadesine, cardiac outcomes

PRINCIPAL INVESTIGATOR: Fontana, John CPT MC
ASSOCIATES: Yee, Lawrence CPT MC

DEPARTMENT: Department of Surgery
SERVICE: Anesthesia-Operative Service

STATUS: Ongoing
APPROVAL DATE: Feb 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To collect perioperative data which will determine whether Acadesine may have an effect on adverse cardiac outcomes following coronary artery bypass graft (CABG).

TECHNICAL APPROACH
This multi-center study is a prospective, randomized, double-blind, placebo-controlled, parallel group protocol. The study involves the perioperative administration of Acadesine, an agent which appears to have protective effects against myocardial ischemia and cardiac arrhythmias. Clinical outcomes will be assessed to determine whether Acadesine may have beneficial effects on patients undergoing CABG surgery.

PRIOR AND CURRENT PROGRESS
A total of 12 patients have been enrolled at WRAMC, and 1,385 patients have been enrolled nationally. All patients were enrolled this past year. This multicenter study is ongoing without changes in the projected completion date. There have been no adverse outcomes thought associated with this study drug. All adverse outcomes will be reported to the IRB, Gensia Pharmaceuticals, and the FDA.

CONCLUSIONS
No conclusions have been drawn at this time.

REPORT DATE: 03/18/94 WORK UNIT # 2065A

DETAIL SUMMARY SHEET

TITLE: Intraoperative Utilization and Effect on Brain Relaxation

KEYWORDS: diuretic, neurosurgery, intracranial pressure

PRINCIPAL INVESTIGATOR: Bettencourt, Joesph MAJ MC
ASSOCIATES: Gordon, Jeff CPT MC

DEPARTMENT: Department of Surgery
SERVICE: Anesthesia-Operative Service

STATUS: Ongoing
APPROVAL DATE: Mar 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To determine if the osmotic diuretic mannitol is as effective in raising the serum osmolality by 10 mOsm as the combination of mannitol and the loop diuretic furosemide.

TECHNICAL APPROACH

Volunteers are randomized by surgeon to either a mannitol only group or a mannitol and furosemide group. Serum osmolality is followed, and the drugs are titrated to achieve an increase of 10 mOsm in the serum osmolality. The surgeon's opinion of brain relaxation on a scale of 1-5 is also recorded.

PRIOR AND CURRENT PROGRESS

A total of 29 patients have been enrolled in the study thus far, 13 during the past year. Initial statistical analysis has shown no signifcant difference in the serum osmolality between groups. There has been a difference between groups in the surgeon's subjective estimate of brain relaxation (mannitol group better), urine output (combined group higher), and serum potassium (combined group lower). There have been no serious or unexpected adverse reactions.

CONCLUSIONS

Mannitol and mannitol combined with furosemide do not differ significantly in raising serum osmolality. More subjects should be studied.

REPORT DATE: 07/11/94 WORK UNIT # 2066A

DETAIL SUMMARY SHEET

TITLE: Multicenter Study of Perioperative Ischemia Research Group - Cardiac Surgery Epidemiologic Database (McSPI-CSEDB)

KEYWORDS: myocardial infarction, CABG

PRINCIPAL INVESTIGATOR: Fontana, John CPT MC

DEPARTMENT: Department of Surgery STATUS: Completed
SERVICE: Anesthesia-Operative Service APPROVAL DATE: May 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To collect basic information on the incidence of myocardial infarction and adverse cardiac outcome following coronary artery bypass graft (CABG) surgery.

TECHNICAL APPROACH
This multi-center study involves the prospective collection of preoperative demographic information, intraoperative anesthetic and surgical data, as well as detailed postoperative follow-up outcome data. This data, obtained from chart reviews, will be filed into a comprehensive data base.

PRIOR AND CURRENT PROGRESS
Approximately 2,500 patients have been enrolled nationally in this multicenter protocol; none from WRAMC. No studywide adverse reactions have been reported.

CONCLUSIONS
None.

REPORT DATE: 06/28/94 WORK UNIT # 2067A

DETAIL SUMMARY SHEET

TITLE: Fiberoptically Assisted Intravenous Catheter Placement

KEYWORDS: fiberoptic device, intravenous catheter

PRINCIPAL INVESTIGATOR: Matson, Michael LTC MC

DEPARTMENT: Department of Surgery STATUS: Completed
SERVICE: Anesthesia-Operative Service APPROVAL DATE: Jun 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To assess the utility of a fiberoptic device in facilitating the placement of intravenous catheters.

TECHNICAL APPROACH
One hundred adult patients presenting for surgery that requires two intravenous catheters will be enrolled into the study. One catheter will be placed using the standard technique, and one will be placed using the fiberoptic system.

PRIOR AND CURRENT PROGRESS
This project was abandoned long ago because it is unfeasible. No patients were enrolled.

CONCLUSIONS
Please see that this project is officially terminated.

REPORT DATE: 10/13/93 WORK UNIT # 2069A

DETAIL SUMMARY SHEET

TITLE: In Vitro Determination of the Response of Skeletal Muscle to Halothane, Caffeine, and Halothane plus Caffeine

KEYWORDS: halothane, caffeine, skeletal muscle

PRINCIPAL INVESTIGATOR: Karan, Steven MAJ MC

DEPARTMENT: Department of Surgery STATUS: Ongoing
SERVICE: Anesthesia-Operative Service APPROVAL DATE: Oct 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine the dose response relationship of halothane, caffeine, and halothane plus caffeine on an in vitro preparation of human skeletal muscle; to determine if intracellular magnesium and potassium levels of peripheral blood cells accurately reflect skeletal muscle magnesium and potassium status; and to identify the role of magnesium and potassium in malignant hyperthermia (MH).

TECHNICAL APPROACH
There are no modifications to the original protocol. Control and diagnostic malignant hyperthermia contracture testing will be performed on human skeletal muscle according to the North American Malignant Hyperthermia Protocol for contracture testing. In addition, potassium and magnesium will be measured in serum, muscle, and blood cells.

PRIOR AND CURRENT PROGRESS
As of this time, no patients have been entered into this protocol due to lack of personnel and patient availability. This situation should stabilize by November 1993. At that time, enrollment of patients should begin.

CONCLUSIONS
The examination of control data continues to be vital in both understanding MH and in evaluating susceptible patients.

REPORT DATE: 02/08/94 WORK UNIT # 2070A

DETAIL SUMMARY SHEET

TITLE: Efficacy of Ketoralac in Reducing the Symptoms of Post Dural Puncture

KEYWORDS: post dural puncture, headache, anesthetic

PRINCIPAL INVESTIGATOR: Guzzi, Louis MAJ MC

DEPARTMENT: Department of Surgery STATUS: Ongoing
SERVICE: Anesthesia-Operative Service APPROVAL DATE: Jan 1993

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To assess the efficacy of ketorolac in reducing or ablating the symptoms of post dural puncture headache (PDPH).

TECHNICAL APPROACH
Parturients who undergo a regional anesthetic (spinal or epidural) for labor and delivery and who subsequently develop a PDPH will be enrolled. Subjects will receive intravenous ketorolac every 6 hours for 24 hours. Degree of pain will then be assessed using a visual analog scale (VAS). Patients with >25% improvement will continue ketoroloc for 5 days. VAS will be completed at 24, 48, 72, and 168 hours.

PRIOR AND CURRENT PROGRESS
No progress has been made on this project. The principal investigator and the Department of Clinical Investigation have been working with the manufacturer, Syntex Laboratories, Inc., to finalize this protocol for approval. There has been excessive delay due to restructuring at Syntex. As of this report, Syntex has approved this protocol, and will be providing the drug at no cost. They are currently working on obtaining the IND number.

CONCLUSIONS
None.

REPORT DATE: 04/15/94 WORK UNIT # 2071A

DETAIL SUMMARY SHEET

TITLE: A Comparison of Caudal vs Lumbar Epidural Steroid Injection with Local Anesthetic in the Treatment of Sciatica

KEYWORDS: sciatica, caudal epidural steroid, lumbar epidural steroid

PRINCIPAL INVESTIGATOR: Karan, Steven MAJ MC

DEPARTMENT: Department of Surgery STATUS: Completed
SERVICE: Anesthesia-Operative Service APPROVAL DATE: Feb 1993

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To compare the efficacy of caudal vs. lumbar epidural steroid injection in the treatment of sciatica.

TECHNICAL APPROACH
Patients that meet the inclusion criteria will be randomized into either the lumbar epidural or caudal canal treatment groups. Each group will receive the same dose of steroid with local anesthetic injected into either the epidural space or caudal canal. The patients will be followed via repeat analog pain scales to determine efficacy of the treatment.

PRIOR AND CURRENT PROGRESS
This study was terminated prior to the enrollment of any patients for the following reasons: 1) The principal investigator of the study was transferred; 2) The case population of the acute and chronic pain clinic changed so that it was no longer feasible to do the study; and 3) The departmental staffing requirements changed so that personnel would not be available to carry out the study.

CONCLUSIONS
N/A.

REPORT DATE: 04/29/94 WORK UNIT # 2072A

DETAIL SUMMARY SHEET

TITLE: Assessment of the Mechanical and Structural Properties of Clots in Healthy Adults and Patients with Known Coronary Artery Disease Using Two Methods

KEYWORDS: platelet function, coronary artery disease, fibrinogen

PRINCIPAL INVESTIGATOR: Greilich, Philip CPT MC
ASSOCIATES: Alving, Barbara COL MC; Chang, Audrey PhD

DEPARTMENT: Department of Surgery
SERVICE: Anesthesia-Operative Service

STATUS: Ongoing
APPROVAL DATE: Apr 1993

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To establish the sensitivity and specificity of platelet force development (PFD) and computerized thromboelastography (CTEG) in assessing platelet function in the surgical patient.

TECHNICAL APPROACH

Blood from two study populations (healthy and known coronary artery disease) will be subjected to three ex vivo tests of platelet function. Each experiment will employ platelet-specific inhibitors in a split plot (or repeated measure) design that includes 15 subjects in a total of 3x4x2 (3 techniques x 4 concentrations x in duplicate) assays. An analysis of covariance (ANCOVA) will be used to establish the sensitivity and specificity of two new methods against the gold standard.

PRIOR AND CURRENT PROGRESS

WRAMC approved this study 27 Apr 93. DCI-funded equipment was approved for order April 1994. WRAIR approved the study 01 Apr 94. USAMRDC funds have permitted leasing of equipment which has been functional since February 1994. The platelet-specific IIb/IIIa monoclonal antibody 7E3 has required an "antibody transfer agreement" with Centocor for in vitro use. This should be completed by May 1994. A full-time research assistant has been assigned to this project beginning May 1994. The first subjects will be enrolled in May 1994. No serious adverse reactions have occurred, and no patients have withdrawn from this study.

CONCLUSIONS

The ability to use the only FDA-approved platelet IIb/IIIa monoclonal antibody inhibitor for human use will add substantial clinical relevance to this study and the potential role of these monitors.

REPORT DATE: 11/10/93 WORK UNIT # 2508

DETAIL SUMMARY SHEET

TITLE: Auditory Supplements to Speechreading

KEYWORDS: auditory-visual, speech perception, hearing-impaired

PRINCIPAL INVESTIGATOR: Grant, Kenneth PhD

DEPARTMENT: Department of Surgery
SERVICE: Army Audiology and Speech Center

STATUS: Ongoing
APPROVAL DATE: Nov 1990

FUNDING: Current FY: $70,975 Previous FYs: $ 0 Total: $ 70,975

STUDY OBJECTIVE

To serve as a grant proposal submitted to the NIH to obtain funding. The goal of the grant is to delineate more fully how auditory and visual cues are combined in bisensory speech perception by hearing-impaired subjects. Three factors assumed to be important for AV performance will be studied. These are the subject's ability to 1) identify consonants, 2) integrate auditory and visual cues, and 3) use context.

TECHNICAL APPROACH

Each of the proposed experiments will include measures of auditory, visual, and auditory-visual identification of speech tokens. Both segmental and connected speech materials will be used. To avoid AV ceiling effects, the auditory signals will be degraded with noise, by filtering, or both. Confusion matrices and overall performance levels on the various experimental tasks will be used as predictors of overall AV benefit for individual subjects.

PRIOR AND CURRENT PROGRESS

This grant is now in its third year of funding from NIH. Laboratory facilities to control auditory and visual speech stimuli have been developed. A study relating to the first project on the grant has been completed (W.U.# 2511), and a manuscript describing the results from 30 normal hearing subjects has been submitted to the Journal of the Acoustical Society of America. A second study (W.U. #2514) describing the effects of noise and filtering on the auditory-visual recognition of medial consonants has been completed, and the results from 10 normal hearing subjects were presented to the Acoustical Society in October 1993. A third study (W.U. #2528) related to the prediction of auditory-visual benefit and auditory-visual integration, is in progress. To date, data from 10 hearing-impaired subjects out of a proposed 30 has been obtained.

CONCLUSIONS

Each experiment proposed in this grant will be carried out under its own work unit number. Descriptions of progress and the use of human subjects will be submitted individually for each project.

REPORT DATE: 01/05/94 WORK UNIT # 2510

DETAIL SUMMARY SHEET

TITLE: Prediction of Stuttering Severity from Physiologic Measures of Speech Motor Systems

KEYWORDS: stuttering, speech kinematics, severity

PRINCIPAL INVESTIGATOR: McClean, Michael PhD
ASSOCIATES: Rock, Donna MA; Cord, Mary MA

DEPARTMENT: Department of Surgery
SERVICE: Army Audiology and Speech Center

STATUS: Ongoing
APPROVAL DATE: Jan 1991

FUNDING: Current FY: $ 1,776 Previous FYs: $ 73 Total: $ 1,849

STUDY OBJECTIVE
To evaluate the association between stuttering severity and kinematic measures of lip, jaw, and laryngeal movements obtained during fluent and disfluent productions of simple speech utterances. A related goal is to carry out a taxonomic description of disfluency types based on orofacial and laryngeal movement.

TECHNICAL APPROACH
Structural displacements of the upper lip, lower lip, and jaw will be recorded with a head-mounted strain gauge transducer system. Vocal fold vibration will be recorded with an electroglottograph, which transduces tissue impedance. These physiologic signals will be digitized at 500 Hz and acquired in 4-sec epochs associated with each speech utterance. Computer-based cursor-controlled measures will be obtained off-line on movement timing, displacement, and velocity. Measures of stuttering severity will be derived from percentage counts of words disfluent as assessed in videotape recordings taken as part of clinical assessments.

PRIOR AND CURRENT PROGRESS
Physiologic recordings were obtained on 36 subjects, 14 during this past year. No subjects have experienced adverse reactions or benefits. A decision was made not to perform fine force control or lip muscle reflex testing as originally planned, but rather to restrict this protocol to kinematic recording as described above. Study 1: Kinematic analyses on the fluent speech of 31 subjects have been completed. Results indicate systematic associations between stuttering severity, movement duration, and timing variability. Study 2: A comparative analysis was completed of speech movement timing in the fluent and disfluent utterances of a subgroup of 10 subjects. Temporal sequencing and movement durations were equivalent for fluent utterances and phonetically-matched utterances immediately following speech disfluencies.

CONCLUSIONS
More severe stutterers showed reduced movement timing variability across utterance repetitions. This is consistent with a recent model of sensorimotor learning indicating greater instability in systems showing less variability in movement output. Unexpected time series effects also have been noted across utterance repetitions. The interaction of these effects with speech disfluency will be explored.

REPORT DATE: 10/06/93 WORK UNIT # 2515

DETAIL SUMMARY SHEET

TITLE: Frequency Resolution and the Detection of Spectral Contrast

KEYWORDS: frequency resolution, hearing-impaired, speech perception

PRINCIPAL INVESTIGATOR: Leek, Marjorie Ph.D.
ASSOCIATES: Summers, W. Van PhD

DEPARTMENT: Department of Surgery
SERVICE: Army Audiology and Speech Center

STATUS: Ongoing
APPROVAL DATE: Oct 1991

FUNDING: Current FY: $ 2,040 Previous FYs: $ 1,150 Total: $ 3,190

STUDY OBJECTIVE

To evaluate the relationship between the loss in contrast between peaks and valleys in the speech spectrum after cochlear processing and the reduction in frequency resolution in hearing-impaired listeners. People with sensorineural hearing loss often have difficulty understanding speech, especially in noisy environments. This may be due in part to a flattening of the peaks and valleys in the speech spectrum caused by reduced frequency resolution accompanying hearing loss.

TECHNICAL APPROACH

Spectral contrast remaining in the post-cochlear internal representation of sounds will be measured by having listeners discriminate a sound with a sinusoidal change in amplitude across the spectrum (rippled spectrum) from a sound with a flat spectrum. The amplitude of spectral change needed for detection will be determined as a function of spacing of the peaks and valleys in the spectra. This function is determined by the spacing of the peaks and the frequency resolution ability of the listener. Independent measures of frequency resolution also will be made. Correlations between discrimination performance and frequency resolution measures will be evaluated.

PRIOR AND CURRENT PROGRESS

Data collection and analysis are complete. A manuscript has been submitted. To discriminate a flat from a peaked spectrum, hearing-impaired listeners required about 4 dB greater amplitude differences between peaks and valleys of complex spectra for all peak/valley spacing than did normal-hearing listeners. However, when the internal cochlear representatives were modeled using measures of frequency resolution, these differences between groups disappeared. A "multiple looks" analysis suggested that listeners require a cumulative total of about 7 dB of internal contrast across a wide-band stimulus for discrimination. Five normal-hearing and five hearing-impaired subjects completed the study; no patients were enrolled during the past year. There have been no adverse reactions, nor has any subject withdrawn from the study. There is no benefit to the subjects.

CONCLUSIONS

Results suggest that, in the analysis of speech sounds by impaired ears, spectral peaks become flattened and formant spacing may be more ambiguous. Both alterations are most likely due to the reduced frequency resolution demonstrated by these patients. The result of this processing may be a distorted internal representation of some speech sounds after cochler analysis.

REPORT DATE: 10/27/93 WORK UNIT # 2516

DETAIL SUMMARY SHEET

TITLE: Orofacial Force Control and Acoustics of Speech Production in Adult Dysarthria Patients

KEYWORDS: adult dysarthria, orofacial force control, acoustic analyses

PRINCIPAL INVESTIGATOR: Thompson, Patryce MA
ASSOCIATES: McClean, Michael PhD; Summers, W. Van PhD

DEPARTMENT: Department of Surgery
SERVICE: Army Audiology and Speech Center

STATUS: Completed
APPROVAL DATE: Oct 1991

FUNDING: Current FY: $ 2,541 Previous FYs: $ 1,315 Total: $ 3,856

STUDY OBJECTIVE

To determine whether nonspeech measures of oromotor performance are correlated with and predictive of the level of speech motor deficit in dysarthric subjects.

TECHNICAL APPROACH

This study will test the fine force control of the lips, tongue, and jaw, and obtain acoustic measures of speech sound production in dysarthric adults. Specialized force transducers and computer software will be used to record and analyze dysarthric subjects' ability to match static force levels with lips, tongue, and jaw. Acoustic analysis of speech will involve computer processing of several productions of /p/ and /t/ consonants. The statistical moments of the amplitude spectra will be used in a discriminant analysis of the two consonants.

PRIOR AND CURRENT PROGRESS

Subjects included nine normal speakers and five dyarthric speakers. In agreement with Forrest et al. (1988), the discriminate analysis procedure showed a high percentage of correct identification of /p/ and /t/ in normal subjects' productions. These results suggest that different physiologic mechanisms may underlie the disordered stop productions of the dysarthric speakers. The two types of production errors were; 1) incorrect place of articulation, causing spectral shift, and 2) inadequate oral pressure or spirantization, causing reduced burst waveform amplitude.

CONCLUSIONS

The present results confirmed the value of the discriminant analysis approach for categorization of stop consonant production in normal speakers. The percent correct measure appears to be more useful than D2 for characterizing differences among dysarthric speakers.

