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ANNUAL PROGRESS REPORT

FY-92

VOLUME II

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

CLINICAL INVESTIGATION PROGRAM
RCS MED-300(RI)

ANNUAL PROGRESS REPORT

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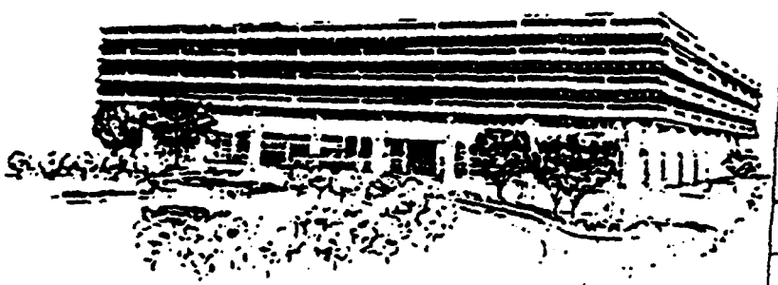
VOLUME II



DEPARTMENT OF CLINICAL INVESTIGATION
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CLINICAL INVESTIGATION PROGRAM
RCS MED-300(RI)

REPORT DATE: 08/10/92 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 LTC(P) MC
ASSOCIATES: Kikendall, James COL MC; Martinez, Miguel MAJ MC

SERVICE: Allergy-Immunology Service STATUS: Ongoing
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 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.

PRIOR AND CURRENT PROGRESS
The intestinal samples in eight normals and two common variable hypogammaglobulinemic patients have been collected. One patient has been followed long term by our service and will be seen in September 1992 for follow-up. This patient is unique in that she has reproducible reversible diarrhea which resolves with adequate intravenous gammaglobulin (IVIG) dosing. The in vitro studies of this patient's secretions before and after IVIG and in comparison with the normals will be worthy of publication. At this point no additional samples will be collected under this protocol.

CONCLUSIONS
Technical difficulties in the G subclass ELISA appear to have been overcome by the availability of purified subclass reagents (previously only in ascites). This accomplishment, with recent improvement in technical support, should allow this work to progress.

REPORT DATE: 08/24/92 WORK UNIT # 3221

DETAIL SUMMARY SHEET

TITLE: The Role of IgG Subclasses in Hymenoptera Hypersensitivity and Immunotherapy

KEYWORDS: IgG subclasses, hymenoptera, immunotherapy

PRINCIPAL INVESTIGATOR: Engler, Renata MAJ MC
ASSOCIATES: Squire, Edward LTC MC; Salata, Kalman PhD

SERVICE: Allergy-Immunology Service STATUS: Ongoing
APPROVAL DATE: Aug 1984

FUNDING: Current FY: $ 0 Previous FYs: $ 21,527 Total: $ 21,527

STUDY OBJECTIVE

To develop a hymenoptera venom specific ELISA assay for the measurement of IgG (IgG1/2/3/4 subclasses to honey bee, wasp, yellow jacket, yellow hornet, white faced hornet); to compare the ELISA assay with the radioimmunoassay; to compare venom-specific IgG and IgG-subclass levels in patients on immunotherapy versus untreated patients with a history of anaphylaxis; and to follow patients on immunotherapy with serial venom specific G measurements.

TECHNICAL APPROACH

Patients will be enrolled during the clinic's routine bee allergy evaluation days. The parameters evaluated in each patient include: a) skin test titration with specific venoms; b) RIA testing for venom specific IgG (VS-G) and IgE; and c) ELISA assays for venom-specific G, G4 and G1. VS-G and G4 levels will be followed sequentially in patients on venom immunotherapy (VIT) and compared to untreated patients. VS-G and G4 levels will be correlated to protection from natural sting reactions and level of severity of previous sting reactions.

PRIOR AND CURRENT PROGRESS

To date, 300 patients have been enrolled. A sensitive and specific ELISA assay for measurement of VS-G1, G4 and total G has been developed; both VS-G and G4 correlate well with a reputable commercial radioimmunoassay. A computerized data base has been utilized to track patients in follow-up and correlate clinical responses to venom and VS-G/G4. Patients on VIT for more than 5 years are being offered the option to stop therapy while they continue to be followed for VS-G/G4 levels and monitored for natural sting rates and responses. Those patients who want to continue VIT, but at increased intervals, are maintaining protective VS-G levels. Twenty patients are being followed after stopping VIT.

CONCLUSIONS

VS-G levels correlate to protection against anaphylaxis in first 3-4 years of VIT; levels decrease after 5 years of VIT, but G4 levels appear to remain elevated. VS-G4 may be a better parameter of protection even after VIT is stopped. Significant levels of VS-G are found in a subset of patients with a history of anaphylaxis and no prior VIT. Some patients have increased VS-G1, particularly with serum sickness. One patient evaluated during rush VIT also had a G4 response.

REPORT DATE: 03/05/92 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 LTC(P), MC
ASSOCIATES: Carregal, Valerie CPT MC; McCormack, Emma CPT MC

SERVICE: Allergy-Immunology Service STATUS: Ongoing
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
Ten subjects have been enrolled in this study. The study has attempted to define optimum conditions for the assays, as well as adequate internal controls. Due to increased clinical demands and decreased technician support available, the project will be continued by Dr. Emma McCormack, an Allergy-Immunology fellow.

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 remains to be elucidated in this system.

REPORT DATE: 08/18/92 WORK UNIT # 3339

DETAIL SUMMARY SHEET

TITLE: Comparison of House Dust Mite Educational Programs on Selected Outcome Variables

KEYWORDS: house dust mites, D.farinae, D.pteronyssinus

PRINCIPAL INVESTIGATOR: Squire, Edward LTC MC
ASSOCIATES: Huss, Karen DNSc; Salata, Kalman PhD

SERVICE: Allergy-Immunology Service STATUS: Ongoing
APPROVAL DATE: Jul 1988

FUNDING: Current FY: $ 253 Previous FYs: $ 3,794 Total: $ 4,047

STUDY OBJECTIVE

To determine if a computerized education program about avoidance measures for house dust mite antigen leads to reduced exposure in patients with asthma. Also, under an addendum, to determine whether benzyl benzoate, when applied to carpeting in those homes in which there remained a substantial residual mite allergen burden, will actually kill mites and thereby lower the mite allergen content of these same carpets.

TECHNICAL APPROACH

This is a randomized trial. Fifty-two patients were followed with symptom diaries and home visits to determine to what extent environmental measures were taken in response to physician' recommendation. Dust was collected from each home and assayed for relevant dust mite allergens, both before and after instruction. Under an addendum, benzyl benzoate, a putative mite-killing agent, and baking soda, the control agent, will be randomly applied to home carpeting of 12 mite-allergic asthmatics. Six asthmatics will apply benzyl benzoate; six will apply baking soda. All will follow manufacturer's instructions.

PRIOR AND CURRENT PROGRESS

Twenty-six mite-allergic asthmatics received conventional instruction (counseling and written instruction), and 26 others received this instruction plus 22 minutes of interactive, computer-assisted instruction. The later group implemented significantly more mite avoidance measures ($p=.0023$) and achieved significantly lower levels of mite allergen in bedroom carpets [allergen levels there fell from 6.5 +/- 7.6 to 2.2 +/- 4.3 mcg/per gram of dust ($p=.004$)]. Corresponding measures for the conventional instruction group did not change significantly. Also, asthmatics in the computer-assisted group became less symptomatic. Benzyl benzoate use did not lower allergen levels further or lead to more symptomatic benefit. The study is closed to patient accrual but remains open for data analysis.

CONCLUSIONS

Conventional instruction on avoidance of mite allergen supplemented with computer instruction led to better mite control, less allergen exposure, and improved asthma. Later use of benzyl benzoate added nothing. Manufacturer's recommendation may be inadequate, or its use may be too complex.

REPORT DATE: 08/07/92 WORK UNIT # 3340

DETAIL SUMMARY SHEET

TITLE: Analysis of Carbohydrate Epitopes on Food Allergen Proteins: A Pilot Study

KEYWORDS: carbohydrate, epitopes, allergens

PRINCIPAL INVESTIGATOR: Salata, Kalman PhD
ASSOCIATES: Birx, Deborah MAJ MC; Engler, Renata LTC MC

SERVICE: Allergy-Immunology Service STATUS: Ongoing
APPROVAL DATE: Aug 1988

FUNDING: Current FY: $ 0 Previous FYs: $ 7,478 Total: $ 7,478

STUDY OBJECTIVE
To identify and characterize carbohydrate epitopes on food allergens which react with specific IgE of patients with food allergy.

TECHNICAL APPROACH
Fluorescent enzyme linked immunosorbent assays (FELISA), sodium dodecylsulfate polyacrylamide gel electrophoresis (SDS-PAGE), isoelectric focusing (IEF), and immunoblotting are used to examine the role of carbohydrate epitopes in food allergy. Glycosidases, lectins, and purified saccharides are used to identify carbohydrate epitopes recognized by specific IgE from patients with food allergy.

PRIOR AND CURRENT PROGRESS
IgE to foods was detected in one subject who was very sensitive to foods. This phenomenon may occur because the IgE is sequestered on mast cells and is not circulating, the food specific IgE is blocking the binding of IgE, or the assay is simply not sensitive enough. Very little can be done about the first possibility. The second possibility is being addressed by selective removal of IgE using protein-A affinity columns. The third possibility is being addressed using a monoclonal anti-human IgE antibody which is being produced in the laboratory in bulk at the moment. Nine subjects have been enrolled; none this year. There have been no adverse reactions, and no one has withdrawn from the protocol.

CONCLUSIONS
So far, food specific IgE antibodies have been detected in one subject with an exquisite sensitivity to foods. IgE has not been detected in other food sensitive subjects. More sensitive assays are being brought on-line to measure the food specific IgE levels in samples from these subjects.

REPORT DATE: 07/29/92 WORK UNIT # 3341

DETAIL SUMMARY SHEET

TITLE: Occurrence of Laryngeal Dysfunction Among Patients Initially Diagnosed as Having Bronchial Asthma

KEYWORDS: asthma, laryngeal dysfunction, laryngeal dyskinesis

PRINCIPAL INVESTIGATOR: Squire, Edward LTC MC
ASSOCIATES: Moyer, Joseph MAJ MC

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

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

STUDY OBJECTIVE
a) Define a standard approach to the evaluation of patients with suspected laryngeal dysfunction. b) Define the frequency of laryngeal dysfunction occurring with and without bronchial asthma among active duty military.

TECHNICAL APPROACH
a) Evaluate patients specifically identified as probably having laryngeal dysfunction. b) Comprehensively evaluate active duty soldiers at Walter Reed who have a profile or seek medical attention for exercise-related lung symptoms.

PRIOR AND CURRENT PROGRESS
This study was designed to define a standardized, multi-option treatment approach, with criteria for success or failure. Since Dr. Moyer's graduation and departure for Womack Army Medical Center, Fr. Bragg, North Carolina, there has not been another allergy-immunology fellow who has chosen to pursue this question. Thus, no progress has occurred, and for this reason the protocol should be closed.

CONCLUSIONS
None.

REPORT DATE: 01/31/92 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: Berger, Teresa BSc(MT); Hershey, Joyce BA

SERVICE: Allergy-Immunology Service STATUS: Ongoing
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; 5 mite allergic subjects and 9 normal subjects, with 1 new patient since the last APR. There were no adverse reactions, no patients withdrew, and there were no benefits to the patients. None of the serum samples collected so far contain measurable IgE against mite proteins. To improve sensitivity, new monoclonal antibody reagents are being prepared. All of the products appeared in initial studies to have the same potency in skin tests.

CONCLUSIONS
A number of in vitro and in vivo methods are being used to measure specific IgE to mite allergens. Initial results indicate that substantial differences exist between extracts from different companies. There are differences in protein content, potency, and spectrum of extract proteins, yet the skin test activity is similar. Few patients have measurable serum anti-mite IgE.

REPORT DATE: 03/10/92 WORK UNIT # 3344

DETAIL SUMMARY SHEET

TITLE: The Effect of UVB (Ultraviolet-B) Light on Immediate, Late and Delayed Hypersensitivity

KEYWORDS: ultraviolet light, skin test, allergy

PRINCIPAL INVESTIGATOR: Carpenter, Gary COL MC

SERVICE: Allergy-Immunology Service STATUS: Ongoing
APPROVAL DATE: Dec 1988

FUNDING: Current FY: $ 0 Previous FYs: $ 5 Total: $ 5

STUDY OBJECTIVE
To assess the effects of ultraviolet light on immediate, late, and delayed allergen skin tests. Ultraviolet-B (UVB) has been investigated as therapy of atopic dermatitis and solar urticaria and cutaneous mastocytosis. This study may help elucidate the mechanisms in which UVB is helpful in these conditions.

TECHNICAL APPROACH
Minimal erythema dose will first be determined. The patient will then receive 1 and 2 MED and 0 MED applied to different randomized areas of the back. The patient is then skin tested at 15 minutes, 24 hours, or 72 hours, and the skin tests are read.

PRIOR AND CURRENT PROGRESS
A total of 12 patients have been studied. Due to the War in the Mideast and increased demands on our service during and following the War, research momentum was lost. At least five more patients need to be recruited for Group 1 of the study. With 16 patients, adequate statistical power to demonstrate clinically and statistically significant effects of UV light on cutaneous reactions to antigen is expected. Groups 2 and 3, who are skin tested 24 or 48 hours after UV radiation, experience too much discomfort with skin testing. The use of topical anesthesia would introduce a new variable, so the study will be closed after finishing Group 1.

CONCLUSIONS
None, so far.

REPORT DATE: 07/16/92 WORK UNIT # 3345

DETAIL SUMMARY SHEET

TITLE: Cross Allergenicity of Pollen Allergens from American Linden and Europen Linden

KEYWORDS: linden, pollen, cross reactivity

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

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

FUNDING: Current FY: $ 0 Previous FYs: $ 330 Total: $ 330

STUDY OBJECTIVE
To compare the cross allogenicity of pollen from American linden and European linden trees.

TECHNICAL APPROACH
Fluorescent enzyme linked immunosorbent inhibition assays (FELISA), sodium dodecylsulfate polyacrylamide gel electrophoresis (SDS-PAGE), isoelectric focusing (IEF), and immunoblotting are used to compare cross allergenicity between American linden and European linden pollen.

PRIOR AND CURRENT PROGRESS
Methods have been developed to measure linden pollen protein in immunoassay techniques and in polyacrylamide gels. One- and two-dimensional techniques use extracts and pollen. Little or no IgE directed against linden protein has been uncovered. Four subjects have been enrolled; none this year. No one has withdrawn, and there have been no adverse reactions.

CONCLUSIONS
Several methods have been devised to analyze linden proteins. Little physiochemical difference was found between pollen proteins from the two species. There are substantial differences between the proteins in commercial extracts and those in whole pollen. Little anti-linden IgE was found in allergic's serum. A monoclonal anti-human IgE may improve sensitivity of the immunoassay; this reagent is being prepared in bulk. IgE may be mostly sequestered on mast cells.

REPORT DATE: 07/17/92 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; Berger, Teresa BSc(MT)

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

FUNDING: Current FY: $ 97 Previous FYs: $ 1,541 Total: $ 1,638

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. One subject has been enrolled; none this year. No one has withdrawn, and there have been no adverse reactions.

CONCLUSIONS
In preliminary studies, 3H-thymidine is probably the best method for measuring lymphocyte proliferation. A simple fluorescent assay for quantitating cultured cells was established. A way of greatly increasing the sensitivity of 96 well plate assays was shown.

REPORT DATE: 08/25/92 WORK UNIT # 3347

DETAIL SUMMARY SHEET

TITLE: A Simple Prick Puncture End Point Titration Procedure to Evaluate the Safety of Switching from Nonstandardized to Standardized Allergen Extracts for Use in Immunotherapy

KEYWORDS: skin test, allergens, immunotherapy

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

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

FUNDING: Current FY: $ 0 Previous FYs: $ 40 Total: $ 40

STUDY OBJECTIVE
To evaluate safety and validity of a simplified skin prick puncture end-point procedure for switching between non-standardized and standardized mite extracts.

TECHNICAL APPROACH
Titrated end-point skin prick puncture tests with mite extracts will be employed.

PRIOR AND CURRENT PROGRESS
Six subjects have been enrolled and tested, and the results have been submitted to Dr. Seltzer who is compiling the data. An additional six subjects will be enrolled and tested in the next week. No subjects have been enrolled this year; a total of nine subjects have been enrolled in the study to date. No one has withdrawn, and there have been no adverse reactions.

CONCLUSIONS
The test seems simple enough, but the final results have not been analyzed, so final conclusions cannot be drawn yet.

REPORT DATE: 03/05/92 WORK UNIT # 3348

DETAIL SUMMARY SHEET

TITLE: Immunotherapy Reactions

KEYWORDS: allergy immunotherapy, venom immunotherapy, adverse reactions

PRINCIPAL INVESTIGATOR: Engler, Renata LTC(P) 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 less supportive nursing staff and clinic shortages, progress in updating data base has been "slowed."

CONCLUSIONS
Increasing IT had significantly more systemic reactions than maintenance IT for both inhalant allergens and venom. 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: 04/02/92 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, Berger, Teresa BSc(MT)

SERVICE: Allergy-Immunology Service STATUS: Ongoing
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 have been enrolled since this study began; no adverse reactions. No new subjects have been enrolled since the last progress report. An additional three subjects need to be recruited to complete accrual. Hopefully these subjects will be entered in the upcoming year.

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 will allow other parameters of the lymphocytes to be measured simultaneously.

REPORT DATE: 04/02/92 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; Berger, Teresa BSc(MT)

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

FUNDING: Current FY: $ 8 Previous FYs: $ 40 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, and NK activity is measured using uncoated cells. Measurements are performed with a flow cytometeer; forward light scatter, side scatter, and two colors of fluorescent light are measured.

PRIOR AND CURRENT PROGRESS
Natural killer and ADCC assays have been devised. Some variability was seen in the ADCC assay that is probably due to the length of the incubation period. In the natural killer cell assay, a 30 minute incubation of the effector and target cells was all that was required. It was possible to measure dead target cells and residual intact target cells. With a 4 hour incubation period, it appeared that the targets were not just dead but disintegrated. A shorter incubation period has worked out well. In addition, performing the assay is much shorter than the traditional method. There have been four new subjects enrolled since the last progress report for a total of seven subjects. There have been no adverse reactions, and no one has withdrawn from the study.

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: 04/15/92 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; Berger, Teresa BSc(MT)

SERVICE: Allergy-Immunology Service

STATUS: Ongoing
APPROVAL DATE: Jan 1990

FUNDING: Current FY: $ 60 Previous FYs: $ 271 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. To improve sensitivity, new monoclonal antibody reagents are being prepared at present. A total of 19 subjects have been enrolled; 10 mite allergic subjects and 9 normal subjects. There were no adverse reactions, no patients withdrew, no new subjects were enrolled in the last reporting period, and there were no benefits to the patients.

CONCLUSIONS

Two in vitro methods were used to measure IgE specific to mite allergens. In initial studies, none of the mite sensitive patients had measurable serum anti-mite IgE. Whether this is due to the sensitivity of the test or because the IgE is sequestered on mast cells is unclear. A hybridoma cell line which produces anti-human IgE is being investigated. A new, more sensitive fluorimeter is being procured to improve the sensitivity of the tests.

REPORT DATE: 04/30/92 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
ASSOCIATES: Lombardo, Fredric MAJ MS

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

FUNDING: Current FY: $ 918 Previous FYs: $ 1,439 Total: $ 2,357

STUDY OBJECTIVE
To establish a consensus as to 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 MTX, 10-30 mg, im or po; qod maintenance TAO, 250 mg/4 mg po; and up to 6 months of daily Gold 3 mg po bid.

PRIOR AND CURRENT PROGRESS

Rx:	# Trials	Successes	Failures
MTX	26	14	12
TAO	12	4	8
Gold	4	1	3

Four of the TAO failures did respond to MTX successfully. One MTX failure also treated with TAO was also a TAO failure.

CONCLUSIONS
Overall, we remain encouraged by the response to MTX. However, in view of the 12 failures experienced with it, an evaluation of alternatives is ongoing, since improved therapy for asthmatics doing poorly on adrenal corticosteroids continues to be sorely and urgently needed.

REPORT DATE: 04/27/92 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; Berger, Teresa BSc(MT)

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 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. No subjects have been enrolled, and no adverse reactions have occurred. No subjects have withdrawn.

CONCLUSIONS
Reports in the literature describe a small population of lymphocyte, contrasuppressors, which bind V. villosa lectin. In preliminary studies it was found that FITC-labeled lectin bound to all lymphocytes. The study will be attempted using a new flow cytometer which has increased resolution.

REPORT DATE: 06/05/92 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: Ongoing
APPROVAL DATE: Apr 1990

FUNDING: Current FY: $ 1,059 Previous FYs: $ 3,344 Total: $ 4,403

STUDY OBJECTIVE
To devise a two-color, simultaneous, two-way mix lymphocyte culture 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
The assay has been established using a purified anti-CD69 antibody and a PE-labeled second antibody. A total of 17 subjects have been enrolled; 2 this past year. No adverse reactions have occurred, and no subjects have withdrawn. The method detects the allogeneic stimulation caused by mixing two individuals' cells. In most cases, little or no stimulation has been seen. In studies with other cell surface markers and the 3H-thymidine, no stimulation was seen. This indicates a problem with the culture conditions. Human serum is being substituted for fetal calf serum to see if that solves the problem.

CONCLUSIONS
An assay of the mixed lymphocyte reaction base on flow cytometry and a fluorescent vital stain have been developed. Unlike other methods, both cell populations may be analyzed simultaneously, and the harsh treatments of current methods are avoided. The cells are allowed to function in a more natural fashion, and additional analyses are possible.

REPORT DATE: 06/18/92 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; Berger, Teresa BSc(MT)

SERVICE: Allergy-Immunology Service

STATUS: Ongoing
APPROVAL DATE: May 1990

FUNDING: Current FY: $ 450 Previous FYs: $ 205 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 is 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 and IL-1 did not affect IL-1 induced ICAM-1 expression. Additional adhesion markers (e.g., VLA-4) are being examined as well. This study does not use any human subjects.

CONCLUSIONS
An IL-1 induced ICAM-1 expression assay was established. Methotrexate does not effect ICAM-1 expression in these cell lines. The anti-inflammatory actions of methotrexate may not be mediated through another adhesion molecule system, and this possibility is being examined.

REPORT DATE: 08/04/92 WORK UNIT # 3356

DETAIL SUMMARY SHEET

TITLE: High Dose Intravenous Immunoglobulin in the Treatment of Chronic Inflammatory Demyelinating Polyneuropathy

KEYWORDS: intravenous, immunoglobulin, CIDP

PRINCIPAL INVESTIGATOR: Davis, William CPT MC
ASSOCIATES: Braverman, Steven CPT MC

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

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

STUDY OBJECTIVE
To evaluate the clinical and immunologic benefits of high dose intravenous immunoglobulin (IVIG) in the treatment of chronic inflammatory demyelinating polyneuropathy.

TECHNICAL APPROACH
Single arm design with patients receiving placebo, then active treatment with IVIG. There will be a detailed statistical evaluation of manual muscle testing, isokinetic muscle testing, functional outcome measures, and nerve conduction velocities.

PRIOR AND CURRENT PROGRESS
This protocol was never given final approval due to the investigational medication IVIG being considered a gift from Sandoz rather than an investigational drug. The request from AR-100 was not completed, and the study was never begun. The study will be closed and replaced by a retrospective review of the use of IVIG in patients with CIDP.

CONCLUSIONS
This study is closed.

REPORT DATE: 09/17/92 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: McCormack, Emma MAJ MC
ASSOCIATES: Engler, Renata LTC(P) MC

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

FUNDING: Current FY: $ 9,911 Previous FYs: $ 3,533 Total: $ 13,444

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 Pneumovac 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
Investigators were trained in techniques of nasal challenge, secretion collection, and assay performance. Thirty-three patient samples have been obtained thus far; 15 controls and 18 with sinusitis. ELISA assays for measurement of nasal secretion components were standardized and performed on 33 patient samples. A data base for study information is being developed. Twenty-seven patients were enrolled this year. No adverse reactions occurred. No one withdrew from the project.

CONCLUSIONS
Study is ongoing; insufficent data for definitive conclusions at this time.

REPORT DATE: 09/15/92 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; Berger, Teresa BSc(MT)

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

FUNDING: Current FY: $ 4,265 Previous FYs: $ 2,097 Total: $ 6,362

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
A mast cell tryptase radioimmunoassay has been established in the laboratory. This assay is very simple and works well with both controls and standards. Twenty-five subjects have been enrolled this year, for a total of 51. A few more subjects will be required to round out some of the groups. Subjects with a wide variety of reactions, as well as control subjects, have been enrolled. There have been no false positives. There have been no adverse reactions, and no subjects have withdrawn from the study.

CONCLUSIONS
It appears that only vigorous anaphylactic reactions produce measurable levels of tryptase in the blood. This test does not appear to be of much utility in diagnosing the milder systemic allergic reactions. A paper describing these results is in preparation.

REPORT DATE: 02/14/92 WORK UNIT # 3359

DETAIL SUMMARY SHEET

TITLE: Leukotriene B4 Receptor Downregulation: Flow Cytometry Analysis

KEYWORDS: leukotriene B4, flow cytometry, down regulation

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

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

FUNDING: Current FY: $ 834 Previous FYs: $ 0 Total: $ 834

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 is used with a flurescein isothiocyanate (FITC) labeled LTB4 to measure receptor down regulation 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 down regulation. LTB4 also competitively inhibits LTB4-FITC binding. A flow cytometric assay has been developed to measure LTB4-FITC binding to granulocytes. Two subjects have been enrolled in total; none in the last year. No subject has withdrawn or had an adverse reaction. There were no benefits to patients.

CONCLUSIONS
LTB4 receptor down regulation can be measured by flow cytometry using an FITC labeled LTB4 conjugate. Brief incubation with LTB4 leads to down regulation of the LTB4 receptor. Further work is required to confirm these results.

REPORT DATE: 02/14/92 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; Berger, Teresa BSc(MT)

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

FUNDING: Current FY: $ 632 Previous FYs: $ 0 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 1uM DIO. A total of 14 subjects have been enrolled to date. 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.

REPORT DATE: 03/16/92 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, Renta LTC(P) MC; Davis, William MAJ MC

SERVICE: Allergy-Immunology 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
A total of 434 patients were contacted and data collected for the data base during the first year. Data is in the process of being analyzed using Excel software. Additional patient calls are required to complete some of the data base.

CONCLUSIONS
To date, the data analysis suggests no significant increase in side effects with booster doses of Pneumova...

REPORT DATE: 04/27/92 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; Berger, Teresa BSc(MT)

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. Lymphocyte subset analysis and HLA typing are the contributions of the two groups at WRAMC.

TECHNICAL APPROACH
Lymphocyte subset analysis is performed using monoclonal antibodies and two-color flow cytometry. HLA typing is performed by a cytotoxicity assay with microscopic examination.

PRIOR AND CURRENT PROGRESS
Lymphocyte subset analysis has been performed on 15 samples. HLA typing has been performed on 11 samples. Subjects are enrolled at Portsmouth Naval Hospital, and blood samples are collected there and distributed to the laboratories conducting tests. Subjects are not enrolled at WRAMC.

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.

REPORT DATE: 05/20/92 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; Berger, Teresa BSc(MT)

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

FUNDING: Current FY: $ 64 Previous FYs: $ 0 Total: $ 64

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
Assays for house dust mite allergen, F1, P1 and cat fel d1 have been established. There are no human subjects involved in this study.

CONCLUSIONS
Sensitive and specific ELISA assays for specific allergens have been established and are working well. The mixtures of allergens will be set up. No conclusions on degradation of specific allergen by proteolytic or physical processes can be drawn yet.

REPORT DATE: 06/18/92 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; Berger, Teresa BSc(MT)

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

FUNDING: Current FY: $ 3,509 Previous FYs: $ 0 Total: $ 3,509

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 chemotactic agents. 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 in which the granulocytes are kept at 4 degrees C will be employed. A total of seven subjects have been enrolled; four in fiscal year 1991 and three in fiscal year 1992. There have been no adverse reactions, and no subjects have withdrawn from the study.

CONCLUSIONS
Whole blood and isolated granuloctye assays of chemotactic agent-induced CD11b expression have been established. FMOC-Leu appears to inhibit granulocyte activation.

REPORT DATE: 04/15/92 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: Davis, William CPT MC
ASSOCIATES: Huh, Michael LCDR MC

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

FUNDING: Current FY: $11,276 Previous FYs: $ 0 Total: $ 11,276

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

TECHNICAL APPROACH
Sequentially measure lymphocyte phenotypes in patients treated with high dose IVIG, observing changes, and correlating these phenotypic changes with clinical response.

PRIOR AND CURRENT PROGRESS
Three subjects have been enrolled, and there have been no adverse reactions. Improved clinical response has been observed in all three subjects, both subjectively and objectively, as measured by manual muscle strength testing and Biodex. Immunologic changes post-IVIG included increased natural killer cell numbers.

CONCLUSIONS
Immunologic changes and a favorable clinical response post-IVIG have been documented. Both parameters were superior with a more rapid IVIG dosing schedule.

REPORT DATE: 08/05/92 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; Berger, Teresa BSc(MT)

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

FUNDING: Current FY: $ 4,027 Previous FYs: $ 0 Total: $ 4,027

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. Bird antigen was found to persist for a very long period of time, up to 18 months after pet birds had been removed from the home. There have been 10 subjects enrolled. None have withdrawn, and there were no adverse reactions.

CONCLUSIONS
Methods have been developed to quantitate bird antigen in dust samples collected in homes. Bird antigen persists for many 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.

REPORT DATE: 09/17/92 WORK UNIT # 4811

DETAIL SUMMARY SHEET

TITLE: Documentation of Irradiated Lymphocyte Inactivation Using the CD69 Surface Marker and Flow Cytometry

KEYWORDS: flow cytometry, irradiator, CD69

PRINCIPAL INVESTIGATOR: Holmes, Kirby Capt BSC
ASSOCIATES: Salata, Kalman PhD; Billups, Lloyd MSc

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

FUNDING: Current FY: $ 6,611 Previous FYs: $ 0 Total: $ 6,611

STUDY OBJECTIVE
To measure mitogen inducible lymphoctye activation in irradiated whole blood using lymphocyte cell surface activation markers and flow cytometry.

TECHNICAL APPROACH
The effects of gamma irradiation of whole blood on mitogen stimulated lymphocyte activation in cultured whole blood or ficoll-hypaque gradient purified lymphocytes will be measured. Immunostaining with fluorescently labelled mouse monoclonal antibodies to lymphocyte cell surface activation markers with two color cytometric analysis, as well as 3 H-thymidine incorporation, will be used to measure lymphocyte activation.

PRIOR AND CURRENT PROGRESS
Whole blood culture proved to be a poor method. Mitogen activation of lymphocytes was not vigorous enough. Freshly isolated lymphoctyes worked best in both thymidine incorporation and flow cytometric methods. CD69 expression worked well and gave results similar to the thymidine incorporation method which served as the gold standard. Interestingly, measurement of cell death worked as well as the other methods. Nineteen subjects have been enrolled this year, which is also the total number. No subject withdrew, and there were no adverse reactions.

CONCLUSIONS
Flow cytometric methods were developed to measure lymphocyte activation in post irradiation whole blood samples using measures of cell death and lymphocyte cell surface activation markers. These methods have the promise of being useful in the quality control of irradiators used to inactivate lymphocytes in units of blood to prevent post transfusio- graft versus host disease.

REPORT DATE: 09/17/92 WORK UNIT # 4812

DETAIL SUMMARY SHEET

TITLE: Quantitation of Red Cell Phenotypes in a Dual Population by Flow Cytometry

KEYWORDS: flow cytometry, red cells, phenotype

PRINCIPAL INVESTIGATOR: Bennett, Charles CPT MS
ASSOCIATES: Billups, Lloyd MSc; Salata, Kalman PhD

SERVICE: Allergy-Immunology Service

STATUS: Ongoing
APPROVAL DATE: Sep 1991

FUNDING: Current FY: $ 2,623 Previous FYs: $ 0 Total: $ 2,623

STUDY OBJECTIVE
To develop methods to differentiate and quantitate red cells in a mixed cell population.

TECHNICAL APPROACH
Immunostaining with standard blood bank serum, Rh immunoglobulin, and fluorescently labeled anti-human IgG in conjunction with three parameter flow cytometry will be used to develop these methods. The parameters used will be forward light scatter (measures size), side light scatter (measures internal cellular complexity), and green fluorescent light output (measures antibody binding).

PRIOR AND CURRENT PROGRESS
Methods were developed to phenotype and quantitate red cells in a mixed cell population. The problem of multicellular aggregates which limit other methods was investigated, and the points where aggregates form were identified. The drawbacks of other methods were overcome using F(ab) fragments of anti-human IgG. In short, quantitative red cell phenotyping methods were developed using standard blood bank typing and commercially available fluorescein labeled anti-human IgG. Human subjects are not involved in this project.

CONCLUSIONS
Flow cytometric quantitative red cell phenotyping methods were developed using standard blood bank typing and commercially available fluorescein labeled anti-human IgG. This method used steadily available commercial reagents and should provide a useful tool for blood bank serologists when faced with mixed red cell populations.

REPORT DATE: 09/17/92 WORK UNIT # 9272

DETAIL SUMMARY SHEET

TITLE: Relationship of Major Histocompatibility Complex Class II Genes to Inhibitor Antibody Formation in Hemophilia A

KEYWORDS: inhibitor, hemophilia A, histocompatibility

PRINCIPAL INVESTIGATOR: Lippert, Lloyd LTC MC
ASSOCIATES: Fisher, Lyman MD PhD; Kapur, Janet BSc(MT)

SERVICE: Allergy-Immunology Service STATUS: Ongoing
APPROVAL DATE: Sep 1988

FUNDING: Current FY: $ 171 Previous FYs: $ 35,445 Total: $ 35,616

STUDY OBJECTIVE
To identify a marker or trait which will prospectively identify the hemophilia A subpopulation at risk for developing anti-factor VIII inhibitor antibodies, and to substantiate a statistical association between the inhibitor phenotype and the major histocompatibility complex (MHC) using HLA testing.

TECHNICAL APPROACH
The HLA phenotypes of both inhibitor and non-inhibitor hemophilia patients will be determined by microlymphocytotoxicity. Restriction fragment length polymorphism (RFLP) analysis will be performed on peripheral blood DNA digested with a battery of restriction enzymes, Southern blotted, and probed with class II MHC alpha and beta gene probes.

PRIOR AND CURRENT PROGRESS
This study continues to enroll subjects at the Medical College of Virginia, Richmond, VA. DNA was extracted on 16 samples for a total of 133 samples. Complete HLA typing by microlymphocytotoxicity methods was performed on five samples. Five new subjects were enrolled this past year, for a total of 50 subjects. The study continues to process samples and acquire data and is nearing the total of 60 subjects proposed in the protocol. The protocol should be completed within the next reporting period.

CONCLUSIONS
No conclusions can be drawn until all the samples are collected and analyzed.

REPORT DATE: 05/12/92 WORK UNIT # 2584

DETAIL SUMMARY SHEET

TITLE: Evaluation of Patients with Obstructive Sleep Apnea Syndrome Following Uvulopalatopharyngoplasty

KEYWORDS: obstructive sleep apnea, uvulopalatopharyngoplasty, polysomnography

PRINCIPAL INVESTIGATOR: Derderian, Sarkis LTC MC
ASSOCIATES: Culpepper, William DAC; Rajagopal, Krishnan LTC MC

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

FUNDING: Current FY: $ 2,161 Previous FYs: $ 2,858 Total: $ 5,019

STUDY OBJECTIVE
To study the perioperative risk following uvulopalatopharyngoplasty (UPPP) for obstructive sleep apnea patients and how psychological test results are affected by surgery.

TECHNICAL APPROACH
Patients are selected for surgery based on clinical and polysomnographic parameters. Patients will be administered polysomnography on the night before surgery, night of surgery, night after surgery, and 3 months following surgery. Sleep parameters, disordered breathing, and oxygenation parameters are compared across studies looking at known perioperative risk factors (i.e., do they worsen or improve). Clinical response to UPPP and psychological status are recorded between the first and last night's assessments.

PRIOR AND CURRENT PROGRESS
The study is closed to enrollment. Twenty-one patients were enrolled and their clinical course followed as outlined above. One paper has been published, and a second paper is in preparation.

CONCLUSIONS
Patients with baseline saturations during sleep of greater than 80% do not need intensive monitoring during the postoperative period.

REPORT DATE: 08/19/92 WORK UNIT # 4801

DETAIL SUMMARY SHEET

TITLE: Fibrinogen Concentration in Two Methods of Cryoprecipitate Preparation

KEYWORDS: cryoprecipitate, fibrinogen, factor VIII

PRINCIPAL INVESTIGATOR: Lippert, Lloyd LTC MS

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

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

STUDY OBJECTIVE
a) To determine if a relationship exists between loss of fibrinogen and factor VIII and the volume of supernatant plasma removed during the preparation of cryoprecipitate from fresh frozen plasma; and b) If a relationship exists, what the relationship is and whether the information could be used to improve yield of fibrinogen and factor VIII in cryoprecipitate.

TECHNICAL APPROACH
Collect aliquots of supernatant plasma at predetermined intervals as the supernatant plasma is removed. Measure fibrinogen and factor VIII content of these aliquots and compare to the content in the starting plasma and final product. Two methods of cryoprecipitate preparation were studied and compared. Utilize linear regression to determine if linear relationship exists between constituent and volume of supernatant plasma.

PRIOR AND CURRENT PROGRESS
This study is being closed due to the transfer of the Principal Investigator and the non-availability of anyone to continue this project.

CONCLUSIONS
Yields of both factor VIII and fibrinogen were significantly greater, and volume of final product was significantly lower for the "slow thaw" prepared product. The original sampling strategy did not, however, allow determination of the relationship between the final volume and yields of the two analytes in the "slow thaw" product.

REPORT DATE: 03/02/92 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: Lippert, Lloyd LTC MS

DEPARTMENT: Department of Clinical Investigation STATUS: Ongoing
APPROVAL DATE: Oct 1989

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

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 you assume that the reticulocytes are from the patient, then the phenotype of the reticulocyte is the patient's phenotype.

PRIOR AND CURRENT PROGRESS
Reticulocyte identification and antigen phenotyping were performed on 319 mixed red blood cell (MRBC) samples prepared from CPDA-1 anticoagulated donor cells and untransfused patient cells in all c(hr') antigen combinations. The flow cytometry profiles allowed clear differentiation between antigen negative and positive cells whether they were the major (75%) or the minor (25%) population. Nearly identical results were obtained in similar experiments with anti-Rho, -K, -Fya, -Fyb, and -Jka. Nineteen patients were tested with an expanded panel of nine antisera. Eighty-seven percent of the flow cytometer results agreed with results from manual testing. Of the 20 inconclusive results, five were in a patient with a very low reticulocyte count and another five were with anti-S. No false positive results were recorded.

CONCLUSIONS
A simple dual-color flow cytometry procedure was developed which correctly determines the red cell antigen phenotype of the transfused patient. It was successfully applied to patients who received a single unit of antigen mismatched blood and to patients who were either chronically or massively transfused.

REPORT DATE: 02/04/92 WORK UNIT # 6276

DETAIL SUMMARY SHEET

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

KEYWORDS: reticulocyte, blood transfusion, flow cytometry

PRINCIPAL INVESTIGATOR: Lippert, Lloyd LTC MS

DEPARTMENT: Department of Clinical Investigation STATUS: Ongoing
APPROVAL DATE: Nov 1990

FUNDING: Current FY: $ 1,294 Previous FYs: $ 0 Total: $ 1,294

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
Specimens were collected and analyzed from 13 hematologically abnormal patients, all but one of which were pediatric patients. In 50% of the patients, donor reticulocytes persisted for 48 hours, and in two cases they were detectable at 72 hours. In two patients with relatively low pretransfusion reticulocye counts, donor reticulocytes predominated soon after transfusion. No other patterns were discernable, which is probably related to the diversity of the patient sample.

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

REPORT DATE: 06/08/92 WORK UNIT # 9263

DETAIL SUMMARY SHEET

TITLE: Neurohumoral Regulation of Ventilation in Patients with Elevated Adrenocorticotropic Hormone (ACTH) and Beta Endorphins (BE)

KEYWORDS: beta endorphine, CRH, respiratory control

PRINCIPAL INVESTIGATOR: Derderian, Sarkis LTC MC

DEPARTMENT: Department of Clinical Investigation STATUS: Completed
APPROVAL DATE: Oct 1985

FUNDING: Current FY: $ 0 Previous FYs: $ 1,446 Total: $ 1,446

STUDY OBJECTIVE
To examine the role of B-endorphine and other neuropeptides in the regulation of respiration.

TECHNICAL APPROACH
To noninvasively assess respiratory function during hypercapnic rebreathing in patients with Addison's disease. Assessments will be performed on four successive days -- a baseline assessment and after administration of naloxone, placebo, and dexamethasone.

PRIOR AND CURRENT PROGRESS
Data was collected on six subjects. Because of technical difficulties and manpower shortages, not all procedures were performed on all subjects. Additionally, after a freezer lost power at WRAIR, many of the early samples were lost. The plans are to close this study and to redesign the procedures to fit within current capabilities.

CONCLUSIONS
The available data has not been analyzed.

REPORT DATE: 10/07/92 WORK UNIT # 9271

DETAIL SUMMARY SHEET

TITLE: The Ventilatory Response to Carbon Dioxide in Compensated Hepatic Cirrhosis

KEYWORDS: GABA, respiratory control, cirrhosis

PRINCIPAL INVESTIGATOR: Derderian, Sarkis LTC MC

DEPARTMENT: Department of Clinical Investigation STATUS: Ongoing
APPROVAL DATE: Sep 1987

FUNDING: Current FY: $ 0 Previous FYs: $ 13,141 Total: $ 13,141

STUDY OBJECTIVE
To examine the potential role for gamma-aminobutyric acid (GABA) in the regulation of respiration.

TECHNICAL APPROACH
Noninvasive assessments of respiratory function and the pattern of breathing during hypercapnic rebreathing will be performed in subjects with cirrhosis of the liver and in normal controls.

PRIOR AND CURRENT PROGRESS
To date, 11 subjects have been entered into this study. None were entered during this past year, and none experienced any untoward or unexpected problems. The group that has been studied thus far has been very heterogenous, and this may explain the diverse responses of those individuals. The future plan is to only enter patients with alcoholic liver disease. Because of the paucity of liver biopsies done at WRAMC and the exclusionary criteria for this group, the subject population is limited. The study will remain open until another five or six patients are enrolled.

CONCLUSIONS
Patients with alcoholic liver disease manifested as cirrhosis have a depressed ventilatory response to carbon dioxide.

REPORT DATE: 01/23/92 WORK UNIT # 9275

DETAIL SUMMARY SHEET

TITLE: Quantitation and Characterization of EGF Levels in Rat Milk

KEYWORDS: EGF, milk, rat

PRINCIPAL INVESTIGATOR: Schaudies, Paul CPT MS

DEPARTMENT: Department of Clinical Investigation STATUS: Ongoing
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
We have identified three biologically active forms of EGF in rat milk. Two of these forms are larger than the native form as determined by their susceptibility to digestion with trypsin. All are immunoreactive and bind the EGF receptor on cultured cells. We are currently examining the potential differential functional roles for these species in the developing gastrointestinal tract. Total number of animals used is unknown. There have been no unexpected or serious adverse reactions or findings.

CONCLUSIONS
Milk is a significant source for EGF in the rat. The EGF is in a biologically active form capable of stimulating DNA synthesis.

REPORT DATE: 05/12/92 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 Clinical Investigation

STATUS: Ongoing
APPROVAL DATE: Feb 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 2,535 Total: $ 2,535

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

One patient with severe scoliosis was entered, and a complete evaluation was performed.

CONCLUSIONS

None to date.

REPORT DATE: 05/26/92 WORK UNIT # 9281

DETAIL SUMMARY SHEET

TITLE: Relationship of Aryl Hydrocarbon Hydroxylase Activity to V-Beta T Cell Receptor Phenotype in Inbred Mouse Strains: A Model for Cancer Risk

KEYWORDS: V-beta T cell receptor, AHH, mls phenotype

PRINCIPAL INVESTIGATOR: Lippert, Lloyd LTC MS

DEPARTMENT: Department of Clinical Investigation STATUS: Completed
APPROVAL DATE: May 1990

FUNDING: Current FY: $ 1,026 Previous FYs: $ 2,253 Total: $ 3,279

STUDY OBJECTIVE
To examine the T cell receptor (TCR) V-beta phenotype of inbred mouse strains and to determine its relationship to inducibility of the P450 enzyme aryl hydrocarbon hydroxylase (AHH) activity.

TECHNICAL APPROACH
Restriction fragment length polymorphism (RFLP) analysis will be performed on DNA extracted from inbred mice spleen cells. The DNA will be digested with several restriction enzymes, Southern blotted, and probed with V-beta 6, 8.1, and 9 gene probes.

PRIOR AND CURRENT PROGRESS
Spleen cells from 14 different inbred mice strains have been used to extract DNA. The DNA was digested with five restriction endonucleases; Hind III, Sac I, Pvu II, Eco RI, and Msp I. The DNA was Southern blotted onto 15 nylon membranes, and these membranes were probed with three V-beta TCR genes. More than 300 restriction fragments were generated.

CONCLUSIONS
The comparison of presence or absence of any of the V-beta TCR genes to that predicted by mls phenotypes of the various mice strains is still to be analyzed. No unexpected fragments were found that correlated with mls phenotypes. The relationship between AHH inducibility and TCR V-beta phenotype was also analyzed. No relationship between the two was established from this research.

REPORT DATE: 03/24/92 WORK UNIT # 9282

DETAIL SUMMARY SHEET

TITLE: Nutrition Knowledge, Dietary Habits, Human Performance and HDL Ratios of Special Forces Soldiers

KEYWORDS: nutrition, performance, soldiers

PRINCIPAL INVESTIGATOR: Coffey, Lauri MAJ SP
ASSOCIATES: Philopena, Ann MAJ SP

DEPARTMENT: Department of Clinical Investigation

STATUS: Completed
APPROVAL DATE: Dec 1990

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

STUDY OBJECTIVE
To determine the relationship of dietary knowledge and dietary habits to the performance of soldiers on forced road march and APRT, as well as HDL levels.

TECHNICAL APPROACH
Sixty male soldiers from Special Forces, Ft. Bragg, North Carolina, volunteered to complete a Nutrition Knowledge Inventory, a Dietary History Inventory, and to have a venous blood draw to determine HDL. Training scores for APRT and for a road march were collected. Descriptive and correlational statistics were used to identify any relationships between nutrition knowledge, dietary habits, performance, and HDL.

PRIOR AND CURRENT PROGRESS
Fifty-five soldiers completed the study in January 1991. There were no adverse or unexpected reactions. No benefits were noted from participating in the study.

CONCLUSIONS
There was no strong relationship between nutrition knowledge, dietary habits, APRT scores, road march time, and HDL. Descriptive statistics revealed elevated LDL levels (mean=139), cholesterol (mean=201), and HDL (mean=43).

REPORT DATE: 07/31/92 WORK UNIT # 9283

DETAIL SUMMARY SHEET

TITLE: Circadian Function in Patients with Sleep Apnea: A Pilot Study

KEYWORDS: sleep apnea, circadian function, pilot study

PRINCIPAL INVESTIGATOR: Culpepper, William DAC

DEPARTMENT: Department of Clinical Investigation STATUS: Completed
APPROVAL DATE: Mar 1991

FUNDING: Current FY: $ 341 Previous FYs: $ 0 Total: $ 341

STUDY OBJECTIVE
To determine whether or not sleep apnea is associated with circadian abnormalities. A majority of patients with sleep apnea continue to experience pathological daytime sleepiness even after the apnea has been successfully treated. This study is designed to assess what role abnormal circadian function may play in persistent daytime sleepiness.

TECHNICAL APPROACH
Routine polysomnography (nPSG) will be performed, as well as continuous temperature monitoring. The nPSG will include 16 AC and DC channels, and the temperature measurements will be made with the core temp system, which requires the patient to ingest a temperature sensing capsule.

PRIOR AND CURRENT PROGRESS
Three patients were entered in this study before the PI left WRAMC. No subjects have been entered since, and the study should be closed.

CONCLUSIONS
None.

REPORT DATE: 05/14/92 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: $ 1,900 Previous FYs: $ 0 Total: $ 1,900

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 on HeLa cell monolayers cultured at WRAIR. The latter is a historical standard that can detect as little as 1 pg of toxin B. 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 utilized. These stools were originally tested by the clinical lab for toxin A by a commercial latex bead agglutination test; however, this test has been discontinued because it does not detect toxin A. To compensate for this missing information, the DCI laboratory 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 by HeLa cell and toxi-titer assays for toxin B.