REPORT DATE: 11/03/93 WORK UNIT # 2518

DETAIL SUMMARY SHEET

TITLE: Prespeech Modulation of Lip Muscle Reflexes in Stutterers and Nonstutterers

KEYWORDS: speech, reflexes, stuttering

PRINCIPAL INVESTIGATOR: McClean, Michael PhD
ASSOCIATES: Clay, John PhD

DEPARTMENT: Department of Surgery
SERVICE: Army Audiology and Speech Center

STATUS: Completed
APPROVAL DATE: Nov 1991

FUNDING: Current FY: $ 1,120 Previous FYs: $ 90 Total: $ 1,210

STUDY OBJECTIVE

To determine whether stutterers and nonstutterers differ in how lip muscle reflexes are modulated during their preparation to speak, and whether reflex modulation is influenced by the speech sound being produced. After work began on this study it became apparent that a test procedure was needed to show consistent reflex modulation effects among the normal subjects.

TECHNICAL APPROACH

EMG recordings are made of reflex and voluntary activity in upper and lower lip muscles. A pulsatile mechanical stretch is given to the mouth's right corner using a servo-control linear motor; this serves as both a reaction time and reflex stimulus. On each trial the EMG and stimulus signals are digitized and saved in computer files for analysis. On every other trial a line on an oscilloscope cues the instruction to say a simple word starting with "p" as soon as the subject feels the mechanical stretch. A no-response trial follows at a fixed interval of 2-4 sec. Software is used to calculate the mean levels of the EMG signals over specified pre- and poststimulus time intervals.

PRIOR AND CURRENT PROGRESS

During the past year, the above procedures were carried out on 18 subjects, bringing the total for the protocol to 28. A significant reflex suppression effect prior to speech was observed in 11 of 14 nonstutterers and in only 4 of 14 stutterers. In addition, two of three stutterers, who showed a large number of disfluencies during the experimental task, showed marked elevations of reflex levels prior to their disfluent speech but significant reflex suppression prior to fluent speech. There have been no serious or unexpected adverse reactions, and there has been no benefit to the patients.

CONCLUSIONS

The observed differences in speech-related suppression of the lip muscle reflexes suggest that stutterers experience disturbances in the control of sensory input prior to speech movements. Procedures similar to those employed in this study have now been extended to a new DCI protocol (WU #2530) in which reflex excitability is being studied in relation to ion levels known to affect neural excitability.

REPORT DATE: 01/05/94 WORK UNIT # 2519

DETAIL SUMMARY SHEET

TITLE: Computer Modeling and Analysis of Lip Muscle Activation for Speech

KEYWORDS: computer modeling, speech, neuromotor control

PRINCIPAL INVESTIGATOR: McClean, Michael Ph.D.
ASSOCIATES: Clay, John PhD

DEPARTMENT: Department of Surgery
SERVICE: Army Audiology and Speech Center

STATUS: Ongoing
APPROVAL DATE: Jan 1992

FUNDING: Current FY: $ 4,034 Previous FYs: $ 546 Total: $ 4,580

STUDY OBJECTIVE

To develop a computer model of neural processes which are likely to underlie muscle activation of a single muscle system for speech motor control. To accomplish this, the activation patterns of lip muscle single motor units during speech production will be described.

TECHNICAL APPROACH

Computer software will be developed which has the capability for interconnection and realistic modeling of several neurons. Neurons are to be modeled as single integrator response functions. EMG and displacement signals from the lip muscle system will be acquired and analyzed with computer. These data along with relevant animal neurophysiologic data will be used to constrain simulated neural circuits intended to model neural systems involved in speech production.

PRIOR AND CURRENT PROGRESS

Physiologic recordings have been obtained on two subjects (one during this past year) for this protocol. There have been no serious or adverse reactions, and there has been no benefit to the subjects. Twelve experimental sessions have been run in which simultaneous single motor unit EMG and movement recordings have been obtained. Specialized software for associated kinematic analysis has been developed. Resulting EMG data are being used to guide initial efforts to model neural circuits controlling lip muscle activation for speech. A computer-based neuron model has been developed which is capable of realistic simulation of neural circuits containing up to 100 neurons. This system is being used in conjunction with neural simulators obtained from other laboratories (BIGNET and SWIM) to model neural circuits which regulate muscle activation patterns underlying rate control for speech.

CONCLUSIONS

Recordings infer that average firing rates tend to increase monotonically with syllable rate (from 15 to 65 imp/s). However, this relationship is nonlinear for some units, and in a few cases firing rate decreases at high syllable rates or motor units cease to discharge. This suggests a distinct change in the nature or mode of muscle activation at high syllable rates and is analogous to control processes described for cat hindlimb during locomotion at different speeds.

REPORT DATE: 05/06/94 WORK UNIT # 2520

DETAIL SUMMARY SHEET

TITLE: Comparison of Linear and K-Amp Hearing Aid Fittings by Experienced Hearing Aid Users

KEYWORDS: hearing aid, trial period, preferred

PRINCIPAL INVESTIGATOR: Surr, Rauna MS
ASSOCIATES: Cord, Mary MA; Walden, Brian PhD

DEPARTMENT: Department of Surgery
SERVICE: Army Audiology and Speech Center

STATUS: Completed
APPROVAL DATE: May 1992

FUNDING: Current FY: $ 1,910 Previous FYs: $ 0 Total: $ 1,910

STUDY OBJECTIVE
To determine whether the benefits provided by Linear Class D and K-Amp hearing aid circuitries differ from each other in routine clinical evaluation and in real-life listening environments.

TECHNICAL APPROACH
Binaural Linear Class D and K-Amp hearing aids will be custom ordered for patients who need replacements for old hearing aids. A two-period cross-over design will be used. The circuitry to be evaluated first will be randomized across subjects. Clinical evaluation will consist of real ear insertion response (REIR) measures using four input levels. A 30-day trial period will follow. The patients will complete a hearing aid benefit questionnaire (PHAB) after each trial. After both trial periods, the patients will retain the circuitry they prefer.

PRIOR AND CURRENT PROGRESS
A total of 18 subjects have been enrolled; none this past year. All the data has been collected and analyzed. A poster was presented at the Annual Convention of the American Academy of Audiology, Phoenix, AZ, in April 1993, and also at the 1994 Military Short Course, Richmond, VA, in April 1994. A manuscript has been submitted to Ear and Hearing in April 1994.

CONCLUSIONS
REIR results indicate that the two circuitries are comparable with 65 dB input levels, but differ with higher input levels. Preference is evenly divided between the two circuitries. PHAB results show no overall difference across subjects but tend to yield higher subscale scores for the preferred circuitry.

REPORT DATE: 05/11/94 WORK UNIT # 2521

DETAIL SUMMARY SHEET

TITLE: Spectral Contrast Perception and the Internal Signal-To-Noise Ration in Hearing-Impaired Listeners

KEYWORDS: spectrum, hearing loss, noise

PRINCIPAL INVESTIGATOR: Leek, Marjorie PhD

DEPARTMENT: Department of Surgery
SERVICE: Army Audiology and Speech Center

STATUS: Ongoing
APPROVAL DATE: May 1992

FUNDING: Current FY: $ 310 Previous FYs: $ 2,236 Total: $ 2,546

STUDY OBJECTIVE

To ascertain the relative importance of two sequelae of impaired frequency resolution in hearing-impaired patients. Individuals with hearing loss often complain of difficulty understanding speech in noisy environments. Poor frequency resolution, often accompanying sensitivity loss in these patients, produces a smearing of the peaks and valleys in speech spectra, as well as a reduced signal-to-noise ratio within processing channels in the cochlea.

TECHNICAL APPROACH

Using highly schematized vowel-like sounds, the amount of contrast between spectral peaks and valleys required for vowel identification will be measured in quiet and in three levels of background noise. Susceptibility to increased noise will be inferred by comparing peak-to-valley differences for equal identification performance at each noise level. Frequency resolution will be measured using a notched-noise masking procedure at two center frequencies. This procedure provides estimates of bandwidth and asymmetry of internal auditory filters within individuals. The results from the identification experiment will be interpreted in light of the degree of impairment in frequency resolution within individuals.

PRIOR AND CURRENT PROGRESS

A total of 15 subjects have been enrolled in the study; none this past year. One subject withdrew before completing the study (no reason given), and two patients were excused because they were unable to perform the auditory identification task. Data has been collected on six hearing-impaired and six normal-hearing subjects. Subjects have experienced no adverse reactions, and they have not received any benefit. Patients with poor frequency resolution are more susceptible to the effects of listening in noise as shown by their need for increased spectral contrast for signal identification. A manuscript describing these results is currently in preparation.

CONCLUSIONS

For both normal-hearing and hearing-impaired listeners, an increase in noise in the listening environment must be accompanied by increased contrast in spectral peaks and valleys of speech sounds to permit accurate stimulus identification. This general effect of noise is exaggerated when frequency resolution is impaired due to damage to the cochlea.

REPORT DATE: 11/12/93 WORK UNIT # 2524

DETAIL SUMMARY SHEET

TITLE: Discrimination of Frequency Transitions by Hearing-Impaired Listeners

KEYWORDS: frequency discrimination, hearing-impaired, frequency transition

PRINCIPAL INVESTIGATOR: Summers, William Ph.D.
ASSOCIATES: Leek, Marjorie PhD

DEPARTMENT: Department of Surgery
SERVICE: Army Audiology and Speech Center

STATUS: Ongoing
APPROVAL DATE: Nov 1992

FUNDING: Current FY: $ 1,801 Previous FYs: $ 0 Total: $ 1,801

STUDY OBJECTIVE

To examine hearing-impaired listeners' ability to discriminate between frequency glides patterned after second formant transitions in English consonant-vowel syllables, and to examine the influence of several stimulus characteristics on performance. Several researchers have suggested that formant transitions may be poorly processed by hearing-impaired listeners and may, as a result, provide reduced segmental information.

TECHNICAL APPROACH

Hearing-impaired and normal-hearing listeners were asked to discriminate between frequency glides as described above. The influences of glide duration, rate, and frequency extent were examined for each group in quiet and in 35-dB spectrum-level broadband noise.

PRIOR AND CURRENT PROGRESS

Data collection was completed during this period. A manuscript based on the results was submitted to the Journal of the Acoustical Society of America. A total of 12 subjects participated in the study, including 6 hearing-impaired listeners and 6 normal-hearing listeners. There have been no adverse reactions from subjects, nor has any subject withdrawn from the study. There is no benefit to the subjects.

CONCLUSIONS

For both groups, reductions in glide duration and the presence of noise each led to significant increases in frequency difference limens for glide onset. The only significant group differences were observed for gradual glides of limited frequency extent. This latter finding was consistent with more accurate processing of "cochlear dispersion" cues on the part of normal-hearing listeners.

REPORT DATE: 12/13/93 WORK UNIT # 2525

DETAIL SUMMARY SHEET

TITLE: A Comparison of the Benefit Derived from Two Classes of Hearing Aids in Patients with Hearing Loss Above 2000 Hz

KEYWORDS: benefit, hearing aid, hearing loss

PRINCIPAL INVESTIGATOR: Beamer, Sharon MA
ASSOCIATES: Grant, Ken PhD; Walden, Brian PhD

DEPARTMENT: Department of Surgery
SERVICE: Army Audiology and Speech Center

STATUS: Completed
APPROVAL DATE: Dec 1992

FUNDING: Current FY: $ 1,078 Previous FYs: $ 0 Total: $ 1,078

STUDY OBJECTIVE

to compare the benefit derived from two classes of hearing aids in patients with hearing loss restricted to the region above 2000 Hz. The two classes of hearing aids differ with regard to the specificity with which amplification can be achieved at selected frequencies. This study examines the differences in perceived benefit for the users of these two classes of hearing aids.

TECHNICAL APPROACH

Subjects were drawn from the patient population of the Army Audiology and Speech Center of WRAMC. All subjects had hearing loss restricted to the region above 2000 Hz and had received binaural amplification within the last 3 years (but at least 8 months prior to the onset of the study). Patients were asked to complete the Profile of Hearing Aid Benefit questionnaire (Cox and Alexander, 1991). Each subject answered 66 questions addressing communication in a variety of environments (e.g., background noise). The questions reflect the amount of problems encountered with the hearing aid and the amount of communication problems without the hearing aid. Benefit is defined as the difference between the two.

PRIOR AND CURRENT PROGRESS

A total of 147 questionnaires were returned to the clinic; 132 were considered acceptable for analysis as they were completed in full. Each questionnaire was analyzed to determine the perceived benefit on seven subscales. Five of the subscales address speech communication, and two of the subscales address perception of environmental sounds. Subjects were divided into two groups depending on the type of amplification they had received. The benefit scores on each subscale were compared for the two groups. Other factors that may influence benefit (such as age, degree and slope of hearing loss, type of Aural Rehab program attended, hours of hearing aid use, etc.) were also examined.

CONCLUSIONS

No significant difference in perceived benefit for the two groups of hearing aid users was observed. Many factors were examined that may influence benefit. However, only hours of hearing aid use and the type of Aural Rehab attended related to hearing aid benefit scores on the PHAB subscales. Patients with hearing loss restricted to the region above 2000 Hz do report benefit from amplification. Consequently, amplification is recommended for this population.

REPORT DATE: 02/14/94 WORK UNIT # 2527

DETAIL SUMMARY SHEET

TITLE: An Investigation of the Role of Hearing Loss in the Perception of a Stop Consonant

KEYWORDS: speech perception, hearing loss, silent interval

PRINCIPAL INVESTIGATOR: Clay, John PhD
ASSOCIATES: Cord, Mary MS

DEPARTMENT: Department of Surgery
SERVICE: Army Audiology and Speech Center

STATUS: Ongoing
APPROVAL DATE: Feb 1993

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To determine whether hearing-impaired listeners differ from normal listeners in the way they use the cues of silent-interval duration, speaking rate, fricative duration, and a precursor word to perceive the stop consonant "/p/."

TECHNICAL APPROACH

Normal-hearing and hearing-impaired listeners will respond to acoustic waveforms comprising the speech sounds "/s/," a variable-length silent interval, and "/lit/" by selecting either the word "slit" or the word "split." Independent variables will include speaking rate, presence or absence of a precursor word, and context provided by the precursor. For each condition, the silent interval corresponding to 50% "split" responses will be determined. The effects of the experimetal variables will be assessed in an analysis of variance.

PRIOR AND CURRENT PROGRESS

Eight normal-hearing and nine hearing-impaired listeners have completed participation. No further listeners will be used. No adverse effects have occurred. There is no benefit to subjects from this study. The data analysis has been completed, and a manuscript is in preparation. One patient was withdrawn from the hearing-impaired group when it was determined that he actually had normal hearing.

CONCLUSIONS

Normal-hearing listeners differed considerably from hearing-impaired listeners in several conditions. In general, hearing-impaired listeners were less responsive to changes in the linguistic and acoustic environment than were normal-hearing listeners.

REPORT DATE: 06/15/94 WORK UNIT # 2528

DETAIL SUMMARY SHEET

TITLE: Relations Among Auditory-Visual Sentence Benefit, Auditory Consonant Recognition, and Auditory-Visual Integration in Hearing-Impaired Listeners

KEYWORDS: speech perception, auditory-visual, speechreading

PRINCIPAL INVESTIGATOR: Grant, Kenneth PhD
ASSOCIATES: Clay, John PhD; Cord, Mary PhD

DEPARTMENT: Department of Surgery
SERVICE: Army Audiology and Speech Center

STATUS: Ongoing
APPROVAL DATE: Jun 1993

FUNDING: Current FY: $ 3,100 Previous FYs: $ 0 Total: $ 3,100

STUDY OBJECTIVE

To evaluate the ability of hearing-impaired (HI) listeners to recognize connected speech when presented audiovisually, and to relate this ability to primary sensory and cognitive factors, such as the ability to recognize speech segments (e.g., consonants) auditorily, and the ability to integrate auditory and visual speech cues.

TECHNICAL APPROACH

This study measures auditory (A), visual (V), and auditory-visual (AV) speech recognition of sentences and consonants presented in a background of noise to 30 HI subjects. In each of the three receptive modalities (A, V, and AV) and for each of the two types of speech materials, subjects must identify the presented speech sample. Consonant data are stored in the form of confusion matrices so that specific stimulus-response confusions may be analyzed. A and V matrices will be subjected to recently developed models of AV integration to predict AV responses. Predicted and obtained AV responses will be compared to determine the degree to which each subject integrates across the two modalities.

PRIOR AND CURRENT PROGRESS

Data collection for 21 of the proposed 30 HI subjects has been completed. Analyses of the confusion matrices and implementation of two quantitative models of consonant integration are underway. A preliminary report of the results is planned for the National Meeting of the Acoustical Society of America to be held 28 Nov 94 - 02 Dec 94. There have been no adverse or unexpected reactions from subjects. Aside from general information and monetary compensation, there has been no benefit to the subjects participating in this protocol.

CONCLUSIONS

Results show that A consonant recognition ability for individual subjects accounts for about 20-30% of the variance observed in AV sentence recognition. Individual differences in V consonant recognition ability, however, can account for as much as 40-50% of the observed variance in AV sentence recognition. The researchers expect that some of the remaining variance can be explained by differences in AV integration ability, and are currently exploring this possibility.

REPORT DATE: 06/10/94 WORK UNIT # 2530

DETAIL SUMMARY SHEET

TITLE: Serum and Urinary Ion Levels and Lip Muscle Reflex rexcitability in Adult Stutterers

KEYWORDS: stuttering, magnesium, reflexes

PRINCIPAL INVESTIGATOR: McClean, Michael PhD
ASSOCIATES: Payne, Matthew CPT MS

DEPARTMENT: Department of Surgery
SERVICE: Army Audiology and Speech Center

STATUS: Ongoing
APPROVAL DATE: Jun 1993

FUNDING: Current FY: $ 1,976 Previous FYs: $ 0 Total: $ 1,976

STUDY OBJECTIVE

To: 1) determine whether there are differences between stutterers and nonstutterers in terms of their serum and urinary magnesium and calcium levels, and lip muscle reflex excitability; and 2) evaluate possible associations between ion levs, reflex excitability, and stuttering severity.

TECHNICAL APPROACH

The experimental method involves obtaining serum and urinary samples on the same day that lip reflex excitability is tested. Ion levels are assessed by means of atomic absorption photospectometry within the support laboratory of DCI. Lip muscle reflexes are quantified by computer acquisition and stimulation. Reflexes are evoked during a passive control condition and prior to a simple speech utterance.

PRIOR AND CURRENT PROGRESS

During the last year, reflex data and serum and urinary samples have been acquired on seven stutterer subjects and eight nonstutterer subjects. There have been no serious or unexpected adverse reactions in any subjects. There has been no benefit to the subjects.

CONCLUSIONS

No conclusions are warranted at this time.

REPORT DATE: 06/14/94 WORK UNIT # 2531

DETAIL SUMMARY SHEET

TITLE: The Effect of Closed-Head Injury on Auditory Information Processing

KEYWORDS: auditory, information-processing, head injury

PRINCIPAL INVESTIGATOR: Podraza, Bonnie PhD
ASSOCIATES: Leek, Marjorie PhD; Clay, John PhD

DEPARTMENT: Department of Surgery
SERVICE: Army Audiology and Speech Center

STATUS: Ongoing
APPROVAL DATE: Jun 1993

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To determine if closed-head-injured subjects differ from control subjects in the way they process auditory information, as measured in a choice reaction-time task. A four-stage linear information processing model was applied to data from head-injured subjects in order to identify specific information-processing stages that might be impaired in this population.

TECHNICAL APPROACH

There have been no modifications to the original protocol. Closed-head injured and control subjects will respond to a 1500 Hz and a 500 Hz tone presented either proximal or distal to the midline of the head over earphones. Experimental manipulation of the following conditions will comprise the independent variables: signal quality, signal discrimination, signal-response compatibility, and foreperiod uncertainty. Thirty-two reaction-time measures will be obtained for each condition. Response accuracy will also be measured. The effects of the experimental variables will be assessed in an Analysis of Variance.

PRIOR AND CURRENT PROGRESS

Ten control and nine head-injured subjects have completed the experiment. One head-injured subject's data will not be used because he was subsequently found to not be head-injured. Two additional head-injured subjects will be tested. No adverse effects have occurred. There is no benefit to subjects from this study.