PRIOR AND CURRENT PROGRESS

The Clinical Microbiology Laboratory estimated that 200 stools per month are processed for C. difficile toxin assay. However, only 352 stools have been received in approximately 13 months. Using the commercial microtiter assay, a batch of 267 stools has been tested, and 27 (approximately 10%) were found positive for toxin A. This percent of toxin positive stools is typical at this medical center. An additional 58 toxin positive specimens will be required to achieve the 85 toxin positive specimens required for statistical analysis. More than the 100 toxin negative specimens statistically needed for testing by HeLa cell and toxi-titer assays are available.

CONCLUSIONS

Twenty-seven of 267 stool specimens tested with a commercial microtiter plate assay are positive for C. difficile toxin A. The low number of stools received for toxin assay (352) during the past year is likely to cause an extension of the collection period, assuming that this rate continues.

REPORT DATE: 04/26/92 WORK UNIT # 9410

DETAIL SUMMARY SHEET

TITLE: Comparison of the Bacterial Flora in Pericoronitis in HIV-Infected Patients and Non-HIV-Infected Patients

KEYWORDS:

PRINCIPAL INVESTIGATOR: White, Ann CPT MC

SERVICE: Dental Clinic STATUS: Completed
APPROVAL DATE: Dec 1990

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

STUDY OBJECTIVE
This study is being closed prematurely due to the death of the PI.

TECHNICAL APPROACH
Study has been closed.

PRIOR AND CURRENT PROGRESS
Study has been closed.

CONCLUSIONS
None. Study has been closed.

REPORT DATE: 05/13/92 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 LTC DC

SERVICE: Dental Clinic STATUS: Ongoing
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.

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
This study is approximately two-thirds completed. There have been no adverse reactions noted in any patient.

CONCLUSIONS
There is inadequate data to draw conclusions regarding efficiency of collagen plugs in preventing dry socket.

REPORT DATE: 04/15/92 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: Bradford, Brant LTC DC
ASSOCIATES: Theberge, Daniel MAJ DC

SERVICE: Dental Clinic STATUS: Ongoing
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
There are 16 patients enrolled in this study; 3 in the control group; 8 in the rigid fixation group (1 complete, 4 with 9-month follow-up pending, and 3 with 6-month follow-up pending); and 5 in the non-rigid fixation group (all with 3-month follow-up pending).

CONCLUSIONS
No analysis at this point.

REPORT DATE: 07/23/92 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: Ongoing
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
Pilot study with demographic data has been completed. The pilot was written up and accepted for abstract at USAFP in Oakland, California, as well as for publication by "Spine." The second aspect of this study has been completed. Currently, data is being analyzed. No more basic trainees are to be enrolled.

CONCLUSIONS
Results from the pilot study document there is a significant incidence and prevalence of LBP in military basic trainees. History of chronic low back problems was associated with difficulty in completing basic training. The role of exercise is being evaluated.

REPORT DATE: 04/01/92 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 by retrospectively reviewing their records.

TECHNICAL APPROACH
Chart review of medical records and laboratory studies on HIV infected patients.

PRIOR AND CURRENT PROGRESS
Medical records and laboratory studies on 172 patients have been reviewed for AZT compliance and for HIV in women.

CONCLUSIONS
Counts decrease with time in an exponential fashion. Life is prolonged with zidovudine (AZT) and/or pneumomystis prophylaxis. With these therapies, CD4 cell counts do not correlate with prognosis. Other prognostic markers are needed in these patients.

REPORT DATE: 04/01/92 WORK UNIT # 1953

DETAIL SUMMARY SHEET

TITLE: The Generation of Human Monoclonal Antibodies to the HIV

KEYWORDS: monoclonal, HIV, human

PRINCIPAL INVESTIGATOR: Drabick, Joseph MAJ MC

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

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

STUDY OBJECTIVE
The purpose of this study is to generate human monoclonal antibodies to commercially available recombinant HIV antigen from the lymphocytes of patients infected with HIV.

TECHNICAL APPROACH
B. lymphocytes from peripheral blood or available lymphoid tissues are separated, then transformed with EBV. The transformed lymphocytes are screened for antibodies to HIV, recombinant HIV antigens, and recombinant soluble CD4. Positive wells are fused to heteromyeloma SHM-D33-0 and screened for specific antibody production. We are currently experimenting with MAB production from EBV transformed B cells and transfect other cell lines for better MAB.

PRIOR AND CURRENT PROGRESS
Further fusions between EBV-immortalized B cells and the fusion partner SHM-D33-0 have been unsuccessful even in one individual who had received immunotherapy with gp120. We have, therefore, imported the necessary technology to attempt to convert B-cell mRNA to cDNA with subsequent amplification by PCR and transfection. We also have established successful sub-industrial cell culture (potentially GMP approved) in our department and have made gram quantities of several hybridomas. We will seed the system with semi-cloned anti-gp120 secreting immortalized lymphoblasts in another attempt to produce workable amounts of MAB. Our final approach has been to produce anti-gp120 MABs in mice by hyperimmunization. Clones with potential therapeutic value can be humanized using recombinant techniques.

CONCLUSIONS
We still feel high levels of neutralizing anti-gp120 antibody could confer protection against primary infection when administered passively. Such a product would be extremely useful in preventing acquisition associated with high risk exposure. We have the capacity to make a monoclonal and take it from culture dish to clinical trial (anti-P. falciparum human IgM MAB) and are exploring new non-traditional avenues of MAB generation.

REPORT DATE: 03/25/92 WORK UNIT # 1958

DETAIL SUMMARY SHEET

TITLE: In Situ Hybridization for Detection of HIV in Langerhans Cells of HIV Infected Patients

KEYWORDS: HIV, Langerhans' cells, macrophages

PRINCIPAL INVESTIGATOR: Hoover, David LTC MC
ASSOCIATES: Kalter, Chester MD

SERVICE: HIV Research STATUS: Completed
APPROVAL DATE: Jul 1987

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

STUDY OBJECTIVE
a) To determine whether HIV genome is present in Langerhans' cells of the skin; and b) To correlate percentage of infected Langerhans' cells with degree of immunosuppression related to HIV infection and with infection on blood monocytes.

TECHNICAL APPROACH
Samples of normal skin will be examined by in situ hybridization for HIV and immunohistochemical methods to mark Langerhans' cells (LC). The percentage of HIV-infected Langerhans' cells will be correlated with clinical stage as determined by the Walter Reed staging system.

PRIOR AND CURRENT PROGRESS
Skin biopsies, shave excisions, and suction blisters were obtained from 28 HIV-positive individuals and 5 controls. LC were identified, studied morphologically, and enumerated by stains for HLA-DR and CD1 (#6). Skin was also stained with mA6 to HIV-1 and compared to known positive control cells. In situ hybridization was performed on skin for HIV-1 mRNA. DNA-PCR for HIV Ltr/gag was performed on both skin sections and epidermal sheets. Skin samples were co-cultured with target HIV-negative monocytes. Electronmicroscopy was also performed on skin samples. No new patients were added to the study since the last annual report.

CONCLUSIONS
Langerhans' cell number was within normal range in HIV-positive patients, regardless of stage of disease. HIV-1 was readily detected in dermal skin samples, but rarely from epidermal only samples. We cannot support previously published views that LC are an important reservoir of HIV-1. This protocol is no longer active.

REPORT DATE: 05/01/92 WORK UNIT # 1970

DETAIL SUMMARY SHEET

TITLE: Treatment IND Protocol for the Use of Videx in Patients with AIDS who are Intolerant to Zidovudine and Patients Exhibiting Significant Deterioration while Taking Zidovudine

KEYWORDS: AIDS, intolerant, zidovudine

PRINCIPAL INVESTIGATOR: Oster, Charles COL MC
ASSOCIATES: Hicks, Charles LTC MC

SERVICE: HIV Research STATUS: Completed
APPROVAL DATE: Feb 1990

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

STUDY OBJECTIVE
To make Videx (DDI) available to many patients with HIV infection who (1) have either developed intolerance or failed zidovudine therapy and (2) cannot enter the Phase II DDI program in the ACTG's due to protocol exclusion or geographic location.

TECHNICAL APPROACH
This study is an open label, uncontrolled evaluation of oral DDI administered every 12 hours at a dose based on the patient's weight: 35-49 kg - 167 mg bid, 50-74 kg - 250 mg bid, and greater than 75 kg - 375 mg bid.

PRIOR AND CURRENT PROGRESS
There were nine patients enrolled in this protocol. Five of the patients had their medication stopped because of side effects; peripheral neuropathy (3), pancreatitis (1), and diarrhea (1). All of these side effects are commonly reported with DDI. One patient had his care transferred to Dwight D. Eisenhower Army Medical Center, Fort Gordon, Georgia. The drug was FDA approved in October 1991, and the treatment IND protocol was closed. The three remaining patients were swiitched to the FDA approved drug.

CONCLUSIONS
DDI was FDA approved in October 1991, and the protocol was closed by the company. Data on this protocol and the Phase II study have not yet been published.

REPORT DATE: 08/17/92 WORK UNIT # 3342

DETAIL SUMMARY SHEET

TITLE: Delayed Type Hypersensitivity Skin Testing: Correlation of Intradermal Injection Vs. Epicutaneous Antigen Placement and CD4 Number in Normals and HIV Seropositive Subjects

KEYWORDS: DTH, skin test, multitest

PRINCIPAL INVESTIGATOR: Birx, Deborah LTC MC

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

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

STUDY OBJECTIVE
Correlate antigen reactivity by intradermal (ID) and epicutaneous injection to circ. CD4 number. Compare subject reactivity to each of the antigens: tetanus, candida, trichophyton IC/multitest correlate anergy by multitest, and ID injection with evidence of HIV disease progression. Develop a standardized anergy panel to clinical staging of HIV infected patients.

TECHNICAL APPROACH
Simultaneous application of the multitest and ID injection of antigens in HIV infected patients.

PRIOR AND CURRENT PROGRESS
This protocol has had difficulties meeting the expected enrollment. There is continued difficulty coordinating accrual through Ward 76. Additionally, there has been a reluctance from some patients to receive the multitest. As a result, only 100 patients have been enrolled to date, making analysis difficult. No significant adverse events have occurred; no volunteers have been disenrolled from the study for these reasons.

CONCLUSIONS
Emphasis will be placed on improving patient accrual to close protocol and allow for complete data analysis.

REPORT DATE: 03/31/92 WORK UNIT # 4806

DETAIL SUMMARY SHEET

TITLE: Pathological Manifestations of HIV Infections at Autopsy

KEYWORDS: cause of death, histology, microbiology

PRINCIPAL INVESTIGATOR: Anderson, David MAJ MC
ASSOCIATES: Clark, Gary COL MC; Turnicky, Ronald LTC MC

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

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

STUDY OBJECTIVE
To 1) perform complete research autopsies on deceased patients with HIV disease, 2) document disease processes causing morbidity and mortality in patients enrolled in WRAMC HIV research, 3) obtain fresh tissue for immuno-histochemical detection phenotyping of immune cells and detection of viral infections, 4) obtain fresh tissue from major organ systems to store in a tissue registry: unfixed at -70 C and formalin-fixed, paraffin-embedded.

TECHNICAL APPROACH
Complete autopsies will be performed as soon after death as a valid research autopsy permit is available. Tissues from all major organ systems will be examined and processed for histochemistry (formalin-fixed, paraffin-embedded) or flash frozen for immune cell phenotyping. Routine histochemistry, special stains, and immune cell phenotyping will be performed, as well as microbiologic culture. Results will be assembled into a research autopsy protocol report which will be returned to the Infectious Disease Service, the deceased patient's chart, and the Jackson Foundation data base.

PRIOR AND CURRENT PROGRESS
Twenty-one research autopsies at WRAMC (15) and NNMC, Bethesda (6) revealed causes of death as follows (6 cases had 2 causes of death each): 6 PCP (1 systemic), 4 Staphylococcus sepsis (3 pneumonias), 4 dilated cardiomyopathy, 2 Karposi's sarcoma (1 visceral, 1 pneumonitic), 2 enteric sepsis, 2 HIV disease only, 2 acute respiratory distress syndrome (ARDS), 1 acute pancreatitis, 1 CMV panencephalitis, 1 aspiration penumonia, 1 sudden death, and 1 pending. Tissue registries exist for all autopsies and have been used to: (a) validate polymerase chain reaction (PCR) detection systems for HIV proviral DNA, Mycobacterium avium-intracellulare, and Pneumocystis carinii DNA in human tissues, and (b) conduct survey of culturable Mycoplasma species from HIV autopsy tissues - no Mycoplasma species cultured from any of 21 autopsies.

CONCLUSIONS
Death still caused by pneumocystis because of poor patient compliance or intolerance of treatment regimens. PCR detection systems of DNA from HIV and opportunistic pathogens are feasible and show good correlations with classic histopathological presentations. Significant, clinically unsuspected diagnosis was found in 15% of autopsies.

REPORT DATE: 09/14/92 WORK UNIT # 6220

DETAIL SUMMARY SHEET

TITLE: Epidemiology of HIV In Pediatric and Perinatal Patients - A Natural History Study

KEYWORDS: immunodeficiency, pediatric, epidemiology

PRINCIPAL INVESTIGATOR: Fischer, Gerald COL MC
ASSOCIATES: Pettett, Gary COL MC; Scott, Robert COL MC

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

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

STUDY OBJECTIVE
The purpose of this study is to develop a Military Pediatric HIV Program for identification of military dependents (spouses and children) of HIV infected personnel. The study will identify basic epidemiologic information and follow these high risk or HIV-infected children over time to assess infection status and disease progression.

TECHNICAL APPROACH
The Military Pediatric HIV Program will identify children at high risk for HIV infection by matching USAHDS reports with the computer linked DEERS data files. All families with one or both spouses infected with HIV will be offered voluntary enrollment in this program. In addition, children with illness or other problems associated with HIV infection may also be voluntarily enrolled in this study. All children followed will be periodically reevaluated using state-of-the-art HIV diagnostic tests. It is anticipated that this program will encompass Army, Air Force, and Navy dependents.

PRIOR AND CURRENT PROGRESS
Over the last year, a major emphasis of the protocol has been to minimize travel and encourage local follow-up with centralization of virologic testing. There are a total of 146 patients on protocol (20 new patients); 75 from WRAMC and 71 from collaborating military centers. There were no known adverse reactions from protocol participation. The intraservice coordination of this protocol between Army, Air Force, and Navy pediatricians has been extremely beneficial to patients in facilitating coordinated medical care. Important research findings include: low perinatal HIV transmission rate and higher normal CD counts in military infants when compared to civilian data.

CONCLUSIONS
This prospective evaluation of HIV-infected women and their babies and "high risk" or HIV-infected children continues to provide important epidemiologic and natural history data on pediatric HIV infections. This information is of great benefit to all children at risk or infected with HIV.

REPORT DATE: 09/14/92 WORK UNIT # 6222

DETAIL SUMMARY SHEET

TITLE: Core Project: Evaluation of Diagnostic Assays for Human Immunodeficiency Virus (HIV) in Children with Evidence of HIV Exposure or HIV Illnesses

KEYWORDS: AIDS, diagnosis, cultures

PRINCIPAL INVESTIGATOR: Fischer, Gerald COL MC
ASSOCIATES: Burke, Donald COL MC; Ascher, David MAJ MC

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

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

STUDY OBJECTIVE
a) To analyze laboratory assays for detection of HIV infection in children; and
b) To correlate the results with the clinical status of the child.

TECHNICAL APPROACH
This protocol will evaluate the usefulness of new diagnostic assays for HIV as they are developed using blood from HIV-infected or high risk children. Blood will be sent to the laboratory for standard ("state-of-the-art") HIV testing (generally those tests that are most developed). The surplus will be utilized for less well developed assays or stored for future analysis. Results from all tests will be compared to conventional assays used to diagnose adult HIV infection (ELISA, Western Blot) to determine their usefulness in children.

PRIOR AND CURRENT PROGRESS
Over the last year, three new patients were enrolled at WRAMC (total of 76 patients). A consolidated Natural History (Protocol Work Unit No. 6220) and Core Diagnostic consent form is available and replaces the two individual forms. Three children lost eligibility for military care and three died of AIDS. There were no known adverse reactions related to protocol enrollment. Utilization of state-of-the-art tests, which provided early diagnosis of HIV infection, was a direct benefit for all HIV infected children. Important research findings include: PCR and HIV cultures were found to detect HIV infection in infants </=6 months of age, HIV-infected infants </=3 months of age may have negative cultures and PCR, and as little as 100 ul of whole blood was sensitive and specific in diagnosing HIV infection in children, but not better than standard HIV cultures for quantitation.

CONCLUSIONS
These studies provide important information concerning diagnostic assays for HIV infection in infants and children. Continuation of these studies will be critical as HIV therapy improves to assess new diagnostic techniques to enhance rapid, early diagnosis in infants and children.

REPORT DATE: 05/11/92 WORK UNIT # 6264

DETAIL SUMMARY SHEET

TITLE: Perinatal HIV Infection: Epidemiology and Natural History

KEYWORDS: natural history, perinatal HIV, epidemiology

PRINCIPAL INVESTIGATOR: Pettett, Gary COL 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
The Pediatric HIV Program has lost funding through NIH. A source of alternative funding is being pursued. Hopefully progress will be made during the next fiscal year.

CONCLUSIONS
None.

REPORT DATE: 05/11/92 WORK UNIT # 6284

DETAIL SUMMARY SHEET

TITLE: Perinatal HIV Tissue Bank

KEYWORDS: fetal HIV infection

PRINCIPAL INVESTIGATOR: Pettett, Philip COL MC

SERVICE: HIV Research STATUS: Ongoing
APPROVAL DATE: Mar 1991

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

STUDY OBJECTIVE
To accumulate placental and fetal membranes from HIV(+) parturient women for the express purpose of diagnosing and quantifying fetal HIV tissue infection.

TECHNICAL APPROACH
Placental and fetal membranes from consenting HIV(+) pregnant women will be collected and stored in preservative media appropriate for microscopic and histochemical identification of HIV infection.

PRIOR AND CURRENT PROGRESS
The Pediatric HIV Program has lost funding through NIH. A source of alternative funding is being pursued. Hopefully, progress will be made during the next fiscal year.

CONCLUSIONS
None.

REPORT DATE: 06/23/92 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: Rundell, James MAJ MC
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, 300 from National Naval Medical Center, and 400 from San Diego Naval Hospital) will be asked to complete anonymous risk behavior assessments. Smaller numbers of infected individuals are 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

Two additional sites have been added to RV26: The National Naval Medical Center (173 currently enrolled) and Womack Community Hospital, Ft. Bragg, North Carolina (33 currently enrolled). Data collection at Wilford Hall (676 currently enrolled) and Walter Reed Army Medical Center (251 currently enrolled) focuses on longitudinal follow-up of seropositive patients already enrolled in the protocol. Approximately 90 seronegative control participants have been enrolled at Walter Reed Army Medical Center. Final approval to see seronegative control participants at NNMC is anticipated in mid-summer 1992. Data collection for the addendum commenced November 1991. Thirty-one subjects have consented and are participating in the study. Data analysis is ongoing. The protocol team is currently developing secondary protocols based on research data that have been analyzed.

CONCLUSIONS

Longitudinal research and collection of seronegative control data are on schedule or ahead of schedule at all sites. Intervention protocol development is on schedule, with two intervention protocols receiving conditional approval by the USAMRDC Retrovirus Clinical Research Committee, pending revisions.

REPORT DATE: 05/28/92 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: Ongoing
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 March 1991, an addendum was approved which allowed for extended follow-up for all participants who agreed to continue and sign a revised informed consent (dated March 1991).

PRIOR AND CURRENT PROGRESS
As part of the VA Cooperative Study Group, Walter Reed Army Medical Center contributed 24 participants to the total of 338 symptomatic HIV-infected patients who were randomized to receive early versus later AZT treatment. The results of this study (Part I) showed that early AZT delayed progression to AIDS (Stage WR 6) but did not affect survival. In Part II, which is ongoing, nine patients from WRAMC Part I (criteria for inclusion) were enrolled and continue to be followed until the final endpoint, death, is reached. To date, two patients have expired due to progression of their disease. Thus far, Part II has shown on extended follow-up that there is still no difference in overall survival. There have been no serious or unexpected adverse reactions, and no patients have withdrawn from Part II.

CONCLUSIONS
Since there was no overall survival benefit to starting AZT early in this study population, clinicians must reexamine the optimal time to starting AZT. Part II of this study is attempting to define further whether there are any other benefits to starting early, such as improved quality of life, or drawbacks, such as development of resistance.

REPORT DATE: 06/10/92 WORK UNIT # 8803

DETAIL SUMMARY SHEET

TITLE: Core Protocol for HIV Developmental Diagnostics (Adults)

KEYWORDS: HIV, AIDS, virus culture

PRINCIPAL INVESTIGATOR: Roberts, Chester, LTC MS
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
Since May 1991, 938 blood specimens have been collected and analyzed. These generated 2,346 co-cultures and approximately 10,000 p24 antigen capture enzyme-linked immunosorbent assays (ELISA), as well as over 700 polymerase chain reaction (PCR) assays. In addition, 1,067 individual serum or plasma p24 antigen determinations were performed using a variety of acid disassociative techniques. PCR detection of HIV and HTLV has progressed to the stage of chemiluminescence and plate-based assays for eventual use in large-batch processing formats.

CONCLUSIONS
HIV can be readily detected in routine clinical samples by tissue culture and PCR. These are now available to all clinicians on a routine basis. This has greatly enhanced the ability to manage patients in all stages of HIV infection.

REPORT DATE: 08/19/92 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
As of August 1992, there are 656 patients actively enrolled in this protocol. From May 1991 to August 1992, there were 50 terminations; 45 were due to death. Two patients withdrew from the protocol, and two were lost to follow-up. New enrollments added to this protocol from May 1991 to August 1992 totalled 186.

CONCLUSIONS
Data is still being collected. Analysis will be done after this center's data is combined with data from National Naval Medical Center (Bethesda, Maryland), Wilford Hall Air Force Hospital (San Antonio, Texas), and Brooke Army Medical Center (San Antonio, Texas).

REPORT DATE: 03/06/92 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: Swango, Philip CAPT USPHS

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, 136 subjects were enrolled, bringing the current total to 685. Of these, 492 have received their initial baseline oral examination, and 308 have also received at least one 6-month follow-up exam. No adverse reactions have been reported, and no patients have withdrawn from the study. Benefit to subjects includes 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: 02/07/92 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: HIV infection, immunotherapy, rgp160

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 immunogenicity and toxicity of recombinant expressed rgp160 in patients with early HIV infection.

TECHNICAL APPROACH
The original vaccine series of this Phase I immunogenicity and toxicity trial was completed, and an addendum was initiated separating the volunteers into two groups: those who responded to the vaccine and those who did not or had poor responses. Responders were vaccinated every 4 months with 160 ug of rgp160; nonresponders were injected with 640 ug of rgp160 at Day 0,7,30,60,90,120 and then every 4 months with 160 ug. Alterations in cellular and humoral immune responses to specific proteins and changes in in vivo and in vitro cellular immune function continued to be assessed.

PRIOR AND CURRENT PROGRESS
Twenty-eight of the 30 original trial volunteers reenrolled into the Phase I rollover. The continued vaccination series in the responders does not seem to result in tolerance; induction of humoral responses and continuation of cellular responses is noted. In the nonresponder arm of the study, eight volunteers have completed the six-shot regime; of which 100% have changed cellular and humoral responses, hence responding to vaccine. Additionally, the stabilization of CD4 cell counts as compared to a matched natural history control group continues to be seen. After up to 24 months of follow-up study, participants decreased 8%, while natural history controls decreased 26%. No systemic toxicity has been noted to date; local toxicity is limited. Five cases of more severe cutaneous reactions have occurred; studies to determine the etiology are ongoing.

CONCLUSIONS
The rgp160 vaccine continues to be safe and immunogenic in early HIV infected individuals. Through the reimmunization of nonresponders we have been able to show universal response rates, regardless of CD4 counts and general health as were originally predicted to limit vaccine applicability. Additionally, the vaccine is shown to continue to elicit immune responses without tolerance.

REPORT DATE: 03/24/92 WORK UNIT # 8808

DETAIL SUMMARY SHEET

TITLE: A Pharmacokinetic Study to Develop a Database to Describe the Relationship Between Zidovudine (ZDV)/Glucuronyl (GZDV) Blood Levels and Drug Toxicity in HIV Infected Patients

KEYWORDS: pharmacokinetics, toxicity, zidovudine

PRINCIPAL INVESTIGATOR: Bjornson, Darrell LTC MS
ASSOCIATES: Lombardo, Fred MAJ MS; Park, Soon PhD

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

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

STUDY OBJECTIVE
To define the relationship of zidovudine (ZDV) and glucuronyl zidovudine (GZDV) peak and trough plasma blood levels with drug toxicity.

TECHNICAL APPROACH
Patients who are prescribed zidovudine for the first time have venous blood samples drawn each month for 12 months: 0, 15, 30, 45, 60, and 75 minutes. Levels of ZDV and GZDV are analyzed with the ZDV-Trac RIA kit, and concurrent toxicity parameters are followed. Multiple regression analysis is used to analyze data.

PRIOR AND CURRENT PROGRESS
Nineteen patients were enrolled and have completed the 12 month pharmacokinetic portion of the study with one-year follow-up on all patients ending in August 1992. There have been no serious or unexpected adverse reactions. There has been no known benefit to the patients. Final analysis of the data is now in process, with subsequent submission for publication in a national pharmacy journal expected this summer (1992). The study will, therefore, be completed this summer.

CONCLUSIONS
Interim analysis in December 1990 (15 patients) suggested an association between hemoglobin decline and peak metabolite GZDV levels and granulocyte decline and peak GZDV and ZDV levels. The best predictor in each case was peak GZDV. There were wide intrapatient variations in plasma concentrations from month to month and wide interpatient variations in plasma concentrations even when corrected for body weight.

REPORT DATE: 06/18/92 WORK UNIT # 8810

DETAIL SUMMARY SHEET

TITLE: Factors Affecting Heterosexual Transmission of Human Immundeficiency Virus

KEYWORDS: HIV, heterosexual, transmission

PRINCIPAL INVESTIGATOR: Bombaugh, Maryann MAJ MC
ASSOCIATES: Levin, Lynn PhD

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

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

STUDY OBJECTIVE
To evaluate the factors which determine the heterosexual venereal transmission of human immunodeficiency virus (HIV) in order to develop preventive and interventive therapies.

TECHNICAL APPROACH
This study is designed in two parts: a cross-sectional, case control study of concordant and discordant HIV infected couples; followed by a prospective study of the discordant pairs.

PRIOR AND CURRENT PROGRESS
No couples have been entered into this study to date. This study is being closed at this time. The objective and technical approach are undergoing revision and will be submitted as a new protocol.

CONCLUSIONS
None.

REPORT DATE: 06/01/92 WORK UNIT # 8811

DETAIL SUMMARY SHEET

TITLE: The Investigation of the Cutaneous Microflora Found in HIV Infected Patients as it Relates to the Onset, Severity and Progression of Disease

KEYWORDS: cutaneous microflora, immunohistochemical stain

PRINCIPAL INVESTIGATOR: Smith, Kathleen LTC MC

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

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

STUDY OBJECTIVE
To document skin changes associated with HIV disease, both clinical and histopathologic, and to follow these changes with progression of disease, with emphasis on histopathologic studies to identify both clinical and subclinical infections, immunohistochemical markers of the inflammatory infiltrate in HIV disease, and microbiologic studies of the cutaneous microflora, both in all stages and with progression of disease.

TECHNICAL APPROACH
Cutaneous exam questionnaire and examination at initial visit. Diagnostic biopsy with a battery of special stains to identify both clinical and subclinical infections and primary diagnosis. Immunohistochemical studies of the inflammatory infiltrate. Cultures of cutaneous microflora in seven designated areas; microbiology done by University of Pennsylvania.

PRIOR AND CURRENT PROGRESS
The study is completed, with 200 HIV-1 positive patients and 200 HIV-1 negative control patients. Total patients enrolled for RV35 is 225; 51 during 1991-92. No adverse effects related to the study were noted. Changes in microflora of HIV-1 positive patients were identified. Also indentified were an increase in Staph Aureus carriage diffusely over skin surface in all stages of HIV disease, and an increase in localized cutaneous infections, with an increase in progression and soft tissue and Staph Aureus sepsis in late stage disease. There are now ongoing studies to develop topical antimicrobial solutions without the drying effects of known antimicrobial solutions.

CONCLUSIONS
This study has led to the development of a treatment protocol for cutaneous Staph Aureus carriage and a protocol to determine possible enterotoxin production resulting from Staph Aureus carriage in HIV-1 infected patients and its relation to disease process. The latter protocol is being conducted at the National Naval Medical Center.

REPORT DATE: 06/01/92 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 LTC MC

SERVICE: HIV Research STATUS: Ongoing
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. The patients are followed every 6 months and may be seen for problems that develop between visits. In addition, seven cutaneous sites are cultured for fungus and bacteria in patients in all stages of disease; repeat cultures are performed if the stage changes.

PRIOR AND CURRENT PROGRESS
The total number of patients enrolled in this study is 972; 395 enrolled 1991-92. Population has been followed for cutaneous disease with clinicohistophathologic and immunohistochemical correlation. Results have shown that skin problems, in general, are increased throughout HIV-1 disease. Some conditions are dramatically increased over HIV negative patients, some of which correlate with progressive WR stage. Other relatively rare conditions are found with increased frequency in HIV disease. A few conditions appear to be found almost exclusively in HIV-1 infected patients.

CONCLUSIONS
Studies will continue in order to see if some cutaneous conditions may be markers of disease progression and, in the future, to see if control of these conditions could delay progression.

REPORT DATE: 08/10/92 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: Bjornson, Darrel COL 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
Currently, all patients on zidovudine and dideoxyinosine have been entered into the data base (a total of 216). The template for the HIV data base (HMJF) has been written, and prescription drug data is currently being entered by physician assistants and protocol nurses. Downloading of drug data from the CHCS system is currently underway by the Data Group at HMJF.

CONCLUSIONS
No conclusions can be drawn from the data at this time. This is an ongoing data collection protocol with long-term follow-up.

REPORT DATE: 08/10/92 WORK UNIT # 8815

DETAIL SUMMARY SHEET

TITLE: Pneumocystis Carinii Pneumonia in HIV Patients: A Cohort Study to Estimate the Protective Effect of Prophylactic Pentamidine Inhalation in Compliant Vs. Noncompliant Patients

KEYWORDS: PCP, HIV, compliance

PRINCIPAL INVESTIGATOR: Bjornson, Darrel COL MS
ASSOCIATES: Oster, Charles COL MC

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

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

STUDY OBJECTIVE

To determine if patients who are compliant with the use of pentamidine inhalation have a decreased risk of developing Pneumocystis carinii pneumonia (PCP) when compared to those who are noncompliant. In addition, we will look to see if there is a difference between monthly and twice monthly regimens regarding compliance.

TECHNICAL APPROACH

A cohort of patients were selected for the study who had been prescribed prophylactic pentamidine inhalation. Incidence of PCP will be collected from the medical records, with compliance data from the pharmacy records. Analysis will determine whether the risk of PCP is greater in patients who are noncompliant with pentamidine therapy versus those who are compliant. In addition, the 300 mg monthly dose will be compared with the 60 mg twice monthly dose regarding compliance.

PRIOR AND CURRENT PROGRESS

This study has now been completed. Patients (n=146) who were prescribed aerosolized pentamidine 60 mg every 2 weeks were more compliant (p=0.006) than those prescribed 300 mg every 4 weeks. In addition, those patients who initially received the 60 mg regimen and were switched to the 300 mg regimen were more compliant when taking the 60 mg dose (p=0.027). There was no association between compliance with either regimen and incidence of PCP. Compliance was generally poor with both regimens.

CONCLUSIONS

Patients on every 2 week regimens of aerosolized pentamidine were more compliant than those on every 4 week regimens. However, regardless of compliance, some patients were not protected by aerosolized pentamidine over the 3.5 year period.

REPORT DATE: 05/02/92 WORK UNIT # 8816

DETAIL SUMMARY SHEET

TITLE: Assessment of Risk Factors for HIV Infection Among AD U.S. Army Personnel with Documented Recent HIV Antibody Seroconversion

KEYWORDS: HIV, seroconversion, risk

PRINCIPAL INVESTIGATOR: McNeil, John MAJ MC

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

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

STUDY OBJECTIVE
To investigate behavioral and other determinants of HIV seroconversion among active duty male soldiers.

TECHNICAL APPROACH
Case control study, blinded, anonymous and confidential interview by civilian disease intervention specialists at 24 sites within CONUS.

PRIOR AND CURRENT PROGRESS
This protocol was never implemented at WRAMC and should be closed.

CONCLUSIONS
None.

REPORT DATE: 02/28/92 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; Tramont, Edmund COL MC

SERVICE: HIV Research STATUS: Ongoing
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
Locally, the protocol RV44 has enrolled eight patients (six at WRAMC and two at NNMC). This multicenter study, as of December 1991, has enrolled 217 patients (35 HIV-infected, 41 consenting to LP). A revised study goal of 600 patients is hoped to be met by the end of 1993. Locally, there have been no adverse events.

CONCLUSIONS
The study locally and nationally is successfully enrolling patients. There are no interim results yet.

REPORT DATE: 06/19/92 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 protocol has completed enrollment with 100 patients (4 patients replaced prior to closure of enrollment) being followed with sequential evaluations and HIV cultures. To date, there have been 19 patients with primary endpoints, with 17 patients developing opportunistic infections and 6 deaths (2 patients died without a preceding opportunistic infection). There have been no unexpected adverse reactions to zidovudine therapy, and the patients and their physicians remain blinded to the results of drug susceptibility testing. Eleven patients have been switched to DDL by their physicians, and 14 patients have withdrawn from the study after having blood drawn.

CONCLUSIONS
Susceptibilities to DDL and DDC decrease approximately tenfold as zidovudine emerges. A cross-sectional analysis of the zidovudine susceptibility data shows that development of zidovudine resistance is associated with significant CD4 decline. The temporal relationship of zidovudine resistance to CD4 decline is being evaluated.

REPORT DATE: 09/14/92 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
To date, 270 patients have been enrolled in military sites (76 from WRAMC as of August 1992); longest duration of follow-up is 600 days. Two hundred and eight volunteers have been enrolled in civilian sites; longest duration of follow-up is 30 days. No vaccine-induced systemic toxicity has been experienced to date. No patient has been discontinued from the trial for safety reasons. An interim analysis was performed in June and evaluated by the Data Safety and Monitoring Board (DSMB). The DSMB reported no safety and toxicity concerns and found immunogenicity to be comparable to Phase I results.

CONCLUSIONS
To date, the vaccine continues to be safe and immunogenic.

REPORT DATE: 09/14/92 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 300ug 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: 300ug q 1 month (15 volunteers); 300ug q 3 months (15 patients); 600ug q 3 months (10 volunteers); and 600ug per original schedule (initial trial placebos).

PRIOR AND CURRENT PROGRESS
Due to the limited immunogenicity of 100ug dose, it was considered premature to attempt a schedule comparison. Therefore, all patients (with the exception of one) were enrolled into the five-injection schedule to match the open label groups. The last patient completed the initial trial in August. A meeting with the sponsor to analyze the data has been arranged for the end of September. The rollover trial was initiated in May 1992. To date, 41 of 43 volunteers have enrolled in this continuation trial. No systemic toxicity has been demonstrated. No patients have been discontinued for safety reasons. One patient was disallowed from entering the continuation trial for noncompliance.

CONCLUSIONS
Preliminary data suggests that the vaccine is safe and immunogenic in early stage HIV-infected individuals. However, overall conclusions are pending the completion of the data analysis later this month.

REPORT DATE: 05/12/92 WORK UNIT # 8821

DETAIL SUMMARY SHEET

TITLE: Sleep Disturbances in HIV+ Patients: A Descriptive Study

KEYWORDS: sleep stage distribution, HIV-positive, HIV-negative

PRINCIPAL INVESTIGATOR: Hendrix, Rose MAJ MC

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

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

STUDY OBJECTIVE
To describe sleep stage distribution and sleep disturbances in HIV-positive patients and in an age and sleep complaint matched HIV-negative control group.

TECHNICAL APPROACH
Patients and controls will undergo a battery of neuropsychological testing and detailed sleep evaluations in an effort to correlate severity of HIV infection with sleep stage changes.

PRIOR AND CURRENT PROGRESS
No progress has been made to date. The PI PCS'd shortly after the protocol was approved. The technical director of the Sleep Lab was assigned the protocol but did not actually recruit patients and was eventually released from government service in the Fall of 1991. Since that time, the laboratory has been struggling to survive due to insufficient staffing and was non-operational for a period of time. Recently, the lab reopened.

CONCLUSIONS
None.

REPORT DATE: 06/09/92 WORK UNIT # 8822

DETAIL SUMMARY SHEET

TITLE: An Open Study of Foscarnet Treatment of First Episode CMV-Retinitis in AIDS Patients

KEYWORDS: Foscarnet, AIDS, retinitis

PRINCIPAL INVESTIGATOR: Oster, Charles COL MC

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

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

STUDY OBJECTIVE
To evaluate the safety and efficacy of Foscarnet induction and three different maintenance regimens for the treatment of AIDS patients with first episode cytomegalovirus (CMV) retinitis; and to determine the pharmacokinetics of intermittent administration of Foscarnet with or without concomitant administration of AZT.

TECHNICAL APPROACH
This is an open-label, prospective, company sponsored compassionate study of Foscarnet for the treatment of first episode CMV retinitis in AIDS patients who have either failed or who have become intolerant to ganciclovir. Patients will be started at an induction dose of 60 mg/kg IV every 8 hours, followed by a maintenance dose of either 60 mg/kg, 90 mg/kg, or 120 mg/kg (randomization determined by the company) IV every day.

PRIOR AND CURRENT PROGRESS
Two patients have been enrolled in this study. The drug was FDA approved in September 1991; therefore, this study has been closed. There were no serious or unexpected adverse events in these patients. Efficacy and safety data were submitted to the company (Astra).

CONCLUSIONS
Foscarnet has been FDA approved, data have been submitted to the company, and the study has been closed. This is a final report.

REPORT DATE: 04/21/92 WORK UNIT # 8823

DETAIL SUMMARY SHEET

TITLE: Safety and Efficacy of Amphotericin B Lipid Complex in Treatment of Cryptococcal Meningitis in Patients with Acquired Immune Deficiency Syndrome

KEYWORDS: AIDS, meningitis, amphotericin B

PRINCIPAL INVESTIGATOR: Oster, Charles COL MC

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

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

STUDY OBJECTIVE
To determine the safety and efficacy of amphotericin B Lipid Complex (ABLC) in the treatment of cryptococcal meningitis in patients with AIDS.

TECHNICAL APPROACH
Dose ranging trial comparing three dosages of ABLC to a standard dosage of amphotericin B.

PRIOR AND CURRENT PROGRESS
Trial halted in February 1992. This study was discontinued by the sponsor, Bristol-Myers Squibb Pharmaceutical Research Institute, in February 1992. No patients from WRAMC were enrolled in this study.

CONCLUSIONS
None. Trial was terminated.

REPORT DATE: 09/10/92 WORK UNIT # 8824

DETAIL SUMMARY SHEET

TITLE: Phase I Study of Alferon N Injection in Persons with Asymptomatic Human Immunodeficiency Virus (HIV) Infection

KEYWORDS: interferon, HIV infection

PRINCIPAL INVESTIGATOR: Skillman, Donald MAJ MC

SERVICE: HIV Research STATUS: Ongoing
APPROVAL DATE: Sep 1991

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

STUDY OBJECTIVE
Phase I study to determine the safety and tolerance of natural interferon alpha (IFN alfa-N3) in HIV-infected persons.

TECHNICAL APPROACH
Twenty HIV-infected persons with CD4+ T cells greater than 400 will be enrolled and screened for adherence to protocol inclusion/exclusion criteria. Those who meet the criteria will self-inject IFN alfa-N3 subcutaneously three times per week for 12 weeks. The dose of the drug varies with time of enrollment: the first 5 volunteers receive 1 million units/dose; the next 10 volunteers start treatment at 2.5 million units/dose and increase to 5 million units/dose for 12 weeks; the last 5 will increase their dose by 2.5 million units/dose/week until 35 million units is reached or toxicity develops. Safety monitoring is continual. A protocol amendment is pending to increase enrollment of volunteers.

PRIOR AND CURRENT PROGRESS
The first 17 patients have been enrolled and started on the study drug. There has been no evidence of significant toxicity or adverse symptoms related to the IFN alfa-N3. Protocol amendments have permitted six of the first nine volunteers to continue on the study drug beyond the initial 12 weeks for further acquisition of safety data. Other patients are still in their initial 12 weeks of treatment and may be eligible for extended therapy as well. A protocol amendment is pending that will permit enrollment of sufficient volunteers so that 20 may be started on the study drug. Two patients enrolled to date did not meet inclusion/exclusion criteria and will not receive the interferon. One volunteer has completed the screening procedure and will begin treatment soon. All patients are seen and treated at the National Naval Medical Center.

CONCLUSIONS
Natural interferon alpha (IFN alfa-N3) appears to be safe and very well tolerated. Unless toxicity is seen in the remaining weeks of the protocol, there appears to be no reason why this drug should not go on to Phase II (efficacy) testing. In vitro evidence of its effects against HIV and published clinical experience with other IFN alpha preparations strongly suggest a potential role for this drug in the treatment of HIV-infected persons.

REPORT DATE: 08/05/92 WORK UNIT # 8400

DETAIL SUMMARY SHEET

TITLE: Relationship Between Marksmanship and Contrast Sensitivity

KEYWORDS: contrast sensitivity, marksmanship

PRINCIPAL INVESTIGATOR: McKee, Morris MAJ MC
ASSOCIATES: Gorski, David MAJ MS

SERVICE: Kenner Army Community Hospital, Fort Lee, VA STATUS: Completed
APPROVAL DATE: Aug 1989

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

STUDY OBJECTIVE
To determine if there is a positive correlation between degree of contrast sensitivity as measured by the VCTS system and performance on the M-16 rifle range.

TECHNICAL APPROACH
A complete optometric examination is performed to rule out disease or other anomalies and visual perculiarities. Then the subject is administered the contrast sensitivity test. The score on the M-16 rifle range is determined. The data are divided into experts and non-qualifiers (or very poor qualifiers). A t-test will be run on the scores to determine if there are any significant differences.

PRIOR AND CURRENT PROGRESS
There has been no activity on this study during the past year; no subjects were enrolled during the past year.

CONCLUSIONS
None. The study is completed without results.

REPORT DATE: 04/17/92 WORK UNIT # 1501

DETAIL SUMMARY SHEET

TITLE: CALGB 8935 Trimodality Therapy for Stage IIIA Non-small Cell Lung Cancer, Phase II

KEYWORDS: tri-modality, non-small cell, lung cancer

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD

DEPARTMENT: Department of Medicine STATUS: Completed
SERVICE: Cancer & Leukemia Group B APPROVAL DATE: Sep 1989

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

STUDY OBJECTIVE
To assess the feasibility, efficacy, and toxicity of neoadjuvant chemotherapy and postoperative, sequential chemotherapy in the treatment of patients with Stage IIIA non-small cell lung cancer.

TECHNICAL APPROACH
Non-randomized study in which all eligible patients are surgically staged, registered, receive anterior chemotherapy, are evaluated for response, go on to thoracotomy, and on the basis of those findings, receive either posterior chemotherapy and radiotherapy or radiotherapy only.

PRIOR AND CURRENT PROGRESS
A total of three patients from WRAMC have been entered on this study. Two patients have died from progressive disease; the third patient is presently undergoing therapy for progressive disease. No patients have been entered this reporting period. No adverse effects have been observed related to protocol therapy. The study reached its accrual goal of 70 patients and closed February 1992.

CONCLUSIONS
Data is being analyzed. No conclusions have been reached.

REPORT DATE: 03/11/92 WORK UNIT # 1502

DETAIL SUMMARY SHEET

TITLE: CALGB 8945 A Phase II Study of Toremifene in Metastatic Breast Cancer

KEYWORDS: breast cancer, metastatic, anti-hormones

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Cancer & Leukemia Group B APPROVAL DATE: Dec 1989

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

STUDY OBJECTIVE

To evaluate the objective response rate of Toremifene in patients with mestastatic breast cancer who are ER and PgR negative. To evaluate duration of response, time to progression, and survival; and to assess the toxicities of Toremifene.

TECHNICAL APPROACH

All eligible patients will be assigned the same dose of oral Toremifene, 200 mg twice/day. Treatment will continue until disease progresses or toxicity occurs. Close monitoring for toxicities will be maintained.

PRIOR AND CURRENT PROGRESS

Two patients were entered into this study from WRAMC during 1991. Both patients were removed from the study due to progressive disease. No major toxicities were observed while they were on therapy. A total of 20 patients have been entered nationwide as of October 1991. The projected accrual was for 20-40 patients. The study was suspended December 1991.

CONCLUSIONS

No conclusions have been reached.

REPORT DATE: 04/17/92 WORK UNIT # 1503

DETAIL SUMMARY SHEET

TITLE: CALGB 8965 Flow Cytometry and Reticulocyte Analysis in Myelodysplastic Syndromes

KEYWORDS: myelodysplasia, flow cytometry

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD

DEPARTMENT: Department of Medicine STATUS: Completed
SERVICE: Cancer & Leukemia Group B APPROVAL DATE: Dec 1989

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

STUDY OBJECTIVE
To study the relationship of DNA content abnormalities to the subtype and cytogenetics of myelodysplastic syndrome and the conversion to acute leukemia.

TECHNICAL APPROACH
Blood and bone marrow samples are obtained upon study entry and repeated if disease progresses.

PRIOR AND CURRENT PROGRESS
This study closed to patient accrual in February 1992. A total of 37 patients were entered nationwide. No patients from WRAMC were entered.

CONCLUSIONS
Data is under analysis. No conclusions have been reached.

REPORT DATE: 03/02/92 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 16 patients from WRAMC have been entered on this study; 5 of them during 1991. The total accrual nationwide is 310. The projected accrual for this study is 400. The blood samples are drawn during routine sampling time while patients are on treatment or follow-up. No adverse reactions have occurred. No patients have been withdrawn from the study. Samples continue to be sent at the specified intervals.

CONCLUSIONS
No conclusions.

REPORT DATE: 01/28/92 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 STATUS: Ongoing
SERVICE: Cancer & Leukemia Group B 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 Sloan-Kettering Memorial.

PRIOR AND CURRENT PROGRESS
This study opened in February of 1990. A total of 60 patients have been entered nationwide. A total of 23 patients from WRAMC have had interviews conducted and have completed questionnaires. This is considered a low risk study; no adverse effects have occurred. No patients have withdrawn their consent to be interviewed.

CONCLUSIONS
Analysis is ongoing; no conclusions have been reached.

REPORT DATE: 03/02/92 WORK UNIT # 1506

DETAIL SUMMARY SHEET

TITLE: CALGB 8922 Interleukin-2 in Acute Myelogenous Leukemia

KEYWORDS: AML, second remission, interleukin-2

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD

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

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

STUDY OBJECTIVE
To determine the activity of interleukin-2 (IL-2) in prolonging remission in acute myelogenous leukemia (AML) patients who are in second remission. To monitor the effect of IL-2 on display.

TECHNICAL APPROACH
Patients will be randomized to receive or not receive 1L-2. If IL-2 is received, it will be given IV by constant infusion 5 days every 2 weeks for 2 months. Blood samples will be drawn before, during, and after treatment. Samples will be drawn twice on patients who do not receive IL-2.

PRIOR AND CURRENT PROGRESS
No patients from WRAMC have been entered into this study. The study was temporarily suspended from patient entry in November 1990. It has not reopened. No further communication has been received.

CONCLUSIONS
None.

REPORT DATE: 01/23/92 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
Since the study opened in October 1990, a total of 76 patients have been entered nationwide. The projected accrual is for 450 patients. One patient has been entered from WRAMC during 1991. The randomized treatment was fludarabine. The patient has completed four courses of treatment with minimal toxicities, mainly hematologic. No adverse effects have occurred. The benefit has been at least a partial response with the assigned treatment. No patients have been entered and then withdrawn from the study.

CONCLUSIONS
The study is ongoing; no conclusions have been reached.