CONCLUSIONS

Preliminary analysis suggests that closed-head injured and control subjects do not differ in either response accuracy or reaction time using this paradigm. The length of the measured auditory reaction times compared to previously reported visual reaction times may be a factor in the failure of the ANOVA to support the independent processing stages predicted by the model under study.

REPORT DATE: 07/14/94 WORK UNIT # 2532

DETAIL SUMMARY SHEET

TITLE: Hearing Loss and the Preception of Complex Sounds

KEYWORDS: hearing impairment, speech, intensity

PRINCIPAL INVESTIGATOR: Leek, Marjorie PhD
ASSOCIATES: Summers, W. Van PhD

DEPARTMENT: Department of Surgery
SERVICE: Army Audiology and Speech Center

STATUS: Ongoing
APPROVAL DATE: Jul 1993

FUNDING: Current FY: $63,912 Previous FYs: $ 0 Total: $ 63,912

STUDY OBJECTIVE

This is a grant proposal submitted to the National Institutes of Health. The degradation of speech understanding in noise experienced by individuals with hearing-impairment may be exacerbated due to the high sound levels necessary for sound to be audible for these listeners. The focus of this program of research is to explore the consequences of listening to sound at high amplitudes by hearing-impaired individuals, with an emphasis on speech and speech-like complex stimuli.

TECHNICAL APPROACH

A number of different experimental techniques will be used for the various studies in this grant. All of them involve earphone presentation of sounds with particular acoustic characteristics such as stimulus intensity, frequency, timing, and bandwidth designed according to the needs of the study. The sequence of studies is designed to first investigate a characteristic of the auditory system, such as frequency resolution, followed by an experiment that is designed to evaluate the possible influence of that mechanism on some aspect of speech understanding by hearing-impaired listeners.

PRIOR AND CURRENT PROGRESS

Funding on this grant began 01 Apr 94. Since that time, two new protocols (W.U.#'s 2535 and 2539) have been approved, and work has begun on experimental programs to collect data. No subjects have been enrolled to date in experiments under this work unit.

CONCLUSIONS

Each experiment proposed in this grant will be carried out under its own work unit number. Descriptions of progress and the use of human subjects will be submitted individually for each protocol.

REPORT DATE: 08/11/94 WORK UNIT # 2588

DETAIL SUMMARY SHEET

TITLE: Hearing Loss and the Perception of Complex Sounds

KEYWORDS: resolution, harmonics, spectral

PRINCIPAL INVESTIGATOR: Leek, Marjorie PhD
ASSOCIATES: Summers, W. Van PhD

DEPARTMENT: Department of Surgery
SERVICE: Army Audiology and Speech Center

STATUS: Completed
APPROVAL DATE: Aug 1988

FUNDING: Current FY: $ 0 Previous FYs: $ 4,031 Total: $ 4,031

STUDY OBJECTIVE

This work unit is a grant proposal submitted to the National Institutes of Health to obtain funding. The goal of the grant is to determine how the impaired spectral and temporal processing accompanying sensorineural hearing loss interferes with the identification and discrimination of speech-like sounds. The proposal includes seven studies, each of which will be submitted for approval as a separate protocol.

TECHNICAL APPROACH

Each of the proposed experiments includes measurements of frequency resolution and a measure of the internal representation of harmonic complexes. Frequency resolution will be assessed using a notched-noise threshold procedure which allows the tracing of the internal auditory filter. Measures of temporal and spectral processing of harmonic complexes will be made by asking subjects to identify sounds which are constructed to have some of the acoustic characteristics of speech. Confusions among selected stimuli will indicate the degree of impairment of the internal representations of those sounds, which will then be related to the measures of frequency resolution.

PRIOR AND CURRENT PROGRESS

During the past year of work on this grant, data collection and analysis have been completed on four experiments (W.U. #'s 2521, 2524, 2590, and 2598 - 2590 is now closed), and pilot work is underway on three others (W.U.#'s 2535, 2538, and 2539). Six patients have participated in protocols associated with this grant this year, for a total enrollment to date of 124 subjects. There have been no adverse reactions. Three patients did not complete one of the studies, due to unwillingness or inability to perform the perceptual task. There is no direct benefit to patients. This NIH grant has been renewed by NIH, and will continue under Work Unit #2532.

CONCLUSIONS

Each experiment proposed in this grant was carried out under its own work unit number. Descriptions of progress and the use of human subjects were submitted individually for each protocol.

REPORT DATE: 05/12/94 WORK UNIT # 2590

DETAIL SUMMARY SHEET

TITLE: Modeling Impaired Frequency Resolution in Normal Ears

KEYWORDS: hearing loss, frequency resolution, auditory models

PRINCIPAL INVESTIGATOR: Leek, Marjorie PhD

DEPARTMENT: Department of Surgery STATUS: Completed
SERVICE: Army Audiology and Speech Center APPROVAL DATE: Jan 1989

FUNDING: Current FY: $ 300 Previous FYs: $ 15,328 Total: $ 15,628

STUDY OBJECTIVE
To determine the feasibility of using signal processing of speech-like sounds to simulate the impaired cochlear processing found in individuals with sensorineural hearing loss. Successful simulation of hearing impairment may lead subsequently to a method for compensating for these impaired processing mechanisms.

TECHNICAL APPROACH
A computer model of impaired cochlear processing is being developed with parameters based on audiological measures from individual subjects. Three subjects with hearing loss will act as "templates" for testing the model. Measurements of frequency resolution are made and entered as parameters into the model. The subjects will then identify sets of vowel-like sounds, producing confusion matrices that reflect the pattern of perceptual distortions they experience. Confusion matrices obtained from normal subjects for the stimulus set processed through the model will be compared to results from the impaired subjects to assess the accuracy of the simulation of hearing loss.

PRIOR AND CURRENT PROGRESS
The application of this model of impaired cochlear function has been greatly expanded by an upgrade to the mathematical analysis software used in the laboratory. Due to limitations in the previous software, only unrealistically short speech signals could be used in this experiment. In addition, an improvement in the analysis of frequency resolution, specifically appropriate to the speech used in this study, has improved the precision of the modeling technique. The stimuli are modeled after three different patterns of frequency resolution obtained from hearing-impaired listeners. One new hearing-impaired subject has been enrolled in the study since January 1993. Three hearing-impaired subjects have previously participated. A manuscript is currently in preparation. There have been no adverse reactions, and no subjects have been withdrawn from the study. There is no benefit to the subject.

CONCLUSIONS
The computer-distorted speech stimuli developed using the cochlear model demonstrated a qualitative similarity to the hypothesized perceptions of patients suffering from hearing loss. Future simulations should be focused on realistic modeling of the phase response of the impaired cochlea to supplement the modeled frequency response, and on attempts to simulate "normal" hearing in hearing-impaired individuals.481

REPORT DATE: 02/14/94 WORK UNIT # 2591

DETAIL SUMMARY SHEET

TITLE: Nonlinear Cochlear Processing in Normal Hearing and Hearing Impaired Listeners

KEYWORDS: spectral contrast, phase, compressive nonlinearity

PRINCIPAL INVESTIGATOR: Leek, Marjorie PhD

DEPARTMENT: Department of Surgery
SERVICE: Army Audiology and Speech Center

STATUS: Completed
APPROVAL DATE: Feb 1989

FUNDING: Current FY: $ 300 Previous FYs: $ 3,755 Total: $ 4,055

STUDY OBJECTIVE

To demonstrate the benefit to vowel identification hypothesized to occur due to a compressive nonlinearity in normal cochlear processing, and to determine whether that benefit is preserved in patients with sensorineural hearing loss.

TECHNICAL APPROACH

An internal enhancement of spectral peaks due to cochlear processing will allow good vowel discrimination even if the actual peaks have reduced amplitude. In a three-alternative forced choice task, listeners are asked to discriminate between /u/ (duke) and /oo/ (book) with the amount of spectral peak-to-valley contrast varying from 1 to 10 dB. The stimuli are presented at either a high or low intensity, and the phase relationships among the spectral components of a sound are controlled to produce either a very peaky or a very flat waveform. A comparison of performance across the intensity and phase conditions will permit assessment of the function of the cochlear nonlinearity.

PRIOR AND CURRENT PROGRESS

A paper describing this work has been published during the last year. No new patients have been enrolled since the last APR. The total number of subjects enrolled in the protocol is 19. There have been no adverse reactions from subjects, nor has any subject withdrawn from the study. There is no benefit to the subjects.

CONCLUSIONS

For normal-hearing subjects, there is a small but consistent enhancement of spectral contrast in harmonic complexes with peaked waveforms at high intensities, suggestive of nonlinear cochlear processing. Hearing-impaired listeners do not, as a group, provide evidence for nonlinear processing of these waveforms at high levels. Signal processing to increase the spectral contrast in speech might improve speech recognition for these patients.

REPORT DATE: 02/14/94 WORK UNIT # 2598

DETAIL SUMMARY SHEET

TITLE: Frequency Resolution on Hearing Impaired and Noise Masked Normal Hearing Listeners

KEYWORDS: frequency resolution, hearing-impaired, masking

PRINCIPAL INVESTIGATOR: Leek, Marjorie PhD
ASSOCIATES: Summers, W. Van PhD

DEPARTMENT: Department of Surgery
SERVICE: Army Audiology and Speech Center

STATUS: Ongoing
APPROVAL DATE: Feb 1990

FUNDING: Current FY: $ 750 Previous FYs: $ 1,995 Total: $ 2,745

STUDY OBJECTIVE

To determine whether the loss in frequency resolution often experienced by hearing-impaired listeners is directly related to their reduced sensitivity, and therefore might be simulated with noise masking in normal-hearing subjects, or whether a separate auditory pathology independent of elevated thresholds coexists in these patients.

TECHNICAL APPROACH

Frequency resolution in two frequency regions will be measured in normal-hearing and hearing-impaired subjects under conditions of quiet and two broadband noise masking conditions. Characteristics of the auditory filters derived from these measurements were determined to allow a comparison of both bandwidth and asymmetry of the filters across subject groups and within subjects as their sensitivity was decreased by the broadband noise floor.

PRIOR AND CURRENT PROGRESS

One paper describing this work has been published, and a second manuscript is in preparation reporting further analyses of these data to examine the additivity of masking in normal-hearing and hearing-impaired persons. No additional subjects have participated in this study during this year. A total of ten subjects have completed this study. There have been no adverse reactions from subjects, nor has any subject withdrawn from the study. There is no benefit to the subjects.

CONCLUSIONS

A new procedure for analyzing auditory filters was developed for this study, suggesting that filter bandwidths increase with increasing signal level more for hearing-impaired listeners than in normal listeners. Using this improved analysis procedure, it was shown that noise masking sufficient to raise subjects' absolute thresholds does not result in increased filter bandwidths, except as accounted for by the increase in signal level.

REPORT DATE: 01/15/93 WORK UNIT # 2060A

DETAIL SUMMARY SHEET

TITLE: The Relationship Between Right Ventilator Volume by Thermodilation Catheter and Left Ventilator Volume by Transesophageal Echo-Cardiography

KEYWORDS: volume, transesophageal, echocardiography

PRINCIPAL INVESTIGATOR: Stoltzfus, Daniel LTC MC
ASSOCIATES: Thwaites, Brian CPT MC; Vernalis, Marian LTC MC

DEPARTMENT: Department of Surgery
SERVICE: Critical Care Medicine Service

STATUS: Terminated
APPROVAL DATE: Jan 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To measure the correlation of right ventricular end-diastolic volume (RVEDV) (thermodilution), pulmonay artery pressures (PAD/PCWP) (Swan-Ganz catheter), and left ventricular end-diastolic volume (LVEDV) during cardiopulmonary bypass.

TECHNICAL APPROACH

Patients scheduled for elective cardiopulmonary bypass grafting (CABG) procedures will have hemodynamic monitor, to include a pulmonary artery catheter (REF-1) and a transesophageal echocardiograph (TEE). At five time points during surgery, measurements will be made of RVEDVI, PAD, PCWP and CVP. Simultaneously, short axis images of the left ventricle will be recorded for "off-line" calculation of LVEDVI.

PRIOR AND CURRENT PROGRESS

This protocol has beeen administratively terminated as requested by the principal investigator.

CONCLUSIONS

None. This protocol has been administratively terminated.

REPORT DATE: 04/20/94 WORK UNIT # 3009

DETAIL SUMMARY SHEET

TITLE: Effect of Empiric Low Dose Amphotericin B on the Development of Disseminated Candidiasis in a Surgical Intensive Care Unit

KEYWORDS: low-dose, amphotericin B, candidiasis

PRINCIPAL INVESTIGATOR: Whatmore, Douglas LTC MC
ASSOCIATES: Aronson, Naomi LTC MC; Longer, Charles LTC MC

DEPARTMENT: Department of Surgery
SERVICE: Critical Care Medicine Service

STATUS: Ongoing
APPROVAL DATE: Mar 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To determine if amphotericin B in low dose (0.3 mg/kg opposed to standard dose of 0.5-1.0 mg/kg) used empirically early in a critically ill patient's course will prevent the dissemination of Candida infections.

TECHNICAL APPROACH

The study will be prospective, randomized, and single-blinded (to the patient/family), with patients receiving low-dose amphotericin B or nothing after obtaining informed consent. Entrance criteria include persistent evidence of sepsis for less than 96 (originally 120) hours on antibiotics, multi-organ system failure involving two organ systems with evidence of Candida at one site (originally did not require evidence of Candida), or Candida isolated from two sites. Evidence of disseminated candidiasis precludes enrollment due to the need for standard dose regimens.

PRIOR AND CURRENT PROGRESS

Two subjects were enrolled during the period 15 Mar 93 to 28 Feb 93, bringing the total enrollment to 26. Both patients completed the protocol. No subject to date has had any unexpected adverse reactions. Benefits have included increased scrutiny for dissemination of Candidal infection. Two significant events have impacted on the progress of the study this year. 1) Because of the decrease in the number of patients infected with Candida at WRAMC, the study was expanded to include the University of Florida, Gainsville (Dr. Stoltzfus) and Madigan AMC (Dr. Low). Approval for a third limb evaluating Fluconazole was also requested. The study has been delayed while waiting for approval in those institutions. 2) Funding approval for MRDC monies was not received by the PI until mid March 1994. The study has been without a research assistant since 01 Oct 93 because of this.

CONCLUSIONS

The study will continue until at least 30 subjects have been enrolled in the original Amphotericin group. A third study limb, evaluating Fluconazole, should be added. This would increase the number of enrollees to at least 45. To date, no conclusions may be reached regarding the potential benefit of early use of low-dose Amphotericin B to prevent dissemination of fungal disease.

REPORT DATE: 02/16/94 WORK UNIT # 3012

DETAIL SUMMARY SHEET

TITLE: Work of Breathing as a Predictor of Failure to Wean from Mechanical Ventilation in Patients with Severe Chronic Obstructive Pulmonary Disease (COPD)

KEYWORDS: work of breathing, mechanical ventilation, COPD

PRINCIPAL INVESTIGATOR: Whatmore, Douglas LTC MC
ASSOCIATES: Harrington, Gerald LTC MC

DEPARTMENT: Department of Surgery STATUS: Terminated
SERVICE: Critical Care Medicine Service APPROVAL DATE: Jan 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine in patients with severe chronic obstructive pulmonary disease (COPD) if there is a difference in work of breathing (WOB) between those who tolerate removal from mechanical ventilation and those who require reintubation.

TECHNICAL APPROACH
An adult patient with COPD, who has required mechanical ventilation for greater than 24 hours, and who is ready (per the primary care team) for extubation, is identified. The patient's WOB is determined via the metabolic cart. The primary team is blinded to the results. The patient is extubated and followed for 24 hours. WOB levels in those patients who tolerate extubation will be compared with those who fail it. The requirement for informed consent was waived because the study only involves the prospective collection of exhaled gas, does not alter the standard of care, and involves no risk to the patient.

PRIOR AND CURRENT PROGRESS
This protocol has been administratively terminated.

CONCLUSIONS
This protocol has been administratively terminated.

REPORT DATE: 02/28/94 WORK UNIT # 3014

DETAIL SUMMARY SHEET

TITLE: The Effect of Leukocyte Filters on the Development of Extravascular Lung Water in Patients Undergoing Coronary Artery Bypass Grafting (CABG)

KEYWORDS: extravascular lung water, thoracic bioimpendance

PRINCIPAL INVESTIGATOR: Ries, Marianne CPT MC
ASSOCIATES: Hetzler, Norman MD; Barry, Michael MD

DEPARTMENT: Department of Surgery
SERVICE: Critical Care Medicine Service

STATUS: Ongoing
APPROVAL DATE: Feb 1993

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To evaluate the effect of leukocyte filters on the development of noncardiogenic pulmonary edema following Coronary Artery Bypass Grafting (CABG) by determining extravascular lung water (EVLW) changes by thoracic bioimpedance (BI).

TECHNICAL APPROACH

This study is a randomized, unbounded, controlled clinical trial with a target enrollment of 106 patients (allowing for dropouts) who are scheduled for elective CABG. Each patient is assigned to undergo CABG with or without a leukocyte depletion (PALL) filter. Patients are stratified into four subgroups according to age (greater than or less than 65 years) and ejection fraction (greater than 50% or less than 50%). All patients undergo measurement of extravascular lung water with thoracic bioimpedance the day before surgery, 2 hours after termination of bypass, 12 hours post-bypass, and 24 hours post-bypass.

PRIOR AND CURRENT PROGRESS

To date, since the procurement of the thoracic bioimpendance monitor in mid-May 1993, 19 patients have been enrolled. The relatively low percentage of eligible patients (of the total cardiothoracic surgery population), and mechanical problems with the monitor (which have been resolved) have resulted in the relatively small number of patients enrolled to date. With the current number of patients, there is no statistically significant difference in EVLW between the control and filter groups, although the trend is towards decreased EVLW in the filter group at 2 and 12 hours post-bypass. There have been no serious or unexpected adverse reactions, and no patients have been withdrawn from the study. There has been no measureable benefit to the patients.

CONCLUSIONS

The trend, to date, is that there is a decrease in EVLW at 2 hours and 12 hours post-bypass in patients randomized to receive a leukocyte depletion filter. This does not achieve statistical significance, to date, with the small number of patients enrolled. With mechanical problems resolved, it is expected that significantly more patients will be enrolled in the coming year.

REPORT DATE: 05/03/94 WORK UNIT # 2061

DETAIL SUMMARY SHEET

TITLE: Prevention of Unresectable Lung Cancer Found at Thoracotomy

KEYWORDS: lung, cancer, surgery

PRINCIPAL INVESTIGATOR: Hale, Douglas MAJ MC

DEPARTMENT: Department of Surgery STATUS: Completed
SERVICE: General Surgery Service APPROVAL DATE: May 1993

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine the identity of reliable predictors of unresectability of lung cancer.

TECHNICAL APPROACH
This will be a retrospective chart review of individuals identified as having unresectable lung cancer from July 1983 through February 1992.

PRIOR AND CURRENT PROGRESS
Thirty-three patients were identified. Data has been abstracted from all of these charts. Due to the limited amount of data, there are no immediate plans to submit this study for publication or presentation.

CONCLUSIONS
With adjustment of CAT scan criteria for extent of disease and the introduction of thoracoscopy, rates of non-resectability may be reduced.

REPORT DATE: 07/12/94 WORK UNIT # 2062

DETAIL SUMMARY SHEET

TITLE: Role of Intracellular Calcium in Bile Acid Induced Injury of Gastric Cells

KEYWORDS: calcium, bile acid

PRINCIPAL INVESTIGATOR: Hale, Douglas MAJ, MC

DEPARTMENT: Department of Surgery STATUS: Ongoing
SERVICE: General Surgery Service APPROVAL DATE: Jun 1993

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine the time course and reversibility of intracellular hypercalcemia in gastric mucosal cells exposed to bile acids.

TECHNICAL APPROACH
A mucosal cell suspension is prepared from rabbit stomach. These cells are then exposed to bile acids or control solutions. The intracellular calcium levels are determined with a FURA fluorescent probe.

PRIOR AND CURRENT PROGRESS
Intracellular hypercalcemia occurs almost immediately after the mucosal cells are exposed to low concentrations of bile acids and plateaus after approximately 20 minutes. This hypercalcemia is reversible as demonstrated by normalizing intracellular calcium levels when a bile acid chelating agent is added to the incubation solutions.

CONCLUSIONS
Intracellular hypercalcemia in injured gastric mucosal cells appears to be a marker of early, reversible cell injury and not a late manifestation of cell death.

REPORT DATE: 08/19/94 WORK UNIT # 2063

DETAIL SUMMARY SHEET

TITLE: Development of Autoradiographic Assay for Detection of Insulin-Like Growtth Factor 1 Receptors in Guinea Pig Mucosa

KEYWORDS: IGF-1, growth factor, receptor

PRINCIPAL INVESTIGATOR: Hale, Douglas MAJ MC

DEPARTMENT: Department of Surgery STATUS: Ongoing
SERVICE: General Surgery Service APPROVAL DATE: Aug 1993

FUNDING: Current FY: $ 2,233 Previous FYs: $ 0 Total: $ 2,233

STUDY OBJECTIVE
To develop a convenient and reproducible assay for insulin-like growth factor receptors (IGF-1) in guinea pig gastric mucosa.

TECHNICAL APPROACH
This study utilizes standard radio-labeled ligand binding techniques and public domain software developed at NIH to analyze the quantity and affinity of IGF-1 receptors. By using a variety of competitive inhibitors and experimental conditions, the receptors are characterized.

PRIOR AND CURRENT PROGRESS
A reliable method of isolating intact guinea pig gastric mucosa has been developed. A specific binding rate of 80% has been achieved by systematically varying experimental parameters (i.e., temperature, duration of incubation, etc.). Currently, work is in progress on the precise quantification of these receptors in different regions of the stomach. Following this, quantification of the binding affinity of this receptor to a host of related ligands will be done. Guinea pig stomachs have been harvested from animals being euthanized for another USUHS protocol. None have been bought through DCI to date.

CONCLUSIONS
IGF-1 receptors are present in guinea pig gastric mucosa. Maximal specific binding of a rabiolabeled IGF-1 ligand is achieved with 24 hour incubations of the specimens at 4 degrees C. There may be significant differences in receptor quantity based upon location in the stomach.

REPORT DATE: 02/07/94 WORK UNIT # 2318

DETAIL SUMMARY SHEET

TITLE: The Effects Upon Ocular Structures of Optical Polycarbonate and of Various Eye Protective Substances Applied to and Incorporated Within It

KEYWORDS: polycarbonate, ocular eye, intraocular

PRINCIPAL INVESTIGATOR: Wertz, Fleming COL MC
ASSOCIATES: Ward, Thomas MAJ MC; Cavallaro, Brian CPT MC

DEPARTMENT: Department of Surgery
SERVICE: Ophthalmology Service

STATUS: Ongoing
APPROVAL DATE: Jan 1990

FUNDING: Current FY: $ 8,882 Previous FYs: $ 0 Total: $ 8,882

STUDY OBJECTIVE

To determine the ocular toxicity, if any, of polycarbonate lenses and various dyes applied to or incorporated within the lenses. Polycarbonate lenses are being issued as eye protection to soldiers. It is anticipated that some of these protective lenses will shatter in combat and that fragments of the lens will be driven into the eye.

TECHNICAL APPROACH

Fragments (0.4 mg) of BLPS lenses and frontserts will be surgically implanted into eyes of albino rabbits. The animals will be randomized into six groups: clear polycarbonate lens, tinted polycarbonate lens, 2 wavelength protective frontsert, 3 wavelength protective frontsert, iron (positive control), and sham operated eyes (negative control). The animals will be given clinical exams, including intraocular pressure and bright-flash ERG's, prior to both fragment implantation and enucleation. The animals will be euthanized at 1, 2, 4, and 26 weeks. An interim clinical exam will be performed at 12 weeks on the 26 week animals. The enucleated eyes will be examined and sectioned for histopathologic evaluation.

PRIOR AND CURRENT PROGRESS

The 3 wavelength particle caused early ERG abnormalities and increased intraocular inflammation as reported last year. Further studies were performed to evaluate potential toxicity of individual dye components of the laser protective frontserts. A total of 32 animals were randomized into four groups: 532 nm absorbing dye; 694 nm absorbing dye; 1064 nm absorbing dye; and Balanced Salt Solution (BSS). A 0.2 ml suspension of 100 ug of dye or BSS alone was injected into midvitreous cavities of right eyes of albino rabbits. Those eyes injected with the 532 nm and 1064 nm absorbing dyes exhibited depressed dark-adapted ERG b-wave amplitudes. One additional animal was used to perfect the injection technique. The total number of animals used is 172. There were no adverse reactions.

CONCLUSIONS

The 532 and the 1064 nm absorbing dyes appear to interfere with normal retinal physiology at early time points (1 week). These changes are consistent with apparent toxicity noted in the previous study employing BLPS fragments in which the fragment containing all three dyes produced significant ERG abnormalities at 1 to 2 weeks.

REPORT DATE: 04/06/94 WORK UNIT # 2319

DETAIL SUMMARY SHEET

TITLE: The Efficacy of Cyanoacrylates in the Primary Closure of Conjunctival Scleral Lacerations

KEYWORDS: cyanoacrylate, scleral, laceration

PRINCIPAL INVESTIGATOR: Wertz, Fleming COL MC
ASSOCIATES: Ward, Thomas MAJ MC; Cavallaro, Brian CPT MC

DEPARTMENT: Department of Surgery
SERVICE: Ophthalmology Service

STATUS: Ongoing
APPROVAL DATE: Jan 1990

FUNDING: Current FY: $ 3,905 Previous FYs: $ 9,915 Total: $ 13,820

STUDY OBJECTIVE

To determine whether scleral lacerations can be effectively closed in New Zealand white rabbits using cyanoacrylate glue, and to determine the ocular toxicity, if any, of the glue. Currently, scleral lacerations are sutured. This is a time-consuming procedure, and it is anticipated that in combat, O.R. time will be of short supply. If lacerations could be quickly closed with glue, it would be very useful under combat conditions.

TECHNICAL APPROACH

A 6 mm scleral laceration will be created and either left open, closed with Vicryl suture in standard fashion, or closed via application of cyanoacrylate (CA) glue. The animals will be followed clinically by monitoring fundus appearance, intraocular pressure (IOP), intraocular inflammation, and ERG. At 48 hours to 2 months after surgery, the animals are euthanized, and the eyes are examined histopathologically. Wound integrity will be evaluated using Siedel testing while increasing the IOP. An transcleral cannula will be connected to both a transducer and a bag of sterile saline. IOP will be elevated by inflating a sphygnomonometer wrapped around the saline or by digital message of the globe.

PRIOR AND CURRENT PROGRESS

A total of 90 animals have been used; none this past year. A manuscript is being prepared for publication.

CONCLUSIONS

This study supports the efficacy of using cyanoacrylate adhesive as a temporary, expedient method of closing scleral lacerations on the battlefield.

REPORT DATE: 06/29/94 WORK UNIT # 2320

DETAIL SUMMARY SHEET

TITLE: Mood and Behavior Changes with Topical Ophthalmic Beta-Adrenergic Blockade

KEYWORDS: B-adrenergic, blockers, glaucoma

PRINCIPAL INVESTIGATOR: Blaydon, Sean CPT MC

DEPARTMENT: Department of Surgery STATUS: Completed
SERVICE: Ophthalmology Service APPROVAL DATE: Feb 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine if topically administered B-adrenergic blockers have an effect on mood.

TECHNICAL APPROACH
To determine subjective mood by having patients who are being treated with a topical B-blocker (or alternative drug) fill out a periodic questionnaire (Beck Depression Inventory).

PRIOR AND CURRENT PROGRESS
No new patients have been recruited into the study since the last Annual Progress Report February 1993. The PI has been on surgical rotations and therefore has not been seeing routine glaucoma cases. A total of 67 patients have been enrolled to date (37 males and 30 females); 14 patients (5 males and 9 females) were enrolled during fiscal year 1993-1994. Approximately 20 more patients are needed to produce statistically interpretable results. No adverse reactions have occured. Recruitment in the past has been according to the protocol. There has been the need to enroll new patients to replace the few removed from the study because of the inability of the randomly assigned medication to control their intraocular pressure/glaucoma.

CONCLUSIONS
No conclusions have been drawn from the preliminary data. This protocol will be resubmitted at Tripler Army Medical Center, and the study will be continued there. Results will be reported to the Departments of Clinical Investigation at Tripler AMC and Walter Reed AMC.

REPORT DATE: 12/02/93 WORK UNIT # 2633

DETAIL SUMMARY SHEET

TITLE: Use of Anti-lymphocyte Preparations in Solid Organ Transplantation

KEYWORDS: anti-lymphocyte, preparations, transplantation

PRINCIPAL INVESTIGATOR: Shaver, Timothy MAJ MC

DEPARTMENT: Department of Surgery STATUS: Completed
SERVICE: Organ Transplant Service APPROVAL DATE: Dec 1989

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine the long-term benefit (1-5 years post transplantation) of anti-lymphocyte preparations used for induction of graft tolerance to prevent rejection episodes, or in the treatment of acute rejection episodes after renal, pancreatic, or hepatic transplantation.

TECHNICAL APPROACH
Minnesota antilymphocyte globulin (MALG) will be given daily for the first 10 postoperative days and every other day for 10 days for a total of 15 doses. This will be given to high immunologic risk patients: a) >20% PRA, b) previously transplanted patients, and c) Black recipients. It will also be given to patients with poor initial renal function; i.e., oliguria <200 cc in the first 6 hours, patients who do not respond to IV diuretics with 100 cc/hour output, and patients whose serum creatinine does not fall >2 mg/dl in the first 24 hours post transplant.

PRIOR AND CURRENT PROGRESS
A total of 31 patients have been enrolled, none during the past year. MALG was withdrawn from use October 1992 due to an FBI investigation into its manufacture and use, and remains withdrawn. Thus, no work was done on this protocol during the past year.

CONCLUSIONS
Due to the unavailability of this drug, the protocol is being closed.

REPORT DATE: 12/10/93 WORK UNIT # 3361

DETAIL SUMMARY SHEET

TITLE: Pneumococcal Polysaccharide Vaccine: Adverse Reactions to Immunization

KEYWORDS: pneumococcal, polysaccharide, immunization

PRINCIPAL INVESTIGATOR: Polly, Shirley MAJ MC
ASSOCIATES: Engler, Renata LTC(P) MC; Davis, William MAJ MC

DEPARTMENT: Department of Surgery
SERVICE: Organ Transplant Service

STATUS: Ongoing
APPROVAL DATE: Dec 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To determine the incidence and prevalence of adverse reactions to primary immunization versus booster immunization with the polyvalent pneumococcal polysaccharide vaccine during the annual influenza vaccination program.

TECHNICAL APPROACH

Charts from patients who have received immunizations in the Allergy-Immunization Clinic of WRAMC were reviewed for types of vaccines received. Patients are called within 6 weeks of vaccination and questioned regarding side effects, including local and systemic reactions, treatment received/required, and duration of symptoms. Data will be entered into a data base for analysis by patient/vaccination characteristics.

PRIOR AND CURRENT PROGRESS

The records of approximately 4,000 patients who had been given either influenza or pneumococcal polysaccharide (PPS) vaccine were reviewed in November 1990. By mid December 1990, 432 of the patients who had received primary or secondary PPS vaccines had been phoned to ascertain possible side effects. No new patients have been enrolled or will be enrolled. Results have been accrued and entered into a computer data base. Data await final review and analysis.

CONCLUSIONS

Since analysis is pending, no statement can be made yet about severity of side effects or benefit to patients. Conclusions are deferred pending completion of data analysis.

REPORT DATE: 08/30/94 WORK UNIT # 2417

DETAIL SUMMARY SHEET

TITLE: A Prospective Study of Back Pain in Pregnancy

KEYWORDS: back pain, pregnancy

PRINCIPAL INVESTIGATOR: McHale, Kathleen MAJ MC

DEPARTMENT: Department of Surgery STATUS: Completed
SERVICE: Orthopaedic Surgery Service APPROVAL DATE: Aug 1989

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To study the natural history of back pain in pregnancy and the occurrence and amount of back pain as it relates to weight gain.

TECHNICAL APPROACH
The explanation of the study and the consent form are given to the prenatal patients at the introductory visit. The questionnaire regarding back symptoms and an orthopaedic physical exam are done along with the obstetric exam once during the first, second, and third trimesters, and then at the first post partum check. If the patient continues to have pain at the post partum exam (6 weeks post partum), then the patient continues to be seen by the Orthopaedic Surgery Service until there is some resolution.

PRIOR AND CURRENT PROGRESS
A total of 43 patients have been enrolled. No new patients were enrolled this past fiscal year due to lack of support personnel for the project. There have been no adverse reactions. New interest in the study has been expressed by women's medical groups. A new proposal has been submitted for funding to the Defense Women's Health Initiative, and a new protocol has also been submitted to the Department of Clinical Investigation.

CONCLUSIONS
Early conclusions show that weight gain is not necessarily related to back pain. Back pain may be related to parity.

REPORT DATE: 10/08/93 WORK UNIT # 2418

DETAIL SUMMARY SHEET

TITLE: Clinical Investigation of the PWB Spine System

KEYWORDS: PWB spine system, spinal fusion

PRINCIPAL INVESTIGATOR: Polly, David Jr MAJ MC

DEPARTMENT: Department of Surgery STATUS: Ongoing
SERVICE: Orthopaedic Surgery Service APPROVAL DATE: Oct 1989

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To evaluate a new pedicle fixation device which is more flexible than previously used rigid devices. It is hypothesized that lumbar and lumbosacral fusion rates will be enhanced.

TECHNICAL APPROACH
This is a multicenter study. All patients to be enrolled are candidates for lumbar or lumbosacral fusions with pedicle fixation. There has been no change in the original protocol. Patients will be followed for 4 years post-procedure.

PRIOR AND CURRENT PROGRESS
Due to a high rate of pseudoarthroses with this device, the implantation was stopped at WRAMC in August 1991, with no further patient accrual to take place. At that time, 24 patients had been entered into this study. PWB instrumentation was removed on 11 of these patients; 9 had a pseudoarthrosis, and 2 had pain over the hardware and a solid fusion on operation. The 2 year follow-up has been completed on all patients. Overall results (all centers) should be ready for FDA review soon.

CONCLUSIONS
Institutional results with this instrumentation system were not as good as with the previous system. The concept of "semi-rigid" fixation in the spine is no longer felt to be advantageous.

REPORT DATE: 04/13/94 WORK UNIT # 2420

DETAIL SUMMARY SHEET

TITLE: MRI Characteristics following Surgical Excision of Soft Tissue Sarcomas and Radiation Therapy in Determining Normal Postsurgical and Radiation Changes from Recurrent Disease

KEYWORDS: MRI, soft tissue sarcoma, recurrent disease

PRINCIPAL INVESTIGATOR: Temple, Thomas MAJ MC

DEPARTMENT: Department of Surgery STATUS: Ongoing
SERVICE: Orthopaedic Surgery Service APPROVAL DATE: Mar 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine what the signal characteristics and differences are between post irradiation changes and recurrences in soft tissue sarcomas of the extremities.

TECHNICAL APPROACH
A retrospective chart review will be made of MRI patients who have undergone surgery and radiation therapy for soft tissue sarcomas of the extremities.

PRIOR AND CURRENT PROGRESS
To date, 14 patients have been admitted to the study, all of them during the past year. Plans are to enroll at least 30 additional patients over the next 2 to 3 months. There has been a delay in progress due to an ETS move by the former PI. This will certainly change over the next 6 months. Also, the study now has an interested radiologist to review the work and a research resident to provide more data base managing. Completion of this project should take no longer than an additional 12 months.

CONCLUSIONS
This is a potentially important study because with the advent of combined treatment for patients with soft tissue sarcomas (i.e., surgery and radiation) the need to differentiate recurrent disease from post surgical and radiation change becomes problematic. The researchers feel that sufficient numbers will be generated in this study to make statistically significant comparisons.

REPORT DATE: 04/11/94 WORK UNIT # 2427

DETAIL SUMMARY SHEET

TITLE: The Effects of Intraoperative Blood Loss on Serum Antibiotic Level in Patients Undergoing Total Joint Arthroplasty

KEYWORDS: total joint arthroplasty, serum antibiotic levels, blood loss

PRINCIPAL INVESTIGATOR: Hopkinson, William COL MC

DEPARTMENT: Department of Surgery STATUS: Completed
SERVICE: Orthopaedic Surgery Service APPROVAL DATE: Mar 1991

FUNDING: Current FY: $ 278 Previous FYs: $ 0 Total: $ 278

STUDY OBJECTIVE
To determine what effect blood loss during surgery has on the serum concentration of the antibiotic.

TECHNICAL APPROACH
At least 48 hours preoperatively, the patient will be given 1 gm Cefazolin IV over 5 minutes. Blood samples will be drawn at 5, 10, 20, 30, 60, 120, 240, and 300 minutes. Intraoperatively, the same procedures will be performed, and EBL and intake will be recorded. The serum concentration of the antibiotic in each sample will be determined by capillary electropheresis. The preoperative and intraoperative serum concentrations will be compared, and the data will be interpreted by the pharmacokineticist.

PRIOR AND CURRENT PROGRESS
A total of 27 subjects have been enrolled, none this past year. All the data has been collected and recorded in this study. This data is still undergoing analysis and statistical review in preparation for presentation at a national meeting. The principals in the study are currently meeting on a monthly basis to prepare this manuscript.

CONCLUSIONS
There are no conclusions yet. The researchers continue to formulate final analysis and manuscript preparation.

REPORT DATE: 11/02/93 WORK UNIT # 2432

DETAIL SUMMARY SHEET

TITLE: Evaluation of the Syndesmosis in Ankle Diastasis Injuries

KEYWORDS: ankle, ligaments, syndemosis

PRINCIPAL INVESTIGATOR: Xenos, John CPT MC
ASSOCIATES: Hopkinson, William COL MC; Olson, Eric MAJ MC

DEPARTMENT: Department of Surgery
SERVICE: Orthopaedic Surgery Service

STATUS: Ongoing
APPROVAL DATE: Oct 1991

FUNDING: Current FY: $ 2,636 Previous FYs: $ 0 Total: $ 2,636

STUDY OBJECTIVE
To evaluate the role of the syndesmotic ligaments when the ankle is exposed to external rotational forces; to evaluate methods of fixation of the syndesmosis; and to evaluate methods of radiographic assessment of syndesmosis injury.

TECHNICAL APPROACH
Fresh frozen cadaver specimens will be used to study subjects. A special apparatus which allows rotational forces to be applied to the ankle was constructed. The ligaments will be incrementally sectioned, and measurements will be made directly on the specimens while radiographs are made at each incremental cut. The radiographs will be read by three independent observers. An addendum is being considered to evaluate the role of the syndesmotic ligaments when the ankle is exposed to internal rotational forces.

PRIOR AND CURRENT PROGRESS
Thirty-three fresh frozen cadavers have been used. This includes four specimens used in a pilot study to perfect technique and determine the merits of the study. No more cadavers will be used. Information has provided extremely useful data which may have significant impact on the methods of diagnosis and treatment of ankle injuries involving the ankle syndesmosis. Plans are to use the data from theis study as a platform for further clinical evaluation.

CONCLUSIONS
1) Extent of syndesmotic ligament disruption correlates with diastasis. 2) Repair of the syndesmosis with screws (one or two) is superior to suture repair of the anterior talofibula ligament. 3) Partial syndesmosis injury can result in diastasis >2mm. 4) Stress lateral radiograph has higher correlation with anatomic diastasis than the stress mortise view (the current gold standard for diagnosis of syndesmosis injuries).

REPORT DATE: 10/14/93 WORK UNIT # 2433

DETAIL SUMMARY SHEET

TITLE: Foot and Ankle Injuries During Operation Desert Storm/Shield: An Analysis

KEYWORDS: foot and ankle, injuries, warfare

PRINCIPAL INVESTIGATOR: Hayda, Roman CPT MC
ASSOCIATES: McHale, Kathleen LTC MC; Lower, Raymond DO

DEPARTMENT: Department of Surgery
SERVICE: Orthopaedic Surgery Service

STATUS: Completed
APPROVAL DATE: Oct 1991

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To analyze open injuries to the foot and ankle in modern warfare, with respect to mechanism, extent of soft tissue and bony injury, treatment complications, and outcome at 1 year, in order to establish diagnostic and treatment guidelines.