REPORT DATE: 01/30/92 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: Ongoing
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
A total of two patients from WRAMC have been entered on this study. Both have completed therapy and are being followed every 3 months. Minimal toxicities from chemotherapy were observed. Both patients had post-radiation pneumonitis. Both patients are rated as having stable disease due to residual mediastinal enlargement. No unexpected reactions were observed. No patients have been withdrawn from the study. Thirty patients have been entered nationwide. The projected accrual is for 50 patients.

CONCLUSIONS
Analysis is ongoing. No conclusions have been reached.

REPORT DATE: 01/30/92 WORK UNIT # 1512

DETAIL SUMMARY SHEET

TITLE: CALGB 8944 A Study of Intensive Combined Modality Therapy for Stage III Breast Cancer

KEYWORDS: Stage III breast cancer, combined therapy, pharmacokinetics

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 response rates, disease-free survival, overall survival, and local recurrence rates of patients treated with pre-op intensive doxorubicin, surgery, cytoxan-methotrexate-5FU (CMF), and radiation therapy; to determine the toxicity of this therapy in otherwise healthy women; to determine the pharmacokinetics of intensive doxorubicin and the relationship to initial response; and to determine the prognostic value of serial serum CA 15-3 levels.

TECHNICAL APPROACH
All eligible patients are to receive four courses of intensive doxorubicin with pharmacokinetics during the first course. This treatment is followed by the appropriate mastectomy, followed by 16 weeks of CMF, followed by radiation. Patients with estrogen receptor (ER) positive tumors will then receive tamoxifen for 5 years.

PRIOR AND CURRENT PROGRESS
Two patients from WRAMC have been entered on this study. No unexpected reactions have been observed. One patient is receiving radiation, and the other is completing the CMF regimen. Both patients have had modified radical mastectomies with no evidence of metastasis. Blood samples continue to be obtained for CA 15-3 analysis. This study was closed as of January 1992. The projected accrual of 100 patients has been reached. No unexpected toxicities have been reported.

CONCLUSIONS
Analysis is ongoing. No conclusions have been reached.

REPORT DATE: 02/20/92 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 factors

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 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
Two patients from WRAMC have been enrolled on this study. One patient failed to achieve a CR, was removed from the study, and died of progressive disease 8 months later. The second patient completed induction, has no evidence of leukemic regrowth, but has had a prolonged course of thrombocytopenia (greater than 7 months). The second patient developed a grade 4 infection during recovery. No other adverse effects were seen. A total of 160 patients have been entered nationwde with a projected accrual of 384. Prolonged thrombocytopenia has been observed in other patients outside of WRAMC after initial induction.

CONCLUSIONS
Analysis is ongoing. No conclusions have been reached.

REPORT DATE: 02/21/92 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 29 patients have been entered nationwide. The projected accrual is for 282 AML patients and 98 CML patients.

CONCLUSIONS
No conclusions have been reached.

REPORT DATE: 03/31/92 WORK UNIT # 1515

DETAIL SUMMARY SHEET

TITLE: CALGB 9022 Intensive Post Remission Therapy for Acute Myelocytic Leukemia

KEYWORDS: AML, untreated, intensive post remission

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 feasibility of administering three distinct courses of intensive post-remission therapy with HIDAC, cyclophosphamide/VP 16, and diaziquone/mitoxantrone to patients in first remission after treatment with standard induction chemotherapy.

TECHNICAL APPROACH
All eligible patients receive standard induction therapy with Ara-C and daunorubicin. Once CR is achieved, all patients receive three post-remission treatments: high dose Ara-C followed by cyclophosphamide/etoposide, followed by diaziquone/mitoxantrone. Prior to the third course of therapy, the patient is re-randomized to receive one of three cohorts using diaziquone, varied doses of mitoxantrone, or no mitoxantrone along with G-CSF. Patients are then followed for recurrence. Addendum #9 added G-CSF to the final treatment.

PRIOR AND CURRENT PROGRESS
Four patients from WRAMC have been entered on this study. Two patients were withdrawn: one failed to achieve a complete remission (CR) after two inductions; the other died of complications of his leukemia. The remaining two patients have completed all therapy and are in CR. Marked and prolonged neutropenia and thrombocytopenia were observed during the three final courses. This problem was addressed with addendum #9 which added G-CSF to the final treatment. No other unexpected side effects were observed. A total of 172 patients have been entered nationwide. This study closed to patient accrual March 1992.

CONCLUSIONS
No conclusions have been reached.

REPORT DATE: 01/21/92 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
This study opened in June 1983 as a companion to ALL treatment studies. A total of 22 patients have been entered from WRAMC. Three of those pateints were entered in 1991. Fourteen patients have died; eight patients are still being followed for possible relapse. No adverse effects from the blood and bone marrow samplings have occurred. No benefit to the patient has been cited. A total of 525 patients have been entered nationwide. The projected accrual is 600 patients. The projected closure date is for January 1993.

CONCLUSIONS
Study is ongoing. No conclusions have been reached.

REPORT DATE: 03/02/92 WORK UNIT # 1517

DETAIL SUMMARY SHEET

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

KEYWORDS: untreated 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 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 18 months total. Patients with stable disease will receive 12 months of treatment.

PRIOR AND CURRENT PROGRESS

No patients from WRAMC have been eligible for this study. A total of 24 patients have been entered nationwide. The projected accrual is for 80 patients.

CONCLUSIONS

No conclusions have been reached.

REPORT DATE: 03/02/92 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. The total nationwide accrual is 89. The projected accrual for the study is 200.

CONCLUSIONS
No conclusions have been reached.

REPORT DATE: 05/18/92 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
A total of seven patients from WRAMC have been entered on this study. All patients were registered during 1991 and have completed their 6 months of therapy. No patients experienced unexpected toxicities, and none were withdrawn during therapy. Three patients are receiving zoladex monthly, one patient is receiving zoladex and tamoxifen, and three patients have completed all therapy.

CONCLUSIONS
The study is ongoing. No conclusions have been reached.

REPORT DATE: 05/18/92 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: Ongoing
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 (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
No patients from WRAMC have been entered on this study due to the requirement for estrogen and progesterone negative receptors.

CONCLUSIONS
The study is ongoing. No conclusions have been reached.

REPORT DATE: 05/19/92 WORK UNIT # 1521-91

DETAIL SUMMARY SHEET

TITLE: CALGB 9194: Comparison of Adjuvant Chemotherapy with Concurrent or Delayed Tamoxifen vs. Tamoxifen Along 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 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
No patients from WRAMC have met the eligibility criteria to be enrolled on this study.

CONCLUSIONS
The study is ongoing. No conclusions have been reached.

REPORT DATE: 09/17/92 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 STATUS: Ongoing
SERVICE: Cancer & Leukemia Group B APPROVAL DATE: Sep 1984

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

STUDY OBJECTIVE
To determine the incidence of specific chromosom 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
This study remains open for patient accrual. A total of 69 patients from WRAMC have been entered; the latest one was registered in March 1991. No new patients have been entered this reporting period. A total of over 1900 patients have been entered nationwide. Samples continue to be sent for analysis on those patients who have relapsed. There has been no incidence of serious or unexpected adverse reactions.

CONCLUSIONS
Analysis is ongoing.

REPORT DATE: 06/10/92 WORK UNIT # 1536-85

DETAIL SUMMARY SHEET

TITLE: CALGB 8582: A Comparison of Pentostatin and Alpha Interferon in Splenectomized Patients with Active Hairy Cell Leukemia

KEYWORDS: pentostatin, alpha-interferon, hairy cell leukemia

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD

DEPARTMENT: Department of Medicine STATUS: Completed
SERVICE: Cancer & Leukemia Group B APPROVAL DATE: May 1985

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

STUDY OBJECTIVE
To compare the effectiveness of pentostatin and alpha-interferon in the treatment of hairy cell leukemia. To evaluate the toxicities of the two drugs.

TECHNICAL APPROACH
Patients entered will be randomized to receive either alpha-interferon SQ 3 X week for 13 weeks or pentostatin IV X 2 days, every 2 weeks for 3 months.

PRIOR AND CURRENT PROGRESS
Only one patient from WRAMC has been entered on this study. That patient subsequently died from a non-disease related condition (1986). No adverse effects from treatment were observed. The study officially closed in May 1992.

CONCLUSIONS
No conclusions have been reached.

REPORT DATE: 08/17/92 WORK UNIT # 1550-86

DETAIL SUMMARY SHEET

TITLE: CALGB 8534: Combination Chemotherapy with Intensive ACE/PCE and Radiation Therapy to the Primary Tumor and Prophylactic Whole Brain Radiation Therapy with or without Warfarin in Limited Small Cell Carcinoma of the Lung

KEYWORDS: lung, chemotherapy, radiation

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD

DEPARTMENT: Department of Medicine STATUS: Completed
SERVICE: Cancer & Leukemia Group B APPROVAL DATE: Aug 1986

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

STUDY OBJECTIVE
To determine the complete response rate and long-term survival of patients treated with a new combined modality program containing three cycles of ACE followed by concurrent radiation and PCE followed by three cycles of ACE.

TECHNICAL APPROACH
Randomized study in which all eligible patients receive the above listed therapy with or without daily doses of warfarin.

PRIOR AND CURRENT PROGRESS
A total of five patients have been entered on this study; the last one was registered in February 1989. No new patients have been registered this reporting period. Three of the five patients have died of their disease; the other two are still being followed for recurrence. No unexpected toxicities have been observed. The study closed August 1992.

CONCLUSIONS
No conclusions have been reached.

REPORT DATE: 08/19/92 WORK UNIT # 1551-86

DETAIL SUMMARY SHEET

TITLE: CALGB 8362: Pharmacokinetics of Ara-C in Patients with Acute Myelogenous Leukemia, A Companion to CALGB 8525

KEYWORDS: pharmacokinetics, Ara-C, leukemia

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD

DEPARTMENT: Department of Medicine STATUS: Completed
SERVICE: Cancer & Leukemia Group B APPROVAL DATE: Sep 1986

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

STUDY OBJECTIVE
To monitor the plasma levels associated with Ara-C induction therapy and the three dosage levels of Ara-C used in the post-remission therapy in CALGB 8525.

TECHNICAL APPROACH
Non-randomized companion study in which all eligible patients give consent to have four samples of blood drawn during induction therapy and again during the first course of intensification therapy. Blood is then processed and sent to a reference laboratory for drug levels.

PRIOR AND CURRENT PROGRESS
This study reopened for accrual in April 1991. No patients have been entered since the reopening date. Previously, 30 patients were entered who were simultaneously entered on CALGB 8525. All samples were collected. No adverse effects were seen. The study closed for accrual on March 30, 1992.

CONCLUSIONS
Data is being analyzed. No conclusions have been reached.

REPORT DATE: 06/12/92 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 under study is elsamitrucin, pending final CALGB approval.

PRIOR AND CURRENT PROGRESS
A total of 11 patients from WRAMC have been entered on this study. Six patients have died of progressive disease; one patient was removed from treatment due to progressive disease, one patient is free of disease, and the remaining three are receiving chemotherapy with stable disease. No adverse, unexpected effects have been observed. No patients have been entered since September 1991.

CONCLUSIONS
The study is ongoing. No conclusions have been reached.

REPORT DATE: 06/12/92 WORK UNIT # 1564-87

DETAIL SUMMARY SHEET

TITLE: CALGB 8692: Intergroup Study in Metastatic Sarcomas

KEYWORDS: chemotherapy, sarcoma

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD

DEPARTMENT: Department of Medicine STATUS: Completed
SERVICE: Cancer & Leukemia Group B APPROVAL DATE: Jun 1987

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

STUDY OBJECTIVE
To determine if the addition of ifosfamide to doxorubicin and dacarbazine significantly changes the response rate, survival, and toxicity in the therapy of metastatic soft tissue sarcomas.

TECHNICAL APPROACH
Randomized study in which all eligible patients receive either doxorubicin and dacarbazine alone or doxorubicin, dacarbazine, and ifosfamide with mesna. Study is no longer randomized, and only patients with bone sarcomas are now eligible. All eligible patients receive doxorubicin, ifosfamide, dacarbazine, and mesna.

PRIOR AND CURRENT PROGRESS
This study was temporarily closed in May 1991 due to limited availability of decarbazine. The study officially closed June 1992 after reaching desired accrual. A total of 11 patients were entered from WRAMC; the most recent one was entered in September 1990. Seven patients have died of progressive disease. Ten patients had progressive disease. One patient's care and follow-up was transferred to another institution, and he was disease free at the time of the last report. No unexpected toxicities were observed and no patients withdrew consents.

CONCLUSIONS
Manuscript submitted with analysis.

REPORT DATE: 01/21/92 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 to 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
This study opened October 1987. A total of five patients have been entered; the latest being in December 1990. No patients were registered during 1991. One patient was removed from the study due to a change in diagnosis and treatment study. The remaining four continue to be followed for relapse. There have been no adverse reactions from the blood and bone marrow samplings. There have been no cited benefits to the patients. The desired accrual for this study remains at 250 patients. A total of 138 patients have been entered nationwide. The projected date of closure is April 1993.

CONCLUSIONS
Analysis is ongoing; no conclusions have been reached.

REPORT DATE: 01/30/92 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
A total of six patients from WRAMC have been entered on this study. One patient was entered during 1991. Bone marrow and blood samples are being obtained when scheduled diagnostic marrows are done. No adverse effects have occurred. A total of 170 patients have been entered nationwide. The projected accrual is for 250 patients; projected closure of the study is April 1993.

CONCLUSIONS
Analysis is ongoing. No conclusions have been reached.

REPORT DATE: 02/19/92 WORK UNIT # 1577-80

DETAIL SUMMARY SHEET

TITLE: CALGB 8361: Immunologic Diagnostic Studies in AML (blood drawing phase); previously CALGB 7921) CALGB 8321: A Comparative Study of 3 Remission Induction Regimens and 2 Maintenance Regimens for AML (treatment phase); previously CALGB 7921

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 59 patients from WRAMC have been entered on this study; five of those patients were entered in 1991. Blood and marrow samples have been sent accordingly. A total of 1625 patients have been entered nationwide. No adverse effects have been seen. No benefits to the patients have been seen. No patients have withdrawn from the study.

CONCLUSIONS

This study is ongoing. No conclusions have been reached.

REPORT DATE: 02/21/92 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 STATUS: Ongoing
SERVICE: Cancer & Leukemia Group B APPROVAL DATE: Jan 1983

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 14 patients from WRAMC have been entered on this study. One patient was entered during 1991. Nationwide, 288 patients have been entered. The projected accrual is for up to 700 patients. Blood samples have been obtained at specified intervals. No withdrawals from study have occurred; no adverse effects have been observed.

CONCLUSIONS
Analysis is ongoing. No conclusions have been reached.

REPORT DATE: 01/02/92 WORK UNIT # 1583-88

DETAIL SUMMARY SHEET

TITLE: CALGB 8862: A Pharmacodynamic Study of Amonafide

KEYWORDS: amonafide, pharmacodynamics

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD

DEPARTMENT: Department of Medicine STATUS: Completed
SERVICE: Cancer & Leukemia Group B APPROVAL DATE: Jul 1988

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

STUDY OBJECTIVE
To determine feasibility of conducting a multi-institutional pharmacodynamic study employing limited sampling points. To examine the relationships between pharmacokinetic characteristics of amonafide and clinical outcome.

TECHNICAL APPROACH
All eligible patients give consent for the collection of blood samples (30cc each, prior to treatment, 45 minutes and 24 hours after treatment) for one course of therapy only. Blood is then processed and sent to a CALGB reference laboratory for analysis.

PRIOR AND CURRENT PROGRESS
Desired accrual was reached for this study, and it was closed in September 1991. No patients from WRAMC were entered. No patients were registered on CALGB Protocol 8642 during the time amonafide was used for treatment.

CONCLUSIONS
Analysis still in progress.

REPORT DATE: 08/19/92 WORK UNIT # 1584-88

DETAIL SUMMARY SHEET

TITLE: CALGB 8896: An Intergroup Study of Adjuvant Therapy of Primary Colon Cancer

KEYWORDS: chemotherapy, adjuvant, colon cancer

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Cancer & Leukemia Group B APPROVAL DATE: Sep 1988

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

STUDY OBJECTIVE
To compare relative toxicity and efficacy of three approaches (low dose leucovorin + 5FU, high dose leucovorin + 5FU, observation) to treatment of patients with Duke's B or C colon cancer post-curative surgery.

TECHNICAL APPROACH
Randomized study in which all eligible patients will be stratified according to extent, obstruction, and metastasis to receive surgery alone or surgery followed by low dose chemotherapy or high dose chemotherapy.

PRIOR AND CURRENT PROGRESS
A total of 12 patients from WRAMC have been entered on this study. Two of those were entered during this reporting period. Those two patients are still receiving treatment. No unexpected toxicities have been observed. Two of the 12 patients have had recurrence of their disease; one has died. Ten patients continue in follow-up and are disease-free. This study closed to patient accrual on July 30, 1992.

CONCLUSIONS
The data is being analyzed. No conclusions have been reached.

REPORT DATE: 11/13/90 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: Completed
SERVICE: Cancer & Leukemia Group B APPROVAL DATE: Jan 1989

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

STUDY OBJECTIVE
1) To identify the maximally tolerated dose of cyclophosphamide, doxorubicin, vincristine, prednisone and etoposide (CHOPE) in the treatment of lymphoma; and 2) 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 would be escalated for the next groups sequentially, until the maximum tolerated dose was reached.

PRIOR AND CURRENT PROGRESS
Study opened January 1989 and was suspended May 1990. Three patients were entered on the study. All three patients have gone off-study due to disease progression.

CONCLUSIONS
This study was suspended in May 1990; accrual goal was reached for the current dose level. Future plans uncertain. Data still being reviewed; no conclusions reached.

REPORT DATE: 05/19/92 WORK UNIT # 1595-89

DETAIL SUMMARY SHEET

TITLE: CALGB 8961 RAS Mutations in Myelodysplasia

KEYWORDS: RAS, oncogenes, myelodysplasia

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Cancer & Leukemia Group B 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 four patients from WRAMC have been entered on this study. No new patients were entered during 1991 or thus far in 1992. The four patients have died of their disease.

CONCLUSIONS
Analysis of samples is ongoing. No conclusions have been reached.

REPORT DATE: 08/18/92 WORK UNIT # 1596-89

DETAIL SUMMARY SHEET

TITLE: CALGB 8897 Evaluation of Adjuvant Therapy for Node Negative Primary Breast Cancer, Phase III

KEYWORDS: adjuvant, node negative, breast cancer

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 disease free survival and overall survival of high risk primary breast cancer patients with negative axillary lymph nodes treated with standard CMF or CAF chemotherapy. To assess value of the addition of tamoxifen in these patients.

TECHNICAL APPROACH
This is a complicated study in which eligible patients are registered as low, uncertain, or high risk patients. Low risk patients are followed with no therapy. Uncertain risk patients undergo flow cytometry to be categorized as low or high. Those categorized as high risk patients, plus all other known high risks, are then randomized to CMF, CMF with tamoxifen, CAF, or CAF with tamoxifen.

PRIOR AND CURRENT PROGRESS
A total of 31 patients from WRAMC have been entered on this study; 7 patients have been entered since the last reporting period. Five of those patients received chemotherapy. No unexpected toxicities were experienced. The other two are still disease free. No patients have withdrawn from the study.

CONCLUSIONS
The study is ongoing. No conclusions have been reached.

REPORT DATE: 08/18/92 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 five patients from WRAMC have been entered on this study. Three patients were entered during 1991 and are still receiving therapy. No unexpected toxicities have been observed. The two original patients remain in complete remission (CR). The other patients are too early to evaluate.

CONCLUSIONS
No conclusions have been reached.

REPORT DATE: 04/30/92 WORK UNIT # 1243

DETAIL SUMMARY SHEET

TITLE: Percutaneous Balloon Valvuloplasty for Patients with Mitral Stenosis or Aortic Stenosis: A Pilot Study

KEYWORDS: valvuloplasty, aortic stenosis, mitral stenosis

PRINCIPAL INVESTIGATOR: Laird, John MAJ MC
ASSOCIATES: Wortham, Dale, COL MC; Prewitt, Kerry MAJ MC

DEPARTMENT: Department of Medicine
SERVICE: Cardiology Service

STATUS: Ongoing
APPROVAL DATE: Oct 1986

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

STUDY OBJECTIVE

To determine the efficacy of percutaneous balloon valvuloplasty (PBV) in adults with aortic or mitral stenosis.

TECHNICAL APPROACH

Symptomatic patients with mitral stenosis and aortic stenosis will be offered PBV as an option to standard surgical valve replacement. PBV will be performed, with immediate and short-term (6 months) hemodynamic, aortographic, and echocardiographic evaluation.

PRIOR AND CURRENT PROGRESS

To date, 42 patients have been enrolled in this study and have undergone balloon aortic valvuloplasty, and 42 patients have undergone balloon mitral valvuloplasty. In the past year, four patients have undergone balloon aortic valvuloplasty, and seven patients have undergone balloon mitral vulvuloplasty. There were no acute complications associated with these procedures. One patient had mild-moderate mitral insufficiency prior to mitral valvuloplasty that worsened following the procedure. He subsequently went on to undergo successful mitral valve replacement. Almost all patients have had significant clinical improvement following the procedure, and the overall complication rate is well within accepted norms.

CONCLUSIONS

The indications for these procedures have been better defined, and the importance of proper patient selection has been delineated. Mitral valvuloplasty appears to be an excellent therapeutic option for selected patients with mitral stenosis. Balloon aortic valvuloplasty appears to have only a limited role as a treatment for patients who are not candidates for surgical valve replacement.

REPORT DATE: 06/22/92 WORK UNIT # 1245

DETAIL SUMMARY SHEET

TITLE: A Double Blind Study of the Safety and Efficacy of Multiple Intravenous Infusions of Disodium EDTA in Patients with Obstructive Peripheral Arterial Disease and Intermittent Claudication

KEYWORDS: EDTA, claudication

PRINCIPAL INVESTIGATOR: Wortham, Dale COL MC
ASSOCIATES: Bigham, Peter CPT MC

DEPARTMENT: Department of Medicine STATUS: Completed
SERVICE: Cardiology Service APPROVAL DATE: Jul 1987

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

STUDY OBJECTIVE
To evaluate the intravenous administration of EDTA in subjects with peripheral vascular disease manifested by intermittent claudicatior

TECHNICAL APPROACH
Thirty weekly intravenous administrations at two different dosage levels will be given. The effect on the symptom of exercise tolerance will be compared, and the drug response will be evaluated by measuring the distances walked during treadmill examination.

PRIOR AND CURRENT PROGRESS
After the enrollment of 26 patients, funding for this study was withdrawn by Wyeth-Ayerst who became the parent company by buying Elkins-Sinn, Inc.

CONCLUSIONS
The study has been interrupted pending receiving new funding. Therefore, this study should be closed at WRAMC.

REPORT DATE: 02/12/92 WORK UNIT # 1249

DETAIL SUMMARY SHEET

TITLE: Multicenter Study of Silent Ischemia

KEYWORDS: silent ischemia, myocardial infarction, unstable angina

PRINCIPAL INVESTIGATOR: Rogan, Kevin MAJ MC
ASSOCIATES: Gorman, Patrick CPT MC

DEPARTMENT: Department of Medicine STATUS: Completed
SERVICE: Cardiology Service APPROVAL DATE: Dec 1987

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

STUDY OBJECTIVE
Heart patients can have brief episodes of silent myocardial ischemia (MI) which are reflected on the electrocardiogram without accompanying symptoms. The meaning of ischemia without symptoms is uncertain. The purpose of this study is to find out whether silent ischemia is a predictor of future complications, such as myocardial infarction, development of unstable angina, or sudden death.

TECHNICAL APPROACH
One to six months after hospitalization for acute MI, unstable angina, or congestive heart failure with ischemic etiology, study subjects will have a physical exam, cardiovascular history taken, a 24-hour Holter recording, routine ECG, a thallium exercise test, and a psychological profile questionnaire. Follow-up visits will include a brief interview to assess health status and, on some occasions, an ECG. The 24-hour Holter recording will be repeated once (at the first follow-up visit).

PRIOR AND CURRENT PROGRESS
Enrollment was completed December 1990; study was completed December 1991. Data processing is in progress in Rochester, NY. Total enrollment was 38 patients. Eight patients are inactive due to relocation to out-of-state areas. There were no adverse events.

CONCLUSIONS
Data analysis in progress.

REPORT DATE: 07/02/92 WORK UNIT # 1256

DETAIL SUMMARY SHEET

TITLE: High Resolution Ambulatory Holter Monitoring in Preoperative Cardiac Evaluation of Vascular Surgery Patients

KEYWORDS: Holter monitor, preoperative evaluation, vascular surgery

PRINCIPAL INVESTIGATOR: Cambier, Patrick CPT MC

DEPARTMENT: Department of Medicine STATUS: Completed
SERVICE: Cardiology Service APPROVAL DATE: Mar 1989

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

STUDY OBJECTIVE
To demonstrate diagnostic utility in high resolution Holter monitoring preoperatively to assess vascular surgical risk of myocardial ischemia.

TECHNICAL APPROACH
Preoperative vascular patients who frequently cannot exercise (to allow traditional stress testing) need alternative means of assessing preoperative cardiovascular risk. High resolution Holter monitoring may provide such insight.

PRIOR AND CURRENT PROGRESS
This study was in progress with enrollment of a limited number of patients when similar data were published in the Journal of the American College of Cardiology. This study surpassed this protocol, and since the principal investigator has undergone a permanent change of station, this study is now closed.

CONCLUSIONS
No significant conclusions can be drawn from the limited number of patients enrolled.

REPORT DATE: 06/29/92 WORK UNIT # 1258

DETAIL SUMMARY SHEET

TITLE: Combined Effects of Angiotensin-Converting Enzyme Inhibitors and Digoxin in the Chronic Treatment of Idiopathic Dilated Cardiomyopathy

KEYWORDS: dilated cardiomyopathy, ACE-inhibitor, digoxin

PRINCIPAL INVESTIGATOR: Hull, Robert CPT MC
ASSOCIATES: Rogan, Kevin MAJ MC; Wortham, Dale COL MC

DEPARTMENT: Department of Medicine
SERVICE: Cardiology Service

STATUS: Completed
APPROVAL DATE: Jul 1989

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

STUDY OBJECTIVE

To study the clinical efficacy of long-term oral digoxin therapy in normal sinus rhythm in patients with underlying idiopathic dilated cardiomyopathy already maintained on chronic ACE-inhibitor therapy. Long-term benefit is to be assessed in terms of overall drug requirements, functional class, quality of life assessment, exercise capacity, and left ventricular ejection fraction.

TECHNICAL APPROACH

Patients will be maintained on oral ACE-inhibitors and undergo baseline assessment as described above. They then will undergo 4-month study periods involving crossover with digoxin/placebo. Study periods will be doubled-blinded, and there will be a 1-month washout period between phases. Each patient will undergo a clinic assessment at the 2-month mark into each period, and at 4 months each patient will have all baseline assessments repeated.

PRIOR AND CURRENT PROGRESS

Just after last year's Annual Progress Report was submitted, an equipment failure (metabolic cart) prohibited the continuation of this study.

CONCLUSIONS

We entered approximately half of our desired number of patients. Three patients were lost to follow-up due to the equipment failure. We reached no meaningful conclusions.

REPORT DATE: 04/02/92 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: Weston, Lawrence MAJ MC

DEPARTMENT: Department of Medicine STATUS: Ongoing
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 multi-center, 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
Fifteen (15) patients have been enrolled in the study to date. During calendar year 1990, 10 patients entered the study, and 5 patients have been enrolled thus far during calendar year 1992. Because of Operation Desert Shield/Storm and the loss of the study nurse, no patients were enrolled in calendar year 1991. Over the 2 year period, a total of five patients have been lost to follow-up or have refused to continue their participation. The remaining patients are doing well; no deaths, serious adverse reactions, or benefits to patients have been encountered.

CONCLUSIONS
With the hiring of a new study nurse, additional patients are being actively recruited for the study.

REPORT DATE: 05/05/92 WORK UNIT # 1262

DETAIL SUMMARY SHEET

TITLE: Utility of Transesophageal Echocardiography in Evaluation of Young Patients with Unexplained Cerebral Ischemia and Infarction

KEYWORDS: stroke, echocardiography, embolism

PRINCIPAL INVESTIGATOR: Gaither, Neal MAJ MC
ASSOCIATES: May, Eugene CPT MC

DEPARTMENT: Department of Medicine
SERVICE: Cardiology Service

STATUS: Completed
APPROVAL DATE: Jan 1990

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

STUDY OBJECTIVE

To evaluate the role of echocardiography for detecting the source of embolic stroke in young patients. To compare the diagnostic yield of transthoracic versus transesophageal echocardiography for detection of "source of embolism" in young patients.

TECHNICAL APPROACH

Transthoracic and transesophageal echocardiography with saline contrast and Valsalva's maneuver. Further evaluation if clinically appropriate.

PRIOR AND CURRENT PROGRESS

Twenty-three patients were enrolled and studied during the first year. Since that time, the associate investigator has transferred to the Neuro-Ophthalmology Service, and continuity of this project with the Neurology Service has not been maintained. This has resulted in an absence of referrals for the study, since almost all patients have come from the Neurology Service. During the preceding 12 months, only four patients have been enrolled. The procedures performed (transthoracic and transesophagel echo) have become a standard part of the evaluation of such patients. Therefore, these patients have been studied by these techniques, but many of those studied were not enrolled in the protocol.

CONCLUSIONS

Since the procedures involved in this investigation have become part of the standard evaluation of young stroke patients, it is recommended that the study be terminated (both investigators will be leaving WRAMC).

REPORT DATE: 02/03/92 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 STATUS: Ongoing
SERVICE: Cardiology Service APPROVAL DATE: Oct 1990

FUNDING: Current FY: $ 517 Previous FYs: $ 0 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
Fourteen animals underwent 24 successful coronary balloon angioplasty procedures. Three deaths occurred (anesthetic - 1; 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 procedures are completed, and no serious or unexpected adverse reactions occurred.

PRIOR AND CURRENT PROGRESS
Immunohistochemical staining of injured venous normal coronary arteries demonstrated TNF within regions of the media 24 hours and 7 days after balloon angioplasty ($p<.05$). Tissue extraction of RNA was completed from seven animals (21 specimens). DOT/BLOT hybridization from TNF mRNA identified greater than twofold induction 24 hours and 7 days after injury in four of seven animals (pNS). Confirmational analysis is in progress. Additional study is in progress to analyze EGF receptor activity in the coronary artery media after injury.

CONCLUSIONS
TNF is present in normal coronary arteries after injury with balloon angioplasty.

REPORT DATE: 01/26/92 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

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Cardiology Service 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 undergo a history, physical examination, and exercise. Patients then wear a Holter monitor for 24 hours during which time they have sexual intercourse. Holter studies are analyzed for ST segment depression, dysrhythmias, and symptoms.

PRIOR AND CURRENT PROGRESS
Fifteen subjects have been enrolled in the study during the past year. There have been no adverse reactions, and no patients have withdrawn from the study. There has been no benefit to patients.

CONCLUSIONS
This study is still ongoing with the hope of enrolling 25-30 patients. Presently no conclusions are available.

REPORT DATE: 07/02/92 WORK UNIT # 1266

DETAIL SUMMARY SHEET

TITLE: Transcoronary Mapping of Ventricular Tachycardia: Catheter Feasibility Study

KEYWORDS: catheter, mapping, intracoronary

PRINCIPAL INVESTIGATOR: Weston, Lawrence MAJ MC

DEPARTMENT: Department of Medicine STATUS: Completed
SERVICE: Cardiology Service APPROVAL DATE: Dec 1990

FUNDING: Current FY: $ 1,321 Previous FYs: $ 0 Total: $ 1,321

STUDY OBJECTIVE
To determine the feasibility of using a newly developed electrode catheter for recording electrograms from the coronary arteries. Feasibility testing is to be performed in a swine model of ventricular tachycardia.

TECHNICAL APPROACH
Under general anesthesia, the coronary mapping catheter will be introduced into the coronary artery tree using standard angioplasty guiding catheters and guidewires. Electrograms will be recorded in sinus rhythm and during ventricular pacing. The animals will be euthanized and the hearts removed for examination.

PRIOR AND CURRENT PROGRESS
A total of five swine were studied. Each major epicardial coronary artery was cannulated in each animal, and high quality electrograms were obtained. No vascular or arrhythmic complications were encountered. Ventricular activation sequences for sinus rhythm and ventricular pacing were readily distinguished using the recorded electrograms.

CONCLUSIONS
Transcoronary activation mapping using this newly developed catheter is feasible, and apparently safe and effective. Further studies are warranted.

REPORT DATE: 06/02/92 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
Patient enrollment was completed in November 1991; WRAMC has four patients in this multi-center study. The study will be ongoing through 1992. Data collection and processing is in progress in Houston, Texas. There has been no incidence of serious or unexpected adverse reactions.

CONCLUSIONS
Data collection and analysis is in progress.

REPORT DATE: 06/22/92 WORK UNIT # 1268

DETAIL SUMMARY SHEET

TITLE: Intracoronary Pacing: Acute and Longterm Safety, Efficacy During Ischemia, and Efficacy in Epicardial Pace-Mapping

KEYWORDS: pacing, coronary, ischemia

PRINCIPAL INVESTIGATOR: Stajduhar, Karl MAJ MC
ASSOCIATES: Hull, Robert MAJ MC; Weston, Lawrence MAJ MC

DEPARTMENT: Department of Medicine
SERVICE: Cardiology Service

STATUS: Ongoing
APPROVAL DATE: Jul 1991

FUNDING: Current FY: $ 2,236 Previous FYs: $ 0 Total: $ 2,236

STUDY OBJECTIVE

To determine extent of acute histologic damage in coronary arteries produced by intracoronary pacing; to determine the spectral resolution of intracoronary pace mapping; and to examine intracoronary pacing thresholds during severe myocardial ischemia.

TECHNICAL APPROACH

For the first objective, an intracoronary pacing electrode will be positioned in different locations and intracoronary cardiac pacing performed. Animals will recover for 1 day, then be euthanized. The coronary arteries will be examined histologically for extent of damage. For the second objective, the intracoronary electrode will be withdrawn during pacing to identify significant surface EKG changes to determine the spectral resolution of this technique. Finally, during coronary pacing, ischemia will be produced by PTCA balloon inflation, and pacing thresholds will be serially assessed.

PRIOR AND CURRENT PROGRESS

The final objective has been completed, with data available on six animals that demonstrate intracoronary cardiac pacing can be sustained with little change in capture threshold for extended durations during severe myocardial ischemia. For the first two objectives, animal data has been obtained, and analysis of this data is ongoing. The EKG data for the pace mapping is being analyzed and histologic study continues of the coronaries post pacing.

CONCLUSIONS

Intracoronary cardiac pacing can be sustained with little change in capture threshold during severe myocardial ischemia. Data analysis is ongoing to determine the histologic damage produced by intracoronary pacing and the spectral resolution of intracoronary pace mapping.

REPORT DATE: 08/14/92 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

PRINCIPAL INVESTIGATOR: Carter, Andrew MAJ MC

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Cardiology Service APPROVAL DATE: Jul 1991

FUNDING: Current FY: $ 5,091 Previous FYs: $ 0 Total: $ 5,091

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
Twenty-five normal Yorkshire pigs have undergone successful placement of tantulum intracoronary stents. Twenty-one of the 25 animals survived the operation (16% mortality). Operative deaths were related to the anesthetic agent (telazol). Nineteen consecutive operations have been completed since substituting ketamine for telazol as the primary anesthetic agent. Angiographic and histologic follow-up assessment at 24 hours (n=3), 7 days (n=7), 14 days (n=3), and 28 days (n=8) confirmed the presence of vascular injury and smooth muscle cell proliferation. The vessels demonstrated consistent degrees of smooth muscle cell proliferation 28 days after injury with a 30-40% luminal stenosis.

CONCLUSIONS
Oversized tantulum mesh stents induce consistent degrees of smooth muscle cell proliferation in normal pig coronary arteries.

REPORT DATE: 08/20/92 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

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Cardiology Service 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 have been enrolled, including 10 patients with lone atrial fibrillation and 2 control patients. No adverse reactions have occurred. No patients have benefited. Seven of the 10 patients have demonstrated some form of atrioventricular conduction anomaly.

CONCLUSIONS
In this highly selected group of patients with atrial fibrillation, an unusually high incidence of atrioventricular conduction anomalies have been identified.

REPORT DATE: 10/05/92 WORK UNIT # 1271

DETAIL SUMMARY SHEET

TITLE: A Retrospective Study of Infective Endocarditis

KEYWORDS:

PRINCIPAL INVESTIGATOR: Hudak, Craig CPT MC

DEPARTMENT: Department of Medicine STATUS: Terminated
SERVICE: Cardiology Service APPROVAL DATE: Aug 1991

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

STUDY OBJECTIVE
This research protocol has been administratively terminated.

TECHNICAL APPROACH
This research protocol has been administratively terminated.

PRIOR AND CURRENT PROGRESS
This research protocol has been administratively terminated.

CONCLUSIONS
This research protocol has been administratively terminated.

REPORT DATE: 07/16/92 WORK UNIT # 1805

DETAIL SUMMARY SHEET

TITLE: Use of Isotretinoin in Prevention of Basal Cell Carcinoma

KEYWORDS: basal cell, prevention, isotretinoin

PRINCIPAL INVESTIGATOR: Benson, Paul MAJ MC
ASSOCIATES: Sperling, Leonard MAJ MC

DEPARTMENT: Department of Medicine
SERVICE: Dermatology Service

STATUS: Completed
APPROVAL DATE: May 1983

FUNDING: Current FY: $ 0 Previous FYs: $ 217,394 Total: $ 217,394

STUDY OBJECTIVE

a) To evaluate the effectiveness of low dosage levels of isotretinoin in reducing the incidence of basal cell carcinomas in a high risk population; b) To examine possible side effects associated with long-term administration of low doses of isotretinoin.

TECHNICAL APPROACH

The study is a double-blind randomized clinical trial to evaluate the efficacy of isotretinoin in reducing the incidence of basal cell carcinoma. A minor modification to the original protocol made during the previous year is that two consecutive fasting triglyceride values less than 211 mg % are required within 3 months prior to randomization. Modification to the original protocol made during the year 1987 recommended a change in interim x-rays. Interim x-rays will only be taken on subjects noted to have DISH documented on the baseline visit (study entry) roentgenogram.

PRIOR AND CURRENT PROGRESS

Of the 135 original study participants, 122 remained active in the study group. The other 13 are accounted for as follows: 4 deceased, 7 dropped out, and 2 left the area. All 122 active patients completed the 3 year intervention phase; 88 patients completed the full 5 year program. Due to time constraints of the study, 34 patients did not receive the total 5 year follow-up: 13 received 4.5 years and 21 received 4 years. There were no cutaneous or noncutaneous adverse experiences during the past year.

CONCLUSIONS

Low dose isotretinoin is ineffective in reducing the occurrence of basal cell carcinoma at new sites in patients with two or more previously treated basal cell carcinomas.

REPORT DATE: 04/06/92 WORK UNIT # 1811

DETAIL SUMMARY SHEET

TITLE: Evaluation of Antibiotic Induced Changes in the Microbial Flora of the External Ear

KEYWORDS: malignant otitis externa, microbial flora

PRINCIPAL INVESTIGATOR: James, William LTC MC

DEPARTMENT: Department of Medicine STATUS: Completed
SERVICE: Dermatology Service APPROVAL DATE: Feb 1989

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

STUDY OBJECTIVE
To evaluate the hypothesis that antibiotics, both systemic and topical, change the flora of the external ear from a predominance of coagulase negative Staphylococcus toward gram negatives (especially Pseudomonas) in outpatients. Results may help identify risk factors for the development of malignant otitis externa following skin cancer surgery on the ear.

TECHNICAL APPROACH
Cultures of outpatient controls, acne, or rosacea patients, on chronic broad spectrum antibiotics and volunteers applying topical bacitracin to the external ear were performed as per the original protocol. Due to various problems, including the need for large bulky bandages and travel problems, we have not been able to recruit ear surgery patients for the protocol. The cultures of the 52 patients studied were negative. Because most Pseudomonas otitis externa occurs in adult diabetics, and in one study antibiotics increased ear Pseudomonas colonization in inpatients, it was felt that it would be more efficient to study this group first. Thus an amendment was submitted to study adult diabetics on antibiotics.

PRIOR AND CURRENT PROGRESS
To date, no patients have been recruited from the Diabetes Clinic, and it appears unlikely any will be enrolled.

CONCLUSIONS
In view of the fact the original primary investigator has been reassigned (diabetic patients are not being recruited) and the results obtained to date have been negative, the study is being closed. In the patient population studied, Pseudomonas is an uncommonly present organism.

REPORT DATE: 08/25/92 WORK UNIT # 1814

DETAIL SUMMARY SHEET

TITLE: Split Thickness Tangential Excision of Tattoos with Correlation to Tattoo Pigment Depth

KEYWORDS: tattoo, Brown dermatome

PRINCIPAL INVESTIGATOR: O'Donnell, Brian MAJ MC
ASSOCIATES: James, William COL MC; Mulvaney, Michael MD

DEPARTMENT: Department of Medicine
SERVICE: Dermatology Service

STATUS: Completed
APPROVAL DATE: Nov 1990

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

STUDY OBJECTIVE

To determine if a thin tangential excision can remove a professionally placed tattoo. Pre-treatment and post-treatment biopsies will be used to correlate tattoo pigment depth with the clinical result of the tangential excision.

TECHNICAL APPROACH

In this pilot study, a tattoo will be excised with a Brown dermatome set at 0.2 mm. Biopsies of involved skin will be obtained before and after the excision. Follow-up evaluation of the treatment sites will occur at 1 week, 1 month, and 6 months. Tattoo pigment depth will be measured with an ocular micrometer. There have been no modifications to the original protocol.

PRIOR AND CURRENT PROGRESS

Five patients have had a tattoo excised. There have been no unexpected adverse reactions. All of the patients have had at least 90% of the tattoo pigment removed. At the 1 month evaluation, there was no significant scarring. The 6-month evaluation is pending.

CONCLUSIONS

It is likely that tangential excision of a professionally placed tattoo with a Brown dermatome will prove to be safe and effective.

REPORT DATE: 04/20/92 WORK UNIT # 1815

DETAIL SUMMARY SHEET

TITLE: Investigation of a Viral Etiology in Pityriasis Rosea

KEYWORDS: pityriasis rosea, picornavirus, polymerase chain reaction

PRINCIPAL INVESTIGATOR: Rowe, Jane MAJ MC
ASSOCIATES: Humphrey, Michael MAJ MC; James, William COL MC

DEPARTMENT: Department of Medicine
SERVICE: Dermatology Service

STATUS: Ongoing
APPROVAL DATE: Jan 1991

FUNDING: Current FY: $ 1,100 Previous FYs: $ 0 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 are done. Blood is drawn at the same time, centrifuged and frozen. A single step method of RNA extraction is done with the acid guanidinum thiocyanate-phenol-chloroform method. The polymerase chain reaction is done on the specimen after RNS using reverse transcriptase reaction initially and then the amplification process.

PRIOR AND CURRENT PROGRESS

Fourteen patients with pityriasis rosea have been enrolled in the study, and 5 control volunteers have been enrolled. All specimens have been processed for RNS extraction using the single step method with phenol-chloroform. Reverse transcriptase and polymerase chain reaction were done once on 11 of the samples, as well as on the positive controls' coxsackie and echo viruses obtained through the ATCC.

CONCLUSIONS

Study not completed, thus no conclusions can be finalized. However, with the samples done, no picornavirus could be found.

REPORT DATE: 03/06/92 WORK UNIT # 1300-88

DETAIL SUMMARY SHEET

TITLE: Postoperative Evaluation of Patients with Differentiated Thyroid Cancer: A Study Comparing 131I, 201Tl and Magnetic Resonance Imaging (MRI)

KEYWORDS: cancer, thyroid, scans

PRINCIPAL INVESTIGATOR: Burman, Kenneth COL MC
ASSOCIATES: Neutze, Janet MAJ MC

DEPARTMENT: Department of Medicine
SERVICE: Endocrine-Metabolic Service

STATUS: Completed
APPROVAL DATE: Jan 1988

FUNDING: Current FY: $ 0 Previous FYs: $ 2,755 Total: $ 2,755

STUDY OBJECTIVE

To determine if thallium and magnetic resonance imaging (MRI) can effectively detect thyroid cancer.

TECHNICAL APPROACH

Patients with known thyroid cancer who are having thyroid scans for their routine care will also have a thallium scan and/or an MRI scan. These tests will then be compared to those results from Iodine 131 scans to determine if thallium is an effective agent.

PRIOR AND CURRENT PROGRESS

Nineteen patients were studied with 24 iodine scans, 33 thallium scans, and 10 MRI's; 17 of them had differentiated thyroid carcinoma, In these 17 cases, all paired studies were concordant for the presence (n=7) or absence (n=10) of disease. One patient showed more extensive disease with thallium than with iodine.

CONCLUSIONS

Thallium is an effective scanning agent.

REPORT DATE: 04/22/92 WORK UNIT # 1302-88

DETAIL SUMMARY SHEET

TITLE: Cholestyramine Treatment of Thyrotoxicosis

KEYWORDS: cholestyramine, thyroid, thyrotoxicosis

PRINCIPAL INVESTIGATOR: Burman, Kenneth COL MC
ASSOCIATES: Solomon, Barbara DNSc; Wartofsky, Leonard COL MC

DEPARTMENT: Department of Medicine
SERVICE: Endocrine-Metabolic Service

STATUS: Ongoing
APPROVAL DATE: Mar 1988

FUNDING: Current FY: $ 0 Previous FYs: $ 15,376 Total: $ 15,376

STUDY OBJECTIVE
To investigate the use of oral cholestyramine as a safe and rapid method of lowering serum thyroxine levels in hyperthyroid patients.

TECHNICAL APPROACH
We will use a randomized placebo crossover controlled design. Subjects will receive 4 grams cholestyramine powder four times a day or an equal amount of placebo powder for 14 days, no powders for 7 days, and then the reciprocal powder for 14 days. Serum T4 and T3 will be measured throughout each period.

PRIOR AND CURRENT PROGRESS
We have studied 16 patients and are continuing to analyze the data. An abstract was presented to the Endocrine Society in 1990 in which we noted that T4 and T3 levels were decreased further on cholestyramine than on control. There have been no serious adverse effects, although several people had mild GI disturbances. There will be no further patient accrual.

CONCLUSIONS
Cholestyramine is a useful adjunctive therapy for the early treatment of thyrotoxicosis.

REPORT DATE: 09/14/92 WORK UNIT # 1303-88

DETAIL SUMMARY SHEET

TITLE: The Clinical Application of In Situ Hybridization to Detect Viral Genomes and Oncogenes in Diseases of the Thyroid and Selected Viral Infections

KEYWORDS: virus, thyroid, probes

PRINCIPAL INVESTIGATOR: Burman, Kenneth COL MC
ASSOCIATES: Humphrey, Michael MAJ MC

DEPARTMENT: Department of Medicine
SERVICE: Endocrine-Metabolic Service

STATUS: Ongoing
APPROVAL DATE: Apr 1988

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

STUDY OBJECTIVE
To determine if viral elements are important in thyroid disease.

TECHNICAL APPROACH
Use both Southern and Northern blots and in situ hybridization studies to determine if viruses are present in thyroid tissue from patients with various thyroid disorders. Polymerase chain reaction (PCR) and cloning techniques will also be employed.

PRIOR AND CURRENT PROGRESS
This study has shown that HIV-like viruses are not present in the thyroid glands or white cells of patients with autoimmune thyroid disease (Lancet 1991;17:337). Since that time, investigators involved in this study have been diligently trying to develop techniques which will allow us to assess the presence of other viruses or virus-like material (i.e., oncogenes). In this regard, about 1 year was spent trying to develop a reliable system of measuring p53 (an oncogenic virus) in samples, but thus far, these attempts have been unsuccessful. Even though Dr. Humphrey has moved to Ft. Bragg, efforts are continuing in this area. Such studies are potentially very important.

CONCLUSIONS
Thus far, the results of this study have not identified a viral-like agent essential to autoimmune thyroid disease.

REPORT DATE: 06/02/92 WORK UNIT # 1306-88

DETAIL SUMMARY SHEET

TITLE: Predicting Energy Requirements in Women with Gestational Diabetes Mellitus (GDM)

KEYWORDS: energy, requirement, gestational diabetes

PRINCIPAL INVESTIGATOR: Coffey, Lauri MAJ SP
ASSOCIATES: Burman, Kenneth COL MC

DEPARTMENT: Department of Medicine
SERVICE: Endocrine-Metabolic Service

STATUS: Completed
APPROVAL DATE: May 1988

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

STUDY OBJECTIVE

To compare various methods of calculating or predicting energy expenditure in women with gestational diabetes mellitus (GDM). Indirect calorimetry will serve as the gold standard.