TECHNICAL APPROACH

The charts of all servicemen treated by the WRAMC Orthopaedic Surgery Service as a result of Desert Storm and Desert Shield will be reviewed. The charts of those who have sustained injuries to the foot and ankle will be reviewed for mechanism of injury, extent of injury to the foot and ankle, associated injury, and treatment. Those with open injuries will be subsequently contacted 12-18 months post-injury. A questionnaire and clinical examination will be carried out when possible. The results will be reviewed using the criteria listed above.

PRIOR AND CURRENT PROGRESS

Follow-up study of 43 patients has been completed. Data has been compiled and tabulated. Write-up of an article for publication is in progress.

CONCLUSIONS

Blast injuries create a wide zone of injury. Strict adherence to surgical principles is critical, with restoration of a functional foot possible in most cases. Patients are able to return to a wide range of sports activities as well as heavy labor.

REPORT DATE: 03/17/94 WORK UNIT # 2434

DETAIL SUMMARY SHEET

TITLE: Aggressive Osteolysis Behind Well-fixed Acetabular Components with Perforations

KEYWORDS: hip, adult, arthroplasty

PRINCIPAL INVESTIGATOR: Xenos, John CPT MC
ASSOCIATES: Hopkinson, William LTC(P) MC

DEPARTMENT: Department of Surgery
SERVICE: Orthopaedic Surgery Service

STATUS: Completed
APPROVAL DATE: Mar 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To evaluate cases of uncemented total hip arthroplasty where radiographic evidence of acetabular component loosening or osteolysis is noted. Only acetabular components with perforations will be included.

TECHNICAL APPROACH

This is a retrospective review of cases performed at Walter Reed and at the Anderson Clinic in Virginia. Cases are reviewed and specimens are obtained at hip revision arthroplasty. Specimens are reviewed at AFIP, and retrieved components are evaluated for explanations for failure or increased component wear.

PRIOR AND CURRENT PROGRESS

A total of five patient charts have been reviewed; three during the past year. All data has been collected for this retrospective review. A manuscript should be completed within 2 months; it is currently being edited prior to submission, and comments/changes from civilian collaborators have yet to arrive.

CONCLUSIONS

There is the possibility of large cystic erosions occuring in the acetabulum behind well-fixed cementless acetabular components.

REPORT DATE: 05/05/94 WORK UNIT # 2435

DETAIL SUMMARY SHEET

TITLE: The Effect of Extracorporeal Shockwaves on Bone and Soft Tissue in Rabbits

KEYWORDS: shockwaves, dose, response

PRINCIPAL INVESTIGATOR: Brown, Maurice CPT MC

DEPARTMENT: Department of Surgery STATUS: Ongoing
SERVICE: Orthopaedic Surgery Service APPROVAL DATE: Apr 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 5,959 Total: $ 5,959

STUDY OBJECTIVE

To: 1) Evaluate ESW's ability to fracture intact bone and determine the accuracy with which such fractures can be created; 2) assess the affect of ESW on soft tissue, as measured by severity of petechiae, ecchymosis, and skin ulceration; 3) examine the dose-response relationship between power delivered and bone and soft tissue injury; and 4) attempt to locate a region of response associated with maximum bone injury and minimum soft tissue injury.

TECHNICAL APPROACH

Power settings of 6, 12, and 19 (6 = 0.42 mJ/mm^2, 12 = 0.78 mJ/mm^2, and 19 = 1.20 mJ/mm^2) will be used, and shockwaves will be administered in salvos of 400, 800, or 1200 waves. Animals will be euthanized at 1, 10, and 28 days or whenever a fracture is noted. Petechiae, echymosis, and ulceration will be measured post treatment and at euthanasia. Radiographs will be taken following shockwave application, at the time of euthanasia, or if a fracture is suspected on the basis of clinical evaluation.

PRIOR AND CURRENT PROGRESS

Animal work was completed during the first year of this study (70 rabbits). The researchers have demonstrated the ability to fracture intact bone in vivo with acceptable soft tissue injury. When dose-response relationships are studied, it is apparent that the largest bone effect with the smallest soft tissue effect occurred at a high power setting with a low number of shocks. This will be helpful data in planning future studies and in formulating treatment approaches in clinical trials. Pathological analysis was recently completed (04 Apr 94), and statistical review of the data is underway.

CONCLUSIONS

Extracorporeal shockwaves can effect fracture in vivo. External soft tissue changes are acceptable. Histological data is currently being reviewed.

REPORT DATE: 07/21/94 WORK UNIT # 2436

DETAIL SUMMARY SHEET

TITLE: Evaluation of Bone Healing in Osteotomies Produced with Excimer Laser and Er:YAG Laser in the Rabbit Model

KEYWORDS: laser, osteotomy

PRINCIPAL INVESTIGATOR: Xenos, John CPT MC

DEPARTMENT: Department of Surgery STATUS: Ongoing
SERVICE: Orthopaedic Surgery Service APPROVAL DATE: Jul 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To evaluate the ability of excimer laser to effectively ablate bone in vivo; to compare zones of adjacent tissue damage in osteotomies performed using excimer laser and Er:YAG (erbium yttrium-aluminum-garnet) laser; and, to compare healing rates of bone in osteotomies performed using excimer laser to those using Er:YAG laser.

TECHNICAL APPROACH
Sterile surgical techniques will be used under controlled conditions with the following procedures performed on each specimen. All skin incisions will be made using a scalpel blade. On one side, each rabbit will undergo either 'cold' osteotomy to the rib using an oscillating saw, osteotomy with excimer laser, or osteotomy with Er:YAG. On the contralateral side, osteotomy will be performed using either excimer or Er:YAG laser.

PRIOR AND CURRENT PROGRESS
The excimer laser has recently become available and functional, and the study will begin as soon as animals are available. Completion of the surgical arm of the study is anticipated between August 1994 and January 1995. The new Principal Investigator is now CPT Milan S. Moore, MC.

CONCLUSIONS
None as yet.

REPORT DATE: 11/16/93 WORK UNIT # 2437

DETAIL SUMMARY SHEET

TITLE: The Role of Topical Antibiotic in the Prevention of Bone Infection of the Rabbit Model. Treatment of Contaminated Open Tibial Fractures Stablized with Internal Fixation

KEYWORDS: infection, bone, antibiotics

PRINCIPAL INVESTIGATOR: Stuart, James CPT MC
ASSOCIATES: Popovic, Neven MD PhD DVM; Jacob, Elliot PhD

DEPARTMENT: Department of Surgery
SERVICE: Orthopaedic Surgery Service

STATUS: Completed
APPROVAL DATE: Nov 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To assess the efficacy of topical cefazolin in experimentally infected tibia fractures in rabbits treated with early internal fixation.

TECHNICAL APPROACH

Transverse osteotomies will be made in the mid-diaphysis of the tibia. Fracture sites will then be inoculated with a standard inoculum of S. aureus. Animals will be randomized to one of four groups: 1) 1 hour treatment with 1000 mg of topical cefazolin powder (experimental treatment) vs. 1 hour of no treatment (control); or 2) 3 hour treatment with 1000 mg of topical cefazolin powder vs. 3 hours of no treatment. Animals will undergo internal fixation with plate and screws. They will be euthanized at 6 weeks. The bones will be harvested using aseptic technique and submitted for quantitative cultures.

PRIOR AND CURRENT PROGRESS

Data analysis demonstrated significant reductions in bacterial counts in experimental groups. Similarly, rates of deep infection were significantly reduced. No significant difference was seen between the 1- and 3-hour treatment groups, with regards to bacterial reduction and rates of deep infection.

CONCLUSIONS

Topical cefazolin appears to have a beneficial effect in decreasing the initial bacterial load in infected open fractures; however, future studies should have larger sample sizes to increase the power in detecting a difference between delays in application of antibiotic.

REPORT DATE: 11/16/93 WORK UNIT # 2438

DETAIL SUMMARY SHEET

TITLE: Techniques for Soft Tissue Reattachment to Bone

KEYWORDS: tendon, fixation, bone

PRINCIPAL INVESTIGATOR: Stuart, James CPT MC

DEPARTMENT: Department of Surgery STATUS: Ongoing
SERVICE: Orthopaedic Surgery Service APPROVAL DATE: Nov 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To compare two separate methods of fixation to bone; cancellous versus cortical bone fixation. Also, to assess the role of local periosteal stripping at the site of reattachment in healing.

TECHNICAL APPROACH
Animal model; New Zealand white rabbit. Patellar tendon will be sectioned sharply at insertion site on tibia (tibial tuberosity). Suture will be placed through tendon and reattached to either cortical or cancellous bone. Knee will be immobilized with K-wire transfixed across the knee. Animals will be euthanized at 12 weeks. Knees will be resected and randomized to either biomechanical testing or histological analysis.

PRIOR AND CURRENT PROGRESS
Biomechanical data obtained demonstrate no significant difference between methods of fixation. However, at necropsy some of the attachment sites were noted to have been pulled apart, which may contribute to inadequate tissue for analysis. Histologic preparations are being conducted at the Department of Orthopaedic Pathology at the AFIP. Histologic analysis and interpretation are currently in progress. A total of 44 rabbits were used for this study. There have been no adverse reactions.

CONCLUSIONS
Preliminary conclusions at this time are limited to biomechanical data, and from that there appears to be no significant difference between techniques with regards to strength of repair. Histological analysis will provide valuable information regarding the nature of the reattachment site and reconstitution of tendon-bone interface.

REPORT DATE: 12/19/93 WORK UNIT # 2439

DETAIL SUMMARY SHEET

TITLE: Results of Coccygectomy for Coccygodynia

KEYWORDS: coccygectomy, coccygodynia

PRINCIPAL INVESTIGATOR: Grosso, Nicholas CPT MC
ASSOCIATES: vanDam, Bruce MD

DEPARTMENT: Department of Surgery
SERVICE: Orthopaedic Surgery Service

STATUS: Ongoing
APPROVAL DATE: Dec 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To review the results of coccygectomy for the treatment of coccygodynia.

TECHNICAL APPROACH
To perform a retrospective review of the results of coccygectomy performed for intractable coccyx pain on 10 patients by 1 surgeon. A chart review as well as a patient questionnaire will be performed.

PRIOR AND CURRENT PROGRESS
Eight of 10 patients were located and contacted. All eight agreed to participate in the study. Five of eight questionnaires were returned from the initial mailing. Chart review is completed. Second mailing of questionnaires and ongoing attempts to contact the remaining three patients are currently being undertaken.

CONCLUSIONS
The study continues to gather data at this time; review of results will be undertaken after all data is compiled.

REPORT DATE: 01/12/94 WORK UNIT # 2440

DETAIL SUMMARY SHEET

TITLE: Methods of Decontaminating Soft Tissue Grafts and Osteoarticular Fragments After Experimental Contamination

KEYWORDS: disinfection, graft, contamination

PRINCIPAL INVESTIGATOR: Stuart, James CPT MC
ASSOCIATES: Uhorchak, John MAJ MC; Hopkinson, William COL MC

DEPARTMENT: Department of Surgery
SERVICE: Orthopaedic Surgery Service

STATUS: Completed
APPROVAL DATE: Jan 1993

FUNDING: Current FY: $ 624 Previous FYs: $ 0 Total: $ 624

STUDY OBJECTIVE

To evaluate the efficacy of three antimicrobial solutions in disinfecting patellar bone-tendon-bone grafts and patellar osteoarticular (OA) fragments after experimental contamination. The solutions used in this study will be chlorhexidine (CHX), povidine-iodine (PI), and chloroxylenol (PCMX); all were compared to normal saline.

TECHNICAL APPROACH

Sixty patellar bone tendon grafts and 60 matched patellar osteoarticular fragments will be obtained from 20 fresh frozen human cadaveric knees. All specimens will be sterilized using 3.5 Mrads of gamma radiation (Cobalt-60). The bacterial broth will contain three representative organisms: coagulase negative Staphylococcus (CNS), Bacillus cereus (BC), and Pseudomonas aeruginosa (PA).

PRIOR AND CURRENT PROGRESS

Group one used a positive control (direct plating of the tissue after contamination); group two used a sterile normal saline; group three used povidine-iodine (PI - 10%); group four used chlorhexidine (CHX-45); and group five used Ultradex (PCMX-3% chlorxylenol). Treatment for the tendon grafts consisted of mechanical scrubbing with the sponge side of the handbrush in a basin containing the treatment solution for 2 minutes. The OA fragments were treated by placing them in a sterile 20 cc syringe containing 15 cc of the treatment solution and shaken for 2 minutes. All specimens were tested, and quantitative culture results were obtained.

CONCLUSIONS

Chlorhexidine is effective in disinfecting experimentally contaminated patellar bone tendon grafts; povidine-iodine appears to be the better antimicrobial solution in disinfecting osteoarticular fragments. This described technique for disinfection using chlorhexidine and povidine-iodine has potential for clinical use in cases of accidental contamination of osteoarticular fragments and bone tendon grafts.

REPORT DATE: 02/07/94 WORK UNIT # 2441

DETAIL SUMMARY SHEET

TITLE: Effectiveness of Ankle Bracing for Lateral Ankle Ligament Sprains

KEYWORDS: ankle, lateral ligaments

PRINCIPAL INVESTIGATOR: DeVries, William CPT MC

DEPARTMENT: Department of Surgery STATUS: Ongoing
SERVICE: Orthopaedic Surgery Service APPROVAL DATE: Jan 1993

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To evaluate: 1) the lateral ankle ligaments during rotational force across the ankle; and 2) the effectiveness of ankle braces to control this motion after ligaments have been sectioned.

TECHNICAL APPROACH
This is a cadaver study. The ligaments will be cut to create an injury; the anterior talofibular ligament, calcaneofibular ligament, posterior talofibular ligament, and anterior tibiofibular ligament. The effect will be evaluated by x-rays obtained during internal rotation. Braces will then be applied, and the x-rays repeated to see if there is stabilization of the ankle joint.

PRIOR AND CURRENT PROGRESS
A total of 24 cadavers have been used. The experimental portion of this study and the data analysis have been completed. A rough draft of a manuscript has been completed. The results have been presented to the Southern Orthopaedic Society, the Eastern Orthopaedic Society, and the Society of Military Orthopaedic Surgeons. This work received the Founder's Award for best militarily relevant research at the Military Orthopaedic Surgeons' Meeting.

CONCLUSIONS
The anterior talofibular ligament was the most important lateral ligament. The mod3 jump brace was the most effective of the three braces tested.

REPORT DATE: 02/03/94 WORK UNIT # 2442

DETAIL SUMMARY SHEET

TITLE: Articular and Meniscal Cartilaginous Response to Nd:YAG and Excimer Laser Exposure in the Rabbit Model

KEYWORDS: laser, meniscus, cartilage

PRINCIPAL INVESTIGATOR: DeVries, William CPT MC

DEPARTMENT: Department of Surgery STATUS: Ongoing
SERVICE: Orthopaedic Surgery Service APPROVAL DATE: Jan 1993

FUNDING: Current FY: $ 726 Previous FYs: $ 0 Total: $ 726

STUDY OBJECTIVE
To compare effects of two different lasers (No: Yag and Excimer) on rabbit knee articular and meniscal cartilage.

TECHNICAL APPROACH
Rabbit knee menisci will be exposed to two different types of lasers, and effects on healing will be evaluated.

PRIOR AND CURRENT PROGRESS
Due to equipment unavailability and assignment of PI outside of WRAMC, the protocol has not been started. Plans are to start in April 1994.

CONCLUSIONS
None yet.

REPORT DATE: 01/05/94 WORK UNIT # 2444

DETAIL SUMMARY SHEET

TITLE: Evaluation of Biodegradable Delivery System to Regenerate Long Bones in Rabbits: Guided Tissue Regeneration in an Ostectomized Radius

KEYWORDS: ostectomy, bone, rabbit

PRINCIPAL INVESTIGATOR: Popovic, Neven DVM MD PhD

DEPARTMENT: Department of Surgery STATUS: Completed
SERVICE: Orthopaedic Surgery Service APPROVAL DATE: Jan 1993

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To establish whether the concept of controlled, guided bone regeneration can be achieved through the use of a novel, biodegradable, polymeric device.

TECHNICAL APPROACH
Under sterile procedures, ostectomy with removal of 2x the diaphyseal diameter of the radius shaft will be performed with an oscillating saw. Biodegradable tube will be secured within the surgical defect, and animals will be observed for 10 weeks.

PRIOR AND CURRENT PROGRESS
A total of 14 animals have been used. There were no adverse effects. This protocol is completed. Surgical ostectomy defects healed except in areas where the biodegradable tube was inserted.

CONCLUSIONS
Biodegradable tube delayed healing of the ostectomy defect.

REPORT DATE: 01/05/94 WORK UNIT # 2445

DETAIL SUMMARY SHEET

TITLE: The Effect of Extracorporeal Shock Waves on Compartment Pressures in the Rabbit Leg

KEYWORDS: shockwaves, lithotripsy, rabbit

PRINCIPAL INVESTIGATOR: Popovic, Neven DVM MD PhD

DEPARTMENT: Department of Surgery
SERVICE: Orthopaedic Surgery Service

STATUS: Completed
APPROVAL DATE: Jan 1993

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To evaluate effects of extracorporeal shockwaves on compartment pressures in rabbits' hind legs.

TECHNICAL APPROACH
Hind legs of rabbits under general anesthesia will be subjected to known intensity of extracorporeal shockwaves, and any changes in the pressures of leg muscles (compartments) will be measured and recorded.

PRIOR AND CURRENT PROGRESS
Project completed; tissue was evaluated and effects on muscle compartments were recorded. Eleven rabbits were used; they experienced no adverse effects.

CONCLUSIONS
Extracorporeal shockwaves cause increase in muscle compartment pressure but not to a level high enough to cause the clinical compartment syndrome. No histologic tissue changes were noted.

REPORT DATE: 01/31/94 WORK UNIT # 2446

DETAIL SUMMARY SHEET

TITLE: The Effects of Different Braces on Pain Relief in Patients with Multiple Myeloma Involving the Spine

KEYWORDS: pain relief, braces, multiple myeloma

PRINCIPAL INVESTIGATOR: Polly, David MAJ MC
ASSOCIATES: Burrell, Linda MAJ M

DEPARTMENT: Department of Surgery
SERVICE: Orthopaedic Surgery Service

STATUS: Ongoing
APPROVAL DATE: Jan 1993

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To evaluate the efficacy and cost effectiveness of three various braces for relieving pain in patients with multiple myeloma involving the spine.

TECHNICAL APPROACH
A prospective, randomized case control study using a modified latin square. Each patient serves as their own control, and wears each of the three braces. Pain relief is assessed by using a modified visual analog scale.

PRIOR AND CURRENT PROGRESS
Two patients have been identified as candidates for this study so far; one completed it, but the other one was required to leave due to disease progression. There have been no serious or unexpected adverse reactions. Conduction of this protocol has been made much more difficult by loss of the orthopaedic research nurse.

CONCLUSIONS
No conclusions to date.

REPORT DATE: 02/04/94 WORK UNIT # 2447

DETAIL SUMMARY SHEET

TITLE: Subtalar Stabilization in Progressive Planovalgus Deformity in Children

KEYWORDS: subtalar stabilization, pediatric planovalgus

PRINCIPAL INVESTIGATOR: McHale, Kathleen LTC MC
ASSOCIATES: DeVries, William CPT MC

DEPARTMENT: Department of Surgery
SERVICE: Orthopaedic Surgery Service

STATUS: Ongoing
APPROVAL DATE: Feb 1993

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To provide an analysis of the outcome of two very classic operations used for stabilization of flat feet in children, and to investigate if a reproducible, classic operation with sound principles can address the clinical problems in all feet regardless of etiology. Previous reports in the literature have reported results when each operation was used for a flat foot of one specific etiology.