TECHNICAL APPROACH

Thirty females with gestational diabetes (Group A) will be recruited for the study. Pregnant women (Group B) will be measured during the third trimester: indirect calorimetry, dietary history, and anthropometric measures will be secured on each patient. Regression analysis will be utilized to analyze the data.

PRIOR AND CURRENT PROGRESS

Fourteen females with gestational diabetes and 14 women who served as controls have completed the study. No new patients were enrolled this year, and no adverse reactions were reported. No direct benefit has been recognized from participating in this study. No further patients will be recruited for this study.

CONCLUSIONS

The measured resting energy expenditure (REE) determined by indirect calorimetry was compared to the calculated REE using the Harris Benedict Equation (HBE) and the Mifflin St. Jordan Predictive Equation (MSJE). Using the subjects' actual body weight, the MSJE underestimated energy expenditure 40% of the time, but there was no significant difference in absolute error between the two equations (P=.451). Both tests are useful and accurate in calculating REE in women with GDM.

REPORT DATE: 02/19/92 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: Ongoing
APPROVAL DATE: Dec 1988

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

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
Three hundred postmenopausal women have been interviewed. One hundred interviews were conducted in 1991. There were no side effects or adverse reactions in patients who participated in the interviews.

CONCLUSIONS
The incidence of fractures was not different in type or number in post-menopausal women taking thyroid hormone from the incidence of fractures in women who did not. Calcium, estrogen, smoking, pregnancy, lactation, geographic location, and alcohol consumption were not different among the women. A previous history of hyperthyroidism and dose of L-T4 did not affect the incidence of fractures. The most common type of fracture for all the women was forearm.

REPORT DATE: 04/28/92 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: Ongoing
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 entered into this study; 5 on tamoxifen and 5 on clomiphene. Two patients in each group were lost to follow-up before any post-treatment information could be collected. Of the remaining three patients completing tamoxifen treatment, one showed an increase in sperm count. Of the three patients completing clomiphene, two showed an increase in sperm count. No patients have been entered into this study since June 1991, apparently due to a fall in the number of patients with oligospermia being referred.

CONCLUSIONS
Too few patients have completed studies to permit any analysis of results.

REPORT DATE: 06/11/92 WORK UNIT # 1313-89

DETAIL SUMMARY SHEET

TITLE: The Influence of Prolonged Polar Residence Upon Cellular Receptors: The Environmental Genome Interaction

KEYWORDS: cold, thyroid, polar

PRINCIPAL INVESTIGATOR: Burman, Kenneth COL MC

DEPARTMENT: Department of Medicine STATUS: Completed
SERVICE: Endocrine-Metabolic Service APPROVAL DATE: May 1989

FUNDING: Current FY: $ 0 Previous FYs: $ 11,346 Total: $ 11,346

STUDY OBJECTIVE
To determine the changes in thyroid hormone kinetics and action in the cold.

TECHNICAL APPROACH
Labelled and unlabelled hormones will be given and kinetics determined. Binding studies will also be performed.

PRIOR AND CURRENT PROGRESS
Although this protocol was approved by DCI, funding was not approved by the Combat Casualty Care Research Program. Despite the fact that this protocol is mission-oriented and is designed to study a mission-related subject (i.e., how soldiers adapt to cold environments) and also despite the fact that USAMRDC requested protocols be submitted, USAMRDC denied funding. Thus, the only portions of the study which we were able to perform were those initiated by Dr. Reed at the National Naval Medical Center.

CONCLUSIONS
No scientific conclusions.

REPORT DATE: 06/02/92 WORK UNIT # 1314-89

DETAIL SUMMARY SHEET

TITLE: The Efficacy of Iodine Restricted Diets in the Treatment of Thyroid Cancer

KEYWORDS: iodine restriction, thyroid, cancer

PRINCIPAL INVESTIGATOR: Coffey, Lauri MAJ SP
ASSOCIATES: Burman, Kenneth COL MC; Solomon, Barbara DNSc

DEPARTMENT: Department of Medicine
SERVICE: Endocrine-Metabolic Service

STATUS: Completed
APPROVAL DATE: May 1989

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

STUDY OBJECTIVE

This study seeks to determine whether the iodine restricted diet (IRD) prescribed at WRAMC increases radioiodine uptake and visualization of thyroid tissue or metastatic lesions in patients following thyroidectomy for thyroid cancer.

TECHNICAL APPROACH

Forty-five thyroid cancer patients will be recruited to participate in this placebo controlled (regular diet) crossover (low iodine diet) study design. This study randomizes the order of treatment assignment and is a multi-variate randomized block (repeated measures of crossover design) analysis of covariance.

PRIOR AND CURRENT PROGRESS

Seventeen patients have completed the study; 6 men and 11 women. No new patients were enrolled this year, and no adverse reactions were reported. There were no direct benefits recognized from participating in this study. No further patients will be recruited for this study.

CONCLUSIONS

The mean age was 50.4 years for the 17 patients participating in this study. Two subjects had metastatic disease at diagnosis, and all but one had both surgery and I-131 as initial treatment. Compliance was measured by urinary iodine excretion. Four patients complied with the iodine restriction, but nine had significant decrease in urine iodine output. Early analysis suggests there is no difference in uptake or tissue visualization between the IRD and regular diet.

REPORT DATE: 10/16/92 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: Ongoing
APPROVAL DATE: Jul 1989

FUNDING: Current FY: $ 0 Previous FYs: $ 5,006 Total: $ 5,006

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
We have utilized differential libraries to identify thyroglobulin, TSH receptor, and peroxidase clones, and we are screening these libraries to identify p53 and HSP 70 clones. We have also shown that some clones do not match previously known sequences and we are now trying to understand their importance. Further, our work has identified the possible pathogenic epitope of thyroglobulin. To date, a total of 40 subjects have been enrolled in this study; 10 during this past year.

CONCLUSIONS
Thyroglobulin antigeneity plays an important role in disease progression. TSH receptor sequence does not seem to be abnormal in these clones.

REPORT DATE: 10/13/92 WORK UNIT # 1317-89

DETAIL SUMMARY SHEET

TITLE: Self Efficacy Beliefs and Diabetes Management Survey

KEYWORDS: diabetes, self-efficacy, self-care

PRINCIPAL INVESTIGATOR: Duncan, William LTC MC

DEPARTMENT: Department of Medicine STATUS: Completed
SERVICE: Endocrine-Metabolic Service APPROVAL DATE: Sep 1989

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

STUDY OBJECTIVE
To determine the influence of diabetes self-efficacy beliefs on the self-care behaviors of adults diagnosed within 3 years with noninsulin-dependent diabetes mellitus.

TECHNICAL APPROACH
Diabetic patients will be evaluated initially and 3 months later with the following instruments: Insulin Management Diabetes Self-Efficacy Scale, Insulin Management Diabetes Health Belief Scale, Insulin Management Diabetes Self-Care Scale, Diabetes Care Profile. An addendum was approved to expand the inclusion criteria and to look at patients at 1 year.

PRIOR AND CURRENT PROGRESS
This study is completed. A total of 60 subjects completed the 3-month protocol. Thirty subjects completed the 1-year protocol.

CONCLUSIONS
Self-efficacy beliefs about diabetes mellitus predicted 64% of the diabetes self-care behaviors after 3 months. The addition of health beliefs accounted for 8% of self-care behaviors after 3 months.

REPORT DATE: 03/17/92 WORK UNIT # 1320-90

DETAIL SUMMARY SHEET

TITLE: Evaluation of Pathological and Normal Thyroid Tissue for the Presence of Retroviral Genomic Nucleotides

KEYWORDS: thyroid, retroviral, HIV

PRINCIPAL INVESTIGATOR: Humphrey, Michael MAJ MC

DEPARTMENT: Department of Medicine STATUS: Completed
SERVICE: Endocrine-Metabolic Service APPROVAL DATE: Jan 1990

FUNDING: Current FY: $ 3,940 Previous FYs: $ 3,304 Total: $ 7,244

STUDY OBJECTIVE
To use molecular biology techniques to identify, purify and sequence retroviral gene sequences located within thyroid tissue.

TECHNICAL APPROACH
Utilization of agarous gel electrophoresis for separation of genomic DNA isolated from Graves' thyrocytes. Followed by Southern transfer to nylon filters and DNA hybridization using HIV specific probes. The polymerase chain reaction (PCR) was also used in an attempt to amplify retroviral sequences from DNA isolated from thyrocytes.

PRIOR AND CURRENT PROGRESS
Utilizing nucleic acid (DNA) isolated from patients with Graves' disease, we were unable to identify in any specimen the presence of DNA sequences related to HIV-1 retrovirus. Primary techniques employed included Southern Blotting and the polymerase chain reaction. There are no experiments on this protocol currently ongoing.

CONCLUSIONS
We have been unable to confirm the presence of HIV-1 related DNA sequences in nucleic acid isolated from Graves' thyroid tissue.

REPORT DATE: 04/15/92 WORK UNIT # 1321-90

DETAIL SUMMARY SHEET

TITLE: Processing of Atrial Natriuretic Peptide (ANP) and Its Receptor on Cultured Human Thyroid Cells: Effect of Thyroid Stimulating Hormone

KEYWORDS: ANP, thyroid, TSH

PRINCIPAL INVESTIGATOR: Tseng, Yueh-Chu PhD
ASSOCIATES: Wartofsky, Leonard COL MC

DEPARTMENT: Department of Medicine
SERVICE: Endocrine-Metabolic Service

STATUS: Completed
APPROVAL DATE: Feb 1990

FUNDING: Current FY: $ 114 Previous FYs: $ 12,689 Total: $ 12,803

STUDY OBJECTIVE

To trace the atrial natriuretic peptide (ANP) processing pathway after its binding to thyroid membrane, and to investigate the effect of thyroid stimulating hormone (TSH) on the processing of ANP in thyroid cells.

TECHNICAL APPROACH

Surgically removed thyroid gland tissue from patients with thyroid diseases will be used to initiate tissue culture for study. [125I]-ANP will be incubated with cells at 4 degrees C for 2 hours. After washing to remove exogenous ANP, cells will be incubated with fresh media in the absence or presence of TSH at 37 degrees C over specific time periods. Radioactivities recovered on cell surface membrane, inside the cells, and in media will be determined to trace the ANP processing pathway. [125I]-ANP and its metabolites in media will be analyzed by HPLC.

PRIOR AND CURRENT PROGRESS

Twenty thyroid tissues were processed for this study. The tissues were leftover samples given to us by pathologists after they removed sufficient tissue for diagnostic testing. There was no adverse effect on patients participating in this study, and patients did not directly benefit. Cultured thyroid cells were used to study ANP receptor binding, ligand (ANP)-receptor internalization, receptor half-life, and ANP degradative pathway after binding to receptors.

CONCLUSIONS

In cultured human thyroid cells: TSH stimulates the internalization of ANP-receptor complex; addition of TSH to binding buffer during assay at 37 degrees C inhibits ANP binding to receptors; and ANP is rapidly degraded by thyroid cells, but the degradation rate is not modulated by TSH.

REPORT DATE: 07/02/92 WORK UNIT # 1322-90

DETAIL SUMMARY SHEET

TITLE: Treatment of Impotence in Diabetic Men

KEYWORDS: impotence, diabetes, yohimbine

PRINCIPAL INVESTIGATOR: Humphrey, Michael CPT MC
ASSOCIATES: Glass, Allan LTC MC

DEPARTMENT: Department of Medicine
SERVICE: Endocrine-Metabolic Service

STATUS: Ongoing
APPROVAL DATE: May 1990

FUNDING: Current FY: $ 1,050 Previous FYs: $ 427 Total: $ 1,477

STUDY OBJECTIVE

To compare the effectiveness, acceptance, and complication rate of an externally applied vacuum device versus yohimbine for the treatment of impotence in the diabetic male population, and to identify any specific characteristics of patients who respond favorably to each therapy.

TECHNICAL APPROACH

Diabetic men presenting to the Endocrine Clinic will be screened to determine the status of erectile function. All subjects with erectile dysfunction will be offered participation. Evaluation will consist of history and physical, routine and endocrine lab testing, and urologic consultation. Testing will be conducted in 3-month phases with yohimbine and Erec-Aid. Initial form of therapy will be randomized with a 3-month washout period between therapeutic periods. The only protocol change involves the urologic examination, which is generally being conducted on an outpatient rather than inpatient basis.

PRIOR AND CURRENT PROGRESS

To date, 22 men have been enrolled. Ten have completed or are completing both arms, and seven others have completed at least one arm. Response to treatment with yohimbine generally has been poor. Response to vacuum device therapy has been better; 7 of 12 individuals who have completed that arm of the protocol claimed good responses. Two of 13 patients were unable to tolerate treatment with yohimbine. No severe side effects were noted. All participants in the study will have completed treatment within 3 months.

CONCLUSIONS

The study is near completion. The vacuum assistance device appears to be an effective, well-tolerated aid for the treatment of some diabetics with erectile dysfunction. Yohimbine was noted to be poorly effective in this small group of patients with erectile dysfunction.

REPORT DATE: 07/24/92 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
There were no patients with untreated Cushing's syndrome presenting for evaluation at Walter Reed Army Medical Center during the past year. Therefore, no CRH tests were performed. In the past, two patients have been studied. The CRH test during inferior petrosal sinus sampling contributed to surgical cure in one Cushing's disease patient by correctly localizing a pituitary ACTH-producing tumor. CRH identified occult ectopic ACTH production, source unknown, and an additional patient is under continued follow-up. There has been no incidence of serious or unexpected adverse reactions.

CONCLUSIONS
CRH testing, particularly during inferior petrosal sinus sampling for ACTH, remains the most discriminating, helpful, and cost-effective means of making the difficult distinction between a pituitary or occult ectopic source of ACTH in Cushing's syndrome. Surgical cure depends upon proper localization. FDA approval of CRH is still pending.

REPORT DATE: 03/03/92 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: Ongoing
APPROVAL DATE: Oct 1990

FUNDING: Current FY: $45,637 Previous FYs: $ 0 Total: $ 45,637

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

We have previously determined that TRH stimulated TSHB gene promoter activity in transiently transfected pituitary GH3 cells is similar to in vivo conditions. The DNA sequences required to mediate TRH action are located -380 to -204 of the transcription start site. Calcium mobilization and protein kinase C activation mimic TRH effects and act through the same DNA sequences. TRH (as well as calcium and protein kinase C activation) stimulates JUN and FOS mRNA accumulation prior to an increase in TSH gene activity or prolactin synthesis.

CONCLUSIONS

TRH stimulation of TSHB gene expression is mediated in part by calcium mobilization and protein kinase C activation. TRH stimulation of JUN and FOS may be key actions in stimulation of TSH synthesis.

REPORT DATE: 03/17/92 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: Humphrey, Michael MAJ MC
ASSOCIATES: Burman, Kenneth COL MC

DEPARTMENT: Department of Medicine
SERVICE: Endocrine-Metabolic Service

STATUS: Ongoing
APPROVAL DATE: Dec 1990

FUNDING: Current FY: $ 236 Previous FYs: $ 0 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

We are currently using the PCR to amplify conserved p53 DNA sequences from DNA isolated from thyroid glands. This amplified DNA has been purified, and sequencing is being actively carried out at this time. Sequencing is a tedious process which requires multiple repeat procedures on each specimen. Immunohistochemical staining will begin in the near future. We are currently awaiting the delivery of key reagents which were ordered in December 1991. Work cannot begin until these are received. We plan to extend immunohistochemical studies to include specimens obtained from multiple other types of endocrine tumors.

CONCLUSIONS

Progress is continuing as stated above.

REPORT DATE: 03/10/92 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: $ 0 Previous FYs: $ 0 Total: $ 0

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
Fourteen patients were enrolled in the first phase of the study. All patients completed the study with no adverse effects. Three patients had hypoglycemic symptoms associated with blood glucose levels less than 60 mg/dl and were discontinued. The eleven remaining patients were enrolled in the open-label, long-term treatment phase of the study. All patients have completed 6 months of treatment on a stable dose of the medication without serious adverse effects and have adequate control of their diabetes. One patient moved from the area after 6 months and was discontinued. All patients are approaching the 9 month treatment evaluation (having been seen every 3 months) and tested for hemoglobin A1C, plasma gluucose, and lipids. To date, no serious adverse effects have occurred. One patient was diagnosed with angina and coronary artery disease by cardiac catheterization and is on medical treatment.

CONCLUSIONS
From our observations, the medication seems to be safe and efficacious in the treatment of NIDDM. Our center is one of 10 sites for the study. Pfizer, Inc., is analyzing the data of all sites for possible publication.

REPORT DATE: 04/29/92 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: Humphrey, Michael MAJ MC

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Endocrine-Metabolic Service APPROVAL DATE: Feb 1991

FUNDING: Current FY: $ 3,221 Previous FYs: $ 0 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
Six patients have entered the study to date. The earliest one has been followed for 1 year. Two of three patients who have undergone follow-up CT's demonstrated significant reductions in goiter size (25% and 50%). One patient developed an elevated left hemidiaphragm 2 weeks after treatment, while a second developed post-treatment hyperthyroidism. These patients were the first two treated. Since that time, patients treated without institution of levothyroxine and with beta blocker prophylactic therapy have not experienced problems.

CONCLUSIONS
Thus far, iodine 131 at moderate doses appears effective in size reduction of multinodular goiters.

REPORT DATE: 03/31/92 WORK UNIT # 1332-91

DETAIL SUMMARY SHEET

TITLE: Thermogenic Agent Promotion of Weight Loss in Obese Soldiers

KEYWORDS: thermogenic, promotion, obese

PRINCIPAL INVESTIGATOR: Solomon, Barbara DNSc

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Endocrine-Metabolic Service APPROVAL DATE: Mar 1991

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

STUDY OBJECTIVE
To test whether thermogenic agents will enhance weight loss while subjects are on a low and maintenance caloric diet.

TECHNICAL APPROACH
Two groups repeated measures design. Groups are either placebo or agent, with further division between men and women.

PRIOR AND CURRENT PROGRESS
Mitchell-Denison Company has informed the Principal Investigator that the agents proposed are available in a pill. They no longer have an interest in pursuing tablet manufacturing or providing the placebo tablets. Therefore, no subjects have been entered into the study.

CONCLUSIONS
Alternative agents are being investigated with the intent to submit an addendum to this protocol.

REPORT DATE: 05/21/92 WORK UNIT # 1333-91

DETAIL SUMMARY SHEET

TITLE: Endothelin and Cultured Human Thyroid Cells

KEYWORDS: endothelin, thyroid, human

PRINCIPAL INVESTIGATOR: Jackson, Sharon Maj MC

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Endocrine-Metabolic Service APPROVAL DATE: Apr 1991

FUNDING: Current FY: $17,635 Previous FYs: $ 0 Total: $ 17,635

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
Thyroid tissues from 14 patients have been studied. These tissues were obtained with informed consent from patients who were scheduled for surgery by their primary physicians, and only tissues released by the pathologist which would otherwise have been discarded were used. Blood (IDCC) was drawn from 40 patients and 15 normal controls for measurement of endothelin levels. No patient has had an adverse reaction as a result of this study or been withdrawn from the study. There has been no direct benefit to any patient from the study.

CONCLUSIONS
We have demonstrated a previously unknown interaction of endothelin in the thyroid. This action of endothelin is likely to be only a part of a complex interaction of growth factors with the thyroid. The specifics of these interactions remain to be determined, as does the significance of elevated endothelin levels in patients with thyroid disorders, if confirmed.

REPORT DATE: 08/04/92 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: $ 1,043 Previous FYs: $ 0 Total: $ 1,043

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
To date, blood has been drawn on 50 patients. Three of the patients with the highest insulin levels were selected for extraction. All three patients were found to have electrophoretic bands corresponding to MW 8300, which is larger than synthetic insulin or that seen in the controls (MW 5800). Pooled sera from 15 other patients did not show this abnormal band. The immunostaining for carbohydrate was positive for all three of these patients. To date, immunostaining for insulin in these patients is negative. Enzymatically deglycosylating the insulin extract in these patients changes the molecular weight to 5800 and prevents staining with the carbohydrate stain.

CONCLUSIONS
This study may have found evidence of an abnormal circulating insulin in a subgroup of patients with NIDDM. Preliminary data suggests that the insulin is glycosylated. The plan is to further characterize this insulin and extend this work to more patients.

REPORT DATE: 08/05/92 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: $28,343 Previous FYs: $ 0 Total: $ 28,343

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, ligate to yeast artificial chromosome vectors JS97/98 or pYAC4, and transform 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
An improved method for creation of high molecular weight DNA has been developed. Currently, transformation experiments are being performed on this DNA. No patient tissue or blood for DNA has been collected in the past year since research is still currently focused on developing the library needed to study such DNA.

CONCLUSIONS
A new method for creating high molecular weight transformant DNA (which should significantly simplify and improve current methods in yeast artificial cloning) has been developed. Creation of a chromosome specific 10 YAC library would represent a major scientific tool for ide..tifying the MEN II gene, as well as any other gene on chromosome 10.

REPORT DATE: 04/24/92 WORK UNIT # 1351-84

DETAIL SUMMARY SHEET

TITLE: Cyclosporin Treatment of Graves' Ophthalmopathy

KEYWORDS: cyclosporine, exophthalmos, Graves' disease

PRINCIPAL INVESTIGATOR: Wartofsky, Leonard COL MC
ASSOCIATES: Burman, Kenneth COL MC

DEPARTMENT: Department of Medicine STATUS: Completed
SERVICE: Endocrine-Metabolic Service APPROVAL DATE: Jan 1984

FUNDING: Current FY: $ 513 Previous FYs: $ 538 Total: $ 1,051

STUDY OBJECTIVE
To assess the effectiveness of cyclosporine in the treatment of severe Graves' ophthalmopathy.

TECHNICAL APPROACH
Patients with severe Graves' ophthalmopathy demonstrating some progression in the prior year are randomized to receiving cyclosporine or high dose prednisone for 3 weeks. There is then a 3-week rest period before crossover to the alternative drug for 3 weeks. Objective improvement is assessed by measurement of proptosis, tonometry, ATA ophthalmopathy index, and serial orbital CT scans.

PRIOR AND CURRENT PROGRESS
In this multicenter study involving all US Army Medical Centers, a total of nine patients have completed the protocol. At WRAMC, three patients have been enrolled, but only two patients have completed the protocol. The other patient drop ed out after 10 days of prednisone due to intolerable gastrointestinal side effects. He did not receive cyclosporine. Our patients receiving cyclosporine had no significant or unexpected side effects. They experienced improvement in soft tissue findings but no decrease in proptosis. Cyclosporine showed no therapeutic advantage over prednisone except for better patient tolerance. No patient has received cyclosporine on protocol in the last 2 years.

CONCLUSIONS
The projected number of study patients has not been realized, and insufficient data has been generated to make valid statistical comment. Reluctantly, we believe the study deserves termination. For unclear reasons, there has been a reduction in the number of patients presenting with moderate to severe ophthalmopathy which precludes progress. At this point, other centers have "scooped" the potential results of a continued study.

REPORT DATE: 07/15/92 WORK UNIT # 1356-84

DETAIL SUMMARY SHEET

TITLE: Ketoconazole-Induced Suppression of Serum Testosterone Levels in Men

KEYWORDS: ketoconazole, testosterone, gonadotropins

PRINCIPAL INVESTIGATOR: Glass, Allan LTC MC

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Endocrine-Metabolic Service APPROVAL DATE: Jul 1984

FUNDING: Current FY: $ 0 Previous FYs: $ 4,352 Total: $ 4,352

STUDY OBJECTIVE
To determine whether the stimulation of serum LH and FSH that follows the ketoconazole-induced reduction in serum testosterone is useful as a test of pituitary gonadotropin reserve.

TECHNICAL APPROACH
Subjects are given ketoconazole 200 mg every 8 hours for 7 days, and serum LH, FSH, testosterone, and 17-OH-progesterone are measured before and after drug administration.

PRIOR AND CURRENT PROGRESS
Normal response to this test was defined in prior years. No suitable patients for this study were seen during the past year.

CONCLUSIONS
Ketoconazole stimulates LH and FSH in normal men. Responses of patients with hypothalamic-pituitary disorders are to be studied as they become available.

REPORT DATE: 04/03/92 WORK UNIT # 1359-85

DETAIL SUMMARY SHEET

TITLE: Newer Investigations into the Immune Mechanisms of Thyroid Disease (1985)

KEYWORDS: immunology, thyroid disease

PRINCIPAL INVESTIGATOR: Burman, Kenneth COL MC
ASSOCIATES: Baker, James MAJ MC

DEPARTMENT: Department of Medicine
SERVICE: Endocrine-Metabolic Service

STATUS: Ongoing
APPROVAL DATE: Feb 1985

FUNDING: Current FY: $ 1,598 Previous FYs: $ 50,128 Total: $ 51,726

STUDY OBJECTIVE
To define the T and B cell abnormalities in patients with thyroid disease, both in the peripheral mononuclear cells, as well as in the intra-thyroidal mononuclear cells.

TECHNICAL APPROACH
There are various aspects of this study: 1) Peripheral mononuclear cells are isolated and cultured in the presence of antigen specific and non-specific stimuli; 2) Similar studies are performed with intra-thyroidal cells; 3) Genes encoding unique or interesting cellular proteins are characterized; and 4) Antigen-specific proteins are characterized.

PRIOR AND CURRENT PROGRESS
We have isolated clones of cells and are studying their antigen specific characteristics. We will try to make hybridomas against interesting proteins, and we have shown that bacterial DNA has TSH receptor homology. We have demonstrated that the genetic response is polyclonal. ANP, lymphokines, and EGF are important in mediating thyroid responses in autoimmune disorders.

CONCLUSIONS
Graves' disease is an autoimmune disease in which there is a heterogeneous activation of T and B cells. We will continue to analyze the genetic responses of interest.

REPORT DATE: 10/13/92 WORK UNIT # 1361-85

DETAIL SUMMARY SHEET

TITLE: 1,25-Dihydroxyvitamin D Action at the Nuclear Level

KEYWORDS: 1,25-Dihydroxyvitamin D, liver, endocrine

PRINCIPAL INVESTIGATOR: Duncan, William LTC MC

DEPARTMENT: Department of Medicine STATUS: Completed
SERVICE: Endocrine-Metabolic Service APPROVAL DATE: May 1985

FUNDING: Current FY: $ 0 Previous FYs: $ 80,475 Total: $ 80,475

STUDY OBJECTIVE
To identify proteins synthesized by the liver in response to 1,25(OH)2D3 treatment.

TECHNICAL APPROACH
The technique of differential hybridization will be used to enrich the poly A-mRNA prior to cell free translation. PCR technology will also be utilized to determine if the vitamin D receptor is present in liver.

PRIOR AND CURRENT PROGRESS
Techniques to conduct this research protocol have been developed to include isolation of hepatic mRNA and Northern analysis, and the rearing of vitamin D deficient rats for the first time at WRAMC. Using the polymerase chain reaction (PCR) methodology, the vitamin D receptor has been detected in rat liver and a human hepatoma cell line (Hep G2). The results from this study have been used to develop a quantitative PCR technique and are the subject of another approved protocol.

CONCLUSIONS
This protocol was central in the effort to understand the molecular basis of vitamin D action. The vitamin D receptor is present in the liver.

REPORT DATE: 02/02/92 WORK UNIT # 1369-86

DETAIL SUMMARY SHEET

TITLE: Magnesium Status and Thyroid Disease

KEYWORDS: magnesium, thyroid, status

PRINCIPAL INVESTIGATOR: Burman, Kenneth COL MC
ASSOCIATES: Dolev, Eran MD; Deuster, Pat PhD

DEPARTMENT: Department of Medicine
SERVICE: Endocrine-Metabolic Service

STATUS: Completed
APPROVAL DATE: Oct 1985

FUNDING: Current FY: $ 0 Previous FYs: $ 4,353 Total: $ 4,353

STUDY OBJECTIVE

To measure magnesium and zinc levels in blood, tissue, and urine in control patients and in patients with hyperthyroidism and hypothyroidism.

TECHNICAL APPROACH

Plasma magnesium and zinc, red blood cell magnesium and zinc, mononuclear cell magnesium and zinc content and 24 hour urine excretion of magnesium and zinc were measured. Red blood cell and white blood cell counts were determined on a counter model ZM, and hemoglobin was measured with a counter electronics hemoglobinometer. Whole blood was hemolyzed by dilution with deionized water, vortexed, and then frozen. Plasma for heparinized tubes was separated from whole blood by centrifugation and frozen for later analysis. Mononuclear cells were isolated by ISOLYMPH, with harvesting and counting of the cells followed by lysis with deionized water and ultrasonication to release magnesium and zinc.

PRIOR AND CURRENT PROGRESS

Twenty-five controls (10 men and 15 women), 11 hyperthyroid and 29 hypothyroid patients volunteered to participate in this study. Magnesium status results indicated that although there was a tendency for patients with hyperthyroidism to have lower plasma concentration of magnesium, as compared to hypothyroid and euthyroid subjects, the differences were not significant. Similarly, red blood cell magnesium did not differ between the groups.

CONCLUSIONS

Plasma magnesium concentrations tended to be lower in hyperthyroid patients, but differences among the groups were not significant. Similarly, red blood cell concentration and mononuclear cell content of magnesium did not differ among the three groups. In contrast, hypothyroid patients showed marked decreases in urinary magnesium excretion as compared to hyperthyroid and euthyroid subjects.

REPORT DATE: 02/24/92 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: Ongoing
SERVICE: Endocrine-Metabolic Service APPROVAL DATE: Nov 1985

FUNDING: Current FY: $ 698 Previous FYs: $ 10,705 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
Work on this project has concentrated on using detection of Y-chromosomal DNA sequences in sperm as a prototype for further detection studies. An abstract detailing preliminary results was presented in April 1991. Since that time, we have been informed of improvements in separation of X and Y-containing sperm and are now using this new procedure to evaluate results. Progress has been hampered in recent months by difficulty obtaining adequate sperm specimens from pathology lab; we are working on this problem. Also carried out were some preliminary results testing various agents to practically decondense DNA in sperm to render it more accessible to DNA probes; results so far are inconclusive. Further studies will be aimed at attempting DNA detection without destroying sperm viability.

CONCLUSIONS
Detection of Y-chromosome-containing sperm by using DNA probes is feasible. Whether this is possible on unkilled sperm is problematic, as is usefulness of albumin-column techniques of sperm separation.

REPORT DATE: 09/30/92 WORK UNIT # 1372-86

DETAIL SUMMARY SHEET

TITLE: Effect of Altered Energy Balance on Sexual Maturation in Rats

KEYWORDS: energy balanc , sexual maturation, hyperthyroidism

PRINCIPAL INVESTIGATOR: Glass, Allan COL MC

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Endocrine-Metabolic Service APPROVAL DATE: Nov 1985

FUNDING: Current FY: $ 4,136 Previous FYs: $ 64,255 Total: $ 68,391

STUDY OBJECTIVE
To determine the effect of alterations in energy balance on sexual maturation in rats.

TECHNICAL APPROACH
Energy balance will be manipulated in rats by food restriction, hyperthyroidism, or catecholamine infusion. Parameters of puberty and growth will be monitored serially, including assessment of such factors as hormone levels, growth rates, timing of vaginal opening, and sperm production.

PRIOR AND CURRENT PROGRESS
Several experiments were carried out to assess the ability of estrogen to induce LH release in hyperthyroid weanling rats. After several preliminary studies to assess dose of estrogen and timing, which turned out to be critical, it could be demonstrated that hyperthyroidism reduced the magnitude of estrogen-induced LH release. Another experiment was completed to assess tissue-specific expression of mRNA for IGF-1 as a possible reason for the differential effects of hyperthyroidism on tissue growth; assays for these are still being conducted. Progress on this study has been slowed by unavoidable delays due to end-of-fiscal-year fund cut-offs and delays in performance of assays by contractors. Thus, for an animal experiment performed in September 1991, final assay results were not received until March 1992.

CONCLUSIONS
Mild hyperthyroidism in weanling rats seems to delay puberty by interfering with hypothalmic function, specifically estrogen-induced LH release. Effect of hyperthyroidism on tissue-specific expression of IGF-1 remains to be determined.

REPORT DATE: 04/27/92 WORK UNIT # 1376-86

DETAIL SUMMARY SHEET

TITLE: Ketoconazole Effects on Vitamin D in Hypercalcemic Patients

KEYWORDS: ketoconazole, hypercalcemia, vitamin D

PRINCIPAL INVESTIGATOR: Glass, Allan COL MC

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Endocrine-Metabolic Service APPROVAL DATE: Apr 1986

FUNDING: Current FY: $ 0 Previous FYs: $ 18,811 Total: $ 18,811

STUDY OBJECTIVE
To determine whether ketoconazole can reduce serum itamin D levels and/or serum calcium levels in hypercalcemic patients, and to assess whether such reduction might be of diagnostic or therapeutic use.

TECHNICAL APPROACH
Measurement of serum calcium, PTH, and vitamin D metabolites in hypercalcemic patients before and after administration of ketoconazole 200 mg every 8 hours for 1 week.

PRIOR AND CURRENT PROGRESS
Previous studies under this protocol defined the effect of ketoconazole on calcium metabolism in normal subjects, patients with primary hyperparathyroidism, and one patient with sarcoidosis. This protocol is being kept active to permit study of additional hypercalcemic patients with sarcoidosis; however, such patients are extremely uncommon, and none were studied during the past year.

CONCLUSIONS
Ketoconazole suppresses production of 1,25-dihydroxyvitamin D in normal subjects, patients with primary hyperparathyroidism, and patients with sarcoidosis.

REPORT DATE: 02/01/92 WORK UNIT # 1385-87

DETAIL SUMMARY SHEET

TITLE: Molecular Biology of Thyroid Disease

KEYWORDS: molecular, thyroid, biology

PRINCIPAL INVESTIGATOR: Burman, Kenneth COL MC
ASSOCIATES: Baker, James MAJ MC; Wartofsky, Leonard COL MC

DEPARTMENT: Department of Medicine
SERVICE: Endocrine-Metabolic Service

STATUS: Ongoing
APPROVAL DATE: Oct 1986

FUNDING: Current FY: $ 2,938 Previous FYs: $ 62,556 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
We are trying to clone the TSH receptor 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.

PRIOR AND CURRENT PROGRESS
We have been successful in isolating two recombinant clones which appear to express thyroid antigens of approximately 18,000 and 65,000 molecular weight that are detected by our monoclonal antibody against the TSH receptor and not by controlled samples. We have also identified proteins to which antibodies are directed.

CONCLUSIONS
The TSH receptor is composed of 18,000 and 65,000 molecular weight antigens. Intrathyroidal lymphocytes from patients with autoimmune disease show a polyclonal heterogeneity. C-myc expression is unchanged in thyroid disease. We have identified a unique area in the TSH receptor that is immunogenic.

REPORT DATE: 03/04/92 WORK UNIT # 1386-87

DETAIL SUMMARY SHEET

TITLE: In Vitro Determination of Messenger RNA Isolated from Porcine Thyroid Glands

KEYWORDS: messenger RNA, porcine, thyroid glands

PRINCIPAL INVESTIGATOR: Burman, Kenneth COL MC
ASSOCIATES: Baker, James MAJ MC; Peele, Mark CPT MC

DEPARTMENT: Department of Medicine STATUS: Completed
SERVICE: Endocrine-Metabolic Service APPROVAL DATE: Dec 1986

FUNDING: Current FY: $ 0 Previous FYs: $ 3,979 Total: $ 3,979

STUDY OBJECTIVE
To utilize in vitro translation of thyroid messenger RNA in order to understand the array of thyroid specific proteins that are encoded and, further, to isolate and characterize important thyroid related proteins, such as the TSH receptor.

TECHNICAL APPROACH
Isolation of messenger RNA from pork thyroid glands is performed by standard GTC extraction techniques. The messenger RNA is obtained by poly A+ RNA chromatography, and the messenger RNA obtained is translated with an S labelled into specific proteins. These specific proteins are then electrophoresed on one or two dimensional gels, with the proteins obtained then identified. Both pork thyroid glands and hepatic samples are used. Also, specific antibodies can be utilized against the proteins to determine which proteins are of interest, such as to recognize the TSH receptor.

PRIOR AND CURRENT PROGRESS
Newer techniques in translation allowed us to perform a variety of tests. We performed about 15 translations and gel electrophoreses but did not identify any new proteins.

CONCLUSIONS
Porcine thyroid glands in a normal state are not associated with aberrant protein formation or with unique oncogenes.

REPORT DATE: 10/13/92 WORK UNIT # 1389-87

DETAIL SUMMARY SHEET

TITLE: 1,25-Dihydroxyvitamin D3 Induction of Ornithine Decarboxylase Activity in Regenerating Rat Liver

KEYWORDS: 1,25-dihydroxyvitamin, ornithine decarboxylase, liver

PRINCIPAL INVESTIGATOR: Duncan, William LTC MC
ASSOCIATES: Wray, H. Linton COL MC

DEPARTMENT: Department of Medicine
SERVICE: Endocrine-Metabolic Service

STATUS: Completed
APPROVAL DATE: May 1987

FUNDING: Current FY: $ 232 Previous FYs: $ 13,020 Total: $ 13,252

STUDY OBJECTIVE
To determine whether 1,25(OH)2D3 induces ornithine decarboxylase (ODC) activity via a receptor (genomic) mechanism in regenerating rat liver.

TECHNICAL APPROACH
ODC activity and oncogene expression are measured in regenerating liver from vitamin D deficient and vitamin D treated rats.

PRIOR AND CURRENT PROGRESS
The hepatic nuclear 1,25(OH)2D3 receptor has been shown to rapidly decrease in regenerating rat liver. Analysis of these changes with time demonstrates that the receptor decreases to 64% of basal concentrations 2 hours after hepatectomy, and slowly returned to pre-hepatectomy values by 32 hours. ODC activity increases after hepatectomy to a maximum at 16 hours. Changes in c-myc proto-oncogene mRNA expression by Northern Analysis are being analyzed. To date, these studies confirm a previous finding using dot blot analysis of a decrease in c-myc mRNA 2 hours after hepatectomy.

CONCLUSIONS
The rise in c-myc and ODC expression during liver regeneration is associated with a fall, not a rise, in expression of the vitamin D receptor. Thus, these activities may not be linked to receptor-mediated 1,25(OH)2D3 action in the regenerating liver.

REPORT DATE: 10/03/92 WORK UNIT # 1390-87

DETAIL SUMMARY SHEET

TITLE: Dynamic Assessment of Zinc Status in Thyroid Disease

KEYWORDS: zinc, hyperthyroidism, hypothyroidism

PRINCIPAL INVESTIGATOR: Burman, Kenneth COL MC
ASSOCIATES: Wartofsky, Leonard COL MC; Solomon, Barbara DNSc

DEPARTMENT: Department of Medicine
SERVICE: Endocrine-Metabolic Service

STATUS: Completed
APPROVAL DATE: May 1987

FUNDING: Current FY: $58,691 Previous FYs: $ 81,905 Total: $ 140,596

STUDY OBJECTIVE
To understand zinc metabolism in thyroid disease.

TECHNICAL APPROACH
Measure zinc blood and urine levels in patients with thyroid disease. A zinc tolerance test is also given. A diet record is kept by the patient.

PRIOR AND CURRENT PROGRESS
Sixteen hypothyroid, five hyperthyroid, and eight normal volunteers have completed the study. All blood and urine samples were analyzed, and the data was computed. Our collaborators at USUHS finished performing their aspects of the study, and we will meet with them again to discuss their results.

CONCLUSIONS
Zinc clearance is altered as the thyroid state changes.

REPORT DATE: 07/10/92 WORK UNIT # 1391-87

DETAIL SUMMARY SHEET

TITLE: Bone Mineral Density (BMD) in Patients with Chronic Renal Failure

KEYWORDS: bone mineral, renal failure

PRINCIPAL INVESTIGATOR: Duncan, William LTC MC
ASSOCIATES: Gouge, Steven MAJ MC; Moore, Jack LTC MC

DEPARTMENT: Department of Medicine
SERVICE: Endocrine-Metabolic Service

STATUS: Ongoing
APPROVAL DATE: Jun 1987

FUNDING: Current FY: $ 0 Previous FYs: $ 814 Total: $ 814

STUDY OBJECTIVE
To correlate bone mineral density measurements at the spine and forearm with clinical and laboratory parameters of patients with chronic renal failure.

TECHNICAL APPROACH
This is a pilot retrospective chart review of patients with chronic renal failure who have had forearm and spine bone mineral density measurements.

PRIOR AND CURRENT PROGRESS
Data collection is completed and analyzed. Results indicate that in chronic renal failure, bone loss is primarily cortical and that measurement of trabecular bone adds little to the evaluation of patients with chronic renal failure. As measurements of the bone mineral density (BMD) accumulate (presently, about 105 patients), over 30 of these patients have repeated BMD's. We are now attempting to correlate the rate of change of the BMD at various bone sites with the clinical parameters already measured.

CONCLUSIONS
Forearm densitometry is the test of choice to follow the status of bone mineral density in patients with chronic renal failure.

REPORT DATE: 10/13/92 WORK UNIT # 1393-87

DETAIL SUMMARY SHEET

TITLE: Regulation of Rat TSH Beta Subunit Gene Expression

KEYWORDS: TSH, gene, rodent

PRINCIPAL INVESTIGATOR: Carr, Frances PhD

DEPARTMENT: Department of Medicine STATUS: Completed
SERVICE: Endocrine-Metabolic Service APPROVAL DATE: Aug 1987

FUNDING: Current FY: $ 1,998 Previous FYs: $ 142,503 Total: $ 144,501

STUDY OBJECTIVE
To determine how the structure of the B-subunit gene of rat thyrotropin defines the functional response of the gene (including hormonal regulation) by thyroid hormones and tissue-specific expression.

TECHNICAL APPROACH
Chimaeric plasmids, encompassing various portions of the 5'-end of the rat TSH B-subunit gene, will be constructed by fusion of the eukaryotic gene sequence with the coding sequence of a reporter enzyme [specifically bacterial chloramphenicol actyl transferase (CAT)]. Transient expression in eukaryotic cells will then be used to identify the cis elements responsible for hormonal regulation in a responsive cell line and those responsible for cell-specific expression in non-responsive cell lines. Then, DNA-protein interaction assay (DNase I protection and gel shift assays) will be used to identify DNA binding proteins that affect transcription, such as the thyroid hormone receptor.

PRIOR AND CURRENT PROGRESS
Deletion analysis of the TSH beta gene revealed that a 57 bp DNA fragment spanning exon 1 contained sufficient DNA sequence to mediate thyroid hormone regulation of gene expression. By continued deletion/mutation analysis, linker scanning of the first exon, two thyroid hormone response elements (TRE's) have been localized. Sequences +18/+27 include the potent TRE absolutely required to mediate thyroid hormone regulation. This sequence binds to thyroid hormone receptors (both alpha and beta isomers) as well as other transcriptional factors, and mediates thyroid hormone action in thyroid hormone receptor deficient cells only with a functional receptor added. Of significance, one mechanism that mediates differential regulation by thyroid hormones is an intrinsic property of the TRE motif.

CONCLUSIONS
Sequences spanning the first exon of the TSH beta subunit gene mediate thyroid hormone regulation in vivo and in vitro. The sequences confer thyroid hormone sensitivity to heterologous promoters. While squelching/quenching and/or steric hindrance may be contributing factors in mediating negative regulation by thyroid hormones, an intrinsic property of the TRE motif is an essential element in differential regulation by thyroid hormones.

REPORT DATE: 10/14/92 WORK UNIT # 1394-87

DETAIL SUMMARY SHEET

TITLE: Molecular Biology of Nutrient Alterations in Rats

KEYWORDS: molecular biology, nutrition, glucose

PRINCIPAL INVESTIGATOR: Burman, Kenneth COL MC
ASSOCIATES: Carr, Frances PhD; Glass, Alan COL MC

DEPARTMENT: Department of Medicine
SERVICE: Endocrine-Metabolic Service

STATUS: Completed
APPROVAL DATE: Aug 1987

FUNDING: Current FY: $ 0 Previous FYs: $ 20,867 Total: $ 20,867

STUDY OBJECTIVE
To examine changes in the insulin receptor and glucose transporter gene and T3 transcript in various states of nutrition.

TECHNICAL APPROACH
Rats are divided into eight dietary groups so that the effect of nutritional alterations can be studied in various aspects of DNA and RNA. There is a control, calorie restricted, high fat, pair fed, high sucrose, and copper deficient group. After 3 months on the appropriate diet, the rats are euthanized, and the organs are studied for transcription of various genes; to include T3, transporter, insulin receptor, erb A, TSH receptor, and other oncogenes and proteins.

PRIOR AND CURRENT PROGRESS
The rat tissues were obtained, but there were no differences found in any genes examined. This study is being closed due to DCI policy and because the investigators do not have the personnel to continue this study.

CONCLUSIONS
None.

REPORT DATE: 09/02/92 WORK UNIT # 1395-87

DETAIL SUMMARY SHEET

TITLE: Oncogenes and Thyroid Receptors

KEYWORDS: oncogenes, thyroid

PRINCIPAL INVESTIGATOR: Burman, Kenneth COL MC
ASSOCIATES: Carr, Frances PhD; Baker, James MAJ MC

DEPARTMENT: Department of Medicine
SERVICE: Endocrine-Metabolic Service

STATUS: Ongoing
APPROVAL DATE: Sep 1987

FUNDING: Current FY: $37,691 Previous FYs: $ 144,669 Total: $ 182,360

STUDY OBJECTIVE

To determine whether oncogenes are expressed variably in thyroid tissue derived from patients with different thyroid diseases. Further, patterns of DNA hybridization will help determine if amplified or rearranged genes exist.

TECHNICAL APPROACH

Nucleotides will be subjected to gel electrophoresis and then transferred to nylon or nitrocellulose. These membranes will then be probed with high specific activity P32 labelled inserts or plasmids. Results will be quantitated visually and by spectrophotometer readings, after autoradiography and development. Abnormal patterns of hybridization may indicate expression abnormalities in RNA or amplification or rearrangement abnormalities in DNA.

PRIOR AND CURRENT PROGRESS

There are a total of 40 subjects entered on this study; 10 during the last year. Over the last year, thyroid tissue for p53 abnormalities has been assessed, but despite numerous sequencing reactions, a nucleotide abnormality in this gene has not been identified. A CDNA library has been constructed from a patient with metastatic thyroid cancer, and the TSH receptor in this tumor has been sequenced and found normal. No viral abnormalities have been identified either. There has been no incidence of serious or unexpected adverse reactions.

CONCLUSIONS

p53 abnormalities and TSH receptor are normal in various thyroid tumors examined, but further investigation in this area is needed.

REPORT DATE: 02/05/92 WORK UNIT # 1399-87

DETAIL SUMMARY SHEET

TITLE: Growth Factors and the Thyroid Gland

KEYWORDS: human thyroid, EGF, ANP

PRINCIPAL INVESTIGATOR: Tseng, Yueh-Chu PhD
ASSOCIATES: Wartofsky, Leonard COL MC; Burman, Kenneth COL MC

DEPARTMENT: Department of Medicine
SERVICE: Endocrine-Metabolic Service

STATUS: Ongoing
APPROVAL DATE: Dec 1987

FUNDING: Current FY: $12,352 Previous FYs: $ 90,498 Total: $ 102,850

STUDY OBJECTIVE

To determine the role of epidermal growth factor (EGF), atrial natriuretic peptide (ANP) and their respective receptors in the maintenance of cultured human thyroid cells derived from surgically removed thyroids in various diseased states.

TECHNICAL APPROACH

1) Primary thyroid cell culture will be established by digesting human thyroid tissues with collagenase, collecting the thyroid cells, then growing cells in proper plates for experiments. 2) EGF and ANP receptors on thyroid cells will be assayed by Scatchard analysis to determine the number of receptor binding sites and their respective binding association constants. 3) Effects of EGF and ANP on thyroglobulin (Tg) secretion by thyroid cells will be determined by assaying Tg concentration media using ELISA. 4) ANP receptor will be characterized by affinity cross-linking using chemical reagent followed by electrophoresis gel separation.

PRIOR AND CURRENT PROGRESS

More than 30 patients had signed the consent forms, but only 12 thyroid tissues were given to us by pathologists to be processed for this study. The tissues obtained were leftover after a pathologist had taken sufficient thyroid for diagnosis. There have been no adverse effects on patients participating in this study, and patients did not directly benefit from the study. Cultured thyroid cells were incubated with growth factors, and cell responses were studied. Cultured medium were assayed for various growth factors secreted by thyroid cells. Thyroid cells were also assayed for receptor bindings to various hormones.