TECHNICAL APPROACH

This will be a retrospective review of pediatric patients with pes planovalgus who have been operated on in the last 7 years by the principal investigator. Pre- and post-operative clinical examinations, x-rays, and charts will be reviewed. New patients will enter the same protocol. Pre-surgical patients with pes planovalgus foot will enter the protocol by virtue of needing surgery, regardless of etiology. An extra-articular Grice-type fusion will be performed on patients under age 11; triple arthrodesis will be done on patients over 11 years old.

PRIOR AND CURRENT PROGRESS

A total of 26 feet have been operated on, and that review is complete. So far, results show that each procedure yields good results regardless of the etiology of the deformity. The review of the retrospective portion is complete.

CONCLUSIONS

The extra-articular arthrodesis for patients under 11 years of age, and the triple arthrodesis for patients older than 11 years of age give good results regardless of etiology of the planovalgus deformity. Subtalar stabilization done before age 11 years appears to give a more normal appearing foot with a higher patient satisfaction.

REPORT DATE: 02/25/94 WORK UNIT # 2448

DETAIL SUMMARY SHEET

TITLE: Thoracoplasty in Scoliosis

KEYWORDS: idiopathic scoliosis, thoracoplasty, posterior spinal fusion

PRINCIPAL INVESTIGATOR: Polly, David MAJ MC

DEPARTMENT: Department of Surgery STATUS: Ongoing
SERVICE: Orthopaedic Surgery Service APPROVAL DATE: Feb 1993

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To compare the mobidity of thoracoplasty in conjunction with posterior spinal fusion for adolescent idiopathic scoliosis versus no thoracoplasty.

TECHNICAL APPROACH
This is a retrospective chart and radiograph review of morbidity parameters (blood loss, length of stay) associated with posterior spinal fusion for adolescent idiopathic scoliosis.

PRIOR AND CURRENT PROGRESS
Charts and records of 24 patients have been reviewed. Data collection and analysis are also complete. A manuscript is currently being drafted.

CONCLUSIONS
Thoracoplasty does not appear to add significant morbidity to posterior spinal fusion for adolescent idiopathic scoliosis.

REPORT DATE: 04/13/94 WORK UNIT # 2449

DETAIL SUMMARY SHEET

TITLE: Measurement of Lumbar Lordosis: Evaluation of Intraobserver, Interobserver and Technique Variability

KEYWORDS: lumbar lordosis

PRINCIPAL INVESTIGATOR: Polly, David MAJ MC

DEPARTMENT: Department of Surgery STATUS: Ongoing
SERVICE: Orthopaedic Surgery Service APPROVAL DATE: Mar 1993

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To assess the intra- and inter-observer variability of the four different methods of measuring lumbar lordosis.

TECHNICAL APPROACH
Using the method of Cobb, lumbar lordosis will be measured in four different ways: 1) inferior endplate T12 to superior endplate of S1; 2) inferior endplate T12 to inferior endplate of L5; 3) superior endplate L1 to superior endplate of S1; and 4) superior endplate L1 to inferior endplate of L5.

PRIOR AND CURRENT PROGRESS
Three observers have measured 60 sets of films using the four different techniques. Each observer did this twice. All measurements have been made, recorded, and entered into the computer; data analysis is progressing. Preliminary results are now available. There is good intra- and inter-observer reliability. The greatest variability is in patients with transitional segment where identification of end vertebra is problematic. Also, patients with large magnitude lordosis (i.e., Scheuermann's disease) have greater variability.

CONCLUSIONS
Confidence intervals can be established, and sources of variation identified.

REPORT DATE: 04/29/93 WORK UNIT # 2450

DETAIL SUMMARY SHEET

TITLE: Regeneration of Segmental Defects in the Radii of Rabbits Using Recombinant Human Bone Morphogenetic-2 Protein

KEYWORDS: rh BMP-2 protein

PRINCIPAL INVESTIGATOR: Popovic, Neven DVM MD PhD

DEPARTMENT: Department of Surgery
SERVICE: Orthopaedic Surgery Service

STATUS: Completed
APPROVAL DATE: Mar 1993

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To establish whether the recombinant human bone morphogenetic-2 (rh BMP-2) protein, in combination with a biocampatible delivery system, can promote the regeneration of critical-size segmental defects in the radii of rabbits.

TECHNICAL APPROACH

The experimental animals will have ostectomy of their radius (3 X diaphyseal diameter) performed, as the bone defect equal to or greater than 2 X the diaphyseal diameter of a long bone will not unite spontaneously. The rabbits will randomly be assigned to one of six treatment groups.

PRIOR AND CURRENT PROGRESS

There has been no progress. Collaborating investigator, Dr. Hollinger, and the Genetics Institute (supplying recombinant morphogenetic-2 protein through Dr. Hollinger) insisted that certain changes be made in the protocol and that certain legal restrictions be placed on any future data. They elected to terminate the protocol versus presenting the protocol changes to The DCI Research Committee.

CONCLUSIONS

None.

REPORT DATE: 06/28/93 WORK UNIT # 2451

DETAIL SUMMARY SHEET

TITLE: Carpal Ligament Injuries in Intra-articular Fractures of the Distal Radius

KEYWORDS: distal radius fractures, carpal ligament injuries

PRINCIPAL INVESTIGATOR: Cook, Jonathan MAJ MC
ASSOCIATES: Popovic, Neven DVM MD PhD; Smith, Allan COL MC

DEPARTMENT: Department of Surgery
SERVICE: Orthopaedic Surgery Service

STATUS: Ongoing
APPROVAL DATE: Apr 1993

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To reproduce intra-articular fractures of the distal radius in cadaveric specimens, and to delineate the type and degree of carpal ligament disruption associated with these fractures.

TECHNICAL APPROACH
Cadaveric specimens will be mounted in a gravity dependent, fast loading machine with the elbows and wrists extended. The load will be applied directly over the transverse carpal ligament. The load will be dropped from heights ranging from 79.0 cm to 60.3 cm; masses varied from 34.1 kg to 12.7 kg. Radiographs will be taken before and after loading. Radius fractures will be classified by the Melone System. The specimens will be dissected, and the type and degree of ligament injury will be noted.

PRIOR AND CURRENT PROGRESS
A total of 11 cadavers have been used. There were five males and six females; far left and far right extremities. Five intra-articular fractures of the distal radius were produced. The remaining specimens sustained other fracture types. By Melone classification, there was one Type I, two Type III, and two Type V. One Type I fracture had complete injury to the dorsal and membranous portion of the scapho-lunate intracarpal ligament (SLIL). One Type V fracture was a grade II open injury with perilunar instability, and complete SLIL, UL, and TFCC injuries with a partial lunotriquetral intracarpal ligament (LTIL) injury. One Type III fracture had a partial LTIL disruption. The carpal ligaments were intact in all other cases.

CONCLUSIONS
Extrinsic carpal ligament injury is not associated with intra-articular fractures to the distal radius. Some degree of intrinsic injury may occur. Numbers are too small to make definitive conclusions.

REPORT DATE: 04/19/94 WORK UNIT # 2452

DETAIL SUMMARY SHEET

TITLE: The Osteoconductive Potential of a Polycaprolactone Foam in the Rat Tibia

KEYWORDS: rat, polycaprolactone foam, osteoconductive potential

PRINCIPAL INVESTIGATOR: Popovic, Neven MD DVM PhD

DEPARTMENT: Department of Surgery
SERVICE: Orthopaedic Surgery Service

STATUS: Ongoing
APPROVAL DATE: Apr 1993

FUNDING: Current FY: $ 910 Previous FYs: $ 0 Total: $ 910

STUDY OBJECTIVE
To study the osteoconductive potential of a polycaprolactone foam in the long bone (tibia) of rats.

TECHNICAL APPROACH
Foam plugs (2mm) in diameter will be inserted in prepared sites of rat tibia. Controls will not receive any plugs.

PRIOR AND CURRENT PROGRESS
A total of 70 rats have been used. All surgery is complete. There have been no serious or unexpected adverse reactions. X-rays were obtained, and all animals were euthanized. The PI is presently waiting for histology to be completed.

CONCLUSIONS
According to x-ray evidence, polycaprolactone foam does not appear to reduce bone proliferation in the rat model.

REPORT DATE: 04/25/94 WORK UNIT # 2453

DETAIL SUMMARY SHEET

TITLE: Evaluation of the Incidence of Progression and Pathologic Fracture of Long Bones Involved with Breast Cancer

KEYWORDS: breast cancer, metastastic, bone

PRINCIPAL INVESTIGATOR: DeVries, William CPT MC

DEPARTMENT: Department of Surgery STATUS: Ongoing
SERVICE: Orthopaedic Surgery Service APPROVAL DATE: Apr 1993

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To evaluate in a prospective manner, the incidence of progression and pathologic fractures of long bones involved with metastatic breast cancer.

TECHNICAL APPROACH
Patients enrolled in the study will have serial x-rays and MRI's performed on the affected extremity. The MRI's will be reviewed by a radiologist in a blinded fashion in an attempt to determine the lesion at risk for progression and/or pathologic fracture.

PRIOR AND CURRENT PROGRESS
No patients have been enrolled to date. The PI has been on TDY for the past 8 months.

CONCLUSIONS
None yet.

REPORT DATE: 05/12/94 WORK UNIT # 2454

DETAIL SUMMARY SHEET

TITLE: Pilot Study on the Use of CO2, Argon, and 808nm Diode Lasers for Laser Welding the Achilles Tendon in the Rat Model: A Comparison

KEYWORDS: laser welding, tendon repair

PRINCIPAL INVESTIGATOR: Choma, Theodore CPT MC

DEPARTMENT: Department of Surgery STATUS: Completed
SERVICE: Orthopaedic Surgery Service APPROVAL DATE: May 1993

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine whether welding of tendons is possible with the application of thermal lasers. Also, to determine the effect of laser energy on tendons.

TECHNICAL APPROACH
Rats will be randomized to different groups. Their achilles tendons will be lacerated and repaired either through suture or one of two different types of thermal lasers. The rats will be randomized to examination through biomechanical testing, histologic evaluation, or electron microscopic examination.

PRIOR AND CURRENT PROGRESS
A total of 82 rats were randomized to different groups. None of the rats experienced adverse reactions. This study was completed in December 1993.

CONCLUSIONS
The study demonstrated that welding of a tendon is possible with the application of laser energy. It was impossible to produce a weld sufficient to withstand significant tensile loads in the immediate postoperative period, but after 2 weeks the strength of the laser-welded tendons was not significantly different than the strength of the suture-repaired tendons.

REPORT DATE: 06/02/94 WORK UNIT # 2455

DETAIL SUMMARY SHEET

TITLE: Effects of Extracorporeal Shockwaves on the Rabbit Physis

KEYWORDS: shockwaves, physis

PRINCIPAL INVESTIGATOR: Popovic, Neven, DVM MD PhD

DEPARTMENT: Department of Surgery STATUS: Ongoing
SERVICE: Orthopaedic Surgery Service APPROVAL DATE: Jun 1993

FUNDING: Current FY: $ 4,360 Previous FYs: $ 0 Total: $ 4,360

STUDY OBJECTIVE
To find the effects of extracorporeal shockwaves on the physis of rabbits. Effects on bone growth and cells of the growth plate will be evaluated.

TECHNICAL APPROACH
Randomly selected rabbit knees will be exposed to extracorporeal shockwaves. Tibia growth will be evaluated via radiographs for up to 12 weeks. Histology will be done after euthanization.

PRIOR AND CURRENT PROGRESS
There was no deviation in either the anesthesia or the protocol. All 19 rabbits experienced no complications. They were treated, x-rayed, and then euthanized. Histology and x-ray evaluation (reading of films) is pending. No fractures were noted, and no disability was noted in experimental limbs.

CONCLUSIONS
Experiment is ongoing. Data needs to be analyzed. No fractures were noted due to extracorporeal shockwaves.

REPORT DATE: 06/08/94 WORK UNIT # 2456

DETAIL SUMMARY SHEET

TITLE: The Effect of Chlorhexidine and Povidine Iodine on Bone Healing in the Rabbit Model: A Histologic and Biomechanical Investigation

KEYWORDS: bone healing, disinfectants

PRINCIPAL INVESTIGATOR: Kilkelly, Francis CPT MC
ASSOCIATES: Popovic, Neven MD DVM PhD

DEPARTMENT: Department of Surgery
SERVICE: Orthopaedic Surgery Service

STATUS: Completed
APPROVAL DATE: Jun 1993

FUNDING: Current FY: $ 9,161 Previous FYs: $ 0 Total: $ 9,161

STUDY OBJECTIVE
To evaluate the effect of two commonly used disinfectants; povodine-iodine and chlorhexidine, on bone healing.

TECHNICAL APPROACH
An osteotomy was made at the attachment of the rabbit's patellar tendon such that a wafer of bone was attached to the tendon only. This wafer of bone was then dipped into hibiclens, povodine-iodine, or saline and then reattached and held with orthopaedic screws. X-rays were taken weekly, and the animals were euthanized at 6 weeks. The specimens were then randomized to biomechanical testing or histologic exam.

PRIOR AND CURRENT PROGRESS
All 41 animals have been euthanized. Biomechanical testing was performed in May of this year. Histologic evaluation and data analysis are being completed at this time. There were no adverse reactions.

CONCLUSIONS
To be determined.

REPORT DATE: 09/08/94 WORK UNIT # 2457

DETAIL SUMMARY SHEET

TITLE: Orthopaedic Injuries in Operation Desert Shield/Storm: A 2-Year Follow-up

KEYWORDS: Desert Storm casualties, war injuries, combat injuries

PRINCIPAL INVESTIGATOR: McHale, Kathleen MAJ MC

DEPARTMENT: Department of Surgery
SERVICE: Orthopaedic Surgery Service

STATUS: Completed
APPROVAL DATE: Jul 1993

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To study, review, and analyze the injuries sustained from combat in Desert Shield/Desert Storm that were evacuated to WRAMC, and to provide historical perspective and an update for war injuries from this conflict.

TECHNICAL APPROACH

Chart review, specific ongoing data collection during treatment, and physical examination will be used to review injuries, and catalog and analyze data.

PRIOR AND CURRENT PROGRESS

This project has been completed and exhibited at the Society of Military Orthopaedic Surgeons' Meeting and at the American Academy of Orthopaedic Surgeons' Meeting. It has been accepted for publication by Military Medicine. The charts of 181 orthopaedic patients were reviewed. An injury analysis revealed that 69 patients sustained a total of 143 fractures, with the remaining patients sustaining soft tissue injuries from traumas, overuse, or pre-existing conditions. Seventy percent of the fractures were open, of which 23% were treated with external fixators; 41% eventually underwent an operative stabilization process.

CONCLUSIONS

The sample principles of treatment that apply to all combat wounds also apply to Desert Shield/Storm wounds. Injuries sustained from blasts produce open fractures which do not fit the Gustil classification well. Early multidisciplinary involvement in the care of these casualties proved to be greatly beneficial.

REPORT DATE: 07/14/94 WORK UNIT # 2458

DETAIL SUMMARY SHEET

TITLE: Evaluation of Rabbit Ulna as a Model for Testing of Bone Substitute Materials

KEYWORDS: rabbit, ulna, bone substitute

PRINCIPAL INVESTIGATOR: Popovic, Neven DVM MD PhD

DEPARTMENT: Department of Surgery STATUS: Ongoing
SERVICE: Orthopaedic Surgery Service APPROVAL DATE: Jul 1993

FUNDING: Current FY: $ 2,330 Previous FYs: $ 0 Total: $ 2,330

STUDY OBJECTIVE
To evaluate the applicability of rabbit ulna as a potential model for testing of various bone substitute materials.

TECHNICAL APPROACH
Ulnar ostectomy will be performed on rabbits. X-rays will be obtained on a routine basis. At completion of the study, the rabbits will be euthanized and prepared for histologic evaluation.

PRIOR AND CURRENT PROGRESS
All surgery was completed, and x-rays were obtained. All 22 rabbits tolerated the surgery well and progressed to full healing. They were all euthanized, and their ulna were prepared for histologic examination.

CONCLUSIONS
All ulnar ostectomy defects healed. Pathology evaluation is pending.

REPORT DATE: 08/04/94 WORK UNIT # 2459

DETAIL SUMMARY SHEET

TITLE: Measurement of Spondylolisthesis Parameters Evaluation of Intraobserver, Interobserver and Technique Reliabilty and Variability

KEYWORDS: spondylolisthesis

PRINCIPAL INVESTIGATOR: Polly, David MAJ MC

DEPARTMENT: Department of Surgery STATUS: Ongoing
SERVICE: Orthopaedic Surgery Service APPROVAL DATE: Aug 1993

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To evaluate various intra- and inter-observer measures of spondylolisthesis.

TECHNICAL APPROACH
Lateral radiographs of subjects with spondylolisthesis will be selected and labeled. Each participant in the study will perform nine of the measurements utilized to evaluate spondylolisthesis. The measurements will be made twice with at least a 2-week interval in between.

PRIOR AND CURRENT PROGRESS
Films of 60 patients were labeled. One physician has completed all measurements. Work is ongoing.

CONCLUSIONS
None yet.

REPORT DATE: 08/15/94 WORK UNIT # 2460

DETAIL SUMMARY SHEET

TITLE: Progression of Idiopathic Scoliosis After Menarche

KEYWORDS: idiopathic scoliosis, post-menarche

PRINCIPAL INVESTIGATOR: Polly, David MAJ MC

DEPARTMENT: Department of Surgery STATUS: Ongoing
SERVICE: Orthopaedic Surgery Service APPROVAL DATE: Aug 1993

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To review the WRAMC Scoliosis Clinic's experience with the progression of scoliosis after menarche.

TECHNICAL APPROACH
All charts in the Scoliosis Clinic on female patients with idiopathic scoliosis will be eligible for inclusion. Any patient with documented progression after menarche will have their radiographs reviewed. The radiographs will then be measured in the standard fashion. Only cases having progression >/= 25 degrees will be included.

PRIOR AND CURRENT PROGRESS
Approximately 1,486 files have been reviewed; 80% were from subjects with idiopathic scoliosis (1,189), and 60 of these appeared to meet inclusion criteria. The radiographs were reviewed by an independent examiner who remeasured all of the films. A total of 31 patients demonstrated post menarchal progression of at least 5 degrees. The average follow-up was 25.4 months (5-71 months). The average curve magnitude was 20 degrees (8-25 degrees). The average Risser sign was one (0-3).

CONCLUSIONS
This review indicated that scoliosis may progress after menarche, though it's not common.

REPORT DATE: 08/03/94 WORK UNIT # 2461

DETAIL SUMMARY SHEET

TITLE: Effects of Extracorporeal Shockwaves on the Rabbit Ulna Cadaver

KEYWORDS: extracorporeal, shockwaves, rabbit ulna

PRINCIPAL INVESTIGATOR: Popovic, Neven MD DVM PhD

DEPARTMENT: Department of Surgery STATUS: Ongoing
SERVICE: Orthopaedic Surgery Service APPROVAL DATE: Aug 1993

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To study the effects of increased dose (power levels) on bones (ulna) of rabbit cadavers.

TECHNICAL APPROACH
Front leg cadavers of rabbits used previously for other experiments will be subjected to measured power levels (0.47 Joules/cm^2 to 1.2+/cm^2). Possible effects (fractures) were observed with x-rays and anatomic dissection.

PRIOR AND CURRENT PROGRESS
A total of 108 front quarter cadavers were used, and various power levels were evaluated. No problems were noted. The laboratory phase of the project is done. The data is currently being analyzed.

CONCLUSIONS
There is a dose/response of rabbit ulna to various power levels of extracorporeal shockwaves.

REPORT DATE: 09/01/94 WORK UNIT # 2462

DETAIL SUMMARY SHEET

TITLE: A Pilot Study: The Effect of Extracorporeal Shockwaves on the Rate of Bone Healing in a Rabbit Radius Diaphysis: Effects on Healing of Autografts, Comminuted Fractures, and Diaphysial Critical Size Bone Defects

KEYWORDS: shockwaves, extracorporeal, bone

PRINCIPAL INVESTIGATOR: Popovic, Neven MD DVM PhD

DEPARTMENT: Department of Surgery
SERVICE: Orthopaedic Surgery Service

STATUS: Ongoing
APPROVAL DATE: Sep 1993

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To study the effects of extracorporeal shockwaves (ESW) on the rate of bone healing of rabbit radii. To show if the ESW will increase or decrease healing of fractures, autografts, or critical size bone defects.