CONCLUSIONS

Transforming growth factor-alpha stimulated thyroid cell growth. TGF-alpha shared the same receptors with epidermal growth factor. Transforming growth factor-beta inhibited thyroid cell growth and thyroglobulin secretion. TGF-beta also inhibited TSH stimulated thyroglobulin secretion by thyroid cells. Tumor necrosis factor inhibited TSH stimulated thyroglobulin secretion by thyroid.

REPORT DATE: 09/30/92 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
SERVICE: Endocrine-Metabolic Service

STATUS: Ongoing
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

No EGF-R abnormalities were identified in these disease states, although a polymorphism was identified. No new subjects were accrued during the reporting period; a total of 4 subjects have been enrolled to date. Patient accrual is complete, and a manuscript has been submitted for publication.

CONCLUSIONS

EGF-R does not seem to be perturbed in these disease states.

REPORT DATE: 10/06/92 WORK UNIT # 4299

DETAIL SUMMARY SHEET

TITLE: T-Cell Dysfunction as a Prognosticator for the Development of Autoimmune Thyroid Disease in Microsomal Antibody Positive Postpartum Women

KEYWORDS: thyroiditis, oncogenes, autoimmunity

PRINCIPAL INVESTIGATOR: Fein, Henry LTC MC
ASSOCIATES: Smallridge, Robert COL MC; Carr, Frances PhD

DEPARTMENT: Department of Medicine
SERVICE: Endocrine-Metabolic Service

STATUS: Ongoing
APPROVAL DATE: Aug 1990

FUNDING: Current FY: $ 575 Previous FYs: $ 13,443 Total: $ 14,018

STUDY OBJECTIVE

To evaluate T cell dysfunction to shed light on pathogenesis of Autoimmune Thyroid Disease (AITD). It is anticipated that thyroid microsomal antigen specific stimulation will reveal alterations in postpartum microsomal antibody positive patients which may better explain causes of AITD and identify women who will develop clinical postpartum thyroid disease. T cells will be used from four groups of women: postpartum MAb positive(+) or negative(-); nonpostpartum MAb + or -.

TECHNICAL APPROACH

T cells will be obtained at 0,3,6 mos from postpartum subjects and once from nonpostpartum subjects. IL-1 stimulation will look for nonspecific enhancement of immune function. Baseline and stimulatory measurements of proto-oncogenes c-fos, c-jun, and c-myc, IL-2 production, and cell proliferation via [3H] thymidine incorporation will be made. Intergroup variations in the response of these assays to various stimuli will reflect alterations in T cell function. MAb levels will be analyzed in relation to incremental changes of oncogenes, IL-2 production, and cell proliferation. Gestational alterations in immune system will be reflected by differences in the three test criteria when comparing the four groups.

PRIOR AND CURRENT PROGRESS

Blood drawing was completed during FY92. The plan was to enroll 20 patients in each group. Final accrual was: Group I (PP, MAb+): 18 subjects had T cells obtained at 0,3,6 mos; 6 others did not complete protocol (bloods obtained at 0 and 3 mos; subjects did not return at 6 mo PP). Group II (PP, MAb-): 15 completed; 6 did not complete. Group III (MAb+): 10 subjects. Group IV (MAb-): 20 subjects. No further patients will be enrolled. T cell function: All samples have undergone IL-1 stimulation; samples obtained for determinations of IL-2 production, cell proliferation. Cells processed to obtain oncogene mRNA levels.

CONCLUSIONS

Data are being actively accumulated at present. No definitive conclusions have been drawn yet.

REPORT DATE: 09/09/92 WORK UNIT # 4300

DETAIL SUMMARY SHEET

TITLE: Atrial Natriuretic Peptide and the Endometrium

KEYWORDS: ANP, endometrium, estrogen

PRINCIPAL INVESTIGATOR: Tseng, Yueh-Chu Ph.D.
ASSOCIATES: Wartofsky, Leonard COL MC

DEPARTMENT: Department of Medicine
SERVICE: Endocrine-Metabolic Service

STATUS: Completed
APPROVAL DATE: Sep 1990

FUNDING: Current FY: $ 900 Previous FYs: $ 9,013 Total: $ 9,913

STUDY OBJECTIVE

To analyze endometrial tissue preparations for the presence of atrial natriuretic peptide (ANP) receptor and to demonstrate binding specificity; to culture endometrial cells in laboratory dishes and study ANP binding to viable cells; and to investigate the effects of sex steroids (estradiol and progesterone) on the development of ANP receptors.

TECHNICAL APPROACH

Frozen endometrium tissues will be homogenized in buffer, and membrane will be prepared by centrifugation. Membrane suspension will be incubated with 125-I-ANP at 4 C to determine specific binding to receptor. Freshly obtained endometriumwill be digested in collagenase to isolate endometrial cells. Stromal cells will be isolated via diffential trypsinization and cultured in 24-well plate at the density of 100,000 cells/well. ANP binding will be studied on cells pretreated with various concentrations of sex steroids.

PRIOR AND CURRENT PROGRESS

Two patients were enrolled in FY 92; 25 patients altogether. There have been no unexpected adverse reactions in patients, and no direct benefit to them. Endometrium was obtained by biopsy in regularly menstruating women, and stromal cells were isolated and cultured for use. ANP competitive binding assays were performed using 125-I-labeled ANP (0.1 nmol/L) and increasing concentrations of unlabeled ANP (0-1000 nmol/L). Optimal binding was obtained after 3 hours incubation at 4 C, and binding characteristics, including dissociation constant and binding site quantity, were estimated by Scatchard analysis. Specific, high affinity (Kd=0.078+/-0.004 nmol/L) and low capacity (4877+/-1951 binding sites/cell) ANP binding was identified. Evaluation of ANP-stimulated cyclic nucleotide production revealed an increase in cGMP production, with a sevenfold increase at 1000 nmol/L ANP and no effect on cAMP production.

CONCLUSIONS

Specific high affinity receptors for ANP were identified in human endometrial cells, suggesting a role for ANP in endometrial cell function and/or development mediated via cGMP production. ANP may affect local salt and water metabolism, be involved in the secretory evolution of glandular and stromal cells, and further facilitate endometrial development via modulation of local vascular tone and endothelial permeability.

REPORT DATE: 06/11/92 WORK UNIT # 9266

DETAIL SUMMARY SHEET

TITLE: The Treatment of Graves' Disease with Anti-Idiotype Therapy Using Intravenous Immunoglobulin

KEYWORDS: Graves' disease, anti-idiotype, IV immunoglobulin

PRINCIPAL INVESTIGATOR: Burman, Kenneth COL MC
ASSOCIATES: Baker, James MAJ MC; Wartofsky, Leonard COL MC

DEPARTMENT: Department of Medicine
SERVICE: Endocrine-Metabolic Service

STATUS: Ongoing
APPROVAL DATE: May 1986

FUNDING: Current FY: $ 0 Previous FYs: $ 23,963 Total: $ 23,963

STUDY OBJECTIVE

To determine if IV immunoglobulin alters thyroid function or antibody levels in patients with Graves' disease.

TECHNICAL APPROACH

Subjects will be infused with 4 grams per kg daily for 3 days. Thyroid hormone levels and TBII and TSI levels before, during, and after the infusion will be determined.

PRIOR AND CURRENT PROCRESS

The three infusions performed were tolerated well by two subjects; the third did not feel well during the infusion. There were apparently no major alterations in the parameters measured. We plan to recruit more patients since we continue to feel these infusions might be helpful in the treatment of Graves' disease.

CONCLUSIONS

None yet.

REPORT DATE: 09/30/92 WORK UNIT # 9273

DETAIL SUMMARY SHEET

TITLE: Identification and Characterization of Thyroid Autoantigens

KEYWORDS: thyroid, antigen, viral

PRINCIPAL INVESTIGATOR: Burman, Kenneth COL MC
ASSOCIATES: Humphrey, Michael CPT MC; Francis, Thomas CPT MC

DEPARTMENT: Department of Medicine
SERVICE: Endocrine-Metabolic Service

STATUS: Ongoing
APPROVAL DATE: Sep 1988

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

STUDY OBJECTIVE
To identify viral-like particles in serum or thyroid tissue from patients with thyroid disease.

TECHNICAL APPROACH
Northern and Southern blots with viral probes, as well as PCR with viral and related particles, EB virus transformation, and hybridoma fusions for T and B cells are to be performed.

PRIOR AND CURRENT PROGRESS
Clones have been identified that have sequences similar to thyroglobulin and are being assessed for sequence mutation. These thyroglobulin clones have also been identified by use of disease-associated monoclonal antibodies in animals. In addition, we have characterized the T cells that respond to local thyroid autoantigens. These cells seem to respond to one particular portion of the TSH receptor (aa 90-120). Attempts are now being made to characterize this T cell receptor. Spectometry will be used to further analyze disease-associated antigens. HIV-like viral particles were not found. Ten new subjects were enrolled, for a total of 13 so far, and no adverse reactions were noted.

CONCLUSIONS
The TSH receptor contains a unique immunogenic portion which can stimulate T cells specifically.

REPORT DATE: 09/17/92 WORK UNIT # 1401

DETAIL SUMMARY SHEET

TITLE: The Effect of Normalization of Intraesophageal pH on Mucosal Proliferation in Barrett's Esophagus

KEYWORDS: Barrett's esophagus, gastroesophageal reflux, proliferation

PRINCIPAL INVESTIGATOR: Murphy, Joseph MAJ MC
ASSOCIATES: Maydonovitch, Corinne BS; Wong, Roy COL MC

DEPARTMENT: Department of Medicine
SERVICE: Gastroenterology Service

STATUS: Ongoing
APPROVAL DATE: Sep 1988

FUNDING: Current FY: $ 718 Previous FYs: $ 5,879 Total: $ 6,597

STUDY OBJECTIVE

Barrett's esophagus (BE) is a columnar epithelium with premalignant potential which develops in response to prolonged and severe gastroesophageal reflux (GER). The study objective is to normalize the intraesophageal pH with omeprazole (Losec) and then observe the effect on mucosal proliferation as assessed by ornithine decarboxylase activity and thymidine uptake.

TECHNICAL APPROACH

Patients (10) with BE, who have reflux by 24 hour ambulatory esophageal pH study, will have esophagogastro-duodenoscopy (EGD) to obtain biopsies of BE to measure mucosal proliferation rate. Losec 20 mg po bid will be started; a pH study will be repeated after 1 week. If the esophageal pH is still <4, the dosage of Losec will be increased and the pH study repeated. When the esophageal pH is >4 on repeat pH study, the Losec will be continued an additional 60 days. EGD with biopsies and pH study will be completed after 30 and 60 days on Losec. Five control patients (with gastric ulcers) will undergo three sequential EGD's with at least one pH study to exclude GER.

PRIOR AND CURRENT PROGRESS

Ten patients with Barrett's esophagus have completed the study. In eight patients the rectal mucosa has been studied for thymidine uptake and ornithine decarboxylase (ODC) activity. Also, in all ten patients the esophageal biopsies have been processed. Proliferation indices are being calculated for the 1100 slides generated. No patients have had an adverse reaction.

CONCLUSIONS

None at this time.

REPORT DATE: 03/06/92 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: Ongoing
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 have been 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 have been enrolled in 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.

CONCLUSIONS
The MC/CC syndrome causes chronic diarrhea. Histologic features correlate with clinical disease. Sulfasalazine appears to be effective in selected patients.

REPORT DATE: 06/22/92 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: Crespo, Israel MAJ MC
ASSOCIATES: Cheney, Christopher LTC MC

DEPARTMENT: Department of Medicine
SERVICE: Gastroenterology Service

STATUS: Ongoing
APPROVAL DATE: Mar 1989

FUNDING: Current FY: $ 2,394 Previous FYs: $ 8,073 Total: $ 10,467

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

A total of 65 patients were enrolled over the past 3 years. Fifty-nine have completed the full protocol, with 43 found to be H. pylori positive and 16 found to be H. pylori negative. There have been no serious complications due to this study, and there have been no withdrawals.

CONCLUSIONS

Treatment efficacy is 80%. Serum antibodies fall with H. pylori treatment eradication. Saliva contains detectable amounts of antibodies to H. pylori. Eradication of H. pylori results in a significant decrement in salivary IgG.

REPORT DATE: 05/20/92 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: Ongoing
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
Charts of 30 previously untreated achalasia patients have been reviewed. Data has been collected from esophageal manometry studies and cornflakes emptying studies performed before dilation and 1, 6, and 12 months after dilation. Data recorded at the time of dilation was also reviewed for several parameters that may influence success of dilation.

CONCLUSIONS
No single parameter examined at the time of dilation could indicate success versus failure. Significant improvement in post-dilation parameters was noted in successfully treated patients.

REPORT DATE: 06/09/92 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: Landes, Tim MAJ MC
ASSOCIATES: Maydonovitch, Corinne BS; Wong, Roy COL MC

DEPARTMENT: Department of Medicine
SERVICE: Gastroenterology Service

STATUS: Ongoing
APPROVAL DATE: May 1989

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

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
Sixty-four manometry/24 hr pH studies done at WRAMC GI clinic 1987-1991 were reviewed. Those charts which demonstrated significant supine reflux (scores > 50, supine reflux > 2% total time) were specifically evaluated. No adverse reactionns from patients during this retrospective review were noted. Dr. Smith (GI Service) is currently evaluating charts from this time period to better define upright reflux.

CONCLUSIONS
Patients who lie down 4 hours following supper have their first reflux episode 30-45 minutes after lying down. During each supine hour, mean esophageal acid exposure time ranges from 17-27 minutes. When comparing patients with low, low normal, and normal lower esophageal sphincter pressure (LESP), there is no significant difference in the time of first supine reflux, longest reflux, and duration of reflux in these three groups.

REPORT DATE: 07/21/92 WORK UNIT # 1409

DETAIL SUMMARY SHEET

TITLE: Comparison of Intravenous H2 Antagonists and Their Influence on Gastric Emptying in Humans

KEYWORDS: gastric emptying, H2 antagonists

PRINCIPAL INVESTIGATOR: Stamm, Carl MAJ MC

DEPARTMENT: Department of Medicine STATUS: Completed
SERVICE: Gastroenterology Service APPROVAL DATE: Aug 1989

FUNDING: Current FY: $ 0 Previous FYs: $ 1,307 Total: $ 1,307

STUDY OBJECTIVE

To evaluate the effect of intravenous bolus administration of three H-2 antagonists (cimetidine, ranitidine and famotidine) on gastric emptying (GE) in humans.

TECHNICAL APPROACH

In a double blinded randomized manner, on four separate study days spaced at least 72 hours apart, subjects will undergo a standard gastric emptying test in Nuclear Medicine after receiving an intravenous bolus of placebo or an H-2 antagonist. Gastric emptying data will be collected for 150 minutes. Blood samples for drug levels will be drawn immediately after.

PRIOR AND CURRENT PROGRESS

A total of nine patients have been studied to date, with no new patients being studied this year. Each of the nine subjects had four gastric emptying studies done after IV bolus injection of a placebo or one of three histamine H2-receptor antagonists. Compared to the placebo, H-2 antagonists affect the early phase solid gastric emptying but not the late phase or overall emptying.

CONCLUSIONS

The finding that early phase gastric emptying is delayed by H-2 antagonists may be of clinical importance in patients with borderline emptying disorders. This study is being closed because the principal investigator is leaving WRAMC.

REPORT DATE: 02/18/92 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
SERVICE: Gastroenterology Service

STATUS: Ongoing
APPROVAL DATE: Oct 1989

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

STUDY OBJECTIVE

To determine possible efficacy of low-dose methotrexate in the treatment of primary sclerosing cholangitis.

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

Three new patients were enrolled in this protocol since January 1991. A total of nine patients have been enrolled to date. There have been no serious or unexpected reactions to the methotrexate. One patient has just completed the 2 year protocol. Two patients have withdrawn from the study voluntarily. One patient has had progression of his disease while on the protocol and currently is on the transplant list at Wilford Hall in Texas. He is the only patient to date who has shown progression of disease while on the protocol.

CONCLUSIONS

Ongoing study.

REPORT DATE: 04/03/92 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: Ongoing
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 been completed. No serious or unexpected adverse reactions have occurred, and none of the volunteers have had to withdraw. None of the patients have derived any benefit from participation in this study.

CONCLUSIONS
Lithium carbonate does not appear to affect gastric emptying or gastrointestinal hormone levels in humans (preliminary).

REPORT DATE: 04/13/92 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: Murphy, Joseph MAJ MC
ASSOCIATES: Sjogren, Maria LTC MC

DEPARTMENT: Department of Medicine
SERVICE: Gastroenterology Service

STATUS: Ongoing
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 7921 consecutive blood donors over a 1 year period were reviewed. Overall, 43 were HCV positive by ELISA. HBcAB was higher in civilian donors compared to military donors.

CONCLUSIONS

Military donors with anti-HCV had lower prevalence of HBcAB. Sporadic transmission of HCV in the civilian population appears to be proportionally higher than in the military population.

REPORT DATE: 04/23/92 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 STATUS: Ongoing
SERVICE: Gastroenterology Service APPROVAL DATE: Feb 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 34,319 Total: $ 34,319

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 seven 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
Active recruitment at WRAMC began in October 1991. The first subject was randomized in November 1991. As of April 1992, 37 subjects have been enrolled in the project. Of these, 31 have also consented to participate in the intermediate endpoint portion of the study. Another 14 individuals completed one or two visits but were determined ineligible and were not enrolled in the study. In March 1992, recruitment efforts were expanded to DeWitt ACH. Nutrition counseling for the project is currently taking place at WRAMC, Ft. Myer, Ft. Meade, and Andrews AFB. All subjects receive close follow-up for adenomas, and intervention subjects receive the benefits of that diet which is compatible with the guidelines of major health organizations. There have been no serious or unexpected adverse reactions.

CONCLUSIONS
It is too early to draw any conclusions as our earliest randomized subjects are only 4 months into their 4 year period of participation.

REPORT DATE: 04/03/92 WORK UNIT # 1414

DETAIL SUMMARY SHEET

TITLE: Case Control Study of Colonic Adenomas

KEYWORDS: colonic adenomas, risk factors, carotenoids

PRINCIPAL INVESTIGATOR: Kikendall, James LTC MC

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Gastroenterology Service APPROVAL DATE: Mar 1990

FUNDING: Current FY: $ 815 Previous FYs: $ 27,722 Total: $ 28,537

STUDY OBJECTIVE
To analyze previously collected data to define risk factors for colonic neoplasia. An amendment provides for analysis of frozen serum samples for gastrin, IGF-1, and 1,25-OH vitamin D.

TECHNICAL APPROACH
Three hundred and sixty-one subjects undergoing colonoscopy donated blood and urine samples and completed a dietary and environmental questionnaire from 1983-1987. Due to funding shortages, analysis of the collected data has been slow, but should be completed in the next few months.

PRIOR AND CURRENT PROGRESS
One paper and two abstracts have recently been submitted. Analysis of the remaining data continues. Preliminary data analysis shows an inverse correlation of beta carotene and cryptoxanthin with adenomas and positive correlations of smoking and alcohol with adenomas. Although these factors are interrelated, they remain significant in multivariate analysis. To date, two papers have been published, and one more has been submitted in addition to seven abstracts/presentations.

CONCLUSIONS
Serum gastrin is not increased in subjects with colonic adenomas. Smoking and alcohol consumption are associated with colonic adenomas. Other conclusions pending further analysis.

REPORT DATE: 06/30/92 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 Pseudoobstruction

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: Ongoing
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 & id 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 completed short-term therapy and remains on long-term therapy for 13 months.

CONCLUSIONS
The drug remains effective in this one patient.

REPORT DATE: 06/10/92 WORK UNIT # 1416

DETAIL SUMMARY SHEET

TITLE: Association of Acromegaly and Intermediate Markers of Neoplasia

KEYWORDS: acromegaly, colonic neoplasia

PRINCIPAL INVESTIGATOR: Murphy, Joseph MAJ MC
ASSOCIATES: Schaaf, Marcus MD; Maydonovitch, Corinne BS

DEPARTMENT: Department of Medicine
SERVICE: Gastroenterology Service

STATUS: Ongoing
APPROVAL DATE: May 1990

FUNDING: Current FY: $ 424 Previous FYs: $ 1,484 Total: $ 1,908

STUDY OBJECTIVE
To find the prevalence of colonic neoplasia in acromegalics, to identify risk factors, and to determine if there is a correlation between disease activity in acromegaly and intermediate markers of mucosal proliferation (ODC activity and tritiated thymidine uptake).

TECHNICAL APPROACH
Patients will have serum drawn for somatomedin C levels, undergo flexible sigmoidoscopy to obtain rectal tissue to measure ODC activity and tritiated thymidine uptake, and receive a colonoscopy to survey for colonic neoplasia.

PRIOR AND CURRENT PROGRESS
Thirty-four patients with acromegaly have been recruited, and flexible sigmoidoscopy and colonoscopy have been performed. Serum somatomedin C and growth hormone have been drawn. Colonoscopy results have been compared to 166 patients referred for heme + stools. No adverse reactions have been noted. Benefits to subjects have included the diagnosis of adenomatous polyps in 15 patients and of adenocarcinoma of the colon in 3 patients.

CONCLUSIONS
There is a higher prevalence of colonic neoplasia in patients over age 50 with acromegaly than with heme + stools. There is a significant correlation between ODC activity in colonic mucosa and serum somatomedin C.

REPORT DATE: 06/18/92 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: $16,412 Previous FYs: $ 3,602 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
Eighteen new subjects were enrolled in this study since May 1991. A total of 34 subjects have been enrolled to date. There have been no serious or unexpected reactions to the ibuprofen, and there have been no complications with the endoscopy. All subjects have completed the study with no withdrawals.

CONCLUSIONS
The data (endoscope and histologic examination) shows no significant difference between ingestion of liquid vs. solid ibuprofen in damage to the stomach.

REPORT DATE: 05/29/92 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 ptients have been withdrawn from the study.

CONCLUSIONS
Ongoing study.

REPORT DATE: 07/06/92 WORK UNIT # 1419

DETAIL SUMMARY SHEET

TITLE: Mechanisms of Gastroesophageal Reflux in Women with Heartburn in the Third Trimester of Pregnancy

KEYWORDS: gastroesophageal reflux, third trimester

PRINCIPAL INVESTIGATOR: Mecredy, Timothy MAJ MC

DEPARTMENT: Department of Medicine STATUS: Completed
SERVICE: Gastroenterology Service APPROVAL DATE: Sep 1991

FUNDING: Current FY: $ 350 Previous FYs: $ 0 Total: $ 350

STUDY OBJECTIVE
To determine the mechanism of reflux events and the circumstances in which they occur in symptomatic pregnant women in their third trimester.

TECHNICAL APPROACH
Simultaneous manometry-pH monitoring and constant LESP measurement before and after a meal are done. The pH probe is left in place, and monitoring continues for another 24 hours. Subjects are studied in third trimester and about 1 month after delivery.

PRIOR AND CURRENT PROGRESS
One patient completed the study. The principal investigator was reassigned.

CONCLUSIONS
Insufficient data to make conclusions.

REPORT DATE: 06/22/92 WORK UNIT # 1450

DETAIL SUMMARY SHEET

TITLE: Adenomatous Colonic Polyps: A Vitamers and MFO Induction

KEYWORDS: colon polyps, vitamin A, beta-carotene

PRINCIPAL INVESTIGATOR: Kikendall, James LTC MC
ASSOCIATES: Burgess, Mary RD; Bowen, Phyllis RD PhD

DEPARTMENT: Department of Medicine
SERVICE: Gastroenterology Service

STATUS: Ongoing
APPROVAL DATE: Jul 1982

FUNDING: Current FY: $ 2,617 Previous FYs: $ 13,484 Total: $ 16,101

STUDY OBJECTIVE

a) Case control portion: To evaluate risk factors for colonic adenomas. b) Intervention portion: To evaluate beta-carotene, 15mg po daily, as a colon cancer chemopreventive agent.

TECHNICAL APPROACH

a) Case control portion: Subjects who report for indicated colonoscopy who meet entry criteria are assessed by dietary and historical interview and sampling of blood and urine. Subjects with polyps (adenomas) and colonoscopy-negative controls are compared. b) Intervention Study: Subjects are randomized to receive placebo or beta-carotene after removal of colonic adenomas. Repeat colonoscopy assesses recurrence over the subsequent 3 years. Although beta-carotene is not known to have any harmful side effects, several potential side effects are monitored.

PRIOR AND CURRENT PROGRESS

There have been 291 subjects enrolled in the intervention portion of this study and 361 subjects enrolled in the case control portion. Accrual was completed in 1990. No serious side effects due to beta-carotene were observed. Beta-carotene, 15 mg po, was determined to be of no benefit in preventing recurrence of colonic adenomas. This was reported at the October 1991 Meeting of the American College of Gastroenterology. The only factor found to predict adenoma recurrence was the number of prior adenomas. This was reported at the American Gastroenterology Association Meeting in May 1992. During the next year, we hope to complete data entry and write manuscripts for both the case control and intervention portions of this study.

CONCLUSIONS

Beta-carotene, 15mg po daily, does not reduce the recurrence of colonic adenomas. The number, but not the size, of previous adenomas predicts recurrence. Both alcohol and cigarette use are associated with initial adenomas.

REPORT DATE: 09/21/92 WORK UNIT # 1462

DETAIL SUMMARY SHEET

TITLE: The Evaluation of Postprandial Supine Reflux Events by Simultaneous Esophageal Manometry, Esophageal pH Monitoring, and Gastroesophageal Scintiscanning in Patients with Hiatus Hernia and Esophagitis

KEYWORDS: reflux, manometry, scintigraphy

PRINCIPAL INVESTIGATOR: Shay, Steven COL MC

DEPARTMENT: Department of Medicine
SERVICE: Gastroenterology Service

STATUS: Completed
APPROVAL DATE: Aug 1983

FUNDING: Current FY: $ 351 Previous FYs: $ 3,141 Total: $ 3,492

STUDY OBJECTIVE

To correlate the presence, approximate volume, and clearance of gastroesophageal reflux by scintiscan with reflux events and clearance as determined by pH changes. To evaluate temporal relationships of hiatal hernia filling and emptying as determined by scintiscan, with gastroesophageal reflux determined by scintiscan and pH changes.

TECHNICAL APPROACH

Patients with symptoms of gastroesophageal reflux and severe endoscopic esophagitis are included. An esophageal pH probe and manometer catheter are passed per nares to measure simultaneous manometry and pH monitoring. The patients ingest a study meal consisting of commercial beef stew, 15 lamb liver cubes, and 250 cc of water, each labeled with 50 uCu of 99m Technetium sulfur-colloid. The patients lie on the left and right side alternately for a total of 4-10 minute recumbent monitoring periods.

PRIOR AND CURRENT PROGRESS

A total of four subjects have completed the protocol. No new subjects were enrolled this past year because of lack of support from Nuclear Medicine due to a decrease in technicians. Also, eligible subjects for this study are difficult to find. No serious or unexpected adverse reactions have occurred in any of the subjects studied. Due to the difficulties recruiting subjects and receiving the Nuclear Medicine support needed for this study, this protocol is being closed.

CONCLUSIONS

Scintigraphy is more sensitive than pH monitoring of the esophagus in identifying postprandial reflux events and their clearance. More subjects need to be studied to explain the role of hiatal hernia in promoting GER in patients with normal lower esophageal sphincter pressure.

REPORT DATE: 05/20/92 WORK UNIT # 1483

DETAIL SUMMARY SHEET

TITLE: Evaluation of Gastroesophageal Reflux as a Cause of Hoarseness

KEYWORDS: hoarseness, reflux, esophagitis

PRINCIPAL INVESTIGATOR: Peller, Thomas MAJ MC
ASSOCIATES: Murphy, Joseph MAJ MC; Maydonovitch, Corinne BS

DEPARTMENT: Department of Medicine
SERVICE: Gastroenterology Service

STATUS: Ongoing
APPROVAL DATE: Apr 1986

FUNDING: Current FY: $ 0 Previous FYs: $ 2,340 Total: $ 2,340

STUDY OBJECTIVE
To determine if gastroesophageal reflux (GER) is a cause of "idiopathic" hoarseness.

TECHNICAL APPROACH
Patients with idiopathic hoarseness and characteristic ENT findings undergo standard GI evaluation for GER. If GER is identified, the patient undergoes baseline voice harmonic analysis and is reevaluated after 8 weeks of medical therapy.

PRIOR AND CURRENT PROGRESS
Seventeen patients referred from the WRAMC ENT Clinic were evaluated for gastroesophageal reflux (GER). Eleven patients agreed to participate, and all of them completed the study. There have been no withdrawals or adverse effects from this study.

CONCLUSIONS
Of the 11 patients studied, 6 were found to have gastroesophageal reflux and underwent medical therapy. Improvement in esophagitis but not voice harmonics was noted after therapy.

REPORT DATE: 06/22/92 WORK UNIT # 1487

DETAIL SUMMARY SHEET

TITLE: Prospective Evaluation of the Effect of Medical Therapy on Plasma and Tissue Zinc Levels in Esophagitis

KEYWORDS: zinc, esophagitis, GERD

PRINCIPAL INVESTIGATOR: Wong, Roy COL MC
ASSOCIATES: Smith, Mark MAJ MC

DEPARTMENT: Department of Medicine
SERVICE: Gastroenterology Service

STATUS: Ongoing
APPROVAL DATE: Jul 1986

FUNDING: Current FY: $ 0 Previous FYs: $ 1,158 Total: $ 1,158

STUDY OBJECTIVE

To prospectively evaluate the effect of anti-gastroesophageal reflux therapy on plasma and esophageal tissue zinc concentrations; and to determine if a correlation exists between degree of esophageal inflammation and plasma and esophageal zinc concentration.

TECHNICAL APPROACH

Patients with endoscopically proven peptic esophagitis undergo esophageal biopsy and phlebotomy for tissue and serum zinc concentration. After standard medical anti-reflux therapy, tissue and blood specimens are obtained for comparison zinc concentrations.

PRIOR AND CURRENT PROGRESS

To date, five new patients have been recruited for participation; three have completed the protocol. The remaining two are undergoing treatment and will be due for final evaluation shortly. Patients continue to be actively recruited. There have been no complications related to study participation. The DCI General Support Lab has been used to analyze samples.

CONCLUSIONS

No conclusions can be drawn at this time.

REPORT DATE: 02/12/92 WORK UNIT # 1489

DETAIL SUMMARY SHEET

TITLE: The Evaluation of Post prandial Supine Reflux Events by Simultaneous Esophageal Manometry, Esophageal pH Monitoring and Gastroesophageal Scintiscanning in Patients with Progressive Systemic Sclerosis with Severe Endoscopic Esophagitis

KEYWORDS: manometry, pH monitoring, scintigraphy

PRINCIPAL INVESTIGATOR: Murphy, Joseph MAJ MC
ASSOCIATES: Peller, Patrick MAJ MC

DEPARTMENT: Department of Medicine
SERVICE: Gastroenterology Service

STATUS: Completed
APPROVAL DATE: Dec 1986

FUNDING: Current FY: $ 1,033 Previous FYs: $ 1,328 Total: $ 2,361

STUDY OBJECTIVE

To determine whether the predominant pathophysiologic abnormality responsible for excessive esophageal exposure in patients with progressive systemic sclerosis (PSS) and severe endoscopic esophagitis is frequent reflux events, poor clearance of a few reflux events, or both.

TECHNICAL APPROACH

Patients with (1) endoscopic reflux esophagitis and abnormal 24 hour pH monitoring, and (2) scleroderma from the study population will be entered in the study. Simultaneous manometry (esophageal motor activity), scintigraphy (reflux volume), and pH monitoring will be performed for 40 minutes after a test meal labelled with 1.0 m Cu 99m Tc sulfur colloid is eaten.

PRIOR AND CURRENT PROGRESS

A total of seven patients with PSS and esophagitis have been enrolled in this study; none in the past year. This has been compared to a group of nine patients with ordinary esophagitis. The study has been completed, and a manuscript has been accepted for publication in Digestive Disease and Science.

CONCLUSIONS

Patients with PSS and esophagitis have fewer reflux events of longer duration than ordinary esophagitis patients. The primary abnormality appears to be decreased smooth muscle peristalsis in these patients.

REPORT DATE: 01/15/92 WORK UNIT # 1495

DETAIL SUMMARY SHEET

TITLE: Effect of Beta-Carotene on Mucosal Proliferation in Patients with Colonic Carcinoma

KEYWORDS: beta-carotene, colon cancer, proliferation

PRINCIPAL INVESTIGATOR: Kikendall, James COL MC
ASSOCIATES: Wong, Roy COL MC

DEPARTMENT: Department of Medicine
SERVICE: Gastroenterology Service

STATUS: Completed
APPROVAL DATE: Oct 1987

FUNDING: Current FY: $ 0 Previous FYs: $ 4,160 Total: $ 4,160

STUDY OBJECTIVE

To determine the effect of beta-carotene on colonic epithelial proliferation in patients with resected adenocarcinoma of the colon or rectum.

TECHNICAL APPROACH

Patients with previously resected colon carcinoma are studied prior to and at 2, 9, 16, 24, and 28 weeks after receiving beta-carotene, 30mg PO QD. At each time point, biopsies and blood samples are obtained. Rectal mucosal biopsies are assayed for cell proliferation by tritiated thymidine uptake and ODC levels. Blood samples and mucosal biopsies are analyzed for beta-carotene levels.

PRIOR AND CURRENT PROGRESS

Twenty patients completed the study. Beta-carotene and ODC assays have been completed, and the thymidine analysis is underway. No more subjects will be enrolled, and no more subjects remain in the trial. There were no serious or unexpected adverse reactions. No subjects were withdrawn from the study. Subjects experienced no direct benefit from participation.

CONCLUSIONS

Beta-carotene administration normalizes rectal mucosal ODC activity and probably mucosal proliferation.

REPORT DATE: 01/30/92 WORK UNIT # 1496

DETAIL SUMMARY SHEET

TITLE: The Effects of Non-Steroidal Anti-Inflammatory Drugs on the Secretion of Human Salivary Epidermal Growth Factor

KEYWORDS: epidermal growth factor, saliva, anti-inflammatory drugs

PRINCIPAL INVESTIGATOR: Wong, Roy COL MC
ASSOCIATES: Maydonovitch, Corinne BS; Dutta, Sudhi MD

DEPARTMENT: Department of Medicine
SERVICE: Gastroenterology Service

STATUS: Ongoing
APPROVAL DATE: Oct 1987

FUNDING: Current FY: $ 0 Previous FYs: $ 525 Total: $ 525

STUDY OBJECTIVE
To determine if therapeutic doses of non-steroidal anti-inflammatory drugs affect salivary epidermal growth factor (EGF) secretion in humans.

TECHNICAL APPROACH
In a double-blind, randomized manner, volunteer subjects receive, on separate occasions two weeks apart, placebo TID for 3 days or indomethacin, 50 mg TID for 3 days. On the following morning, after a final drug dose, saliva is collected in a centrifuge tube, centrifuged, stored at -70C and analyzed by radioimmunoassay for EGF. Serum samples are collected and analyzed for indomethacin levels.

PRIOR AND CURRENT PROGRESS
A total of 21 volunteer subjects have been enrolled in this study. No new subjects were enrolled during this past year. One volunteer erroneously received placebo twice and was dropped from the study. There were no serious or adverse reactions related to the study. There is no direct benefit for participation in this study. This study is closed to further patient accrual, and remains open for follow-up only.

CONCLUSIONS
Indomethacin significantly decr ases salivary epidermal growth factor. This may play a role in the ulcerogenic properties of indomethacin. A manuscript is in progress.

REPORT DATE: 01/30/92 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, rectosigmoid, laser Doppler

PRINCIPAL INVESTIGATOR: Murphy, Joseph MAJ MC
ASSOCIATES: Pacicco, Thomas MAJ MC

DEPARTMENT: Department of Medicine
SERVICE: Gastroenterology Service

STATUS: Ongoing
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 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 also be obtained to measure tissue prostaglandin levels, and blood samples will be taken to measure indomethacin levels.

PRIOR AND CURRENT PROGRESS
No new subjects were added during the previous year. The fiberoptic probes have been found to be sensitive to incandescent lights. An opaque jacket was installed, so new subjects can now be recruited. A total of 10 subjects have been studied previously as controls. No serious or unexpected adverse reactions have occurred in any of the subjects studied.

CONCLUSIONS
Recent adjustments to optic probes will permit additional study subjects.

REPORT DATE: 03/16/92 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: Shay, Steven COL MC
ASSOCIATES: Maydonovitch, Corinne BS

DEPARTMENT: Department of Medicine
SERVICE: Gastroenterology Service

STATUS: Ongoing
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, are studied. Three hour electrogastrograms and 24 hour antral motility evaluations are performed after treatment with placebo and Cisapride. Changes in symptoms are measured using a questionnaire. A double-blind crossover design is employed so that each subject receives both placebo and Cisapride.

PRIOR AND CURRENT PROGRESS

A total of six patients have been enrolled and completed the protocol; one this past year.

CONCLUSIONS

None at this time, as study is a double-blinded, placebo controlled study, and more patients are to be enrolled.

REPORT DATE: 09/25/92 WORK UNIT # 2031

DETAIL SUMMARY SHEET

TITLE: Gastrointestional Blood Loss During Marathon Running and the Effect of Cimetidine on its Prevention

KEYWORDS: GI blood loss, marathon running, cimetidine

PRINCIPAL INVESTIGATOR: Moses, Frank LTC MC

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Gastroenterology Service APPROVAL DATE: Sep 1988

FUNDING: Current FY: $ 3,293 Previous FYs: $ 602 Total: $ 3,895

STUDY OBJECTIVE
To determine the frequency and severity of gastrointestinal blood loss during marathon and endurance exercise, and the effects of cimetidine on its prevention.

TECHNICAL APPROACH
Qualitative and quantitative stool hemoglobin analyses are performed before and after runners complete endurance competitive events.

PRIOR AND CURRENT PROGRESS
Two 100-mile ultramarathon events have been completed. GI bleeding occurred in the majority of subjects, and symptoms were severe at times. Cimetidine protected runners in the unblinded portion of the study. Thirty of the planned 250 marathon runners have been studied, and results show a trend toward improvement when cimetidine is used. A protocol modification was submitted last fiscal year to allow endoscopy of some participants in order to localize bleeding. During this year seven runners completed all or part of the modified protocol, including panendoscopy following the marathon. No complications or untoward effects were noted.

CONCLUSIONS
Data suggests cimetidine may be of benefit in improving GI symptoms associated with endurance running and reduction of GI bleeding. Further evaluation and study of this condition is warranted and planned.

REPORT DATE: 04/23/92 WORK UNIT # 1026

DETAIL SUMMARY SHEET

TITLE: Dizziness: A Prospective Study of Patient Characteristics and Outcome

KEYWORDS: dizziness, etiology, prognosis

PRINCIPAL INVESTIGATOR: Kroenke, Kurt LTC MC
ASSOCIATES: Wehrle, Allen LTC MC; Rosenberg, Michael LTC MC

DEPARTMENT: Department of Medicine
SERVICE: General Medicine Service

STATUS: Completed
APPROVAL DATE: Jan 1990

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

STUDY OBJECTIVE

To prospectively evaluate patients with a chief complaint of dizziness in order to determine the most common causes, the psychiatric and functional characteristics, the value of physical and laboratory examination, and the outcome at 4 and 12 months of follow-up.

TECHNICAL APPROACH

Patients seen for dizziness in four clinical areas (Internal Medicine Clinic, Outpatient Clinic, Neurology Clinic, and Emergency Room) are entered in a log book and contacted by phone to determine their willingness to participate. Participants were seen in the Dizziness Clinic where they underwent medical and psychiatric interviews, laboratory testing, audiologic testing, neuro-ophthalmologic examination, and detailed determination of their functional status. Follow-up (by mail) was performed at 4 and 12 months to determine outcome. Controls from the same clinical areas were recruited and underwent identical evaluation.

PRIOR AND CURRENT PROGRESS

We evaluated 100 dizzy patients and 25 controls (as planned) in our Dizziness Clinic (completed this phase April 1991). Presented abstract at National Institute of Mental Health Disorders in Primary Care Conference in September 1991, and Society of General Internal Medicine Annual Meeting in May 1992. First manuscript is being submitted (currently being forwarded through Department of Clinical Investigation for approval) for publication on etiology; second manuscript is being completed on psychiatric findings; third paper will be written this summer when one-year follow-up (per mail) is completed.

CONCLUSIONS

Regarding etiology, most common cause of dizziness in primary care is vestibular (54%), followed by psychiatric (16%). However, over half of patients have two or more causes. One-third of dizzy patients get better at two-week follow-up. Primary care physician could evaluate most dizzy patients initially with a directed history and physical exam that could be accomplished in approximately 10 minutes.

REPORT DATE: 01/24/92 WORK UNIT # 1027

DETAIL SUMMARY SHEET

TITLE: Symptoms in the Community: Prevalence, Etiology and Psychiatric Co-Morbidity

KEYWORDS: symptoms, psychiatric, epidemiology

PRINCIPAL INVESTIGATOR: Kroenke, Kurt LTC MC

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: General Medicine Service APPROVAL DATE: Nov 1990

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

STUDY OBJECTIVE
To analyze a large data base (Epidemiologic Catchment Area Survey) to determine the community prevalence, patient-attributed etiology, and psychiatric co-morbidity related to common medical symptoms.

TECHNICAL APPROACH
Used data base tapes. Analyzed them using logistic regression analysis.

PRIOR AND CURRENT PROGRESS
Analysis completed. Abstract published in Clinical Research. Manuscript 95% completed and will be submitted for publication by February 1992.

CONCLUSIONS
Community prevalence of symptoms is very high. Only 20% are considered by patients to be "minor." About 35% of the symptoms are potentially psychiatric in etiology. The presence of any one of the 15 most common symptoms is associated with a two- to threefold increased risk of a concomitant psychiatric disorder.

REPORT DATE: 08/11/92 WORK UNIT # 1028

DETAIL SUMMARY SHEET

TITLE: Termination of the Physician-Patient Relationship in a Primary Care Clinic

KEYWORDS: primary care, patient satisfaction, continuity of care

PRINCIPAL INVESTIGATOR: Roy, Michael CPT MC

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: General Medicine Service APPROVAL DATE: Aug 1991

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

STUDY OBJECTIVE
To identify independent predictors of patient satisfaction with the process of transferring their care from a graduating resident physician to a new resident. An addendum is planned to determine whether interventions can improve patient satisfaction.

TECHNICAL APPROACH
An attitudinal survey will be given to consecutive patients returning to the clinic for their first visit with a new physician and will be mailed to patients not returning within 4 months of the physician change. The questions will elicit the patients' degree of satisfaction with the transfer process, as well as potential predictors of satisfaction. Univariate and multivariate analyses will be performed using SAS to identify the independent predictors of patient satisfaction.

PRIOR AND CURRENT PROGRESS
The initial study has been completed. A total of 237 surveys were completed by patients returning for their first visit with a new physician. Surveys mailed were returned by 139 of 152 patients. Thus, a total of 376 patients have participated. This phase was successful in identifying five independent predictors of patient satisfaction with the transfer process and serves as a springboard for the addendum. The addendum involves two interventions; with questionnaires used to determine whether either or both of the interventions can improve satisfaction. There have been no serious or adverse reactions. Patients have been very positive about the study, and none have expressed any objections.

CONCLUSIONS
Independent predictors of patient satisfaction are: personal notification by the departing physician; discussion of feelings about the transfer; belief that the discussion was sufficient; positive impression of the institution; and agreement that the doctor did everything possible to ease the transfer.

REPORT DATE: 07/16/92 WORK UNIT # 1507

DETAIL SUMMARY SHEET

TITLE: WRAMC 9010: A NCI-WRAMC Collaborative Phase I Study of Tetraplatin

KEYWORDS: Phase I, Tetraplatin, pharmacokinetics

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD

DEPARTMENT: Department of Medicine STATUS: Completed
SERVICE: Hematology-Oncology Service APPROVAL DATE: Aug 1990

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

STUDY OBJECTIVE
To establish the maximum tolerated dose, to carefully ssess toxicities, to measure pharmacokinetics and DNA adduct formation, and to assess antitumor activity using Tetraplatin.

TECHNICAL APPROACH
Cohorts of three patients will be evaluated at each dose level until the maximum tolerated dose is reached. Initial dose of 4.3mg/m2, with escalation according to Fibonacci scheme, will be given; we are now dosing at the 8th dose level. Close monitoring for toxicities will be maintained. Treatment will continue in each patient until progression of disease or six cycles have been given.

PRIOR AND CURRENT PROGRESS
Nine patients from WRAMC were enrolled and treated on study. None of the patients' cancers responded to Tetraplatin. Significant neurotoxicity was seen in four of the nine patients treated. The dose range that produced the neurotoxicity was from 51mg/m2 to 90mg/m2 given every 4 weeks. The maximum tolerated dose will be reported as 90mg/m2. The study has been closed per Dr. Michael Christian, Medicine Branch, NCI. The remainder of the drug will be returned to NCI. The official closure date was July 15, 1992.

CONCLUSIONS
No tumor responses were statistically significant. Dose limiting toxicity seen was neurological (PNS). Further testing of the drug has been terminated at this time.

REPORT DATE: 01/30/92 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: Ongoing
SERVICE: Hematology-Oncology Service 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, followed by two additional courses of chemotherapy.

PRIOR AND CURRENT PROGRESS
Four patients have been entered on this study from WRAMC. Two patients have completed therapy and are being followed for recurrence. Two patients are still receiving preradiation chemotherapy. No unexpected toxicities have been observed; no patients have withdrawn. The nationwide accrual rate has been higher than projected. Approximately 30 patients per month have been registered. The total accrual is 692. The desired accrual is 1335 patients; 334 patients on each arm.

CONCLUSIONS
Too early for data analysis.

REPORT DATE: 04/16/92 WORK UNIT # 1516-90

DETAIL SUMMARY SHEET

TITLE: Recombinant DNA GM-CSF in Compassionate Circumstances

KEYWORDS: GM-CSF

PRINCIPAL INVESTIGATOR: Ward, Frank LTC MC
ASSOCIATES: Diehl, Louis COL MC; Lombardo, Frederic MAJ MS

DEPARTMENT: Department of Medicine
SERVICE: Hematology-Oncology Service

STATUS: Completed
APPROVAL DATE: Dec 1990

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

STUDY OBJECTIVE
To assess effectiveness and side effects of granulocyte-macrophage colony stimulating factor (GM-CSF) when used by a single patient on a compassionate basis.

TECHNICAL APPROACH
Patient will be treated with 5 ug/kg/d SQ GM-CSF to maintain an absolute granulocyte count of 500-1000 with dose adjustment downward (25% or more) for WBC greater than 10,000. The medication will be periodically held to see if the patient could maintain an absolute granulocyte count in the normal range without GM-CSF.

PRIOR AND CURRENT PROGRESS
Patient last received GM-CSF on February 14, 1991. The patient has maintained an acceptable granulocyte count since that time. The study has been completed, effective April 6, 1991, and the remainder of the GM-CSF will be returned to the sponsor. There were no serious or unexpected side effects or reactions.

CONCLUSIONS
GM-CSF was effective and safe for the support of this patient during bone marrow hypoplasia with associated granulocytopenia consequent to consolidation chemotherapy for acute myelocytic leukemia.

REPORT DATE: 05/19/92 WORK UNIT # 1522-91

DETAIL SUMMARY SHEET

TITLE: CALGB 9064: Analysis of Neuroendocrine Markers on Tissue Blocks in Patients with Stage IIIA NOn-Small Cell Lung Cancer

KEYWORDS: tissue blocks, retrospective analysis

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Hematology-Oncology Service APPROVAL DATE: Apr 1991

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

STUDY OBJECTIVE
To analyze pathology specimens before and after chemotherapy for neuroendocrine markers, carcinoembryonic antigen (CEA), and p185neu to determine if correlation exists between response and/or survival with these markers. To compare pre and post chemotherapy specimens for intensity and percentage of cells positive for neuroendocrine markers, CEA, and p185neu. To correlate light microscopic characteristics with neuroendocrine markers, CEA, and p185neu and clinical parameters.

TECHNICAL APPROACH
Patients must first be registered on the treatment study CALGB 8935. The patient is then registered for this companion study. Tissue blocks are mailed to the reference laboratory for analysis. At completion of the review, tissue blocks will be returned to WRAMC.

PRIOR AND CURRENT PROGRESS
Three patients have been entered on this study during 1991 from WRAMC. All three patients were treated on CALGB 8935 and have died of their disease. No risk or benefit to the patient exists from this protocol.

CONCLUSIONS
Analysis is ongoing. No conclusions have been reached.

REPORT DATE: 05/22/92 WORK UNIT # 1639-86

DETAIL SUMMARY SHEET

TITLE: Characterization of Human Antineutrophil Antibodies

KEYWORDS: neutropenia, anti-neutrophil, autoantibodies

PRINCIPAL INVESTIGATOR: Hartman, Kip MAJ(P) MC
ASSOCIATES: Wright, Daniel COL MC

DEPARTMENT: Department of Medicine
SERVICE: Hematology-Oncology Service

STATUS: Completed
APPROVAL DATE: Mar 1986

FUNDING: Current FY: $ 3,678 Previous FYs: $ 445 Total: $ 4,123

STUDY OBJECTIVE

To characterize the neutrophil antigens recognize by naturally occurring anti-neutrophil antibodies in autoimmune neutropenia.

TECHNICAL APPROACH

Sera from patients with neutropenia of suspected autoimmune origin are screened for the presence of anti-neutrophil antibodies. Further studies are then performed to further characterize these antibodies, including Western blotting, affinity chromatography separation of suspected autoantibodies, and immunofluorescence studies of autoantibody activity.

PRIOR AND CURRENT PROGRESS

Eighty patients have been identified by the screening assay as having positive anti-neutrophil antibodies over the 6 years of the study (17 during the past year). Additional blood was collected after informed consent from two of these patients during the past year. As this is a blood collection study only, there have been no unexpected or adverse reactions, and no patients have withdrawn from study. There has been no direct benefit to patients other than diagnostic information provided to clinicians regarding the anti-neutrophil status of the patients. The study is now closed, and has been superseded by a new study protocol approved in 1992.

CONCLUSIONS

Autoantibodies specific for the neutrophil adhesion glycoprotein complex CD11b/CD18 were identified in the sera of several patients with autoimmune neutropenia. This autoantibody specificity may contribute to the morbidity of infections associated with autoimmune neutropenia, by interference with neutrophil adhesion and opsonin receptor function. Further studies are needed to confirm these findings.

REPORT DATE: 04/28/92 WORK UNIT # 1650-87

DETAIL SUMMARY SHEET

TITLE: Exploratory Dose Finding Study to Assess the Efficacy and Safety of Intravenous AHR 11190B (Zacopride Hydrochloride) in the Prevention of Cisplatin-Induced Emesis

KEYWORDS: Zacopride Hydrochloride, IND, drug

PRINCIPAL INVESTIGATOR: Lombardo, Fredric MAJ MS
ASSOCIATES: Adams, Jonathan DCR PHS; Knight, Robert LTC MC

DEPARTMENT: Department of Medicine
SERVICE: Hematology-Oncology Service

STATUS: Ongoing
APPROVAL DATE: Nov 1987

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

STUDY OBJECTIVE

To assess the efficacy and safety of single doses of Zacopride Hydrochloride in the prevention of cisplatin-induced emesis, and to investigate the dose-response effect of Zacopride Hydrochloride for prevention of emesis caused by cisplatin.

TECHNICAL APPROACH

Protocol outline methodology. A particular dose of Zacopride is given 30 minutes prior to cisplatin infusion. If patients have six or more emetic episodes, Zacopride would be considered a filum, and other antiemetics will be administered.

PRIOR AND CURRENT PROGRESS

Unfortunately, there is still no indication as to when this protocol will be reactivated by the holder of the IND (A.H. Robins, Inc.). As previously noted, this is a multi-institutional study in which the original dose of the agent caused side effects. The company is still in the process of amending the original protocol. We have not placed any patient on this protocol. The protocol should remain open until the dose modulation issue is resolved. Now that the Research Department of A.H. Robins has been reorganized under a new organization, this issue should be resolved. If this is not resolved this year, I will suggest the termination of this project.

CONCLUSIONS

Zacopride is still considered a very interesting antiemetic agent with a novel mechanism of action. It will offer our patients a potentially effective treatment with minimal side effects, as has been demonstrated by collateral studies.

REPORT DATE: 06/02/92 WORK UNIT # 1656-88

DETAIL SUMMARY SHEET

TITLE: Magnetic Resonance Imaging in the Staging and Evaluation of Response to Therapy in Small Cell Carcinoma of the Lung

KEYWORDS: MRI, small cell carcinoma, conventional staging

PRINCIPAL INVESTIGATOR: Burrell, Linda MAJ MC
ASSOCIATES: Perry, James MAJ MC; Lee, Nicole CPT MC

DEPARTMENT: Department of Medicine
SERVICE: Hematology-Oncology Service

STATUS: Completed
APPROVAL DATE: May 1988

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

STUDY OBJECTIVE

To compare conventional staging (CS) to a single MRI imaging study for detection of extrathoracic metastases of small cell lung cancer; to compare CS versus MRI in assessing response of the disease to therapy; and to do a cost comparison of CS versus MRI.

TECHNICAL APPROACH

MRI protocol will observe spine, head, pelvis and femur as compared to conventional staging methods.

PRIOR AND CURRENT PROGRESS

This study was closed after the enrollment of 40 patients.

CONCLUSIONS

MRI appeared to be more accurate in detecting disease in small cell carcinoma than CS. A single study appeared to be comparable in cost.

REPORT DATE: 06/15/92 WORK UNIT # 1657-88

DETAIL SUMMARY SHEET

TITLE: Long Term 5-FU Infusion for Recurrent Head and Neck Cancer, A Phase II Pilot Study

KEYWORDS: 5-fluorouracil, cancer, continuous infusion

PRINCIPAL INVESTIGATOR: Ward, Frank MAJ MC
ASSOCIATES: Lombardo, Frederick MAJ MC; Cobb, Patrick CPT MC

DEPARTMENT: Department of Medicine
SERVICE: Hematology-Oncology Service

STATUS: Completed
APPROVAL DATE: Jun 1988

FUNDING: Current FY: $ 0 Previous FYs: $ 13,650 Total: $ 13,650

STUDY OBJECTIVE

a) Assess effectiveness of a continuous infusion of 5-FU in patients with recurrent head and neck cancer; and b) Assess the toxicity of a continuous infusion of 5-FU in patients with recurrent head and neck cancer.

TECHNICAL APPROACH

All adult patients with recurrent head and neck cancer who meet the eligibility requirements and consent to the protocol will have a central venous catheter placed (if one is not already in place) and will be subsequently treated with 24 hour per day continuous infusion 5-FU at 300 mg/m2/day dose, along with oral vitamin B6 to reduce the skin toxicity of the drug (in regard to hand-foot reaction). The drug will be continued in the absence of tumor progression or serious toxicity.

PRIOR AND CURRENT PROGRESS

No additional patients have been accrued to this study. The study has been reopened at Fitzsimons Army Medical Center where additional patients will be accrued.

CONCLUSIONS

Our limited experience suggests continuous infusion 5-fluorouracil is well tolerated. Our institutional data do not allow a conclusion as to efficacy. Additional patients will be provided by accrual at our collaborative institution (Fitzsimons Army Medical Center). The level of interest in this protocol at WRAMC does not justify continuation of the study here.

REPORT DATE: 07/18/92 WORK UNIT # 1658-88

DETAIL SUMMARY SHEET

TITLE: Verification of the Heterogeneity of Lupus Anticoagulant Using Purified IgG and IgM from Patients with Lupus Anticoagulant

KEYWORDS: lupus anticoagulant, cardiolipin antibody

PRINCIPAL INVESTIGATOR: Alving, Barbara LTC MC

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Hematology-Oncology Service APPROVAL DATE: Jul 1988

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

STUDY OBJECTIVE
To obtain blood from patients who have a lupus anticoagulant for the purpose of purifying and characterizing the antiphospholipid activity as being in the IgG or IgM fraction.

TECHNICAL APPROACH
IgG and IgM will be purified by column chromatography using DEAE cellulose from patient plasma.

PRIOR AND CURRENT PROGRESS
A total of 18 patients have been studied; 2 of these during the past year. There have been no adverse reactions to the blood drawing. The study is of no immediate benefit to the patients. New developments in the field indicate that another plasma protein, beta2-microglobulin, may determine how well antiphospholipid antibodies are detected in a solid-phase assay for cardiolipin. Therefore, research is continuing with purified forms of the antibodies in the presence of beta2-microglobulin.

CONCLUSIONS
Antibodies demonstrate marked heterogeneity toward phospholipids, and multiple plasmas need to be studied to define the range of the heterogeneity.

REPORT DATE: 09/06/92 WORK UNIT # 1659-88

DETAIL SUMMARY SHEET

TITLE: Antisickling Effect of Erythrocyte 2,3-DPG Depletion

KEYWORDS: sickle cell, 2,3-DPG, hemoglobin S

PRINCIPAL INVESTIGATOR: Kark, John COL MC
ASSOCIATES: Poillon, William PhD; Hicks, Cecil

DEPARTMENT: Department of Medicine
SERVICE: Hematology-Oncology Service

STATUS: Completed
APPROVAL DATE: Aug 1988

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

STUDY OBJECTIVE

a) To evaluate the extent of the antisickling effect produced by in vitro depletion of erythrocyte 2,3-DPG (2,3-diphosphoglycerate) in red cells from patients with sickle cell disease; b) To measure the contributions made by each of several mechanisms for this effect; and c) To define optimum conditions for minimal levels of enzyme activators to achieve this effect.

TECHNICAL APPROACH

Small amounts of whole blood (30 ml) are drawn from patients with sickle cell disease or trait; the cells are washed, resuspended with activators of red cell 2,3-DPG phosphatase activity (glycolate or metabisulfite) or in control media, incubated for several hours, washed, resuspended in buffer and equilibrated with varying levels of po2, and fixed. The percentage of sickled cells are compared for treated versus control samples. Oxygen affinity, 2,3-DPG, ATP, pH, and drug levels are measured in both types of cells.

PRIOR AND CURRENT PROGRESS

Prior to these studies, red blood cell (RBC) 2,3-DPG was thought to have little effect on sickle cell disease. However, this study found that depletion of 2,3-DPG from isolated hemoglobin (Hb) greatly inhibited deoxy-Hb S polymer in vitro. Experiments with whole RBC's showed unexpected RBC dehydration due to a K+ leak which was an artifact of in vitro treatment. Using media to prevent this cell dehydration, this study confirmed greater than 50% reduction in RBC sickling when 2,3-DPG content of sickle RBC's was reduced by about 90%.

CONCLUSIONS

2,3-DPG plays an unexpectedly important role in the production of sickle cell disease among patients with the S hemoglobinopathies. The findings in this study provide novel evidence for the potential effectiveness of agents which would reduce 2,3-DPG in patients with sickle cell disease or sickle cell trait.

REPORT DATE: 05/01/92 WORK UNIT # 1660-88

DETAIL SUMMARY SHEET

TITLE: Assessing the Usefulness of a Quantitative Measure of Mucosal Neutrophils in Profoundly Neutropenic Patients

KEYWORDS: mucosal, neutrophil, neutropenia

PRINCIPAL INVESTIGATOR: Hargis, Jeffrey CPT MC
ASSOCIATES: Knight, Robert LTC MC; Wright, Daniel COL, MC

DEPARTMENT: Department of Medicine
SERVICE: Hematology-Oncology Service

STATUS: Terminated
APPROVAL DATE: Oct 1988

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

STUDY OBJECTIVE

To determine whether quantitative measurements of oral neutrophils may provide information of clinical importance that supplements the information derived from blood neutrophil counts alone in defining the host defense defects of patients with profound neutropenia.

TECHNICAL APPROACH

Oral mucosal neutrophils are obtained by a daily saline mouthwash. The specimen is centrifuged and then stained with fluorescent acridine orange. Mucosal neutrophils are then counted by fluorescence microscopy in a hemocytometer chamber.

PRIOR AND CURRENT PROGRESS

This research protocol has been administratively terminated.

CONCLUSIONS

This research protocol has been administratively terminated.

REPORT DATE: 08/03/92 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 eight lymphoma patients have been treated with ABMT at WRAMC. Four patients were treated with the original 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. Four patients have been treated with the modified regimen, which eliminated the Ara-C and decreased the BCNU to 600 mg. This modified regimen was tolerated well, without major toxicities being noted. All patients are in remission. One patient was harvested and will be transplanted September 1992.

CONCLUSIONS

In conclusion, using the 3-drug regimen with decreased BCNU caused no major toxicities in the four patients done to date. All patients who have been treated on the 3-drug regimen, and one patient from the 4-drug regimen, remain in remission with short term follow-up.

REPORT DATE: 09/10/92 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 year, 11 adult patients have been treated with high dose chemotherapy with autologous bone marrow support for solid tumors. The tumors have been metastatic breast cancer in 10 patients and refractory testicular carcinoma in 1. There were no treatment related deaths. There were four PR's, one CR, one SD, and one with progressive disease at day +60 evaluation. The rest have not had day +60 evaluation at present.

CONCLUSIONS
In conclusion, the regimen has been well tolerated with no mortality and acceptable morbidity. The addition of an increased dose of cyclophosphamide has not increased organ toxicity. Responses have been seen with this regimen, and it will be continued with possible consideration for a double transplant as a follow-up study to see if results may be improved.

REPORT DATE: 06/15/92 WORK UNIT # 1672

DETAIL SUMMARY SHEET

TITLE: 5-Fluorouracil and Low Dose Leucovorin After Ultrasound Guided Laser Ablation of Colorectal Carcinoma Metastatic to the Liver

KEYWORDS: 5-fluorouracil, leucovorin, liver

PRINCIPAL INVESTIGATOR: Ward, Frank MAJ MC
ASSOCIATES: Dawson, Nancy LTC MC; Dachman, Abraham MD

DEPARTMENT: Department of Medicine
SERVICE: Hematology-Oncology Service

STATUS: Ongoing
APPROVAL DATE: May 1990

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

STUDY OBJECTIVE

To assess the effectiveness of 5-fluorouracil and low-dose leucovorin as therapy for metastatic colorectal carcinoma to the liver after laser ablation of the hepatic metastases, when compared to historical controls. Primary endpoint is survival. Disease-free interval, progression-free interval, and palliative effect of chemotherapy in conjunction with laser ablation are secondary endpoints.

TECHNICAL APPROACH

Patients who have undergone laser ablation of metastatic colorectal carcinoma to the liver will receive leucovorin (20 mg/m2/d) immediately followed by 5-fluorouracil (425 mg/m2/d) by rapid intravenous injection for 5 consecutive days. Courses will be repeated at 4 weeks, 8 weeks, and every 5 weeks thereafter in the absence of progressive disease or unacceptable toxicity. Survival will be calculated from the date of study entry. Doses will be modified for toxicity.

PRIOR AND CURRENT PROGRESS

No patients have been accrued to this study. This is a direct result of the poor accrual rate to the protocol employing laser therapy for the ablation of colorectal carcinoma metastatic to the liver, from which patients for this study are referred. However, the laser ablation study is a significant attempt to impact on the care of patients with metastatic disease confined to the liver.

CONCLUSIONS

This study should remain open as long as the laser ablation study is available for patient accrual.

REPORT DATE: 06/12/92 WORK UNIT # 1673

DETAIL SUMMARY SHEET

TITLE: Molecular Basis of the Maturation of Bone Marrow Granulocytes: Isolation, Purification and Characterization of Granulocyte Maturation Regulators from Normal Human Serum

KEYWORDS: granulocytes, maturation, regulator

PRINCIPAL INVESTIGATOR: Bednarek, Jana PhD
ASSOCIATES: Wright, Daniel COL MC; Ward, Frank LTC MC

DEPARTMENT: Department of Medicine
SERVICE: Hematology-Oncology Service

STATUS: Ongoing
APPROVAL DATE: May 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 5,469 Total: $ 5,469

STUDY OBJECTIVE

To isolate, purify, and characterize the granulocyte maturation-inducing activity detected in normal human serum in our previous pilot study (Work Unit #1649-87).

TECHNICAL APPROACH

Chromatographic and electrophoretic procedures will be used to isolate, purify, and characterize the activity which we suspect is a protein or peptide. As the purification proceeds, at every step, we plan to assay for biological activity. This is accomplished in cultures of normal neutrophilic precursors from bone marrow. We will also attempt to use leukemic cell lines. When sufficiently purified, the molecule will be characterized by determination of molecular weight and amino acid composition. If it contains carbohydrates, we will determine its composition as well as its importance for biological activity/activities.

PRIOR AND CURRENT PROGRESS

There were 7 subjects enrolled during the last fiscal year, for a total of 15. The purification of maturation activity was carried out to a fourth step. Step 4 used electrophorectic separation and transblot of the protein. Activity is easily lost; to maintain it will require further experiments. Effects on CD-34 cells and leukemic cell lines were very promising and attracted the attention of Miles Labs, who is proposing collaboration. Experiments were stopped temporarily because: a) principal investigator was reassigned, b) several associates and collaborators retired, and c) two interested new fellows have other assignments.

CONCLUSIONS

Purification of the activity that is involved in initiation or substantial regulation of maturation of granulocytes proceeded, so that we have a partially purified material showing three major bands and several minor bands (visible on overload of electrophorsis). Biological assays with step 1 and 2 CD-34 cells shows reactions consistent with induction or recruitment by maturation factor. Leukemic cell lines Red-3 and HL-60 can be stopped from dividing.

REPORT DATE: 08/04/92 WORK UNIT # 1674

DETAIL SUMMARY SHEET

TITLE: Ifosfamide for Metastatic or Unresectable Primary Transitional Cell Carcinoma of the Urothelial Tract: A Phase II Pilot Study

KEYWORDS: ifosfamide, transitional cell, carcinoma

PRINCIPAL INVESTIGATOR: Reid, Thomas MAJ MC
ASSOCIATES: Ward, Frank LTC MC; Lombardo, Fred MAJ MSC

DEPARTMENT: Department of Medicine
SERVICE: Hematology-Oncology Service

STATUS: Completed
APPROVAL DATE: May 1990

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

STUDY OBJECTIVE

To determine the efficacy of intravenous ifosfamide therapy in patients with transitional cell carcinoma of the urothelial tract who have failed standard therapy.

TECHNICAL APPROACH

Patients will be treated with ifosfamide 1.5 g/m2/d intravenous infusion over 2 hours per day for 5 days. Initial dose modifications will be made for previous pelvic irradiation and/or extent of previous chemotherapy. No modifications of the original protocol have been made.

PRIOR AND CURRENT PROGRESS

Last year was the second year of the protocol, and no additional patients were enrolled. A total of two patients were enrolled in the protocol. There were no serious or unexpected adverse reactions. One patient progressed after his first course of therapy and was removed from further treatment. The other patient received two cycles and had stable disease but was removed from study for progressive cachexia. Both patients have since died of their cancer. The present pilot protocol was started at a local level in anticipation of eventually expanding to several institutions in CALGB; that is, to convince the larger group some efficacy was to be shown at the local level. ECOG, however, thought the idea interesting enough to have a groupwide study at the outset.

CONCLUSIONS

No definitive conclusions can be made about the efficacy of this drug. In the second year of this study, ECOG developed a similar protocol and accrued patients more rapidly. Because of the competing ECOG study, it is reasonable to enroll patients on this more rapidly accruing study. The present study will be considered completed.

REPORT DATE: 06/12/92 WORK UNIT # 1675

DETAIL SUMMARY SHEET

TITLE: WRAMC 9004 A Study of Interferon Alpha-2A in Combination with 5FU Plus Leucovorin in Metastatic or Recurrent Colorectal Cancer

KEYWORDS: colorectal cancer, interferon, 5FU/leucovorin

PRINCIPAL INVESTIGATOR: Weiss, Raymond MD

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Hematology-Oncology Service APPROVAL DATE: Jun 1990

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

STUDY OBJECTIVE
To test the efficacy of the 3-drug regimen in 30 previously untreated metastatic or recurrent colorectal cancer patients.

TECHNICAL APPROACH
Non-randomized study in which all patients receive subcutaneous injections of interferon alpha, high dose IV leucovorin, and standard IV doses of 5FU every 3 weeks.

PRIOR AND CURRENT PROGRESS
A total of eight patients from WRAMC have been entered on this study; three were entered in 1992. One patient died of progressive disease, one patient died (suicide), and one patient was removed from treatment recently due to disease progression after a partial response. Five patients remain on treatment. No unexpected toxicities have been observed. The GI toxicity has been grade 2-3 in all patients. No patients have withdrawn consent for treatment. Four out of the remaining five patients have had a clinical partial response.

CONCLUSIONS
Study is ongoing. No conclusions have been reached.

REPORT DATE: 09/14/92 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: Ongoing
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
There has been no progress on this project during the past year; however, the investigators plan to continue trying to accrue patients for one more year. So far, only a total of three patients have been enrolled. The topic is of importance since clinical interest in patients with the antiphospholipid syndrome continues to grow, and appropriate lab testing has not yet been well defined. There is no direct benefit to the patients, other than they will also have a profile of their coagulation status in addition to the rheumatologic studies.

CONCLUSIONS
Important findings anticipated include ascertaining the best methods for recognition of patients with the antiphospholipid syndrome and determining how well the coagulation assays and solid phase assays for the detection of antiphospholipid antibodies correlate.

REPORT DATE: 05/13/92 WORK UNIT # 1677

DETAIL SUMMARY SHEET

TITLE: Flludarabine 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: Ongoing
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 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 patient had a partial response to the therapy. Patient was continued on therapy and had continued response with marked decrease in the adenopathy and bone marrow involvement. Dose reductions have occurred as outlined in the group C protocol. The patient is currently being monitored off therapy and will be restarted at time of disease progression.

CONCLUSIONS
This agent is very effective in decreasing the tumor burden in this patient. As this drug is now commercially available, it will continue to be used for this patient if needed. As she was enrolled in the group C protocol, it will continue to be provided at no cost for this patient.

REPORT DATE: 10/06/92 WORK UNIT # 1678

DETAIL SUMMARY SHEET

TITLE: Tiazofurin Treatment of Adults with Chronic Myelogenous Leukemia in Blast Crisis

KEYWORDS:

PRINCIPAL INVESTIGATOR: Wright, Daniel COL MC

DEPARTMENT: Department of Medicine STATUS: Terminated
SERVICE: Hematology-Oncology Service APPROVAL DATE: Aug 1991

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

STUDY OBJECTIVE
This research protocol has been administratively terminated.

TECHNICAL APPROACH
This research protocol has been administratively terminated.

PRIOR AND CURRENT PROGRESS
This research protocol has been administratively terminated.

CONCLUSIONS
This research protocol has been administratively terminated.

REPORT DATE: 02/03/92 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: La Russa, Vincent PhD
ASSOCIATES: Salvado, August COL MC; Ward, Frank LTC MC

DEPARTMENT: Department of Medicine
SERVICE: Hematology-Oncology Service

STATUS: Ongoing
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

Studies have continued on the role of ribonucleotide metabolism and the regulation of myelopoiesis. Recently, the culture system has been used to study the pathophysiology of viral infections of bone marrow of military importance. In addition, the culture system has been used to predict marrow engraftment by primitive cells after immunotoxin treatment, supporting its future usefulness as a purging agent for AML. In other studies of marrow transplantation, the usefulness of highly purified CD34+ cells from HLA mismatched unrelated donors has been evaluated and has been found to be efficient in establishing hematopoiesis as autologous CD34+ cells in our culture system.

CONCLUSIONS

The results from these studies will elucidate on mechanisms involved in the regulation of hematopoiesis in normal and disease-state.

REPORT DATE: 08/04/92 WORK UNIT # 1956

DETAIL SUMMARY SHEET

TITLE: Neutrophil Function in Patients with Diabetes Mellitus

KEYWORDS: diabetes mellitus, neutrophil, myeloperoxidase

PRINCIPAL INVESTIGATOR: Cross, Alan COL MC
ASSOCIATES: Glass, Allan COL MC; Duncan, William LTC MC

DEPARTMENT: Department of Medicine
SERVICE: Infectious Disease Service

STATUS: Ongoing
APPROVAL DATE: Jun 1987

FUNDING: Current FY: $ 0 Previous FYs: $ 7,236 Total: $ 7,236

STUDY OBJECTIVE

To assess 1) neutrophil function of patients with diabetes mellitus and determine if impaired functional responses of diabetic neutrophils are related to a defect in the incorporation of exogenous inositol into hormonally sensitive phosphatidyl inositol pools, 2) lymphocyte function in diabetics by measuring expression of 1L2 receptors, HLA-DR antigens, and IL2 production, and 3) neutrophil function by measuring calcium levels, and membrane depolarization.

TECHNICAL APPROACH

Since submitting an amendment to this protocol in 1988, the most significant finding has been that the initial rates of superoxide formation in diabetics is twice that of controls; however, 10 minutes after stimulation, the neutrophils of diabetic patients generate levels of superoxide that are 25% that of controls. Resting, but not stimulated, intracellular calcium levels also differed between the two groups. The expression of IL2 receptors in response to some stimuli differed between the two groups. We are now correlating these differences with clinical parameters.

PRIOR AND CURRENT PROGRESS

A total of 40 patients and 26 controls have been enrolled in this study. Since the last report of July 1991, no further subjects have been entered. Consequently there have been no serious or unexpected adverse reactions, and no patient has withdrawn from the study. Analysis of the patients to date reveals no gross differences in myeloperoxidase (MPO) activity between patients with types I and II diabetes. There has been no clear benefit to patients entered into this study. Work will continue at WRAIR with neutrophils from healthy donors in which conrolled amounts of glucose and myoinositol will be added to assess their effects on MPO activity.

CONCLUSIONS

Despite clear evidence of a susceptability to infection among diabetic patients, no clear defect in neutrophil function has been documented in this study or by others. Because of the complexity of the condition of many of the patients in this study, further work will be needed to better define optimal neutrophil assay conditions.

REPORT DATE: 05/07/92 WORK UNIT # 1965

DETAIL SUMMARY SHEET

TITLE: Treatment of Cutaneous Leishmaniasis with Pentostam

KEYWORDS: leishmaniasis, Pentostam, IND

PRINCIPAL INVESTIGATOR: Oster, Charles COL MC
ASSOCIATES: Magill, Alan MAJ MC; Gasser, Robert Jr. LTC MC

DEPARTMENT: Department of Medicine
SERVICE: Infectious Disease Service

STATUS: Ongoing
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

Twenty-one patients have been treated with Pentostam in the last year; a total of 141 patients have been enrolled in this protocol. A relative increase in numbers was seen this year due to patients from Desert Storm. Two unexpected adverse reactions were seen. Both patients had no adverse clinical sequelae. Elevated pancreatic enzymes were detected in one patient and have now been detected in most patients treated to date. This appears to be a common and previously unrecognized toxicity associated with Pentostam. Many have asymptomatic increases in serum amylase and lipase, but many also have clinical symptoms consistent with pancreatitis. Long experience with the drug does not indicate a chronic problem resulting from this drug exposure. Treatment guidelines are currently being defined.

CONCLUSIONS

Pentostam is still the drug of choice for treating all the leishmaniases. Patients with cutaneous and viscerotropic disease are cured of their disease with this drug. No other drug is currently available to treat this disease that is more effective or less toxic. As we continue to use this drug in Americans with leishmaniasis, a more complete picture of the side effect profile will emerge.

REPORT DATE: 08/04/92 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

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Infectious Disease Service 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
Administer the immunoglobulin and bleed people, then subject the ELISA results to pharmacokinetic analysis.

PRIOR AND CURRENT PROGRESS
As noted in an addenum submitted in January 1991, nine patients were entered into the protocol during June and July 1990. There will be no further patient enrollment to this study. Serum specimens obtained for up to 35 days were analyzed for serotype-specific antibody levels. Since obtaining that data, no further patients have been entered into the study. The data have been subjected to pharmacokinetic analysis by Dr. Shmuklarsky at the Division of Experimental Therapeutics, WRAIR. In combination with a similar study at the Division of Experimental Therapeutics, WRAIR. In combination with a similar study in healthy volunteers done at the University of Maryland, there is surprising evidence that this passive antibody may actively induce new antibody formation.

CONCLUSIONS
Based on the persistence of elevated levels of type-specific antibody long after the known half-life of IVIG, we plan to address the possibility that IVIG can act as an immunogen. Per the addendum of January 1991, after developing a sensitive ELISpot assay to detect new antibody formation by B lymphocytes, healthy volunteers will be infused with this hyperimmune immunoglobulin, and antibody production of these lymphocytes will be assessed.

REPORT DATE: 01/21/92 WORK UNIT # 1972

DETAIL SUMMARY SHEET

TITLE: Cytokine Release by Amphotericin B

KEYWORDS: amphotericin B, cytokines, tumor necrosis factor

PRINCIPAL INVESTIGATOR: Chung, Raymond COL MC

DEPARTMENT: Department of Medicine STATUS: Completed
SERVICE: Infectious Disease Service APPROVAL DATE: Oct 1990

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

STUDY OBJECTIVE
To test whether the cytokines (interleukin-1, interleukin-6, and tumor necrosis factor) are released in blood when amphotericin B is given to humans. The release of these cytokines has been postulated as the cause of the fevers and chills seen with amphotericin B administration.

TECHNICAL APPROACH
Patients receiving amphotericin B have blood drawn at specified intervals. The blood specimens are tested for cytokines. Several controls, who would not get amphotericin B, would also have blood drawn and tested.

PRIOR AND CURRENT PROGRESS
One control patient was done. Cytokine kits, although ordered, had not arrived by June 1991. Because the principal investigator was reassigned to Saudi Arabia in support of Operation Desert Storm, the study was ended in June 1991.

CONCLUSIONS
None.

REPORT DATE: 04/27/92 WORK UNIT # 1973

DETAIL SUMMARY SHEET

TITLE: Prospective, Controlled Randomized Study Comparing the Efficacy and Safety of Intravenous Ciprofloxacin with Standard Antibiotic Therapy in the Treatment of Selected Tissue Infections

KEYWORDS: ciprofloxacin

PRINCIPAL INVESTIGATOR: Magill, Alan MAJ MC

DEPARTMENT: Department of Medicine STATUS: Completed
SERVICE: Infectious Disease Service APPROVAL DATE: Oct 1990

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

STUDY OBJECTIVE
To compare intravenous ciprofloxacin to standard intravenous antibiotics in the treatment of pneumonias, complicated urinary tract infections, and soft tissue infections due to susceptible organisms.

TECHNICAL APPROACH
Patients who meet the entry criteria are enrolled.

PRIOR AND CURRENT PROGRESS
Study ended by the protocol director because WRAMC failed to enroll patients. Timely referrals were difficult to obtain from the housestaff, fellows, etc. No patients were enrolled in this study.

CONCLUSIONS
WRAMC is a poor site to conduct studies of this nature. Common infections are frequently treated at other facilities and do not need to be referred to WRAMC. There is no incentive for the housestaff to increase their burden with protocol patients, as other effective antibiotics are available. It was impossible for already busy clinicians to conduct the study. A protocol nurse/data management person would be mandatory before attempting a similar protocol in the future.

REPORT DATE: 01/10/92 WORK UNIT # 1974

DETAIL SUMMARY SHEET

TITLE: Phase I Trial of a Polyvalent Escherichia Coli-Toxin A Conjugate Vaccine

KEYWORDS: E. coli, vaccine, polysaccharide

PRINCIPAL INVESTIGATOR: Artenstein, Andrew CPT MC
ASSOCIATES: Cross, Alan COL MC

DEPARTMENT: Department of Medicine
SERVICE: Infectious Disease Service

STATUS: Ongoing
APPROVAL DATE: Nov 1990

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

STUDY OBJECTIVE
To determine whether a polyvalent E. coli O-polysaccharide-toxin A conjugate vaccine is safe and immunogenic when administered to humans.

TECHNICAL APPROACH
This is a Phase I study of a polyvalent polysaccharide vaccine against common bacteremic strains of E. coli. A group of healthy volunteers will be injected with this product, and serial serum chemistries, side effect diaries, and various antibody measurements will be assessed on each subject.

PRIOR AND CURRENT PROGRESS
The data collection portion of the study has been completed. Fourteen subjects were enrolled in the study for vaccination; five of these received booster doses at day 90 as well. There have been no serious or unexpected adverse reactions related to the immunization, and no patients were withdrawn from the study. As noted in the original protocol, there are no benefits to the subjects. Currently, the laboratory and immunologic responses of the subjects to the vaccine are being analyzed.

CONCLUSIONS
The immunization schedule and subsequent data collection period was completed in early December 1991. As the data is currently undergoing anlaysis, no conclusions can be drawn at this point.

REPORT DATE: 05/20/92 WORK UNIT # 1975

DETAIL SUMMARY SHEET

TITLE: A Double Blind Randomized Prospective Controlled Study of the Safety, Immunogenicity and Efficacy of Gram-Negative Bacterial Vaccines in Wounded Soldiers

KEYWORDS: gram-negative, bacterial vaccines

PRINCIPAL INVESTIGATOR: Artenstein, Andrew CPT MC
ASSOCIATES: Cross, Alan COL MC

DEPARTMENT: Department of Medicine STATUS: Completed
SERVICE: Infectious Disease Service APPROVAL DATE: Feb 1991

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

STUDY OBJECTIVE
To determine the relative safety and efficacy of three different gram-negative bacterial vaccines in a susceptible population.

TECHNICAL APPROACH
Each candidate will receive one of two regimens based on a randomization scheme. Following vaccination they will be followed for certain clinical endpoints and immunologic parameters.

PRIOR AND CURRENT PROGRESS
Study aborted in March 1991 prior to the enrollment of any patients due to the abrupt end of the conflict in the Persian Gulf.

CONCLUSIONS
None.

REPORT DATE: 05/29/92 WORK UNIT # 1152

DETAIL SUMMARY SHEET

TITLE: In Vitro Analysis of Removal of Radiocontrast Agents (RCA) by Artificial Membranes

KEYWORDS: dialysis, radiocontrast, transport

PRINCIPAL INVESTIGATOR: Gouge, Steven MAJ MC
ASSOCIATES: Moore, Jack LTC MC

DEPARTMENT: Department of Medicine
SERVICE: Nephrology Service

STATUS: Completed
APPROVAL DATE: Jun 1987

FUNDING: Current FY: $ 0 Previous FYs: $ 1,332 Total: $ 1,332

STUDY OBJECTIVE

1) To study removal of radiocontrast agents (RCA) by three types of artificial membranes. 2) To determine performance curves depicting clearance as a function of operating parameters to assist in assessing optimal conditions for RCA removal.

TECHNICAL APPROACH

An in vitro system consisting of standard dialysis machines and solutions will be used. Test perfusates were made by adding urea and one of two RCA to normal saline. These solutions were run through three types of dialyzers to different flow and pressures to assess RCA clearance.

PRIOR AND CURRENT PROGRESS

RCA mass transport was measured with cuprophan (CU) and polyacrylanitrile (PA) dialyzers. Both hexabrix and renografin RCA were used. Clearance of renografin exceeded clearance of hexabrix in both types of dialyzers and is attributed to the lower molecular weight of the former. Clearance of both RCA's was affected by TMP in only PA dialyzers and is due to convective transport. Diffusive transport accounted for RCA removal in cuprophan dialyzers. PA dialyzers are best for removal of RCA.

CONCLUSIONS

Demonstration of optimum operational characteristics will allow investigation in a prospective study of patients at high risk for RCA toxicity. A paper has been published in Blood Purification.

REPORT DATE: 09/15/92 WORK UNIT # 1155

DETAIL SUMMARY SHEET

TITLE: The Effect of Thyroid Hormone Administration in Acute Renal Failure

KEYWORDS: renal failure, thyroxine, dialysis

PRINCIPAL INVESTIGATOR: Moore, Jack LTC MC
ASSOCIATES: Johnson, John COL MC; Burman, Kenneth COL MC

DEPARTMENT: Department of Medicine
SERVICE: Nephrology Service

STATUS: Completed
APPROVAL DATE: Sep 1987

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

STUDY OBJECTIVE

To determine whether patients with acute renal failure (ARF) have improved survival when treated with thyroxine (T4) compared to patients who do not receive T4; to determine whether T4 alters the severity of ARF; to assess the thyroid axis in patients with ARF; and to determine whether T4 effects severity and mortality of ARF in parallel, or are these effects disparate.

TECHNICAL APPROACH

Adults with renal failure are stratified into two groups based on entry serum creatinine and urine output. They then receive either T4 or placebo in a double blind, placebo controlled study. Thyroid hormones are measured at intervals, and renal function is assessed. Data are analyzed in context with survival variables, thyroid function parameters, and dialysis requirements.

PRIOR AND CURRENT PROGRESS

Three patients have been entered into this study since its approval in 1987; none this past fiscal year. The plan was to enroll subjects from the Persian Gulf war, but there were none. Identifying patients with ARF in a sufficiently timely fashion to make this protocol practical has proved impossible. Thus, this study should be closed.

CONCLUSIONS

No conclusions can be drawn. Two other medical centers (both civilian) have had no success accruing patients for this type of protocol presumably because most prospective subjects are critically ill.

REPORT DATE: 01/3 . . WORK UNIT # 1156

DETAIL SUMMARY SHEET

TITLE: Retrospective Analysis of the Use of Renal Ultrasound at Walter Reed Army Medical Center

KEYWORDS: ultrasound, kidney, obstruction

PRINCIPAL INVESTIGATOR: Welch, Paul MAJ MC
ASSOCIATES: Lockard, Jerry MAJ MC; Moore, Jack Jr. LTC MC

DEPARTMENT: Department of Medicine
SERVICE: Nephrology Service

STATUS: Completed
APPROVAL DATE: Oct 1987

FUNDING: Current FY: $ 0 Previous FYs: $ 1,131 Total: $ 1,131

STUDY OBJECTIVE

1) To survey the application of diagnostic ultrasonography at WRAMC by all requesting physicians. 2) To classify as standard or non-standard the indications for performing the sonogram, and to determine the relative frequency of abnormal versus normal results based on this distinction.

TECHNICAL APPROACH

All ultrasound reports in 6-month increments are collated, and the appropriate records are reviewed. Information from the records are then categorized into a) the indication for the ultrasound, b) the type of requesting physician, and c) the result of the ultrasound. A and C are subclassified into different strata which assist in data analysis. Data are then analyzed in a matrix format.

PRIOR AND CURRENT PROGRESS

The original Principal Investigator was in the process of completing data collection when he left the Army. No further work has been completed, and the study has been closed.

CONCLUSIONS

None.

REPORT DATE: 04/05/92 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: ANP, thyroid hormone, kidney

PRINCIPAL INVESTIGATOR: Moore, Jack LTC MC
ASSOCIATES: Tseng, Yueh-Chu PhD

DEPARTMENT: Department of Medicine
SERVICE: Nephrology Service

STATUS: Ongoing
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 was identified and characterized under control conditions, and in cells grown in T3-free media and media enriched with T3. The ANP receptor was characterized using hot and cold ANP. Guanylate cyclose (cyclic G) was measured using kit.

PRIOR AND CURRENT PROGRESS

PCDC exhibited very low specific binding at 37 C and 25 C. At 4 C, a receptor Kd of 11nM and 1,500,000 binding sites/cell were identified. When cells were grown in T3-free media, or media enriched with T3, no change in specific binding was noted. ANP did produce significant changes in cyclic GMP; however, T3 did not affect cyclic G levels.

CONCLUSIONS

Any thyroidal influence on the renal cellular response to ANP is not mediated directly by changes in the number or binding affinity of ANP receptors in the PCDC model. A manuscript describing these findings is in preparation.

REPORT DATE: 05/08/92 WORK UNIT # 1158

DETAIL SUMMARY SHEET

TITLE: Tumor Necrosis Factor and Interleukin-1 Levels in Patients with Systemic Lupus Erythematosis

KEYWORDS: lupus, tumor necrosis factor, lupus nephritis

PRINCIPAL INVESTIGATOR: Welch, Paul MAJ MC
ASSOCIATES: Moore, Jack LTC MC; Strickland, Roger MAJ MC

DEPARTMENT: Department of Medicine
SERVICE: Nephrology Service

STATUS: Completed
APPROVAL DATE: Mar 1989

FUNDING: Current FY: $ 0 Previous FYs: $ 1,463 Total: $ 1,463

STUDY OBJECTIVE

To correlate clinical markers of systemic lupus erythematosis (SLE) disease activity with levels of tumor necrosis factor (TNF) and interleukin-1 (IL-1).

TECHNICAL APPROACH

Part A: Patients with SLE with and without lupus nephritis will be prospectively recruited from the Rheumatology and Nephrology Clinics. Clinical parameters for disease activity will be correlated with TNF and IL-1 levels measured by RIA. Part B: Patients with SLE and sera stored in the Rheumatology sera bank will have TNF levels correlated with clinical disease activity retrospectively.

PRIOR AND CURRENT PROGRESS

No further patient samples have been obtained since early 1990. Recruitment stopped due to original investigator leaving WRAMC and problems with the TNF assay. Subsequently, published literature from other institutions have addressed many of the questions this study was attempting to answer. Current investigation by other investigators is focusing at cellular and molecular regulation of TNF and IL-1 in SLE which is beyond the scope of our services.

CONCLUSIONS

Close study due to reasons stated above.

REPORT DATE: 08/20/92 WORK UNIT # 1160

DETAIL SUMMARY SHEET

TITLE: Hemodynamic and Renal Response in the Rate to Hemorrhagic Hypotension in the Presence of ANF Antibody and in the Presence of Thiorphan, A Selective Metalloendoprotease Inhibitor

KEYWORDS: kidney, shock, atrial natriuretic

PRINCIPAL INVESTIGATOR: Yuan, Christine CPT MC
ASSOCIATES: Pamnani, Motilal, PhD; Moore, Jack Jr. LTC MC

DEPARTMENT: Department of Medicine
SERVICE: Nephrology Service

STATUS: Completed
APPROVAL DATE: Aug 1989

FUNDING: Current FY: $ 0 Previous FYs: $ 17,731 Total: $ 17,731

STUDY OBJECTIVE

To evaluate the physiologic role of atrial natriuretic factor (ANF) in hemorrhagic hypotension, and to assess the effects of exogenously administered ANF and/or Thiorphan (a selective metallendoprotease inhibitor which inhibits the catabolism of ANF) on renal function during hemorrhagic shock.

TECHNICAL APPROACH

Male Wistar rats, anesthetized with pentobarbital sodium, underwent hemorrhage to MAP=50 using a Wiggers-Jamson method. Hypotension was maintained for 3 hours. Inulin clearance, urine sodium excretion, c-GMP excretion, urine output, and plasma renin activity and immunoreactive ANF levels were measured hourly. Animals were then euthanized, and wedge sections of the right kidney were preserved in buffered formalin. Animals received ANF, Thiorphan, both ANF and Thiorphan, or the vehicle during the first hour of hemorrhage.

PRIOR AND CURRENT PROGRESS

The experiments outlined in the protocol have been completed. Two abstracts have been published on the results of this work, and a paper has been submitted for publication and is in review. All animals approved for the protocol have been used (100 rats).

CONCLUSIONS

ANP and Thiorphan given in combination during hemorrhagic hypotension produces an increase in urine output, inulin clearance, and cGMP excretion compared to controls. ANP given alone during hemorrhagic hypotension has no effect on urine output, inulin clearance, or cGMp excretion, despite high plasma levels.

REPORT DATE: 03/03/92 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, Christine CPT MC

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Nephrology Service APPROVAL DATE: Nov 1990

FUNDING: Current FY: $ 3,530 Previous FYs: $ 0 Total: $ 3,530

STUDY OBJECTIVE

To study the effects of atrial natriuretic peptide (ANP) and thiorphan in renal function during hemorrhagic shock in the rat model. We have previously found that renal function and urine output are acutely improved by this drug combination. We 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

Renal blood flow experiments are nearly done. Ten to 20 more animals will have to be entered to complete this part of the study. Chronic survival experiments are underway. Seven animals have been completed.

CONCLUSIONS

Renal blood flow appears to be preserved in animals receiving ANP/thiorphan, even with mean arterial BP of 50 mmHg, while that of controls and animals receiving vehicle declines markedly. The chronic studies are incomplete. However, the protocol works well, and animals are surviving hemorrhage with about 10% mortality, as had been expected.

REPORT DATE: 04/15/92 WORK UNIT # 1162

DETAIL SUMMARY SHEET

TITLE: The Regulation of Insulin-like Growth Factor I and Insulin-like Growth Factor Binding Protein Gene Expressionin 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: Ongoing
APPROVAL DATE: Jan 1991

FUNDING: Current FY: $ 8,598 Previous FYs: $ 0 Total: $ 8,598

STUDY OBJECTIVE

To elucidate the molecular and cellular biologic events which lead to the development of glomerulosclerosis. In particular, we are studying 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).

TECHNICAL APPROACH

We are examining matrix synthesis and degradation display 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 provide a murine model for non-proliferative glomerulosclerosis. Gene expression of ECM, MMP, and TIMP is 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 are measured by standard techniques. Renal histology is assessed by light and immunofluorescence microscopy.

PRIOR AND CURRENT PROGRESS

In vitro studies: Normal and bGH mesangial cells express type IV collagen, TIMP-1, and 72 kDa gelatinase mRNA and protein. Changes in cell density do not have a significant effect on the steady state mRNA levels of these molecules. In contrast, only the normal mesangial cells express 92 kDa gelatinase activity. In vivo studies: Normal mouse glomeruli express 72 kDa gelatinase mRNA in vivo, but no TIMP-1. Preliminary studies of bGH mice reveal a two- to threefold elevation in glomerular 72 kDa gelatinase mRNA over normals.

CONCLUSIONS

RT-PCR provides a sensitive technique for quantifying mRNA in cultured cells and in murine glomeruli. The major phenotypic difference between normal and bGH mesangial cells in vitro is expression of 92 kDa gelatinase in normals only. Normal mouse glomeruli in vivo express the 72 kDa gelatinase mRNA, and this expression is up-regulated in bGH mice.

REPORT DATE: 04/03/92 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, Christine 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: $ 3,485 Previous FYs: $ 0 Total: $ 3,485

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

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

Experiments have been largely completed. Cyclosporine stimulated endothelin production in a dose-dependent manner, as well as stimulating prostacyclin production. Cell viability declined in a dose-dependent manner; phosphoramidon inhibited both endothelin and prostacyclin production but not the decline in cell viability. We plan to enlarge these studies to study the behavior of the endothelin receptor upon stimulation with cyclosporine.

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: 05/14/92 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

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Nephrology Service APPROVAL DATE: Apr 1991

FUNDING: Current FY: $16,810 Previous FYs: $ 0 Total: $ 16,810

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

Ten (10) patients have been studied; 5 with renal cancer (normal), 1 with GN, and 4 normals from NIH (collaborator). We have shown that we can successfully isolate glomeruli in vivo, isolate mRNA, transcribe it into cDNA, and then use competitive PCR to both detect and quantify the amount of mRNA for both TIMP 1 and TIMP 2. Morphometric analysis of tissue suggests a strong correlation between the amount of TIMP expressed and the degree of glomerulosclerosis. There have been no adverse effects on patients and none have withdrawn. There has been no benefit to patients.

CONCLUSIONS

Detection of the molecular precursors of glomerular sclerosis is possible. This information may be of great use in understanding the natural history of GN, as well as designing future treatment trials.

REPORT DATE: 08/11/92 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

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Nephrology Service APPROVAL DATE: Aug 1991

FUNDING: Current FY: $ 2,587 Previous FYs: $ 0 Total: $ 2,587

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
Cell viability was maintained except at the highest concentration of cisplatin used. Cisplatin did not stimulate endothelin or prostaglandin production when measured at 24 hours. The plan is to repeat these experiments with measurements of cell viability, endothelin, and prostacyclin production at varying time intervals - 4 hours, 8 hours, 16 hours, and 48 hours after cisplatin exposure.

CONCLUSIONS
Cisplatin does not stimulate endothelin or prostacyclin production in endothelial cells after 24 hours of exposure to a range of drug concentrations.

REPORT DATE: 05/12/92 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 STATUS: Ongoing
SERVICE: Pulmonary Disease Service APPROVAL DATE: Feb 1981

FUNDING: Current FY: $ 520 Previous FYs: $ 11,267 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
To date, 13 patients have been studied on this protocol since 1981. Ten of these patients were studied in 1990 and 1991. No patients have been entered into this study over the last year because of manpower limitations in the lab and the lack of available software programs to perform the occlusion pressure responses. With the hiring of a new lab director and the completion of the software development it is anticipated that major progress should be made in the forthcoming year.

CONCLUSIONS
The degree of nocturnal hypoxemia can be predicted from age and daytime hemoglobin saturation in patients with underlying fibrotic lung disease.

REPORT DATE: 10/21/92 WORK UNIT # 1714

DETAIL SUMMARY SHEET

TITLE: Mechanisms Limiting Exercise Ventilation in Chronic Obstructive Lung Disease

KEYWORDS: exercise, ventilation, COPD

PRINCIPAL INVESTIGATOR: Dillard, Thomas LTC MC
ASSOCIATES: Derderian, Sarkis LTC MC

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Pulmonary Disease Service APPROVAL DATE: Sep 1983

FUNDING: Current FY: $ 0 Previous FYs: $ 220 Total: $ 220

STUDY OBJECTIVE
To determine factors that limit ventilation at maximum exercise in patients with chronic obstructive lung disease (COPD).