TECHNICAL APPROACH

Extracorporeal shockwaves will be applied to rabbit radii that sustained fractures or application of autografts or critical size defects. Radiographs will be obtained at periodic time intervals to study bone healing.

PRIOR AND CURRENT PROGRESS

Funding for this protocol was approved in the Spring of 1994. However, no animals have been entered yet due to the PI's lack of time. It is anticipated that this study will begin in October 1994.

CONCLUSIONS

None yet.

REPORT DATE: 08/18/94 WORK UNIT # 2522

DETAIL SUMMARY SHEET

TITLE: Vocal Cord Function and Voice Quality Evaluation of Active Duty U.S. Army Drill Instructors

KEYWORDS: videostroboscopy, hoarseness

PRINCIPAL INVESTIGATOR: McKenzie, Pearline CPT MC
ASSOCIATES: Mann, Eric MAJ MC; Gurevich-Uvera, Joyce MA

DEPARTMENT: Department of Surgery
SERVICE: Otolaryngology-Head & Neck Service

STATUS: Ongoing
APPROVAL DATE: Aug 1992

FUNDING: Current FY: $50,050 Previous FYs: $ 0 Total: $ 50,050

STUDY OBJECTIVE
To prospectively document the laryngeal pathology and describe the acoustic effects of voice abuse in active duty U.S. Army drill instructors.

TECHNICAL APPROACH
State-of-the-art videostroboscopic techniques and a computerized speech lab will be used to accurately assess the vocal pathology of drill instructors during the first week of intense field training. The information gained through this study could form a basis for future treatment modalities.

PRIOR AND CURRENT PROGRESS
Money for this project has been allocated, and the sole source has been approved. Purchase of the necessary equipment has been completed. The researchers are now waiting for the arrival of the equipment. They will begin to document pathology and record data once the equipment arrives and the travel money is allocated.

CONCLUSIONS
None.

REPORT DATE: 01/25/94 WORK UNIT # 2526

DETAIL SUMMARY SHEET

TITLE: Radiation Effects on Salviary Epithelial Growth Factor (EGF): A Pilot Study

KEYWORDS: radiation therapy, cancer

PRINCIPAL INVESTIGATOR: Cukier, Andrew CPT MC

DEPARTMENT: Department of Surgery STATUS: Ongoing
SERVICE: Otolaryngology-Head & Neck Service APPROVAL DATE: Jan 1993

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To study the quantitative effect of radiation therapy on salivary epithelial growth factor in patients treated for cancer of the head and neck region.

TECHNICAL APPROACH
A 5 minute whole saliva collection will be done once per week.

PRIOR AND CURRENT PROGRESS
Seven subjects were enrolled in the study to date. There have been no adverse reactions, and no withdrawals. There has been no benefit to patients as expected.

CONCLUSIONS
This is an ongoing study collecting data. Results will potentially benefit future patients by providing improved radiation mucositis therapy.

REPORT DATE: 10/12/93 WORK UNIT # 2910

DETAIL SUMMARY SHEET

TITLE: The Use of Bone Repair Materials for Maxillary Alveolar Clefts

KEYWORDS: bone, repair, materials

PRINCIPAL INVESTIGATOR: Mayer, Michael LTC MC
ASSOCIATES: Hollinger, Jeffrey COL DC

DEPARTMENT: Department of Surgery
SERVICE: Plastic Surgery Service

STATUS: Completed
APPROVAL DATE: Oct 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To compare the standard of care for bone regeneration, the autogenous bone graft, to experimental materials consisting of a biodegradable carrier and a bone inductive protein (BIP).

TECHNICAL APPROACH
The model for this comparison will be maxillary alveolar clefts in dogs. Initially, the alveolar clefts will be created along with an oronasal fistula lined with epithelium. Six dogs each will be randomized into four treatment groups: untreated control, autologous bone graft, biodegradable carrier, and biodegradable carrier with BIP. Four months after the clefts are treated, the recipient beds, including the experimental materials, will be recovered and evaluated by quantitative microscopy and histology.

PRIOR AND CURRENT PROGRESS
A total of 26 dogs have been used for this study, none this past year. There were no serious or unexpected adverse reactions. The goal for the model was to produce a cleft that was a critical-size defect (CSD) in the maxilla. Unless a CSD is treated with a bone regenerating material (i.e., autogenous cortico-cancellous graft), wound repair progressses to a fibrotic scar rather than to new bone formation. The overall goal for the study was to regenerate bone in the maxilla using 200 ug rhBMP-2 combined with bioerodible particles (BEP) and autogenous blood. In addition, two other treatments were evaluated: 1) BEP and autogenous blood, and 2) autografts from the posterior iliac crest. At 2 and 4 months post-operatively, dogs were euthanized, and the recipient beds with contiguous bone were recovered and processed for radiographs and histology.

CONCLUSIONS
The autograft treated defects had more new bone than the other two treatments. A disappointing response to the rhBMP-2 may have been due to an inappropriately delivered dose, and inability of the delivery system to maintain the rhBMP-2 at the recipient bed, due to the bleeding and soft tissue displacement.

REPORT DATE: 10/12/93 WORK UNIT # 2911

DETAIL SUMMARY SHEET

TITLE: Orbital Floor Reconstruction with Bone Repair Materials

KEYWORDS: bone, repair, materials

PRINCIPAL INVESTIGATOR: Mayer, Michael LTC MC
ASSOCIATES: Hollinger, Jeffrey COL DC

DEPARTMENT: Department of Surgery
SERVICE: Plastic Surgery Service

STATUS: Completed
APPROVAL DATE: Oct 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To compare the use of resorbable PLA:PGA plus a bone inductive protein (BIP) with PLA:PGA alone, and with controls of post-operative, non-reconstructed animals, in the surgical reconstruction of the orbital wall and orbital floor defects.

TECHNICAL APPROACH
The model will be orbital wall/floor defects in the non-human primate species (NHPS) (Macaca mulatta). Initially, the orbital floor/wall defects will be created and repaired with a biodegradable carrier or biodegradable carrier plus BIP. The three treatment groups will consist of the biodegradable carrier, the carrier plus BIP, or the untreated defect. Eighteen NHPS will be utilized. Three months post-treatment, the specimens and experimental materials will be retrieved and evaluated by quantitative microscopy and histology.

PRIOR AND CURRENT PROGRESS
Due to the lack of highly purified BIP, facilities, non-human primates, and funding, the project could not be completed this fiscal year. No animals have been used for this study.

CONCLUSIONS
None.

REPORT DATE: 10/12/93 WORK UNIT # 2912

DETAIL SUMMARY SHEET

TITLE: Rigid Skeletal Fixation of the Immature Craniofacial Skeleton

KEYWORDS: rigid, skeletal, fixation

PRINCIPAL INVESTIGATOR: Mayer, Michael LTC MC
ASSOCIATES: Hollinger, Jeffrey COL DC; Bley, Jack MAJ VC

DEPARTMENT: Department of Surgery
SERVICE: Plastic Surgery Service

STATUS: Ongoing
APPROVAL DATE: Oct 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To evaluate the effects of rigid skeletal fixation on skull growth and bone repair in both osteotomized and non-osteotomized, immature, non-human, primate species calvaria.

TECHNICAL APPROACH
Through a coronal approach, a frontal bone flap and supraorbital bar will be made and either fixed in place or advanced with either semi-rigid (wire fixation) or rigid fixation (plates and screws). The fifth treatment group will be the controls. At 6 months, three non-human primate species from each group will be euthanized, and the skulls evaluated using topographical landmarks and a three SPACE digitizer. The cranial module will be calculated for each skull. Individual cranial metric measurements will be divided by the individual cranial modules. The remainder of the primates will be euthanized 1 year post-treatment, and the skulls evaluated. Use of eight new primates was authorized via a FY93 addendum.

PRIOR AND CURRENT PROGRESS
A total of 27 non-human primates have undergone surgery (25 during the past year); 10 have been maintained as controls. One non-human primate expired secondary to anesthesia complications. The initial two non-human primates (who underwent surgery during FY92) were maintained 1 year post-operatively, then euthanized. The skulls are waiting for 3-D analysis. Eight non-human primates have been added via an addendum approved, August 6, 1993, to investigate the use of biodegradable rigid fixation and are in quarantine waiting for surgery.

CONCLUSIONS
No preliminary conclusions can be drawn at this time.

REPORT DATE: 10/05/93 WORK UNIT # 2713

DETAIL SUMMARY SHEET

TITLE: Secondary Prospective Study for the Evaluation of the Safety and Effectiveness of Cryopreserved Human Allograft Heart Valves (LifeNet)

KEYWORDS: cryopreserved human valve, valved allograft conduits

PRINCIPAL INVESTIGATOR: Zurcher, Robert MAJ MC

DEPARTMENT: Department of Surgery STATUS: Ongoing
SERVICE: Thoracic Surgery Service APPROVAL DATE: Oct 1991

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine via a prospective study the efficacy and side effects of the use of cryopreserved human valves for use in patients.

TECHNICAL APPROACH
Diseased valves will be replaced with human cryopreserved allografts using standard cardiac surgical techniques. Addtionally, valved allograft conduits will be used in children in whom there may be a congenital absence or deficiency of a native valve.

PRIOR AND CURRENT PROGRESS
No subjects have been entered into this protocol to date due to lack of patient referral. However, one patient is on the schedule for the end of November.

CONCLUSIONS
None available.

REPORT DATE: 10/05/93 WORK UNIT # 2714

DETAIL SUMMARY SHEET

TITLE: Cryovalve Heart Valve Allografts, Replacement Heart Valve Allograft (CryoLife)

KEYWORDS: cryopreserved human valve, valved allograft conduits

PRINCIPAL INVESTIGATOR: Zurcher, Robert MAJ MC

DEPARTMENT: Department of Surgery STATUS: Ongoing
SERVICE: Thoracic Surgery Service APPROVAL DATE: Oct 1991

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
A prospective study to determine the efficacy and side effects of the use of cryopreserved human valves for use in patients.

TECHNICAL APPROACH
Diseased valves will be replaced with human cryopreserved allografts using standard cardiac surgical techniques. Additionally, valved allograft conduits will be used in children in whom there may be a congenital absence or deficiency of a native valve.

PRIOR AND CURRENT PROGRESS
No subjects have been entered into this protocol to date due to lack of patient referral. However, one patient is on the schedule for the end of November.

CONCLUSIONS
None available.

REPORT DATE: 02/08/94 WORK UNIT # 2837

DETAIL SUMMARY SHEET

TITLE: NPCP 2200 A Comparison of Leuprolide with Leuprolide and Flutamide in Previously Untreated Patients with Clinical Stage D2 Cancer of the Prostate

KEYWORDS: leuprolide, flutamide, prostate cancer

PRINCIPAL INVESTIGATOR: McLeod, David COL MC

DEPARTMENT: Department of Surgery STATUS: Ongoing
SERVICE: Urology Service APPROVAL DATE: Feb 1985

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To try to determine if the antiandrogen flutamide will increase the efficacy of leuprolide.

TECHNICAL APPROACH
Patients are randomized to receive leuprolide and flutamide or leuprolide and placebo. At the time of progression, the blind is broken, and patients not receiving flutamide will be given the drug.

PRIOR AND CURRENT PROGRESS
This is a multiple group cooperative study. Accrual ended in April 1986; patients are being seen for follow-up only. Altogether, 600 patients have been entered. WRAMC randomized a total of 24 patients; 1 is being followed on drug, 2 are being followed off drug, 1 is lost to follow-up, and 20 have died due to prostate cancer. No serious or unexpected adverse reactions have been reported.

CONCLUSIONS
The researchers concluded that in patients with advanced prostate cancer, treatment with leuprolide and flutamide is superior to treatment with leuprolide alone.

REPORT DATE: 10/14/93 WORK UNIT # 2843

DETAIL SUMMARY SHEET

TITLE: ECOG EST 1887 A Phase III Trial of Cystectomy Alone Vs. Neoadjuvant M-VAC + Cystectomy in Patients with Locally Advanced Bladder Cancer

KEYWORDS: cisplatin, cystectomy, bladder cancer

PRINCIPAL INVESTIGATOR: McLeod, David COL MC

DEPARTMENT: Department of Surgery STATUS: Ongoing
SERVICE: Urology Service APPROVAL DATE: Oct 1988

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To compare the survival in patients with locally advanced bladder cancer who are treated with cystectomy alone to those who are treated with M-VAC (methotrexate/vinblastine/Adriamycin/cisplatin) followed by cystectomy in a randomized Phase III neoadjuvant trial; and to quantify the "tumor downstaging" effect of neoadjuvant M-VAC.

TECHNICAL APPROACH
This is a randomized, multicenter, Phase III trial for patients with T2-T4a, NO, MO transitional cell carcinoma of the bladder with or without squamous differentiation. Patients are randomized to radical cystectomy or M-VAC plus radical cystectomy.

PRIOR AND CURRENT PROGRESS
A total of 156 patients have been enrolled; 76 of them during the past year. Two WRAMC patients have been enrolled, none of them during the past year. One WRAMC patient, randomized to M-VAC plus radical cystectomy in 1990, continues to be followed and is doing well. The second WRAMC patient was randomized to cystectomy alone in 1991, and died of metastatic bladder cancer in May 1992. There have been no serious or unexpected adverse reactions.

CONCLUSIONS
None.

REPORT DATE: 09/15/94 WORK UNIT # 2859

DETAIL SUMMARY SHEET

TITLE: SWOG 8894 A Comparison of Bilateral Orchiectomy with or without Flutamide for the Treatment of Patients with Histologically Confirmed Stage D2 Prostate Cancer

KEYWORDS: cancer, prostate, orchiectomy

PRINCIPAL INVESTIGATOR: McLeod, David COL MC

DEPARTMENT: Department of Surgery STATUS: Completed
SERVICE: Urology Service APPROVAL DATE: Sep 1989

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To test the hypothesis that total androgen blockade (orchiectomy plus flutamide) may be better than orchiectomy alone.

TECHNICAL APPROACH
This is a prospective, randomized, double-blind, placebo-controlled study.

PRIOR AND CURRENT PROGRESS
A total of 35 patients have been accrued to this protocol. A total of 21 patients have died due to prostate cancer. The 14 remaining patients on this protocol are being followed in the Urology Clinic every 3 months or sooner if necessary. Of these patients, seven are followed on study drug (flutamide vs placebo), six are being followed off drug, and one is being followed on open labeled flutamide. Three patients were enrolled in 1994. This protocol has met its accrual goals and is completed as of 15 Sep 94. Follow-up will continue as planned. No new patients have been enrolled since 27 Jul 94.

CONCLUSIONS
None at this time.

REPORT DATE: 07/26/94 WORK UNIT # 2864

DETAIL SUMMARY SHEET

TITLE: ECOG EST 9887 A Phase III Trial of Treatment of Pathologic Stage C Carcinoma of the Prostate with Adjuvant Radiotherapy

KEYWORDS: prostate cancer, pathologic Stage C, adjuvant radiotherapy

PRINCIPAL INVESTIGATOR: Moul, Judd MAJ MC
ASSOCIATES: McLeod, David COL MC

DEPARTMENT: Department of Surgery STATUS: Ongoing
SERVICE: Urology Service APPROVAL DATE: Jul 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 500 Total: $ 500

STUDY OBJECTIVE
To compare in a randomized study, the disease-free survival rates in completely resected patients with pathologic Stage C (T3NOMO) carcinoma of the prostate assigned to be treated with adjuvant external beam radiotherapy to that in patients assigned to receive no adjuvant therapy. To assess the qualitative and quantitative toxicities of patients with pathologic Stage C carcinoma of the prostate when treated with external beam radiotherapy.

TECHNICAL APPROACH
After prostatectomy with pelvic lymphadenectomy and no evidence of regional lymph node or metastatic disease, the patient is randomized to receive adjuvant radiation therapy or no adjuvant therapy. All patients are off treatment 1 year after randomization or at disease progression.

PRIOR AND CURRENT PROGRESS
Eventhough all men who undergo radical prostatectomy and are pathologic Stage C are offered this protocol, no patients were accepted for randomization during the past year. Altogether, four subjects have been enrolled. There have been no serious or unexpected adverse reactions. ECOG and SWOG are re-evaluating this protocol because of poor national accrual; it remains open pending a decision from ECOG.

CONCLUSIONS
Although the study remains open, it has accrued poorly. It may be closed by ECOG/SWOG in the near future.

REPORT DATE: 07/25/94 WORK UNIT # 2865

DETAIL SUMMARY SHEET

TITLE: A Randomized Trial of Transurethral Resection of the Prostate Vs. Open Prostatectomy or Nonoperative Treatment

KEYWORDS: prostate, TURP, BTOPS

PRINCIPAL INVESTIGATOR: Sihelnik, Stephen LTC MC

DEPARTMENT: Department of Surgery STATUS: Ongoing
SERVICE: Urology Service APPROVAL DATE: Jul 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To determine whether long-term mortality rates vary in men treated for symptomatic benign prostatic hypertrophy (BPH) by non-operative strategies vs operative means; to establish efficacy of non-operative treatment strategies vs TURP for men with symptomatic BPH; and to compare short- and long-term outcomes of TURP vs open prostatectomy for men with symptomatic BPH and large prostate glands.

TECHNICAL APPROACH

This is a multicenter clinical trial randomizing patients on a stratified basis (prostate size, anti-hypertensive, prostate anatomy) to receive either open prostatectomy, transurethral prostatectomy, or non-operative strategies (balloon dilation, alpha blockers, or watchful waiting control arm). Patients are evaluated with an initial symptom score and objective flow parameters and are followed periodically for procedure efficacy and overall mortality. Amendments necessitated by funding constraints have now limited the study to two arms; TURP vs. balloon dilation.

PRIOR AND CURRENT PROGRESS

A total of 73 patients were enrolled into this protocol; 53 wwere randomized (5 drug, 9 balloon, 11 watchful waiting, 2 open, and 26 TURP). Twenty subjects were non-randomized (2 drug, 0 balloon, 5 watchful waiting, 2 open, and 11 TURP). Recruitment and randomization for this protocol were discontinued in January 1993. Final data collection was completed for all non-randomized patients and those randomized to the alpha blocker terazosin. Follow-up continues bi-annually for the remaining patients randomized to TURP, watchful waiting, or balloon dilation until a 3 year visit is completed. Follow-up continues for 24 patients (15 TURP, 5 watchful waiting, and 4 balloon dilation). There were no serious or unexpected adverse events during this study. Benefits to study subjects are pending the completion of the research protocol.

CONCLUSIONS

There have been no conclusions to date.

REPORT DATE: 09/20/94 WORK UNIT # 2868

DETAIL SUMMARY SHEET

TITLE: Randomized Prospective Study Comparing Radical Prostatectomy Alone Versus Radical Prostatectomy Preceded by Androgen Blockade in Clinical B2 (T2bNxMo) Prostate Cancer

KEYWORDS: androgen blockage, prostate cancer, Stage B2

PRINCIPAL INVESTIGATOR: McLeod, David COL MC
ASSOCIATES: Moul, Judd MAJ MC

DEPARTMENT: Department of Surgery STATUS: Ongoing
SERVICE: Urology Service APPROVAL DATE: Sep 1991

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To evaluate the safety and efficacy of a combination of leuprolide and flutamide prior to radical prostatectomy in clinical Stage B2 prostate cancer as compared to no therapy before radical prostatectomy.

TECHNICAL APPROACH
This is a multicenter, randomized study which will compare the safety and efficacy of leuprolide plus flutamide prior to radical prostatectomy to radical prostatectomy alone.

PRIOR AND CURRENT PROGRESS
A total of 300 patients have been enrolled studywide (24 during the past year); WRAMC has enrolled 22 patients (one this past year). Ten patients have been randomized to receive androgen blockage before surgery. Twelve patients have been randomized to prostatectomy along. All patients have had surgery and have done well postoperatively. The enrollment phase for this study was completed 23 Dec 93. All previously enrolled patients have completed the active drug administration and the surgical portion of the study. The patients will be followed at 6-month intervals until there is evidence of disease progression. There have been no adverse reactions.

CONCLUSIONS
None as yet.