TECHNICAL APPROACH
Continuous physiologic measurements will be made on a bicycle ergometer during graded resistance exercise, with esophageal balloon in place for the measurement of pleural pressure to determine the work of breathing.

PRIOR AND CURRENT PROGRESS
A total of 13 patients were enrolled in this study. Patient accrual is completed. Data has been collected and consists of analog tracings of respiratory pressures, flows, and volumes during incremental cycle exercise while breathing on a mouthpiece to measure ventilation and oxygen consumption. The methods used required conversion of analog data to numeric values by hand. This process was the main focus of activity during the past year. Interpretation of data and development of a manuscript for submission can be expected during the next year.

CONCLUSIONS
The magnitude of tidal peak expiratory pressure (PEP) increases during exercise in COPD patients. This rise in PEP is disproportionately more than the magnitude of increase in expiratory airflow rate.

REPORT DATE: 06/17/92 WORK UNIT # 1717

DETAIL SUMMARY SHEET

TITLE: Prediction of Maximum Exercise Response from Resting Pulmonary Function in Patients with Chronic Obstructive Pulmonary Disease

KEYWORDS: exercise, ventilation, COPD

PRINCIPAL INVESTIGATOR: Dillard, Thomas LTC MC
ASSOCIATES: Hnatiuk, Oleh MAJ MC

DEPARTMENT: Department of Medicine
SERVICE: Pulmonary Disease Service

STATUS: Ongoing
APPROVAL DATE: May 1985

FUNDING: Current FY: $ 0 Previous FYs: $ 1,090 Total: $ 1,090

STUDY OBJECTIVE

To test the hypothesis that assessment of inspiratory function in addition to expiratory function can improve the prediction of the exercise response of patients with chronic obstructive pulmonary disease (COPD).

TECHNICAL APPROACH

To evaluate parameters of both inspiratory and expiratory function in COPD patients, and to perform exercise tests in this group. Using these variables, prediction formulae with the highest r2 values will be identified for maximum exercise ventilation and oxygen consumption. Data will be collected through record review.

PRIOR AND CURRENT PROGRESS

Progress on this protocol includes two published articles; one article published since the last annual report. A third article has been prepared for peer review. Data collected under this protocol consists of records from 105 patients.

CONCLUSIONS

Inspiratory testing improves the description of maximum ventilation and oxygen consumption in patients with chronic obstructive pulmonary disease.

REPORT DATE: 05/12/92 WORK UNIT # 1720

DETAIL SUMMARY SHEET

TITLE: Pilot Study On the Use of Conjunctival Oxygen Tension Monitoring in the Sleep Apnea Syndrome

KEYWORDS: oxygen, sleep apnea, conjunctival monitor

PRINCIPAL INVESTIGATOR: Derderian, Sarkis LTC MC
ASSOCIATES: Mohr, Lawrence LTC MC

DEPARTMENT: Department of Medicine
SERVICE: Pulmonary Disease Service

STATUS: Completed
APPROVAL DATE: Apr 1987

FUNDING: Current FY: $ 0 Previous FYs: $ 30,192 Total: $ 30,192

STUDY OBJECTIVE

To compare conjunctival oxygen tension monitoring with ear oximetry in Black sleep apneic patients.

TECHNICAL APPROACH

Using polysomnography (PSG) we plan to compare the two devices. In that skin pigmentation affects oximetry, the conjunctival monitor should be a reliable index.

PRIOR AND CURRENT PROGRESS

This study was completed and a paper submitted for review in January 1992.

CONCLUSIONS

Pulse oximetry in Blacks is not affected by skin pigmentation.

REPORT DATE: 04/29/92 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 MAJ MC
ASSOCIATES: Berg, Benjamin CPT MC

DEPARTMENT: Department of Medicine
SERVICE: Pulmonary Disease Service

STATUS: Ongoing
APPROVAL DATE: Jan 1988

FUNDING: Current FY: $ 3,079 Previous FYs: $ 1,979 Total: $ 5,058

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

All data collection planned under this protocol has been completed and there will be no further accrual of subjects. Data analysis and reporting continues. Several reports remain to be completed. These pertain to the change in spirometry with altitude, change in diffusing capacity with altitude, hemodynamic effects of altitude, and adaptation to altitude. All but one of these has been developed to some extent. Three manuscripts developed under this protocol were published this past year.

CONCLUSIONS

Work continues under this protocol. We expect to conclude work on this project in three years.

REPORT DATE: 05/12/92 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: Ongoing
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
Because of manpower limitations, no patients have been entered into the study over the past 12 months. We currently have plans to have a summer student undertake and complete the project within the next 6 months.

CONCLUSIONS
None to date.

REPORT DATE: 06/15/92 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: Ongoing
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

Four patients have completed the protocol at this time. Patients with this isolated upper airway obstruction are difficult to find. However, the project is certainly worth pursuing to completion. As these patients sometimes come in groups, it is difficult to say how much longer the protocol must be maintained. It is hoped that the study can be completed in the near future. No untoward effects have been noted in the cases studied.

CONCLUSIONS

Suggest that the protocol be maintained for the upcoming year.

REPORT DATE: 10/07/92 WORK UNIT # 1732

DETAIL SUMMARY SHEET

TITLE: Pleural Pressure Measurements in Normal Healthy Volunteers During the Administration of Nasal Continuous Positive Airway Pressure (NCPAP)

KEYWORDS: nasal CPAP, pleural pressure, esophogeal pressure

PRINCIPAL INVESTIGATOR: Derderian, Sarkis LTC MC

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Pulmonary Disease Service APPROVAL DATE: Sep 1988

FUNDING: Current FY: $ 328 Previous FYs: $ 5,187 Total: $ 5,515

STUDY OBJECTIVE
The objective of this pilot study is to quantify the increase in pleural pressure due to nasal continuous positive airway pressure (NCPAP). This will be accomplished by measuring pleural pressure at several levels of NCPAP in normal healthy volunteers.

TECHNICAL APPROACH
To measure pleural pressure at different levels of NCPAP using the esophageal balloon technique and, in addition, to continuously record chest/wall and abdominal motion.

PRIOR AND CURRENT PROGRESS
To date, two subjects have been studied. The protocol was temporarily halted during late 1991 due to the loss of technical support staff. Recently, several days have been spent relocating necessary transducers and amplifiers and recompiling the breathing circuit to study additional subjects. This study should be kept open since it is expected to yield pilot information for future studies.

CONCLUSIONS
None to date. There is no new information in this area, and the work should yield important information for future studies.

REPORT DATE: 04/03/92 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 symptons.

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

To date, six patients have completed the 6 month protocol. There have been no untoward side effects noted and no patient withdrawals. Although data has not yet been statistically reviewed, objective and subjective improvements have been observed in both patients' reports of decreased pulmonary symptoms and increased pulmonary function tests.

CONCLUSIONS

Preliminary results are encouraging in that all patients have improved under therapy. Since all results are still blinded, no conclusion can be made yet regarding the efficacy of high dose inhaled triamcinolone acetonide in the treatment of pulmonary sarcoidosis.

REPORT DATE: 06/08/92 WORK UNIT # 1737

DETAIL SUMMARY SHEET

TITLE: Predicting Exercise Responses in COPD Patients

KEYWORDS: exercise, COPD, emphysema

PRINCIPAL INVESTIGATOR: Dillard, Thomas MAJ MC

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Pulmonary Disease Service 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
The data collection phase of this protocol has enrolled and completed study of a total of 46 cases, more than one-third of the originally planned maximum sample size. This includes 12 cases added during the past year.

CONCLUSIONS
Additional data collection is planned during the coming year. The protocol remains active in the data collection phase.

REPORT DATE: 07/14/92 WORK UNIT # 1738

DETAIL SUMMARY SHEET

TITLE: Incidence of Arrhythmias During Pentamidine Therapy

KEYWORDS: arrhythmia, pentamidine

PRINCIPAL INVESTIGATOR: Eliasson, Arn MAJ MC

DEPARTMENT: Department of Medicine STATUS: Completed
SERVICE: Pulmonary Disease Service APPROVAL DATE: Jul 1990

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

STUDY OBJECTIVE
To determine the incidence of arrhythmias during pentamidine therapy.

TECHNICAL APPROACH
Patients at WRAMC receiving IV or inhaled pentamidine will be evaluated prospectively for risk factors for arrhythmias. They will be followed with periodic EKG's and other cardiologic studies including echocardiograms and Holter monitors. Specific endpoints include changes in QT intervals and frequencies of arrhythmias correlated with the dose of pentamidine administered.

PRIOR AND CURRENT PROGRESS
Ten patients were enrolled in the past year, bringing the total number to 17. Because this study brought new attention to the problem of IV pentamidine toxicity, very few patients have received this antibiotic therapy during the past year. Patient enrollment has been adversely affected as a result. Several individual patients had their antibiotic regimens altered due to the increased monitoring afforded by this protocol. This may have had a positive impact on their outcome by sparing them pentamidine toxicity. Data collection is complete, and analysis shows that arrhythmic toxicity may be predicted by following the QTc interval on daily standard EKG's. This knowledge greatly improves the safety of IV pentamidine.

CONCLUSIONS
Arrythmic toxicity may be predicted following the QTc interval on daily standard EKG's and greatly improves the safety of IV pentamidine.

REPORT DATE: 07/14/92 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: $ 0 Previous FYs: $ 0 Total: $ 0

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.

PRIOR AND CURRENT PROGRESS
During the past year, three half-time study coordinators were hired and trained in data collection, file maintenance, and generation of reports. Sixty-one patients in the MICU were screened, and 15 patients were enrolled. Data collection is completed on all subjects. These subjects, in combination with the other patients enrolled at other medical centers, formed a data base which proved the efficacy of this therapy against Klebsiella. The effect against Pseudomonas was not the same. Study supervisors and planners have decided to amend this protocol to use a higher dose of the polyclonal antibody preparation against Pseudomonas. When received, these changes will be submitted for review and approval.

CONCLUSIONS
Patient enrollment is complete under the initial protocol. Data analysis and manuscript preparation is being performed by study designers. An amendment is being written and will be submitted within the next 2 months.

REPORT DATE: 07/22/92 WORK UNIT # 1740

DETAIL SUMMARY SHEET

TITLE: The Effect of Diltiazem on Pulmonary Gas Exchange in Patients with Chronic Obstructive Lung Disease at Rest, with Exercise, with Exposure to a Hypoxic Environment and during Sleep

KEYWORDS: Ca channel, COPD, gas exchange

PRINCIPAL INVESTIGATOR: Moores, Lisa CPT MC
ASSOCIATES: Phillips, Yancy LTC MC

DEPARTMENT: Department of Medicine STATUS: Ongoing
SERVICE: Pulmonary Disease Service APPROVAL DATE: Jul 1990

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

STUDY OBJECTIVE
To evaluate the potential of calcium channel antagonists to blunt the pulmonary vasoconstrictive response to hypoxemia, thus lowering pulmonary vascular resistance, increasing ventilation-perfusion mismatching, and worsening hypoxemia.

TECHNICAL APPROACH
Prospective study in patients with severe airflow obstruction and mild hypoxemia -- all subjects undergo baseline studies of ABG, pulmonary function, resting cardiac output, and incremental cardiopulmonary exercise before and after two hours of acute administration of 60 mg diltiazem. Subjects are then randomly assigned to receive four weeks of either diltiazem or a placebo, 60 mg TID, at which time all tests are repeated 2 hours after a medication dose.

PRIOR AND CURRENT PROGRESS
There have been 14 patients meeting the above criteria who have been completely studied. Plans are to continue the study in an attempt to look at the cardiopulmonary effects of chronic diltiazem use during sleep.

CONCLUSIONS
Examination of the data from the first 14 patients reveals no effect of acute or chronic diltiazem use on cardiac output, oxygen delivery, pulmonary function, or exercise performance. There was a trend toward a protective effect of diltiazem on pulmonary gas exchange at altitude which is being investigated.

REPORT DATE: 01/21/92 WORK UNIT # 1742

DETAIL SUMMARY SHEET

TITLE: The Effect of Pyridostigmine on Bronchial Hyperreactivity

KEYWORDS: pyridostigmine, asthma, airway hyperreactivity

PRINCIPAL INVESTIGATOR: Roach, James CPT MC
ASSOCIATES: Phillips, Yancy LTC(P) MC; Eliasson, Arn LTC MC

DEPARTMENT: Department of Medicine
SERVICE: Pulmonary Disease Service

STATUS: Completed
APPROVAL DATE: Oct 1990

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

STUDY OBJECTIVE
To examine the effect of pyridostigmine on bronchial hyperreactivity (BHR) in normal smoking and non-smoking subjects and in subjects with known mild asthma.

TECHNICAL APPROACH
This study is a randomized, double-blinded, placebo controlled, prospective crossover trial. Bronchial hyperreactivity is measured by the bronchoprovocation challenge known as "eucapnic voluntary hyperventilation." There have been no modifications to the original protocol.

PRIOR AND CURRENT PROGRESS
The study is completed and closed to enrollment. A total of 30 subjects (10 in each group) were enrolled. There were no serious or adverse reactions. There was no particular benefit to patients who completed the study. A number of patients were withdrawn from the study; in the majority of instances it was because they were called to participate in Operation Desert Storm prior to completing the study. A few patients declined to participate in the second day of testing after completing the first day.

CONCLUSIONS
Pyridostigmine, at a dose of 30 mg po twice daily has no effect on bronchial hyperreactivity as measured by eucapnic voluntary hyperventilation in the population studied. The implication is that pyridostigmine can be safely administered (from a respiratory standpoint) to soldiers that are in danger of being exposed to nerve gas.

REPORT DATE: 02/04/92 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: $ 660 Previous FYs: $ 0 Total: $ 660

STUDY OBJECTIVE

To examine the validity of previously developed methods for prediction of maximum voluntary ventilation (MVV) in normal patients and 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

There have been a total of 23 patients enrolled in the protocol to date; 12 in the last year. There have been no serious or unexpected adverse reactions associated with this study. This study does not directly benefit the patients unless their physicians request and utilize the collected data. Data collected while reviewing files to identify eligible patients was analyzed retrospectively and showed that maximum inspiratory flow rate (MIFR) was a determinant of MVV.

CONCLUSIONS

Prospectively collected data has not been analyzed. Patient identification, procurement, and testing continue.

REPORT DATE: 04/14/92 WORK UNIT # 1745

DETAIL SUMMARY SHEET

TITLE: Beta Agonist Bronchodilator Inhalation in Mechanically Ventilated COPD Patients: A Comparison of Nebulizer and Metered Dose Inhaler with IspirEase

KEYWORDS: inhaled bronchodilators, COPD, mechanical ventilation

PRINCIPAL INVESTIGATOR: Torrington, Kenneth LTC MC
ASSOCIATES: Phillips, Yancy COL MC; Andresen, Paul CRTT

DEPARTMENT: Department of Medicine
SERVICE: Pulmonary Disease Service

STATUS: Ongoing
APPROVAL DATE: Jan 1991

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

STUDY OBJECTIVE

To determine the optimal method for administering inhaled beta agonist bronchodilator medications to COPD patients requiring mechanical ventilation.

TECHNICAL APPROACH

Mechanically ventilated COPD patients will be studied as they are recovering from the condition(s) that exacerbated their chronic disease. Physiologic responses will be compared to inhaled metaproterenol, administered either via a metered dose inhaler or an updraft nebulizer. The study will be double-blinded and placebo-controlled. The protocol has not been modified since approval.

PRIOR AND CURRENT PROGRESS

During the past year, no patients have been enrolled into the study. This lack of activity is primarily the result of insufficient interest by the respiratory therapy investigator, who was responsible for finding appropriate patients. This individual has retired and has been replaced by Paul Andresen, CRTT, an enthusiastic and qualified practitioner.

CONCLUSIONS

The proposed study will provide important scientific information which will enable physicians to choose the optimal method for administering inhaled bronchodilator medications to mechanically ventilated patients.

REPORT DATE: 05/15/92 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

To date, 95 patients have been enrolled in the protocol. Three of these patients experienced hemo/pneumothorax. This value is well below usual values reported in the literature. There have been no adverse outcomes to patients as a result of this study. There has been no benefit to patients participating in this study.

CONCLUSIONS

Data collection is ongoing. No conclusions can be reached at this time based on data available.

REPORT DATE: 04/30/92 WORK UNIT # 1747

DETAIL SUMMARY SHEET

TITLE: Increased Use of Repeat Fiberoptic Bronchoscopy: Utility in Patients with Suspected Bronchogenic Carcinoma

KEYWORDS: RFB, fiberoptic bronchoscopy, suspected malignancy

PRINCIPAL INVESTIGATOR: Torrington, Kenneth LTC MC
ASSOCIATES: Poropatich, Ronald MAJ MC

DEPARTMENT: Department of Medicine
SERVICE: Pulmonary Disease Service

STATUS: Ongoing
APPROVAL DATE: Aug 1991

FUNDING: Current FY: $ 3,003 Previous FYs: $ 0 Total: $ 3,003

STUDY OBJECTIVE

To document the increased use of repeat fiberoptic bronchoscopy (RFB) at Walter Reed Army Medical Center; to evaluate indications for repeat procedures; and to determine the value of RFB in patients with suspected carcinoma.

TECHNICAL APPROACH

This study is a retrospective chart review of all patients undergoing bronchoscopy in the WRAMC Pulmonary Clinic between 1986 and 1990. Patients who have had two or more procedures will be identified and sorted on the basis of the indication for the repeated bronchoscopy.

PRIOR AND CURRENT PROGRESS

Bronchoscopy reports on 1,598 patients were collected between January 1986 and December 1990 and were screened to find 207 patients who underwent RFB. Repeated procedures increased progressively from 11% of all procedures in 1986 to 20% in 1990. Fifty-nine percent of the repeat bronchoscopies were performed in patients with suspected carcinoma. Data analysis for this group has been completed, and the report has been accepted for publication by Chest. The second largest group was composed of immunocompromised patients with pulmonary infiltrates. Data on the 18% of patients presenting with immunocompromised status and pulmonary infiltrates will be evaluated in the future.

CONCLUSIONS

RFB increased steadily 1986-1990, primarily because of its use (1) in previously diagnosed cancer patients presenting with second primary lesions, pulmonary metastases, or progressive disease requiring therapeutic interventions; and (2) in infected Human Immunodeficiency Virus patients. For patients with new suspected malignancies, RFB is often diagnostic when the initial procedure has shown endobronchial or submucosal tumor, but biopsy specimens were nondiagnostic.

REPORT DATE: 07/29/92 WORK UNIT # 1748

DETAIL SUMMARY SHEET

TITLE: Utility of Fiberoptic Bronchoscopy in Stage I Bronchogenic Carcinoma

KEYWORDS: fiberoptic bronchoscopy, bronchogenic carcinoma, solitary pulmonary

PRINCIPAL INVESTIGATOR: Torrington, Kenneth LTC MC
ASSOCIATES: Kern, Joseph MAJ MC; Weidner, Sara CPT MC

DEPARTMENT: Department of Medicine
SERVICE: Pulmonary Disease Service

STATUS: Ongoing
APPROVAL DATE: Aug 1991

FUNDING: Current FY: $ 663 Previous FYs: $ 0 Total: $ 663

STUDY OBJECTIVE
To determine the value of performing fiberoptic bronchoscopy in patients presenting for evaluation of solitary pulmonary nodules suspicious for bronchogenic carcinoma.

TECHNICAL APPROACH
This study is a retrospective chart review of patients bronchoscoped in the Walter Reed Army Medical Center Pulmonary Clinic as part of their preoperative evaluation for a solitary pulmonary nodule. The study will correlate bronchoscopic and surgical findings and will determine whether a preoperative diagnosis of malignancy affected the duration of surgery.

PRIOR AND CURRENT PROGRESS
Charts of 260 patients were screened to find approximately 100 potential cases. Final data are being reduced and analyzed, and a draft manuscript has been written. Preliminary data were presented in abstract form and were discussed at the 1992 American Thoracic Society Annual Conference in May 1992.

CONCLUSIONS
Definitive conclusions await final data analysis. A final report is expected by the end of October 1992.

REPORT DATE: 10/21/92 WORK UNIT # 1749

DETAIL SUMMARY SHEET

TITLE: Air Transport of Patients with Pulmonary Defects

KEYWORDS: altitude, hypoxia, emphysema

PRINCIPAL INVESTIGATOR: Dillard, Thomas LTC MC
ASSOCIATES: Berg, Benjamin CPT MC; Phillips, Yancy LTC MC

DEPARTMENT: Department of Medicine
SERVICE: Pulmonary Disease Service

STATUS: Ongoing
APPROVAL DATE: Sep 1991

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

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 cooximetery; exposure of subjects to 15% oxygen; ascent to simulated altitude conditions of 3000 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

Twenty-nine subjects have completed the protocol. No serious complications have occurred. Four subjects had minor complications which did not require change in protocol or medical treatment. These consisted of vagal reactions without syncope (1 patient, 1 control) and ear pain (1 control, 1 flight crewman). No sequelae occurred in any of these instances. In one case (control), arterial catheter could not be inserted.

CONCLUSIONS

Progress has been made in the area of data collection.

REPORT DATE: 08/26/92 WORK UNIT # 1971

DETAIL SUMMARY SHEET

TITLE: Early Diagnosis of Tuberculosis Using the Polymerase Chain Reaction

KEYWORDS: tuberculosis, polymerase chain reaction

PRINCIPAL INVESTIGATOR: Poropatich, Ron MAJ MC

DEPARTMENT: Department of Medicine STATUS: Completed
SERVICE: Pulmonary Disease Service APPROVAL DATE: Jul 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 4,308 Total: $ 4,308

STUDY OBJECTIVE
To develop a polymerase chain reaction (PCR) assay applicable to clinical specimens at WRAMC and then to assess its specificity, sensitivity and overall feasibility as a clinical tool to diagnose tuberculosis. Because a quick test is especially useful in cases of smear negative but culture positive cases, this protocol specifically examined this population.

TECHNICAL APPROACH
Oligonucleotide primers were synthesized using known gene sequences from the TB genome. By a process of trial and error, using purified mycobacterial genomic DNA as templates, two pairs of nested primers (from Pab protein gene) were found to be specific for TB. They were then used on over 50 clinical specimens. PCR using nested primers can eliminate the necessity of doing confirmatory Southern blots and thus make the results of this test available in 24 hours.

PRIOR AND CURRENT PROGRESS
Nested primer paris (NPP) were designed from regions of Pab (38k MW) gene of M. tuberculosis (Mtb). Primer parts were used in sequential PCR's (sPCR), with Mtb genomic DNA as initial template, to amplify a 589 bp and then a 353 bp segment. NPP did not amplify genomic DNA from M. avium, M. intracellulare, M. kansasii, M. fortuitum, or M. scrofulaceum. sPCR was able to detect Mtb DNA in dilutions of Mtb culture positive sputum that were negative by Bactec culture. Aliquots of 44 decontaminated and concentrated clinical specimens that were fluorochrome-negative and culture-positive for mycobacteria were saved. DNA was extracted by boiling (x 15 min), treatment with lysozyme, 1% SDS, phenol/chloroform and alcohol precipitation. NPP sPCR's done on these specimens showed 66% sensitivity, 100% specificity, 100% positive predictive value, and 95% negative predictive value compared with culture. This assay can be performed within a 24 hr period.

CONCLUSIONS
Although the sensitivity was 66%, the expectation is that sensitivity could be improved with smear-positive specimens. Unfortunately, the study was completed before testing these specimens.

REPORT DATE: 07/15/92 WORK UNIT # 3220R

DETAIL SUMMARY SHEET

TITLE: An Experimental Model of Seronegative Lupus - A Study of Biological Role of Anti-Ro/SSA and La/SSB Antibodies

KEYWORDS: Anti-Ro/SSA, La/SSB, autoantibodies, sero-negative lupus

PRINCIPAL INVESTIGATOR: Tesar, Joseph MD
ASSOCIATES: Molina, Rudolph MD

DEPARTMENT: Department of Medicine
SERVICE: Rheumatology Service

STATUS: Completed
APPROVAL DATE: May 1984

FUNDING: Current FY: $ 3,775 Previous FYs: $ 21,244 Total: $ 25,019

STUDY OBJECTIVE

To develop in vitro and in vivo models of seronegative and neonatal lupus using anti-Ro/SSA and La/SSB antibodies. The study has implications for subacute cutaneous lupus and primary Sjogren's syndrome. The Ro/SSA and La/SSB antibodies in these diseases probably mediate some of the clinical manifestations, such as small vessel vasculitis and cutaneous inflammation.

TECHNICAL APPROACH

The study will define the effect of immune complex formation in situ at the surface of epithelial cells. The effect of environmental agents such as UV radiation on release of Ro and La antigens from epithelial cells will be studied using immunofluorescent techniques. An animal model of cutaneous and neonatal lupus will be developed using the above immunological reagents. The techniques developed will be used also in clinical publications pertaining to Sjogren's syndrome and neonatal lupus.

PRIOR AND CURRENT PROGRESS

Methods have been developed for isolation and quantitation of Ro and La antigens and antibodies. Release of Ro and La antigens from epithelial cell line by UV radiation and adenoviral agents has been demonstrated. Immune complexes of IgG anti-SSA/SSB and SSA/SSB antigen composition activate human complement as demonstrated by fixation of C3 at the cell surface by immunofluorescent technique. A new type of neonatal lupus with cutaneous manifestations associated with Sm and RNP antibodies was demonstrated. Involvement of Ro/SSA and La/SSB antibodies was demonstrated in pathology of Sjogren's syndrome with CNS manifestations and optic neuropathy.

CONCLUSIONS

Complement activating immune complexes were induced on the surface of epithelial cells (Hep-2) by UV radiation and adenoviral agents in the presence of anti-Ro and La nuclear antibodies and complement. Purified anti-Ro and anti-La antibodies activate the classical pathway of complement after interaction with the homologous antigens. Ro/SSA and La/SSB antibodies also have a pro-inflammatory effect in primary Sjogren's syndrome.

REPORT DATE: 06/01/92 WORK UNIT # 3703

DETAIL SUMMARY SHEET

TITLE: Autoimmune Phenomena in Patients with Inflammatory Osteoarthritis and Primary Nodal Osteoarthritis

KEYWORDS: autoimmunity, osteoarthritis

PRINCIPAL INVESTIGATOR: Strickland, Roger MAJ MC
ASSOCIATES: Riordan, Kathryn MD

DEPARTMENT: Department of Medicine
SERVICE: Rheumatology Service

STATUS: Completed
APPROVAL DATE: May 1988

FUNDING: Current FY: $ 0 Previous FYs: $ 723 Total: $ 723

STUDY OBJECTIVE

To determine the extent of autoimmune features with inflammatory osteoarthritis (OA) and primary nodal osteoarthritis.

TECHNICAL APPROACH

One hundred and forty Caucasian patients with primary nodal osteoarthritis or inflammatory OA will be screened with x-rays and laboratory tests for evidence of autoimmune disease.

PRIOR AND CURRENT PROGRESS

Twelve patients have been studied with erosive osteoarthritis. Eight of the 12 had evidence of sicca, and 9 of the 12 had thyroid abnormalities. These thyroid abnormalities included Grave's disease, thyroiditis, hypothyroidism, or thyroid antibodies. Six patients have been studied with osteoarthritis with predominant Heberden's nodes, but they did not have erosive OA. Four of these six had sicca, and two had thyroid abnormalities. In contrast, of seven patients with the more usual nodal OA, none had sicca and only one had a thyroid problem.

CONCLUSIONS

These results suggest that patients with erosive osteoarthritis and those with Heberden's nodes may represent distinct subsets of OA associated with immune aberrations with sicca features and thyroid abnormalities.

REPORT DATE: 06/01/92 WORK UNIT # 3704

DETAIL SUMMARY SHEET

TITLE: Iontophoresis Therapy for Rheumatoid Arthritis

KEYWORDS: iontophoresis, rheumatoid arthritis

PRINCIPAL INVESTIGATOR: Strickland, Roger MAJ MC
ASSOCIATES: Klipple, Gary COL MC; Mewshaw, Betsy RN, MSN

DEPARTMENT: Department of Medicine
SERVICE: Rheumatology Service

STATUS: Ongoing
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

Eleven patients have been randomized and entered into the study. Each has had 3-5 joints treated. No results at this point; the data is not analyzed and the study is still ongoing. No adverse reactions have been encountered of any significance. Due to the PCS move of MAJ Strickland, the new principal investigator will be COL Gary Klipple, MC.

CONCLUSIONS

No conclusions can be drawn yet.

REPORT DATE: 06/01/92 WORK UNIT # 3705

DETAIL SUMMARY SHEET

TITLE: Iontophoresis Therapy for Osteoarthritis

KEYWORDS: iontophoresis, osteoarthritis

PRINCIPAL INVESTIGATOR: Strickland, Roger MAJ MC
ASSOCIATES: Klipple, Gary COL MC; Mewshaw, Betsy RN MSN

DEPARTMENT: Department of Medicine
SERVICE: Rheumatology Service

STATUS: Ongoing
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
Two patients with osteoarthritis have been randomized and entered into the study. No results are available to provide conclusions at this time (i.e., not enough patients are studied as yet). No significant adverse reactions have been encountered. Due to a PCS move of MAJ Strickland, the new principal investigator will be COL Gary Klipple, MC.

CONCLUSIONS
Too early to draw conclusions.

REPORT DATE: 06/01/92 WORK UNIT # 3706

DETAIL SUMMARY SHEET

TITLE: Iontophoresis Therapy for Bursitis and Tendinitis

KEYWORDS: iontophoresis, bursitis, tendinitis

PRINCIPAL INVESTIGATOR: Strickland, Roger MAJ MC
ASSOCIATES: Klipple, Gary COL MC; Mewshaw, Betsy RN MSN

DEPARTMENT: Department of Medicine
SERVICE: Rheumatology Service

STATUS: Ongoing
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
Nine patients with a variety of soft issue rheumatism problems have been randomized and entered into the study. It is too early to draw meaningful conclusions and interpret the results. No adverse reactions of any significance have been reported. Due to the PCS move of MAJ Strickland, COL Gary Klipple, MC, will be the new principal investigator for this protocol.

CONCLUSIONS
Too early to draw conclusions.

REPORT DATE: 09/11/92 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: Ongoing
APPROVAL DATE: Aug 1990

FUNDING: Current FY: $ 9,315 Previous FYs: $ 2,329 Total: $ 11,644

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

There have been 22 subjects enrolled in the study, and there have been no adverse reactions or patients withdrawn from the study. Preliminary data have been generated from the stored sera of these patients, and certain of these sera have been shown to have enhanced binding of IgG to neutrophils and to the cultured cell line THP-a. The immunobead antigen capture assay, which has been used to identify antibody specificities for these specimens, is currently being modified. The study remains open, pending evaluation of the current study specimens with the modified immunobead assay.

CONCLUSIONS

None yet.

REPORT DATE: 06/10/92 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: Ongoing
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
Eighteen patients have been entered in the study at this time and have received baseline and 6-month evaluations at the NIH.

CONCLUSIONS
None to date.

REPORT DATE: 06/18/92 WORK UNIT # 7138

DETAIL SUMMARY SHEET

TITLE: Investigation of the Usefulness of Motor Evoked Potentials in Neurological Disorders

KEYWORDS: motor evoked potentials, magnetic, motor system

PRINCIPAL INVESTIGATOR: Jabbari, Bahman COL MC

SERVICE: Neurology Service STATUS: Completed
APPROVAL DATE: May 1988

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

STUDY OBJECTIVE
To evaluate the yield of the newly invented magnetic evoked potentials in neurological disorders. This test can noninvasively measure the conduction times in the motor pathways of the brain and the spinal cord.

TECHNICAL APPROACH
Focal magnetic stimulation to the neural tissue is provided by a Nicolet 2000 unit. On each patient, the response will be recorded for the abductor pollicis and anterior tibialis muscles, and the nervous system will be stimulated at the wrist, Erb's point (brachial plexus), C6 cervical level, scalp, and at the region of hand and leg motor cortex. Absolute latency values for the peripheral and central potentials and the central conduction times will be compared with the normals for age and height provided in the literature. All patients will sign the informed consent prior to testing.

PRIOR AND CURRENT PROGRESS
A total of 232 patients were tested in different categories of neurological disorders. There were 76 patients with definite or probable multiple sclerosis, 14 with amyotrophic lateral sclerosis, 30 with peripheral neuropathy, 23 with osteoarthritis, 25 with intraspinal lesions, 10 with hydrocephalus, 40 with other neurological disorders, and 12 with hysterical paralysis. The incidence of magnetic motor evoked potential (MMEP) abnormality was 86% in definite and 64% in probable multiple sclerosis, 95% in ALS, 80% in intraspinal lesions, 92% in peripheral neuropathies, 86% in hydrocephalus, and 0% in hysterical hemiparesis.

CONCLUSIONS
The results of this study demonstrate a high yield for MMEP in multiple sclerosis, amyotrophic lateral sclerosis, and spinal cord pathology.

REPORT DATE: 06/02/92 WORK UNIT # 7141

DETAIL SUMMARY SHEET

TITLE: Recombinant Beta Interferons as Treatment for Multiple Sclerosis: A Multicenter Protocol

KEYWORDS: beta-interferon, multiple sclerosis

PRINCIPAL INVESTIGATOR: Salazar, Andres COL MC

SERVICE: Neurology Service STATUS: Ongoing
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.

PRIOR AND CURRENT PROGRESS
Twenty-seven patients have been entered at WRAMC, and a total of 207 patients have been entered in the entire multicenter study. There have been no adverse experiences attributable to the drug.

CONCLUSIONS
Beta-interferon is safe and well tolerated when administered at a dose of 6 million units IM for over 1 year to patients with multiple sclerosis.

REPORT DATE: 06/10/92 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: Ongoing
APPROVAL DATE: Mar 1989

FUNDING: Current FY: $ 0 Previous FYs: $ 295 Total: $ 295

STUDY OBJECTIVE
To determine the toxicity and tolerance of low doses of poly-ICLC and CCNU in patients with malignant gliomas.

TECHNICAL APPROACH
Patients will be administered poly-ICLC at 10, 20, 50, and 100 mcgm/kg twice weekly for 1 year.

PRIOR AND CURRENT PROGRESS
Nineteen patients with malignant gliomas have been entered to date. Poly-ICLC has been exceptionally well tolerated at the doses used to date, including 10 and 20 mcgm/kg twice weekly and 50 mcgm/kg weekly for up to 1-1/2 years. Mean survival is now 18 months for the entire group (range 6 to 36 months) and >14 months for Grade IV glioblastomas. Seven patients dropped out early in the study unrelated to Poly-ICLC toxicity, and five with advanced and highly malignant tumors ave died. The rest remain well, with a relatively good quality of life.

CONCLUSIONS
Poly-ICLC can be safely administered to patients with malignant gliomas over 18 months with virtually no toxicity. Preliminary findings suggest increased survival and tumor regression in most patients.

REPORT DATE: 04/07/92 WORK UNIT # 7143

DETAIL SUMMARY SHEET

TITLE: Investigation of the Effectiveness of Nimodipine in Movement Disorders

KEYWORDS: nimodipine, movement disorder, calcium channel blocker

PRINCIPAL INVESTIGATOR: Jabbari, Bahman COL MC

SERVICE: Neurology Service STATUS: Ongoing
APPROVAL DATE: Nov 1989

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

STUDY OBJECTIVE
To evaluate the effectiveness of calcium channel blocker nimodipine in movement disorders.

TECHNICAL APPROACH
Patients with involuntary movement disorders (chorea, myoclonus, dystonia, tremor) will be enrolled. Each patient will be videotaped prior to treatment. Nimodipine 30 mg will be prescribed qid for 10 days. Patient's improvement will be evaluated by a clinical rating scale and a second videotape. An unbiased observer will rate the tapes.

PRIOR AND CURRENT PROGRESS
We have studied 19 patients with a variety of movement disorders. There were eight patients with torticollis, six with tremor, two with chorea, two with myokymia, and one with myoclonus. All three patients with cerebellar tremor showed remarkable improvement as seen in videotapes and clinical rating scales. One patient with myokymia of lower leg muscle also showed significant improvement. No side effects were noted.

CONCLUSIONS
The calcium channel blocker drug nimodipine when given at a daily dose of 120 mg was effective in some patients with disabling cerebellar tremor. More patients are needed to be studied in this category.

REPORT DATE: 06/24/92 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
Aproval and funding for this project was received from DVA, and supplemental funding was received from DoD. Personnel were hired and trained. Evaluation instruments were developed, and data entry forms were prepared. Six patients were piloted with the evaluation and treatment program. Thirteen patients have been accrued to date. Eleven patients have completed treatment.

CONCLUSIONS
None.

REPORT DATE: 03/28/92 WORK UNIT # 7145

DETAIL SUMMARY SHEET

TITLE: Dyesthetic Pain: A Blinded and Controlled Study of Treatment with Capsaicin 0.075%

KEYWORDS: pain, capsaicin

PRINCIPAL INVESTIGATOR: Harper, Michael LTC MC
ASSOCIATES: Sinoff, Stuart MAJ MC; Bolt, Jodie CPT MC

SERVICE: Neurology Service STATUS: Ongoing
APPROVAL DATE: Dec 1990

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

STUDY OBJECTIVE
To ascertain in the context of a double-blinded, placebo controlled study whether capsaicin 0.075%, when applied topically to the skin, will alleviate or improve burning, superficial dysesthetic pain caused by meralgia paresthetica, reflex sympathetic dystrophy (sympathetically maintained pain), burning peripheral neuropathies, or other non-specified neuropathic (burning) pain.

TECHNICAL APPROACH
This is a multi-center study. Patients will be randomly enrolled into the four groups delineated above. After an initial evaluation, patients will apply test ointment (cream) to affected areas four times daily for a 6 week period. They will return every 2 weeks for questioning and completion of a case report form. Patients will complete the case report forms at specified times at home, foregoing travel to Walter Reed every 2 weeks. These forms will be returned at the time of the conclusion visit (6 weeks).

PRIOR AND CURRENT PROGRESS
To date, we have enrolled 16 of the projected 49 patients. There have been no serious or unexpected adverse reactions. It is difficult for the blinded patients and physicians to know if there have been any improvements, but for whatever reasons, some patients have reported lessening of their burning dysesthetic pain. The code of placebo versus treated patients has not been broken. Enrollment of more reflex sympathetic dystrophy patients was anticipated, but there have not been many despite the study's location at a large tertiary referral center. One patient withdrew from the study at 4 weeks. Additional patients in all categories are being actively sought for enrollment as appropriate.

CONCLUSIONS
Currently, there are few conclusions that can be drawn. It does appear that the blinding of the study is good, for it does not appear that either patients or physicians can accurately predict which patients are receiving placebo and which are receiving investigational drug. All patients appear to be experiencing some burning due to cream application.

REPORT DATE: 04/15/92 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: Ongoing
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
Three normal subjects and one patient with a solitary pontine lesion have been studied. Two of three normal subjects showed significant slowing of heart rate during exposure to cold water and breath-holding. There were no EEG changes. The patient with pontine lesion paradoxically demonstrated an increased heart rate while exposed to cold water and breath-holding.

CONCLUSIONS
The small number of subjects studied to date does not allow any definite conclusions. Preliminary data suggest that normal subjects differ from patients with brain stem lesions in their cardiovascular response to cold water and breath-holding.

REPORT DATE: 05/21/92 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: $ 1,744 Previous FYs: $ 0 Total: $ 1,744

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 81 tapes were reviewed on 22 patients with respect to a clinical sign termed dystonia. Dystonia was seen in 7 of 22 (30%) patients (average 4 seizures per patient). All six patients with unilateral dystonia demonstrated it contralateral to the discharging focus; one patient had alternating dystonia, but the first dystonic limb was contralateral to the area of the brain damage. Currently, the localizing value of "head turning" during seizures is being evaluated.

CONCLUSIONS
Epileptic dystonia is an important localizing sign when it occurs during a seizure. Dystonia points to the contralateral hemisphere as the side of pathology.

REPORT DATE: 07/29/92 WORK UNIT # 9200

DETAIL SUMMARY SHEET

TITLE: Anatomical and Functional Sequelae of Head Injuries Incurred in Vietnam

KEYWORDS: penetrating head injury, post traumatic epilepsy, neuropsychological

PRINCIPAL INVESTIGATOR: Salazar, Andres COL MC

SERVICE: Neurology Service STATUS: Ongoing
APPROVAL DATE: Jun 1980

FUNDING: Current FY: $ 0 Previous FYs: $ 6,875 Total: $ 6,875

STUDY OBJECTIVE
To examine selected veterans who received head injuries in Vietnam, plus Vietnam veterans who received no head injuries as a control group.

TECHNICAL APPROACH
Each subject will receive a neurological exam, CT scan, speech pathology exam, motor exam, audiology exam, electrophysiology battery, and neuropsychological exam. In addition, an American Red Cross caseworker has interviewed each subject and family to complete a field study.

PRIOR AND CURRENT PROGRESS
Inpatient phase completed as of October 1984. There were 520 head injury subjects enrolled, plus 86 uninjured controls. Contact is maintained with VHIS subjects, and selected patients are reevaluated at WRAMC periodically; however, these contacts are not for the purpose of further data collection. Data analysis continues. Recent analyses have centered on return to work after penetrating head injury. Fifty percent (50%) of our population is employed; return to work can be predicted from analysis of neurologic and cognitive status.

CONCLUSIONS
The VHIS data base represents an invaluable asset on computer tape and microfiche that will continue to provide room for analysis for years to come. While many of the questions posed in the original protocol have already been answered, new and often more exciting questions have arisen and will continue to arise as investigators explore the data.

REPORT DATE: 07/06/92 WORK UNIT # 7520

DETAIL SUMMARY SHEET

TITLE: The Relationship of the Sense of Coherence and Hardiness to the Nutritional Status of Anorectic Head and Neck Cancer Patients Currently Undergoing Radiation Therapy

KEYWORDS: hardiness, sense of coherence, nutritional status

PRINCIPAL INVESTIGATOR: Sarnecky, Mary LTC MC
ASSOCIATES: Forlaw, Loretta LTC AN

DEPARTMENT: Department of Nursing

STATUS: Completed
APPROVAL DATE: May 1990

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

STUDY OBJECTIVE

To investigate the relationship between the personality traits' sense of coherence and hardiness and the nutritional status of patients with head and neck cancer who are receiving radiation therapy.

TECHNICAL APPROACH

Experimental, correlational design study. Descriptive statistics will be used to summarize demographic information. Pearson product moment correlations will be used to explain the relationship between the sense of coherence, hardiness, and nutritional status, as well as the subscales of the Orientation to Life Questionnaire and the Health Related Hardiness Scale. The significant difference between the mean Body Mass Index at diagnosis and subsequent means for weeks 1-8 of radiation therapy will be assessed using the repeated measure t-test. Step-wise multiple regression will be applied to explain the statistical differences among variables.

PRIOR AND CURRENT PROGRESS

Subjects enrolled total 26 male and 13 female ambulatory head and neck cancer patients. No adverse reactions or patient withdrawals have occurred. No patient benefits ensued. Using Pearson Product Moment Correlations for each of the scale and subscales of the Orientation to Life Questionnaire and the Health Related Hardiness Scale, it was determined that hardiness was not significantly related to nutritional status during radiation therapy in this sample. Scores on the Orientation to Life Questionnaire did demonstrate a significant relationship between the sense of coherence and maintenance of nutritional status during radiation therapy. That is, those who maintained or improved nutritional status tended to score higher in sense of coherence. As would be expected, sense of coherence and hardiness were positively related.

CONCLUSIONS

It appears that the Orientation to Life Questionnaire is more sensitive than the Health Related Hardiness Scale in explaining differences between patients who maintain their nutritional status and those who do not.

REPORT DATE: 06/30/92 WORK UNIT # 7521

DETAIL SUMMARY SHEET

TITLE: Pregnancy Attitudes, Ambivalence and Symptom Distress

KEYWORDS: pregnancy attitudes, ambivalence, symptom distress

PRINCIPAL INVESTIGATOR: Biskey, Valerie COL AN

DEPARTMENT: Department of Nursing STATUS: Ongoing
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 pre-paid mailer.

PRIOR AND CURRENT PROGRESS
Six hundred and two questionnaries were sent out from three different collection sites; 433 were returned (104 were from WRAMC). The response rate was 72%. Data analysis of the quantitative portion of the study is nearly complete, as it is anticipated that this work will be completed and an article prepared for publication by January 1993.

CONCLUSIONS
The Pregnancy Questionnaire is an 86-item instrument with coefficient alphas of 0.97 for the general pregnancy scale and 0.98 for the ambivalence scale.

REPORT DATE: 04/20/92 WORK UNIT # 7522

DETAIL SUMMARY SHEET

TITLE: A History of Walter Reed Army Medical Center: 1909-1990

KEYWORDS: medical history, WRAMC

PRINCIPAL INVESTIGATOR: Sarnecky, Mary LTC AN

DEPARTMENT: Department of Nursing STATUS: Ongoing
APPROVAL DATE: Feb 1991

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

STUDY OBJECTIVE
To produce an accurate, up-to-date, scholarly history of Walter Reed Army Medical Center.

TECHNICAL APPROACH
This study used the historical methodology. A problem statement, conceptual framework, and study questions will be articulated. Data will be collected and assessed for validity and reliability. The data will be organized, integrated, analyzed, and synthesized as well. A research report will be written, a manuscript will be prepared and submitted for publication. No modifications to the approach specified in the original protocol have been employed.

PRIOR AND CURRENT PROGRESS
As outlined above, all steps of the methodological process have been completed with the exception of the final step. This final step is the preparation of the research report and a manuscript for publication.

CONCLUSIONS
Thus far, findings reveal that Walter Reed Army Medical Center has had an illustrious history. It has been consistently a premier institution in the vanguard of scientific advances. Its contribution to both military and civilian medicine has been significant.

REPORT DATE: 06/23/92 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 LTC AN

DEPARTMENT: Department of Nursing

STATUS: Ongoing
APPROVAL DATE: Jul 1991

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

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

Nurse knowledge data collection has been completed. There are 42 nurse subjects (21 in each group). Nurse intervention and patient pain relief data collection have been completed on the pre-SLM set of 20 patients. The post-SLM set requires two more subjects. There have been no adverse reactions or subjects withdrawn from the study. Subjects may benefit from the knowledge they gain by participating in the study, but preliminary findings from the pre- and post-SLM patient sets do not show a change in nurse interventions or in patient pain relief.

CONCLUSIONS

Nurses' knowledge increased significantly. Nurses' interventions and patients' pain relief may not have changed. We plan to begin quality assurance work on the six wards and to distribute the SLM to all nurses, with support provided by the Nursing Service.

REPORT DATE: 04/23/92 WORK UNIT # 7523

DETAIL SUMMARY SHEET

TITLE: Families Coping with Combat Injury

KEYWORDS: family coping, combat injury

PRINCIPAL INVESTIGATOR: Reeder, Jean LTC AN
ASSOCIATES: Tijerina, Maria LTC AN; Swartz, Ann MAJ AN

DEPARTMENT: Department of Nursing
SERVICE: Nursing Research Service

STATUS: Ongoing
APPROVAL DATE: Mar 1991

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

STUDY OBJECTIVE
To describe the family-related, patient-related, and injury-related variables to determine how they influence the way that families cope with combat injury.

TECHNICAL APPROACH
Data were collected three times from two family members of combat injured soldiers hospitalized at WRAMC: (1) within 1 week after the family arrived at WRAMC to visit the injured family member; (2) 1 month after they completed the first questionnaire; and (3) 1 year following administration of the first questionnaire. Families were asked to complete four questionnaires that measured: family coping, family perception of the injury event, family member perceived stress, and family "pile-up" of the file events.

PRIOR AND CURRENT PROGRESS
Data were collected from 25 families of patients injured during Operation Desert Storm. Due to the low number of casualties actually returned to WRAMC, the sample size for regression analysis was not met. No adverse effects of participation were reported. Several family members said they were glad to share this information with "the Army" if it would help others. Due to the importance of the information obtained during the first wave, data collection continued as planned. Third round questionnaires are now being returned.

CONCLUSIONS
Data analysis of the first two rounds revealed sources of anxiety and frustration for families centered on problems in obtaining timely and accurate notification and information about injury, patient location, and progress and prognosis. Fear and anger were common during the first round and depressive symptoms the second. Mean scores were comparable to a previous study.