REPORT DATE: 10/13/93 WORK UNIT # 2869

DETAIL SUMMARY SHEET

TITLE: Response Patterns to DDAVP (Desmopressin Acetate) in the Treatment of Nocturnal Enuresis as a Function of Change in Urine Osmolality

KEYWORDS: nocturnal enuresis, urine osmolality

PRINCIPAL INVESTIGATOR: Sihelnik, Stephen LTC MC

DEPARTMENT: Department of Surgery STATUS: Completed
SERVICE: Urology Service APPROVAL DATE: Oct 1991

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To examine the long-term safety and efficacy of DDAVP and response patterns to changes in urine osmolality in patients with primary nocturnal enuresis.

TECHNICAL APPROACH
Patients will be randomized to receive DDAVP placebo after a 2 week baseline period in a double-blind fashion for 4 weeks. They will then receive open label drug for 4 months. During the lead-in and double-blind period, urine osmolalities will be assessed.

PRIOR AND CURRENT PROGRESS
A total of 19 patients have been randomized according to the protocol, 7 during the past year. Seventeen evaluable patients completed the study; one patient was dropped due to ineffectiveness of therapy, and one patient was dropped due to shortness of breath. The protocol was closed to enrollment in March 1993. There were no incidents of serious or unexpected adverse reactions.

CONCLUSIONS
No conclusion to date.

REPORT DATE: 01/13/94 WORK UNIT # 2871

DETAIL SUMMARY SHEET

TITLE: A Randomized, Comparative Trial of Casodex Versus Flutamide Used in Combination with Medical Castration in Patients with Untreated Metastatic Prostate Cancer

KEYWORDS: casodex, medical castration, prostate cancer

PRINCIPAL INVESTIGATOR: McLeod, David COL MC

DEPARTMENT: Department of Surgery STATUS: Ongoing
SERVICE: Urology Service APPROVAL DATE: Jan 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To compare the efficacy and safety of casodex versus flutamide used in combination with LHRH analogs, in patients with untreated metastatic prostate cancer according to: time to treatment failure, quality of life, tolerability, subjective response, and survival.

TECHNICAL APPROACH
This is a randomized, comparative, multicenter trial. Patients will be randomized to zoladex implant or leuprolide depot in a 2:1 ratio, and between one of two antiandrogens (casodex or flutamide) in a 1:1 ratio.

PRIOR AND CURRENT PROGRESS
A total of 814 patients have been entered into this study (600 during the past year). WRAMC has entered 10 patients (3 during the past year): 5 are receiving zoladex plus antiandrogen (casodex or flutamide); four are receiving leuprolide plus antiandrogen; and one died due to prostate cancer. All other patients are doing well on their assigned therapies. No WRAMC patient has experienced a serious or unexpected adverse reaction. All study-wide adverse reactions have been reported to the HUC/IRB. Patient accrual ended 24 Sep 93. This study remains open for patient follow-up.

CONCLUSIONS
None at this time.

REPORT DATE: 02/18/94 WORK UNIT # 2872

DETAIL SUMMARY SHEET

TITLE: EOG EST C-0490: Phase II Study of Difluromethylornithine (DFMO) in Patients with Superficial and Superficially-Invasive Bladder Cancer

KEYWORDS: DEMO, bladder, cancer

PRINCIPAL INVESTIGATOR: Moul, Judd MAJ MC
ASSOCIATES: Abt, Mary Beth RN; McLeod, David COL MC

DEPARTMENT: Department of Surgery
SERVICE: Urology Service

STATUS: Completed
APPROVAL DATE: Feb 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine the safety and efficacy of oral difluromethylornithine (DEMO) in superficial and superficially invasive cell carcinoma of the urinary bladder.

TECHNICAL APPROACH
Prospective randomized trial of four dose schedules of oral DEMO in patients with pathologically proven Ta No Mo or T1 No Mo transitional cell carcinoma of the bladder. Patients will be monitored every 3 months with labs, cystoscopy, bladder cystologies, and audiograms.

PRIOR AND CURRENT PROGRESS
A total of 54 patients, including 4 WRAMC patients have been enrolled. During the past year, 37 patients have been enrolled; none of them have been from WRAMC. This protocol was closed to patient accrual 17 Feb 94. All four WRAMC patients continue follow-up in the Urology Clinic; one of them discontinued the drug 2 months early due to a right tonsil lesion and tinnitis. This adverse reaction report was submitted to the IRB/HUC in May 1993.

CONCLUSIONS
None at this time.

REPORT DATE: 10/14/93 WORK UNIT # 2873

DETAIL SUMMARY SHEET

TITLE: Evaluation of the P53 Tumor Suppressor Gene in Human Testicular Cancer

KEYWORDS: testicular cancer, P53, immunohistochemistry

PRINCIPAL INVESTIGATOR: Lewis, Donald MAJ MC

DEPARTMENT: Department of Surgery STATUS: Ongoing
SERVICE: Urology Service APPROVAL DATE: Oct 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To evaluate the P53 tumor suppressor gene protein immunostaining in the primary tumor of adult testicular germ cell cancer, and to assess if P53 expression would serve as a clinically useful tumor marker.

TECHNICAL APPROACH
Histopathologic review of all H and E slides from orchiectomy cases will be performed by a single pathologist. The slide most representative of the tumor will be selected, and the corresponding paraffin block obtained. Immunostaining with the P53 antibody will be done. Review by the same pathologist for aberrant staining will be noted, and clinical correlation applied.

PRIOR AND CURRENT PROGRESS
During the first year of this study, 152 cases have been reviewed, and immunostaining has been completed. Multivariate logistic regression analysis for prognostic factors used to help predict occult nodal disease in the clinical Stage I NSGCT tumor patient (with P53 immunostaining also applied) has been completed. From the results, it appears a better prediction can be made of which patients with clinical Stage I NSGCT cancer will have nodal disease at the time of their lymphadenectomy.

CONCLUSIONS
Aberrant P53 expression is present in testis cancer. The difference in P53 staining for the embryonal carcinoma component is statistically significant between the pathologic stage I and II groups. The relative risk for occult nodal disease in the clinical stage I NSGCT group increases with increased P53 staining for the embryonal carcinoma component.

REPORT DATE: 12/08/93 WORK UNIT # 2874

DETAIL SUMMARY SHEET

TITLE: Multicenter Study of Intravenously Administered 111 In-CYT-356 in the Evaluation of Patients with Primary Prostate Cancer Prior to Staging Pelvic Lymph Node Dissection (Protocol 356In15)

KEYWORDS: 111 In-CYT-356, prostate, cancer

PRINCIPAL INVESTIGATOR: McLeod, David COL MC

DEPARTMENT: Department of Surgery STATUS: Ongoing
SERVICE: Urology Service APPROVAL DATE: Dec 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To evaluate the efficacy of intravenous infusion(s) of 111-CYT-356 in identifying occult prostate cancer in patients who have undergone primary prostatectomy for the treatment of prostate cancer; to evaluate the safety of intravenous infusion(s) of 111 In-CYT-356 in patients with prostate cancer; and to determine the incidence and timing of HAMA development and immune complex formation following intravenous infusion of 111 In-CYT-356.

TECHNICAL APPROACH
This is an open-labelled, non-randomized, uncontrolled, multicenter study.

PRIOR AND CURRENT PROGRESS
Two WRAMC patients have been enrolled in this protocol. Both of them tolerated administration of the antibody well. No serious or unexpected adverse reactions or toxicities were reported. Centerwide enrollment is unknown.

CONCLUSIONS
None at this time.

REPORT DATE: 12/08/93 WORK UNIT # 2875

DETAIL SUMMARY SHEET

TITLE: Administration of Intravenous Doses of 111 In-CYT-356 in the Detection of Occult Prostate Carcinoma (Protocol 356In14)

KEYWORDS: 111 In-CYT-356, prostate, cancer

PRINCIPAL INVESTIGATOR: McLeod, David COL MC
ASSOCIATES: Moul, Judd MAJ MC

DEPARTMENT: Department of Surgery STATUS: Completed
SERVICE: Urology Service APPROVAL DATE: Dec 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine the sensitivity and specificity of 111 In-CYT-356 imaging for the detection of non-contiguous extraprostatic disease in prostate cancer patients scheduled for staging pelvic lymph node dissection. To evaluate the ability of the 111 In-CYT-356 imaging to effect the management of patients with primary prostate cancer when used in conjunction with standard diagnostic staging procedures.

TECHNICAL APPROACH
This is an open-labelled, non-randomized, uncontrolled, multicenter study.

PRIOR AND CURRENT PROGRESS
Two WRAMC patients were enrolled during the first year of this study. Both tolerated the administration of the antibody well, with no adverse reactions or toxicities reported. Studywide enrollment is unknown. This study is being closed at this time and is being replaced by a new protocol (to be reviewed in January 1994).

CONCLUSIONS
None at this time.

REPORT DATE: 12/08/93 WORK UNIT # 2876

DETAIL SUMMARY SHEET

TITLE: Detection of the c-erbB-2 Oncogene Protein in Serum and Tissue of Patients with Prostate Cancer, Benign Prostate Conditions, and No Prostate Disease

KEYWORDS: c-erbB-2 oncogene, prostate, cancer

PRINCIPAL INVESTIGATOR: Moul, Judd MAJ MC

DEPARTMENT: Department of Surgery STATUS: Ongoing
SERVICE: Urology Service APPROVAL DATE: Dec 1992

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine if the c-erbB-2 oncoprotein is detectable in the serum and prostate tissue of patients with prostate cancer, in those with benign prostate hyperplasia, and in normal control subjects.

TECHNICAL APPROACH
A serum sample will be collected from consenting WRAMC subjects, and a laboratory assay will be performed for the oncogene protein determination.

PRIOR AND CURRENT PROGRESS
This study is ongoing; serum has been collected from 16 patients. No results are available at this time. There have been no serious or unexpected adverse reactions.

CONCLUSIONS
Not applicable at this time.

REPORT DATE: 02/15/94 WORK UNIT # 2877

DETAIL SUMMARY SHEET

TITLE: Detection of Cathepsin D in the Seminal Plasma and Tissues of Patients with Prostate Cancer, Benign Prostate Conditions, and No Prostate Disease

KEYWORDS: prostate, cancer, cathepsin D

PRINCIPAL INVESTIGATOR: Moul, Judd MAJ MC

DEPARTMENT: Department of Surgery STATUS: Ongoing
SERVICE: Urology Service APPROVAL DATE: Feb 1993

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To determine the expression of the cathepsin D protein in seminal plasma and protate tissue of prostate cancer patients, benign prostate disease patients, and normal control patients; and to determine if these levels correlate to cancer grade, stage, and outcome.

TECHNICAL APPROACH
Standard tissue immunohistochemistry utilizing cathepsin-D specific antibody and standard ELISA assay for cathepsin-D level in seminal plasma will be performed.

PRIOR AND CURRENT PROGRESS
No patients have been enrolled, but recruitment efforts continue. Accrual has been slow because patients have been unwilling or unable to provide ejaculation for study.

CONCLUSIONS
Study in progress.

REPORT DATE: 07/15/94 WORK UNIT # 2878

DETAIL SUMMARY SHEET

TITLE: Treatment of Begign Prostatic Hyperplasia: Pilot Study

KEYWORDS: prostate, medical therapy, BPH

PRINCIPAL INVESTIGATOR: Sihelnik, Stephen

DEPARTMENT: Department of Surgery STATUS: Ongoing
SERVICE: Urology Service APPROVAL DATE: Jul 1993

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To ascertain if medical therapy (finasteride and/or doxazosin) delays or prevents the symptomatic progression of benign prostate hyperplasia (BPH), and to assess differences over time between treatment groups. To investigate prognostic indicators and biologic parameters regarding response to therapy. To gain insight into biologic and physiologic natural history of prostate growth.

TECHNICAL APPROACH
Patients must have symptomatic BPH (an AUA symptom score greater than 8) without confounding lower urinary tract pathology. Patients will be randomized to one of four areas: alpha blocker vs. finasteride vs. alpha blocker + finasteride vs. placebo. Endpoints are symptom progression or urinary retention. Urodynamic and ultrasound parameters will be evaluated secondarily.

PRIOR AND CURRENT PROGRESS
This is a master protocol. Please see the individual protocol (W.U. #2879) for further information.

CONCLUSIONS
See individual protocol (W.U. #2879) for further information.

REPORT DATE: 07/19/94 WORK UNIT # 2879

DETAIL SUMMARY SHEET

TITLE: Early Medical Treatment of BPH

KEYWORDS: prostate, medical therapy, BPH

PRINCIPAL INVESTIGATOR: Sihelnik, Stephen LTC MC

DEPARTMENT: Department of Surgery
SERVICE: Urology Service

STATUS: Ongoing
APPROVAL DATE: Jul 1993

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To ascertain if medical therapy (finasteride and/or doxazosin) delays or prevents the symptomatic progression of benign prostate hyperplasia (BPH) and to assess differences over time between treatment groups. To investigate prognostic indicators and biologic parameters regarding response to therapy. To gain insight into biologic and physiologic natural history of prostate growth.

TECHNICAL APPROACH
This is a pilot study to assess the feasibility of a full-scale trial. Patients are recruited and followed for a minimum of 2 months and a maximum of 12 months. The study is a multi-centered, placebo-controlled, double-masked clinical trial in which patients who have been diagnosed with symptomatic BPH are randomly assigned to either of three drug treatment arms or a placebo control once all entrance criteria have been fulfilled. All patients are monitored closely and will undergo follow-up evaluations at 3, 6, 9, and 12 months for efficacy, adverse effects, and overall mortality.

PRIOR AND CURRENT PROGRESS
Recruitment of eligible patients began November 1993. To date, 14 patients have been enrolled at WRAMC; none have experienced serious or unexpected adverse reactions. Studywide patient enrollment and adverse reaction data are unknown at this time. Benefits to study subjects will be unknown until the protocol is completed.

CONCLUSIONS
No conclusions; data collection is ongoing.

REPORT DATE: 07/22/94 WORK UNIT # 2880

DETAIL SUMMARY SHEET

TITLE: Nerve Growth Factor and Basic Fibroblast Growth Factor in the Urine of Patients with Prostatism and Interstitial Cystitis

KEYWORDS: nerve growth factor, prostatism, interstial cystitis

PRINCIPAL INVESTIGATOR: Zorn, Burkhardt MAJ MC

DEPARTMENT: Department of Surgery
SERVICE: Urology Service

STATUS: Ongoing
APPROVAL DATE: Jul 1993

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To determine if neurotropine in urine correlates or predicts outcomes with irritative or obstructive bladder pathology.

TECHNICAL APPROACH

Will perform routine evaluation for patients with prostatism or intersitital cystitis and obtain urine for determination of level of Nerve Growth Factor (NGF). Will follow patients longitudinally with or without treatment.

PRIOR AND CURRENT PROGRESS

A total of 19 patients have been enrolled in the study. They are being accrued at a rate of appoximately two per month. Accrual will continue until a goal of 25-30 subjects is met. The ELISA for determination of urine NGF has produced indeterminate data. Optimization for the ELISA is currently being investigated. No adverse reactions have occurred.

CONCLUSIONS

Until the ELISA is optimized, the determination of urine levels is limited in correlation with clinical parameters.

REPORT DATE: 08/11/94 WORK UNIT # 2881

DETAIL SUMMARY SHEET

TITLE: Program for Treatment of Erectile Failure with MUSE (Medicated Urethral System for Erection)

KEYWORDS: erectile, MUSE, failure

PRINCIPAL INVESTIGATOR: Costabile, Raymond MAJ MC
ASSOCIATES: McLeod, David COL MC

DEPARTMENT: Department of Surgery STATUS: Ongoing
SERVICE: Urology Service APPROVAL DATE: Aug 1993

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To: 1) obtain pretreatment information on patients'/spouses' quality of life; 2) determine optimal dose for each patient according to open-label titration schedule; 3) judge effect of optimal dose on patients'/spouses' quality of life after 4 weeks, 3 months, and 6 months of treatment; 4) evaluate effect of medications on erectile process; 5) determine long term efficacy in a maintenance protocol; and 6) evaluate safety of various medications delivered by MUSE.

TECHNICAL APPROACH
This protocol is a four phase study that consists of: 1) Non-treatment phase lasting 4 weeks consisting of quality of life data collection; 2) Tritration phase during which the patient will be tested at various doses in the clinic to find optimal dose tolerated for home use; 3) Treatment phase lasting 1 month during which patients will continue on chosen medication; and 4) Maintenance phase lasting 6 months during which patients will continue on medication. Patients/spouses will return at various intervals for follow-up, PE's, and quality of life collection.

PRIOR AND CURRENT PROGRESS
WRAMC has enrolled a total of 46 patients; total enrollment has been 600 patients studywide. This protocol is closed for new enrollment, and open only to current patients. Three patients were treatment failures and did not respond to the medication; two were ineligible after screening; four experienced hypotension and syncope and were taken off study (adverse reactions were reported to DCI/IRB and VIVUS); eleven are continuing through the maintenance phase of the protocol; two were lost to follow-up; and the remainder will be switched to the new protocol starting August 1994 (W.U. #2889). Other side effects include burning, pain, tingling, and pressure in the penis. No new side effects have been noted. The medication now consists of Alprostadil alone (not in combination with Prazosin).

CONCLUSIONS
None at this time.

REPORT DATE: 08/11/94 WORK UNIT # 2882

DETAIL SUMMARY SHEET

TITLE: Incidence of Stool Guaiac Conversion Following Extracorporeal Shock Wave Lithotripsy (ESWL)

KEYWORDS: lithotripsy, guaiac, bowel

PRINCIPAL INVESTIGATOR: Irby, Pierce LTC MC
ASSOCIATES: Watson, Richard MD

DEPARTMENT: Department of Surgery
SERVICE: Urology Service

STATUS: Ongoing
APPROVAL DATE: Aug 1993

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE

To determine if extracorporeal shock wave lithotripsy (ESWL) is associated with stool guaiac conversion following treatment, and to determine the incidence of such conversion.

TECHNICAL APPROACH

Patients have guaiac testing pre- and post-ESWL. Results are documented. Any subjects who convert from negative to positive undergo colonoscopy ASAP to evaluate any potential trauma or lesion. There have been no modifications from the original protocol. The accrual goal is 50 patients.

PRIOR AND CURRENT PROGRESS

A total of 14 patients have been enrolled since the study began accrual in March 1994. One patient has shown conversion, and was found to have a colon polyp. All others tested negative. Protocol enlistment has been lower than expected. Many patients are ineligible because they are referred air-vac and are unable to stay for the entire protocol. There have been no adverse reactions, and no complications.

CONCLUSIONS

Study is in progress. Conclusions are pending. No data analysis has been done yet.

REPORT DATE: 06/22/94 WORK UNIT # 8101

DETAIL SUMMARY SHEET

TITLE: The Effect of Antituberculosis Drugs on Human Gingival Indices - A Clinical Study

KEYWORDS: gingival, indices, isoniazid

PRINCIPAL INVESTIGATOR: Zuehlke, Robert MAJ DC
ASSOCIATES: Kerns, David LTC DC; Greenwell, Henry MS, JD, DMD

DEPARTMENT: Ireland AH, Fort Knox, KY

STATUS: Completed
APPROVAL DATE: Jun 1993

FUNDING: Current FY: $ 0 Previous FYs: $ 0 Total: $ 0

STUDY OBJECTIVE
To investigate the possible influence of INH on a modified gingival index (mGI), a modified plaque index (mPI), and a modified Periodontal Screening and Recording (mPSR) of patients taking the drug.

TECHNICAL APPROACH
Patients taking routine doses of INH had mPI, mGI, and mPSR scores recorded at a baseline examination, 1 month later, and at least 3 months after completion of chemotherapy (experimental group). Patients from the control group were examined in a similar manner, except they did not receive any antibiotics during or 6 months prior to the study.

PRIOR AND CURRENT PROGRESS
A total of 17 patients (aged 21-38 years) were given examinations for the experimental group. Sixteen patients (21-39 years) were examined in a similar manner for the control group. There were no serious or unexpected adverse reactions.

CONCLUSIONS
Results of this pilot study indicated that there were no statistically significant differences between the experimental and control groups for all parameters tested at any time.

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