REPORT DATE: 04/28/92 WORK UNIT # 7524

DETAIL SUMMARY SHEET

TITLE: Determinants of Intent to Leave Among Nurses with Doctoral Degrees by Occupational Setting

KEYWORDS: turnover, job satisfaction, causal models

PRINCIPAL INVESTIGATOR: Gurney, Cynthia LTC AN

DEPARTMENT: Department of Nursing STATUS: Completed
SERVICE: Nursing Research Service APPROVAL DATE: Apr 1991

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

STUDY OBJECTIVE
To determine the differences in factors relating to turnover among nurses with doctoral degrees, based on occupational setting; and to determine those factors that would serve to promote retention of the Army Nurse Corps' doctorally prepared officers.

TECHNICAL APPROACH
This study involves secondary analysis of survey research data. Statistical studies include descriptive analysis of the sample, factor analysis, and T-tests to identify statistically significant differences.

PRIOR AND CURRENT PROGRESS
The sample consisted of 1062 members of a professional nursing organization. The study showed an 82% response rate with an N of 869. The sample was divided into two groups, those occupied in academic settings and those in hospital settings, before multigroup analysis. The study was completed during the summer of 1991. Statistical analysis was completed in the winter of 1991 using computer resources at DCI and the Department of Biostatistics at WRAIR.

CONCLUSIONS
The two populations were essentially similar, except that doctorally prepared nurses in the hospital setting were younger ($p</=.05$), and hospital-based nurses valued resource adequacy and promotion to a greater extent than the academically-based nurses. Theory implies that Army nurse doctorates will behave more similarly to the hospital-based nurses; therefore, these factors should be of primary concern in designing strategies to retain nurse researchers in the Army.

REPORT DATE: 04/28/92 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
SERVICE: Nursing Research Service

STATUS: Ongoing
APPROVAL DATE: Apr 1991

FUNDING: Current FY: $ 29 Previous FYs: $ 0 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

The questionnaire was developed between October 1990 and July 1991. U.S. Army PERSINSCOM participated in questionnaire development and approved the final survey. The sample data base was compiled in PERSINSCOM between July and December 1991, with data collection also beginning in December. Currently, data collection is still underway. The data base provided did not contain the most accurate addresses for the sample, and additional processes are being used to obtain accurate home or unit addresses for the persons to be polled.

CONCLUSIONS

None at this time.

REPORT DATE: 04/20/92 WORK UNIT # 9303

DETAIL SUMMARY SHEET

TITLE: Hospital Liquid Diet Evaluation

KEYWORDS: advanced liquid diet, standard liquid diet, full liquid diet

PRINCIPAL INVESTIGATOR: Patterson, Richard LTC SP

SERVICE: Nutrition Care Directorate STATUS: Completed
APPROVAL DATE: Mar 1990

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

STUDY OBJECTIVE
To evaluate the acceptability of commercially produced advanced hospital liquid diets developed by the U.S. Army Natick Research, Development and Engineering Center, in terms of overall appearance, flavor, consistency, texture, ease of sipping, and portion size.

TECHNICAL APPROACH
One hundred oncology, wired-jaw, or other inpatients with a diet order for an advanced liquid diet, will be used to evaluate the new menu of commercially produced hospital liquid diets. Patients who agree to participate in the study will be served the new advanced liquid diets instead of the standard liquid diets for three meals on one day only.

PRIOR AND CURRENT PROGRESS
No subjects who met the inclusionary criteria have volunteered to participate in the study; therefore, this protocol is being closed. There are no direct benefits to subjects in this study. There have been no serious or unexpected adverse reactions reported as a result of using these products.

CONCLUSIONS
The product has demonstrated wide acceptability at other testing sites.

REPORT DATE: 04/08/92 WORK UNIT # 4243

DETAIL SUMMARY SHEET

TITLE: The Effect of Vaginal Lubricants on Sperm Motility in the Postcoital Test

KEYWORDS: lubricants, sperm, motility

PRINCIPAL INVESTIGATOR: Klein, Thomas COL MC

DEPARTMENT: Department of Obstetrics and Gynecology STATUS: Completed
APPROVAL DATE: Feb 1987

FUNDING: Current FY: $ 0 Previous FYs: $ 50 Total: $ 50

STUDY OBJECTIVE
To determine sperm motility in vivo following the use of vaginal lubricants. The use of vaginal lubricants occasionally becomes an issue for infertile couples. We seek to determine if in vivo use of lubricants is likely to affect sperm-cervical mucus interaction.

TECHNICAL APPROACH
The sperm-cervical mucus interaction will be assessed after a standard postcoital test (PCT). The results of the tests will be compared from each couple after a PCT with, and one without, the use of vaginal lubricants. The physician will be blinded to the patient's use of lubricant.

PRIOR AND CURRENT PROGRESS
No further patients have been accrued at WRAMC. The former PI is stationed at Bethesda Naval Hospital, and because of WRAMC staff departures, no staff have been able to actively recruit patients. The protocol will remain active at the National Naval Medical Center but completion is requested at WRAMC.

CONCLUSIONS
None.

REPORT DATE: 06/22/92 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: Barnhill, Danny LTC MC
ASSOCIATES: Park, Robert MD

DEPARTMENT: Department of Obstetrics and Gynecology

STATUS: Ongoing
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

To date, 72 patients have been entered into this study. Walter Reed has entered eight patients. No significant toxicity has been reported thus far.

CONCLUSIONS

Too early.

REPORT DATE: 10/10/92 WORK UNIT # 4279

DETAIL SUMMARY SHEET

TITLE: Epidermal Growth Factor and Endometrial Growth

KEYWORDS: EGF, endometrium, radioreceptor

PRINCIPAL INVESTIGATOR: Klein, Thomas COL MC
ASSOCIATES: Schaudies, Paul CPT MS

DEPARTMENT: Department of Obstetrics and Gynecology

STATUS: Completed
APPROVAL DATE: Jul 1989

FUNDING: Current FY: $ 218 Previous FYs: $ 908 Total: $ 1,126

STUDY OBJECTIVE

To study the epidermal growth factor (EGF) receptor and its ligand during the normal human menstrual cycle in an attempt to document receptor and ligand alterations in response to the morphologic changes normally seen in the endometrium during the normal menstrual cycle.

TECHNICAL APPROACH

The recruitment of participants and the ligand assay are being performed as presented in the initial protocol. The endometrial membrane preparation for the EGF receptor assay has been modified as follows. The endometrium is homogenized in 5 volumes of ice cold 10 mM Tris-HCL, pH 7.5 containing 25 mM sucrose and 1 mM EDTA in a Dounce homogenizer. The homogenates are centrifuged in a Beckman JA-20 rotor at 3400 rpm at 4C for 10 min. The nuclear pellets are discarded, and the resultant clear supernatants are centrifuged in a Beckman 60Ti rotor at 40,000 rpm at 4C for 60 min. These supernatants are discarded, and the resultant endometrial plasma membrane pellets are resuspended in 0.2% MEM/BSA solution.

PRIOR AND CURRENT PROGRESS

No additional patient accrual has taken place during the past year; a total of 60 patients were enrolled since this study began. The data have been published and the study is complete.

CONCLUSIONS

The endometrial EGF receptor content is cycle-dependent, being maximal during the periovulatory period and minimal in the perimenstrual phase of the cycle. This cyclic variation in receptor content may be the result of the physiologic fluctuations in sex steriod hormone levels. These findings further suggest a role for EGF and its receptor in endometrial proliferation and differentiation.

REPORT DATE: 06/29/92 WORK UNIT # 4301

DETAIL SUMMARY SHEET

TITLE: Pelvic Ureter Identification During Laparoscopy: A Prospective Study

KEYWORDS: laparoscopy, complications, ureter

PRINCIPAL INVESTIGATOR: Allen, Rodney CPT MC

DEPARTMENT: Department of Obstetrics and Gynecology STATUS: Completed
APPROVAL DATE: Apr 1991

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

STUDY OBJECTIVE
To determine the visibility of the pelvic portion of the ureter and, from this information, the susceptibility of the ureter to injury during laparoscopic procedures.

TECHNICAL APPROACH
Subjects will be recruited from patients presenting to the Department for conditions indicative for laparoscopy. During the procedure, data concerning the pathology will be assessed, the degree of abdominal insufflation will be observed, the ureter visualized, and the time required for visualization will be recorded.

PRIOR AND CURRENT PROGRESS
This study has been concluded and the results reported.

CONCLUSIONS
Visibility of the ureters may play a role in the accidental injury to this structure during the course of the laparoscopic procedure. Pelvic pathology was the most likely reason that ureters were not seen. Further study with a larger cohort is required to investigate these issues and confirm our impressions.

REPORT DATE: 03/05/92 WORK UNIT # 4113

DETAIL SUMMARY SHEET

TITLE: Cooperative Gynecologic Oncology Group

KEYWORDS: gynecologic, oncology, group

PRINCIPAL INVESTIGATOR: Barnhill, Danny LTC 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
Approximately 798 patients have been entered into GOG protocols from Walter Reed. There have been 61 patients entered since the last report.

CONCLUSIONS
Detailed in individual reports.

REPORT DATE: 04/13/92 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: Barnhill, Danny LTC MC
ASSOCIATES: Park, Robert MD

DEPARTMENT: Department of Obstetrics and Gynecology STATUS: Ongoing
SERVICE: Gynecologic Oncology Group 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
There have been 563 patients entered into this protocol for the entire GOG; 7 have been entered from Walter Reed. Combinations of cis-platinum and other chemotherapeutic agents are in the process of being tested in other GOG protocols. This protocol is closed to patients with squamous and nonsquamous cell carcinoma of the cervix, epithelial ovarian carcinoma, endometrial adenocarcinoma, vaginal carcinomas, vulvar carcinomas, and for first-line uterine sarcomas and endometrial adenocarcinomas. There has been one grade 4 renal toxicity, one grade 4 neurotoxicity, and one grade 4 GU toxicity.

CONCLUSIONS
Cis-platinum has marked activity as first-line chemotherapy in squamous cell carcinoma of the cervix, endometrial cancer, and mixed mesodermal sarcomas of the uterus. It is active as second-line therapy for advanced ovarian adenocarcinoma and mixed mesodermal sarcoma of the uterus, and may have limited activity in treating cervical adenocarcinomas. It seems inactive as first or second-line therapy against endometrial and vulvar carcinomas and for uterine leiomyosarcoma.

REPORT DATE: 04/23/92 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: Barnhill, Danny LTC MC
ASSOCIATES: Park, Robert COL MC

DEPARTMENT: Department of Obstetrics and Gynecology STATUS: Ongoing
SERVICE: Gynecologic Oncology Group 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 191 patients have been entered from the entire GOG. Walter Reed has entered one patient. It is currently closed to squamous and nonsquamous cancer of the cervix, cancer of the vulva and vagina, epithelial ovarian carcinoma, adenocarcinoma and adenosquamous carcinoma of the uterus, leiomyosarcomas, and mixed mesodermal tumors of the uterus. There has been only one grade 4 hematologic toxicity.

CONCLUSIONS
The data includes minimal activity with 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. Patients with non-squamous carcinoma of the cervix, endometrium, vulva, vagina, as well as uterine sarcomas, have minimal response to DHAD.

REPORT DATE: 03/05/92 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: Barnhill, Danny LTC MC
ASSOCIATES: Park, Robert MD

DEPARTMENT: Department of Obstetrics and Gynecology STATUS: Ongoing
SERVICE: Gynecologic Oncology Group APPROVAL DATE: Jan 1983

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

STUDY OBJECTIVE
This protocol will constitute a Phase II design to determine the efficacy of aminothiadiazole in treating advanced pelvic malignancies.

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 151 patients accrued by the GOG. One patient has been entered by Walter Reed. The protocol currently is closed for epithelial ovarian cancer, squamous cell cancer of the cervix, non-squamous cell cancer of the cervix, endometrial adenocarcinoma, and leiomyosarcomas. There have been two grade 4 hematologic toxicities reported.

CONCLUSIONS
Aminothiadiazole used in this dose and schedule has minimal activity in previously treated patients with ovarian carcinoma and squamous cell carcinoma of the cervix, non-squamous cell carcinoma of the cervix, and endometrial adenocarcinoma.

REPORT DATE: 06/29/92 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, potential

PRINCIPAL INVESTIGATOR: Barnhill, Danny LTC MC
ASSOCIATES: Park, Robert MD

DEPARTMENT: Department of Obstetrics and Gynecology STATUS: Ongoing
SERVICE: Gynecologic Oncology Group 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 456 patients entered into this study; 402 of whom are evaluable. Walter Reed has entered 26 patients into this study. No significant toxicities have been reported among the patients treated. This protocol was closed to patient entry on March 7, 1992.

CONCLUSIONS
Too early.

REPORT DATE: 06/30/92 WORK UNIT # 4224

DETAIL SUMMARY SHEET

TITLE: GOG 26S: A Phase II Trial of Teniposide (VM-26) in Patients with Advanced Pelvic Malignancies

KEYWORDS: teniposide, pelvic, malignancy

PRINCIPAL INVESTIGATOR: Barnhill, Danny LTC MC
ASSOCIATES: Park, Robert MD

DEPARTMENT: Department of Obstetrics and Gynecology STATUS: Completed
SERVICE: Gynecologic Oncology Group APPROVAL DATE: Jul 1985

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

STUDY OBJECTIVE
To determine the efficacy of teniposide (VM-26) in the treatment of 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 for treatment. The treatment consists of VM-26, 100mg/m2 IV every week, until progression of disease or evidence of adverse effects prohibits further therapy.

PRIOR AND CURRENT PROGRESS
The entire GOG has entered 117 patients into this protocol. Walter Reed has entered no patients. Entry is now closed to patients with ovarian epithelial tumors, squamous cell carcinoma of the cervix, and non-squamous and endometrial adenocarcinoma. Two grade 4 toxicities were reported - granulocytopenia. The protocol was closed in November 1991.

CONCLUSIONS
Teniposide produced only modest activity in previously treated patients with epithelial ovarian cancer, squamous cell carcinoma of the cervix, non-squamous cell carcinoma of the cervix, or carcinoma of the endometrium.

REPORT DATE: 06/30/92 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: Barnhill, Danny LTC MC
ASSOCIATES: Park, Robert MD

DEPARTMENT: Department of Obstetrics and Gynecology
SERVICE: Gynecologic Oncology Group

STATUS: Ongoing
APPROVAL DATE: Jul 1985

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

STUDY OBJECTIVE

To evaluate the role of adjunctive extrafascial hyste ectomy 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

To date, 282 patients have been entered into this protocol by the entire GOG. Walter Reed has entered 10 patients. There have been five grade 4 gastrointestinal toxicities. Of the other four grade 4 toxicities, one was urinary, one was neurologic, and two were cardiovascular. This protocol was closed to patient entry on November 18, 1991.

CONCLUSIONS

Too early.

REPORT DATE: 04/23/92 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: Barnhill, Danny LTC 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
This study seeks to identify additional active agents for treating advanced or recurrent endometrial adenocarcinoma by studying single new drugs in patients witl. 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
GOG #86 is a master protocol. See individual protocols.

CONCLUSIONS
See individual protocols.

REPORT DATE: 06/20/92 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: Barnhill, Danny LTC 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. The study design will involve treating an average sample size of 30 patients per drug studied for each of the following cell categories: mixed mesodermal tumor (MMT), 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 a chemotherapeutic regimen as outlined in each segment of the protocol.

PRIOR AND CURRENT PROGRESS
There have been 92 patients entered into GOG 87-B and 79 patients entered into GOG 87-C. Walter Reed has entered six patients into 87-B and one patient into GOG 87-C. The grade 4 adverse effects for 87-B include one thrombocytopenia, six granulocytopenias, two neurotoxic effects, nine leukopenias, and one anemia. There has been one death related to therapy. The grade 4 adverse effects for 87-C include two leukopenias and six neutropenias. The protocol 87-B was closed for MMT on March 7, 1988, and for leiomyosarcomas on June 13, 1989. Protocol 87-C was closed for MMT on July 17, 1989, and leiomyosarcomas on May 6, 1991.

CONCLUSIONS
See individual protocols.

REPORT DATE: 06/29/92 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: Barnhill, Danny LTC 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
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 five days every 4 weeks until disease progression or adverse effects prohibit further therapy.

PRIOR AND CURRENT PROGRESS
There have been 92 patients entered into this protocol for the entire GOG; 86 of whom are evaluable. Walter Reed has entered six patients into this study. Of all the patients treated, nine experienced grade 4 leukopenia, one experienced grade 4 thrombocytopenia, six experienced grade 4 granulocytopenia, two experienced grade 4 neurotoxic effects, and one experienced grade 4 anemia.

CONCLUSIONS
Ifosfamide/Mesna may be the most active single agent therapy for advanced mixed mesodermal tumors of the uterus.

REPORT DATE: 07/29/92 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: Barnhill, Danny LTC MC
ASSOCIATES: Park, Robert MD

DEPARTMENT: Department of Obstetrics and Gynecology STATUS: Ongoing
SERVICE: Gynecologic Oncology Group APPROVAL DATE: Aug 1986

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

STUDY OBJECTIVE
The objective of this study is 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 218 patients into this study. Walter Reed has entered five 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 10 grade 4 toxicities: 4 thrombocytopenias, 4 granulocytopenias, 1 neurotoxicity, and 1 bronchospasm.

CONCLUSIONS
Ifosfamide is an active Phase II drug in relapsed epithelial ovarian carcinoma, although nephro-toxicity is a limiting factor in this patient population. Ifosfamide possesses minimal activity in previously treated squamous cell carcinoma of the cervix.

REPORT DATE: 04/13/92 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: Barnhill, Danny LTC MC
ASSOCIATES: Park, Robert MD

DEPARTMENT: Department of Obstetrics and Gynecology
SERVICE: Gynecologic Oncology Group

STATUS: Ongoing
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 ble mycin (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
To date, 67 patients have been entered into this protocol by all GOG member institutions. Walter Reed has entered no patients. There have been 40 episodes of grade 4 granulocytopenia, 7 episodes of grade 4 thrombocytopenia, 3 episodes of grade 4 GI reactions, 1 episode of grade 4 dermatologic reaction, and 1 episode of grade 4 allergic reaction.

CONCLUSIONS
Too early.

REPORT DATE: 04/24/92 WORK UNIT # 4246

DETAIL SUMMARY SHEET

TITLE: GOG 94: A Phase II Study of the Treatment of Papillary Serous Carcinoma of the Endometrium Stage I and II and Maximally Debulked Advanced Endometrial Carcinoma with Total Abdominal Radiation Therapy

KEYWORDS: papillary, carcinoma, endometrium

PRINCIPAL INVESTIGATOR: Barnhill, Danny LTC MC
ASSOCIATES: Park, Robert COL MC

DEPARTMENT: Department of Obstetrics and Gynecology
SERVICE: Gynecologic Oncology Group

STATUS: Completed
APPROVAL DATE: Apr 1987

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

STUDY OBJECTIVE
This protocol is designed to determine the survival and progression-free interval of patients with maximally debulked advanced endometrial carcinoma treated with abdominal radiation therapy.

TECHNICAL APPROACH
All patients with primary endometrial carcinoma, clinical and surgical Stages III and IV disease (all histologic types), all clinical and surgical stages of clear cell carcinoma, and all clinical and surgical stages of papillary serous carcinoma are eligible. Tumor must be maximally debulked at 2 cm or less.

PRIOR AND CURRENT PROGRESS
There have been 262 patients entered into this study from the entire GOG; Walter Reed has entered 5 patients. There have been seven grade 4 GI toxicities, three grade 4 hematologic toxicities, and one grade 4 hepatic toxicity out of 173 evaluable patients. This protocol was closed to patient entry in February 1992. We are currently following four patients.

CONCLUSIONS
None.

REPORT DATE: 06/29/92 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: Barnhill, Danny LTC MC
ASSOCIATES: Park, Robert COL MC

DEPARTMENT: Department of Obstetrics and Gynecology
SERVICE: Gynecologic Oncology Group

STATUS: Ongoing
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

There have been 152 patients entered into this study from the entire GOG; Walter Reed has entered 7 patients. Thirty-three patients have developed grade 4 neutropenia and one patient has developed a grade 4 thrombocytopenia.

CONCLUSIONS

Too early.

REPORT DATE: 06/22/92 WORK UNIT # 4251

DETAIL SUMMARY SHEET

TITLE: GOG 26W: A Phase II Trial of Echinomycin in Patients with Advanced Pelvic Malignancies

KEYWORDS: echinomycin, pelvic malignancies

PRINCIPAL INVESTIGATOR: Barnhill, Danny LTC MC

DEPARTMENT: Department of Obstetrics and Gynecology STATUS: Ongoing
SERVICE: Gynecologic Oncology Group APPROVAL DATE: Jun 1987

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

STUDY OBJECTIVE
To determine the efficacy of echinomycin in the treatment of advanced or recurrent pelvic malignancies.

TECHNICAL APPROACH
Eligible patients include those who 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
To date, the entire GOG has entered 101 patients into this study. Walter Reed has entered four patients. There has been one grade 4 GI adverse reaction reported. This study has been closed to patients with epithelial ovarian carcinoma, squamous cell carcinoma, and nonsquamous cervical carcinoma, but remains open to patients with other types of gynecologic malignancies.

CONCLUSIONS
Echinomycin displays minimal activity in patients with squamous cell carcinoma of the cervix, nonsquamous carcinoma of the cervix, and epithelial ovarian carcinoma who have had prior chemotherapy.

REPORT DATE: 06/30/92 WORK UNIT # 4253

DETAIL SUMMARY SHEET

TITLE: GOG 81F: A Phase II Trial of Tamoxifen Citrate in Patients with Advanced or Recurrent Endometrial Carcinoma Responsive to Progestins

KEYWORDS: tamoxifen, endometrial, carcinoma

PRINCIPAL INVESTIGATOR: Barnhill, Danny LTC MC
ASSOCIATES: Park, Robert MD

DEPARTMENT: Department of Obstetrics and Gynecology
SERVICE: Gynecologic Oncology Group

STATUS: Completed
APPROVAL DATE: Jul 1987

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

STUDY OBJECTIVE
To determine whether patients with endometrial carcinoma who have responded to medroxyprogesterone acetate and then progressed will respond to a second hormonal manipulation in the form of tamoxifen citrate.

TECHNICAL APPROACH
To be eligible, patients must have histologically confirmed advanced, persistent, or recurrent endometrial carcinoma with documented disease progression after local therapy. Patients must have measurable disease. Patients must have been treated with medroxyprogesterone acetate and have been partial responders.

PRIOR AND CURRENT PROGRESS
The entire GOG has entered 82 patients into this study to date. Walter Reed has entered no patients. No grade 4 toxicities have been reported. The protocol was closed to patient entry in May 1992.

CONCLUSIONS
None.

REPORT DATE: 06/30/92 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: Barnhill, Danny LTC 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
The entire GOG has entered 63 patients into this study. Walter Reed has entered no patients. There has been one grade 4 (hematologic, GI, and surgical) adverse effect from the entire GOG experience with this protocol.

CONCLUSIONS
Too early.

REPORT DATE: 08/27/92 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: Barnhill, Danny LTC 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
To date, 117 patients have been entered into this study from the entire GOG. Walter Reed has entered one patient. Nine patients have had grade 4 leukopenia. Two patients have had grade 4 GI toxicity, one patient has had a grade 4 dermatologic toxicity, three patients have had grade 4 thrombocytopenia, and 41 patients have had grade 4 granulocytopenia. This protocol is closed to patient entry, but two patients are still being followed.

CONCLUSIONS
Too early for analysis.

REPORT DATE: 03/05/92 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: Barnhill, Danny LTC MC
ASSOCIATES: Park, Robert MD

DEPARTMENT: Department of Obstetrics and Gynecology STATUS: Ongoing
SERVICE: Gynecologic Oncology Group 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
Two hundred and nineteen patients have been entered into this protocol through the entire GOG. One hundred and eighty-three are evaluable. Walter Reed has entered 13 patients. There has been one grade 4 GI toxicity on review of the entire GOG data.

CONCLUSIONS
Too early.

REPORT DATE: 06/22/92 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: Barnhill, Danny LTC MC
ASSOCIATES: Park, Robert MC

DEPARTMENT: Department of Obstetrics and Gynecology STATUS: Ongoing
SERVICE: Gynecologic Oncology Group 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
To date, 50 patients have been entered into this protocol from the entire GOG. No patients have been entered from Walter Reed. One grade 4 anemia has been reported in past fiscal years. This study has been closed to patients with epithelial ovarian carcinoma but remains open to patients with other gynecologic malignancies.

CONCLUSIONS
Gallium nitrate has modest activity in previously treated patients with epithelial ovarian carcinoma.

REPORT DATE: 06/22/92 WORK UNIT # 4265

DETAIL SUMMARY SHEET

TITLE: GOG 102 A-B (Master Protocol): Intraperitoneal Administration of Cisplatin and 5-FU in Residual Ovarian Carcinoma, Phase II

KEYWORDS: cisplatin, 5-fluorouracil, ovarian carcinoma

PRINCIPAL INVESTIGATOR: Barnhill, Danny LTC MC
ASSOCIATES: Bosscher, James LTC MC

DEPARTMENT: Department of Obstetrics and Gynecology STATUS: Ongoing
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
There have been 48 patients entered into this protocol for the entire GOG. No patients have been entered from Walter Reed. There has been one grade 4 leukopenia, four grade 4 neutropenias, one grade 4 anemia, and one grade 4 hepatic toxicity. GOG 102B was closed to new patient entry in December 1988; however, the Master Protocol 102A remains in effect.

CONCLUSIONS
This is an active salvage regimen in small volume, cisplatin-sensitive tumors.

REPORT DATE: 06/27/92 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: Barnhill, Danny LTC 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. Walter Reed has two 76 protocols approved: 76-I and 76-S. The entire GOG has entered 394 patients into 76-I, of which 3 have been from Walter Reed. The GOG has entered 32 patients into 76-S, of which 1 has been from Walter Reed. There have been approximately 40 grade 4 toxicities: 21 leukopenias, 10 neutropenias, 1 cutaneous, 2 neurotoxicities, 1 fever, 4 thrombocytopenias, and 1 hypocalcemia. Both protocols were closed to patient accrual (76-I on February 26, 1990, and 76-S on May 21, 1990).

CONCLUSIONS
See individual protocols.

REPORT DATE: 03/05/92 WORK UNIT # 4268

DETAIL SUMMARY SHEET

TITLE: GOG 26DD: A Phase II Trial of Amonafide in Patients with Advanced Pelvic Malignancies

KEYWORDS: amonafide, pelvic, malignancies

PRINCIPAL INVESTIGATOR: Barnhill, Danny LTC 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
There have been 51 patients entered into this protocol from the entire GOG. Walter Reed has entered 3 patients. There have been 10 grade 4 hematologic toxicities, 1 grade 4 GI toxicity, and 1 grade 4 renal toxicity reported. No treatment deaths have been reported. The protocol is closed to squamous cell cancer of the cervix and epithelial ovarian cancer.

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: 03/05/92 WORK UNIT # 4272

DETAIL SUMMARY SHEET

TITLE: GOG 87C: A Phase II Trial of Hydroxyurea, *Dacarbazine, and Etoposide* in Patients with Advanced or Recurrent Uterine Sarcomas

KEYWORDS: hydroxyurea, dacarbazine, etoposide

PRINCIPAL INVESTIGATOR: Barnhill, Danny LTC MC

DEPARTMENT: Department of Obstetrics and Gynecology STATUS: Completed
SERVICE: Gynecologic Oncology Group APPROVAL DATE: Dec 1988

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. The study design will involve treating 30 patients per each drug studied for each of the following cell types: mixed mesodermal tumor, leiomyosarcoma, and other sarcomas.

TECHNICAL APPROACH
Eligible patients must have histologically confirmed advanced, persistent, or recurrent uterine sarcoma with documented disease progression after appropriate local therapy. Histologic types to be included in this study include leiomyosarcoma, mixed mesodermal tumor, endometrial stromal sarcoma, and other uterine sarcomas. All patients must have measurable disease and must be considered incurable.

PRIOR AND CURRENT PROGRESS
To date, 79 patients have been entered into the protocol by the entire GOG. One patient has been entered by Walter Reed. There have been nine hematologic grade 4 toxicities reported. There have been no treatment deaths. The protocol is now closed.

CONCLUSIONS
None.

REPORT DATE: 03/05/92 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: Barnhill, Danny LTC 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 258 patients. Seven patients have been entered from Walter Reed. There have been 31 grade 4 neutropenia episodes reported and 7 grade 4 thrombocytopenic episodes reported. There have been no reported deaths.

CONCLUSIONS
Too early.

REPORT DATE: 04/13/92 WORK UNIT # 4275

DETAIL SUMMARY SHEET

TITLE: GOG 107 A Randomized Study of Doxorubicin Vs. Doxorubicin Plus Cisplatin in Patients with Primary Stage III and IV Recurrent Endometrial Adenocarcinoma, Phase III

KEYWORDS: doxorubicin, cisplatin, endometrial

PRINCIPAL INVESTIGATOR: Barnhill, Danny LTC MC

DEPARTMENT: Department of Obstetrics and Gynecology STATUS: Ongoing
SERVICE: Gynecologic Oncology Group APPROVAL DATE: Mar 1989

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

STUDY OBJECTIVE
The major objective of this study is to determine whether the addition of cisplatin to doxorubicin offers significant improvement in the frequency of objective response, the duration of progression free interval, and the length of survival as compared to doxorubicin alone.

TECHNICAL APPROACH
Eligible patients must have Stage III, Stage IV, or recurrent endometrial carcinoma. Patients must have measurable disease. Patients may have received prior hormonal therapy or therapy with biologic response modifiers.

PRIOR AND CURRENT PROGRESS
To date, 141 patients have been enrolled by the entire GOG. No patients have been entered from Walter Reed. There have been 22 grade 4 granulocytopenic toxicities, 4 grade 4 thrombocytopenic toxicities, 1 grade 4 anemia, and 4 grade 4 GI toxicities.

CONCLUSIONS
Too early.

REPORT DATE: 06/27/92 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: Barnhill, Danny LTC 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

There have been 71 patients entered into this study from the entire GOG. Walter Reed has entered no patients. There have been 27 grade 4 neutropenias, 8 grade 4 thrombocytopenias, and 2 grade 4 GI adverse effects.

CONCLUSIONS

Too early.

REPORT DATE: 06/30/92 WORK UNIT # 4278

DETAIL SUMMARY SHEET

TITLE: GOG 26EE A Phase II Trial of Didemnin B in Patients with Advanced Pelvic Malignancies

KEYWORDS: Didemnin B, pelvic, malignancies

PRINCIPAL INVESTIGATOR: Barnhill, Danny LTC MC

DEPARTMENT: Department of Obstetrics and Gynecology STATUS: Ongoing
SERVICE: Gynecologic Oncology Group APPROVAL DATE: Jul 1989

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

STUDY OBJECTIVE
The objective of this study is to determine the efficacy of Didemnin B in the treatment of advanced or recurrent pelvic carcinomas.

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
To date, 43 patients have been entered into this study by the entire GOG. Walter Reed has entered no patients. One grade 4 gastrointestinal toxicity has been reported. The protocol is closed to patients with squamous cell carcinoma of the cervix and epithelial ovarian carcinoma patients.

CONCLUSIONS
Didemnin B is ineffective with the schedules utilized.

REPORT DATE: 03/05/92 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: Barnhill, Danny LTC 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, 34 patients have been accrued by the entire GOG. Walter Reed has entered 5 patients. No toxicity reports are available at this time.

CONCLUSIONS

Too early.

REPORT DATE: 03/05/92 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: Barnhill, Danny LTC 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, 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, 20 patients have been accrued by the entire GOG. Walter Reed has entered 5 patients. No toxicity reports are available at this time.

CONCLUSIONS

Too early.

REPORT DATE: 06/29/92 WORK UNIT # 4292

DETAIL SUMMARY SHEET

TITLE: GOG 26HH A Phase II Trial of 5-Fluorouracil and Leucovorin in Advanced Metastatic or Recurrent Pelvic Malignancies

KEYWORDS: 5-fluorouracil, pelvic, malignancies

PRINCIPAL INVESTIGATOR: Barnhill, Danny LTC MC
ASSOCIATES: Park, Robert MD

DEPARTMENT: Department of Obstetrics and Gynecology STATUS: Completed
SERVICE: Gynecologic Oncology Group APPROVAL DATE: May 1990

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

STUDY OBJECTIVE
To determine the efficacy of 5-fluorouracil (5-FU) and leucovorin in advanced metastatic or recurrent pelvic malignancies.

TECHNICAL APPROACH
Patients with histologically confirmed advanced, persistent, metastatic, or local gynecologic cancer with documented disease progression will be eligible. Leucovorin will be administered in a dose of 20 mg/m2 daily x 5 days and repeated at 4 and 8 weeks and thereafter every 5 weeks. 5-FU will be administered in a dose of 425 mg/m2 daily x 5 days to infuse immediately after the leucovorin has been given and will be repeated at 4 and 8 weeks and thereafter every 5 weeks.

PRIOR AND CURRENT PROGRESS
To date, 49 patients have been accrued by the entire GOG. Walter Reed has entered no patients. Three grade 4 neutropenias have been reported. No treatment-related deaths have been reported. The protocol was closed to squamous cell carcinoma of the cervix and to ovarian epithelial tumors in April 1990. This protocol was terminated November 1991.

CONCLUSIONS
This schedule has minimal activity in epithelial tumors of the ovary and squamous cell carcinoma of the cervix.

REPORT DATE: 06/22/92 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: Barnhill, Danny LTC MC
ASSOCIATES: Bosscher, James LTC MC

DEPARTMENT: Department of Obstetrics and Gynecology
SERVICE: Gynecologic Oncology Group

STATUS: Ongoing
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
There have been 274 patients entered for the entire GOG. No patients from Walter Reed have been entered.

CONCLUSIONS
Too early.

REPORT DATE: 06/22/92 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: Barnhill, Danny LTC MC
ASSOCIATES: Bosscher, James LTC MC

DEPARTMENT: Department of Obstetrics and Gynecology
SERVICE: Gynecologic Oncology Group

STATUS: Ongoing
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
There have been 108 patients entered for the entire GOG. Two patients have been entered from Walter Reed Army Medical Center.

CONCLUSIONS
Too early.

REPORT DATE: 06/22/92 WORK UNIT # 4296

DETAIL SUMMARY SHEET

TITLE: GOG 8810 Flow Cytometrically Determined DNA Content in Endometrial Carcinoma

KEYWORDS: flow cytometry, DNA, adenocarcinoma

PRINCIPAL INVESTIGATOR: Barnhill, Danny LTC MC
ASSOCIATES: Bosscher, James LTC MC

DEPARTMENT: Department of Obstetrics and Gynecology
SERVICE: Gynecologic Oncology Group

STATUS: Ongoing
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

Two hundred and ninety-three patients have been entered for the entire GOG. Five patients have been entered by Walter Reed Army Medical Center. The protocol was closed to patient entry in November 1991. Four patients are still being followed on this study.

CONCLUSIONS

Too early.

REPORT DATE: 06/22/92 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: Barnhill, Danny LTC MC
ASSOCIATES: Bosscher, James LTC MC

DEPARTMENT: Department of Obstetrics and Gynecology STATUS: Ongoing
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 321 patients entered into this protocol for the entire GOG. Nine patients have been entered from Walter Reed (two pending, seven evaluable). There have been 143 grade 4 leukopenias, one grade 4 anemia, one grade 4 thrombocytopenia, 3 grade 4 GI advserse effects, and one grade 4 cardiac toxicity noted. This protocol was closed to patient entry in March 1992. Nine patients are still being followed on this study.

CONCLUSIONS
Too early.

REPORT DATE: 06/29/92 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, malignancies

PRINCIPAL INVESTIGATOR: Barnhill, Danny LTC MC
ASSOCIATES: Park, Robert MD

DEPARTMENT: Department of Obstetrics and Gynecology STATUS: Ongoing
SERVICE: Gynecological Oncology Group 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, 45 patients have been accrued by the entire GOG. Walter Reed has entered one patient. Four cases of grade 4 neutropenia, two cases of grade 4 leukopenia, and one case of grade 4 sepsis have been reported. No treatment related deaths have been reported. This protocol was closed to squamous cell carcinoma of the cervix on June 12, 1990, and to epithelial ovarian carcinoma on September 1, 1990.

CONCLUSIONS
Too early.

REPORT DATE: 06/08/92 WORK UNIT # 4809

DETAIL SUMMARY SHEET

TITLE: The Effects of Storage on Irradiated Red Blood Cells: An In Vitro and In Vivo Study

KEYWORDS: potassium, irradiated blood

PRINCIPAL INVESTIGATOR: Knoll, Susan CAPT BC

DEPARTMENT: Department of Pathology and Area Laboratories STATUS: Completed
APPROVAL DATE: Mar 1991

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

STUDY OBJECTIVE
To determine if stored irradiated blood has significantly increased levels of potassium as compared to non-irradiated stored controls and at what storage time the effects become statistically significant; and to determine the survival of stored irradiated red blood cells using a fluorescent lipophilic probe in a dog model.

TECHNICAL APPROACH
Part I. Ten units of human donor blood were aliquoted into two equal portions. One aliquot of each pair was irradiated with 3000 RADS of gamma radiation. Both aliquots were stored under normal Blood Bank conditions. Aliquots were sampled at 0,1,3,5,7,10,14,21,28 and 35 days post irradiation and analyzed for plasma potassium content. Part II. Blood from five dogs was drawn into standard blood collection bags and was transformed into packed red blood cells. Units from test animals were irradiated with 3000 RADS and stored under normal Blood Bank conditions for 7 days. Units were labeled with a fluorescent tag and reinfused. Blood samples were drawn to calculate RBC survival.

PRIOR AND CURRENT PROGRESS
Part I. A significant increase in potassium levels in the irradiated aliquots was observed from day 1 after irradiation that continued through the entire storage period. This increase was as much as two times the levels measured in the non-irradiated aliquots. Part II. Red blood survival was not clearly affected by irradiation, but all irradiated units had poorer 24-hour survival than the non-irradiated control. Using the fluorescent tag instead of a radioactive label for measurement of the survival times worked well and could work for other studies involving tracking red blood cells in vivo. A total of five animals were used in this study. There were no serious adverse reactions.

CONCLUSIONS
Results from both studies indicate irradiation damages red blood cells, affecting them in storage and after transfusion. Further studies to confirm findings in the in vivo portion of the study and to determine more specifically the damage that occurs could impact upon the use of irradiated red blood cells for transfusion.

REPORT DATE: 09/18/92 WORK UNIT # 4810

DETAIL SUMMARY SHEET

TITLE: Immunohistochemistry of Type II Pneumocytes in Hyperplasia and Neoplasia

KEYWORDS: pneumocytes, bronchoalveolar, carcinoma

PRINCIPAL INVESTIGATOR: Adair, Carol MAJ MC

DEPARTMENT: Department of Pathology and Area Laboratories STATUS: Completed
APPROVAL DATE: May 1991

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

STUDY OBJECTIVE
To compare the immunohistochemical staining patterns of reactive hyperplasia of type II pneumoctyes and bronchoalveolar carcinoma of the lung, a neoplasm of the alveolar cells or pneumoctyes. The reactive and neoplastic processes involving pneumoctyes are, at times, difficult to distinguish histologically; immunohistochemistry may be useful.

TECHNICAL APPROACH
Cases of reactive hyperplasia and bronchoalveolar carcinoma will be stained for the following antigens: Leu M1, CEA, human milkfat globule protein, and B 72.3. Presence of positive staining in reactive or neoplastic pneumocytes will be evaluated to determine whether these immunostains are of utility in distinguishing between the reactive and neoplastic processes. The material used will be archival paraffin-embedded tissue from cases identified from the file of Surgical Pathology at WRAMC.

PRIOR AND CURRENT PROGRESS
This study has been completed. Twenty cases each of reactive hyperplasia and bronchoalveolar carcinoma were stained. The data has been reviewed with the statisticians in Department of Clinical Investigation. A manuscript has been written and should be submitted for publication in the next 2 weeks.

CONCLUSIONS
Immunohistochemical staining for Leu M1 and B 72.3 are the most helpful in distinguishing between type II pneumocyte hyperplasia and bronchoalveolar carcinoma; however, there is some overlap of staining patterns between carcinomas and reactive pneumocytes in cases of advanced fibrosing interstitial pneumonitis.

REPORT DATE: 06/23/92 WORK UNIT # 6038

DETAIL SUMMARY SHEET

TITLE: Collection and Cryopreservation of Spleen Cells for the Production of Monoclonal Antibodies

KEYWORDS: spleen, cryopreservation, lymphocyte

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Fischer, Gerald COL MC

DEPARTMENT: Department of Pediatrics

STATUS: Ongoing
APPROVAL DATE: Apr 1983

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

STUDY OBJECTIVE
To use cryopreserved spleen cells from a bank as a source of growth factors and tumor monoclonal antibodies.

TECHNICAL APPROACH
After splenectomy, spleen is dissected and single cell suspensions are made. These cells are cryopreserved in liquid nitrogen for later use.

PRIOR AND CURRENT PROGRESS
There have been no new registrants on this protocol in the past year. Dr. Gerald Fischer of USUHS is the supervisor of the laboratory where the spleen cells are currently being stored. He reported in June that he would not be available to discuss the status of research using these cells until mid-July of 1992.

CONCLUSIONS
Study remains open, pending Dr. Fischer's decision.

REPORT DATE: 11/05/92 WORK UNIT # 6059

DETAIL SUMMARY SHEET

TITLE: Malondialdehyde Production by Neonatal Erythrocytes

KEYWORDS: vitamin E, free radicals, neonate

PRINCIPAL INVESTIGATOR: Poth, Merrily MD

DEPARTMENT: Department of Pediatrics

STATUS: Completed
APPROVAL DATE: Sep 1986

FUNDING: Current FY: $ 0 Previous FYs: $ 3,031 Total: $ 3,031

STUDY OBJECTIVE

The objective of this study is to determine whether free radical production of red blood cell membranes of neonates would reflect vitamin E deficiency in this population.

TECHNICAL APPROACH

Neonatal red blood cells were exposed to hydrogen peroxide and malondialdehyde (MDA) production measured to attempt to determine whether this measure of vitamin E sufficiency/deficiency would help to resolve the questioned need for vitamin E supplement of newborns, individually or as a group.

PRIOR AND CURRENT PROGRESS

There was no initiation of this project since it was approved. Prior work by this group revealed that many newborn infants showed an increased MDA production by RBC's, with persistence for variable periods of time.

CONCLUSIONS

Increased MDA production is seen by some neonatal RBC's. There does not appear to be a simple explanation why certain infants exhibit this phenomenon nor of the effects of diet on this phenomenon.

REPORT DATE: 04/20/92 WORK UNIT # 6063

DETAIL SUMMARY SHEET

TITLE: The Effect of Mestinon on Growth in Non-growth Hormone Deficient Short Children

KEYWORDS: short stature, growth hormone, pyridostigmine

PRINCIPAL INVESTIGATOR: Poth, Merrily MD

DEPARTMENT: Department of Pediatrics STATUS: Ongoing
APPROVAL DATE: Feb 1988

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

STUDY OBJECTIVE
To determine whether Mestinon (pyridostigmine) has a physiological effect on growth hormone secretion and hence on growth.

TECHNICAL APPROACH
Mestinon (60 mg) or placebo will be given each night at bedtime to short, non-growth hormone deficient children. Growth rate and serum somatomedin C will be compared (between 6 months of Mestinon therapy and 6 months of placebo) for placebo versus drug treatment.

PRIOR AND CURRENT PROGRESS
A total of 11 patients have been enrolled in this study. To date, seven have completed the entire protocol; three will complete the protocol by July 1991, and one is a recent enrollee. There are no differences, so far, in growth rate, bone age or somatomedin C levels between pyridostigmine or placebo periods. There have been no serious or unexpected adverse reactions. No patients have withdrawn from the study. Records and signed consent are present for all patients enrolled.

CONCLUSIONS
Follow-up on a larger number of patients will be required before any other statement may be made on the efficacy of pyridostigmine in treatment of short stature.

REPORT DATE: 07/23/92 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: Ongoing
APPROVAL DATE: Aug 1989

FUNDING: Current FY: $ 9,531 Previous FYs: $ 9,154 Total: $ 18,685

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
Fibroblast cultures have been established and studied. Results show: 5-alpha-reductase activity is not changed by either IGF-1 or growth hormone, androgen receptors are not changed by IGF-1 or GH, and cell polifecation is increased by IGF-1 but not GH.

CONCLUSIONS
IGF-1 has proliferation effects in foreskin fibroblasts. As yet, no interaction has been identified with androgens. Current study is proceeding to evaluate the effect of androgens on IGF-1 production by foreskin fibroblasts.

REPORT DATE: 10/01/92 WORK UNIT # 6215

DETAIL SUMMARY SHEET

TITLE: The Enteral Absorption of Human IgG by the Neonatal Guinea Pig and Its Retention of Opsonic Activity Type III Group B Streptococcus

KEYWORDS: immunoglobulin, enteral absorption, guinea pig

PRINCIPAL INVESTIGATOR: Jesse, Steven CPT MC
ASSOCIATES: Weisman, Leonard LTC MC

DEPARTMENT: Department of Pediatrics

STATUS: Completed
APPROVAL DATE: May 1988

FUNDING: Current FY: $ 0 Previous FYs: $ 8,545 Total: $ 8,545

STUDY OBJECTIVE

The human newborn has been classically described as a "nonabsorber" of breastmilk antibody. Using an animal model which resembles the human neonate (in a GI sense), we are attempting to demonstrate the absorption of Human IgG via the gut after gavaging the subject with a known amount of IgG shortly after birth. We also hope to identify variables which may influence enteral absorption of IgG.

TECHNICAL APPROACH

Vaginally delivered Hartley Guinea Pig pups are gavaged with a 10% human IgG preparation shortly after birth. Cohorts receive either 5 gm/kg or 1 gm/kg po either once or three times. Controls receive either 5 gm/kg or 1 gm/kg ip once. Serial samples (0.3cc) are then obtained via a femoral cutdown at 24, 48, and 72 hours; and at 1 and 2 weeks after IgG administration. Pups remain with their dam and suckle ad lib; all being euthanized after 2 weeks. A Competitive Inhibition Enzyme Immunoassay is being used to compare serum human IgG levels in all animals, over time, and between 5gm/kg and 1gm/kg groups.

PRIOR AND CURRENT PROGRESS

Animal and laboratory work are completed. Analysis is completed. Draft publications are in preparation.

CONCLUSIONS

None yet.

REPORT DATE: 07/20/92 WORK UNIT # 6219

DETAIL SUMMARY SHEET

TITLE: Chronic Stress, Change in Social Support, and Uncertainty

KEYWORDS: chronic stress, reactions to stress

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Blaney, Susan MAJ MC; Edwards, E. Glenn MAJ MC

DEPARTMENT: Department of Pediatrics

STATUS: Ongoing
APPROVAL DATE: Jul 1988

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

STUDY OBJECTIVE

a) To evaluate psychological, physiological, and behavioral responses to ongoing chronic stress; b) To examine the role of change in the stress-social support relationship; and c) To determine the role of ambiguity or uncertainty in stress.

TECHNICAL APPROACH

A multi-modal (endocrine, hematologic, psychiatric, immunologic) evaluation is used for family members of children with malignancies. This study is in conjunction with the Department of Psychiatry, USUHS. Families are screened by a hematology-oncology nurse specialist.

PRIOR AND CURRENT PROGRESS

There have been 45 parents of children with chronic illnesses, 29 parents of children with autism or learning disabilities, and 21 parents with children who do not have chronic or life-threatening illness enrolled in study. Subject recruitment has been completed, and medical charts are being reviewed.

CONCLUSIONS

Study should remain open.

REPORT DATE: 04/06/92 WORK UNIT # 6223

DETAIL SUMMARY SHEET

TITLE: Ceftriaxone for Outpatient Management of Suspected Occult Bacteremia: A Multicenter Cooperative Study

KEYWORDS: occult, bacteremia, ceftriaxone

PRINCIPAL INVESTIGATOR: Zawadsky, Peter COL MC

DEPARTMENT: Department of Pediatrics STATUS: Ongoing
APPROVAL DATE: Oct 1988

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

STUDY OBJECTIVE
To compare ceftriaxone and augmentin in the treatment of febrile infants and children who have no obvious focus of infection and who, therefore, may have occult bacteremia.

TECHNICAL APPROACH
This is a collaborative, tri-service multicenter study with Colonel James Bass, Tripler AMC, serving as study monitor. Outpatients fulfilling study entry criteria and consenting to participate are evaluated for occult bacteremia with blood cultures, exam, and other studies as indicated. They are then randomized to therapy with either augmentin PO or ceftriaxone IM, and follow-up exam is performed 24 hours later. Further evaluation and therapy varies according to symptoms and blood culture results. Data sheets at entry and for each follow-up are compiled. Patients with positive blood cultures will form the study group for comparing the two antibiotic regimens.

PRIOR AND CURRENT PROGRESS
A total of nine patients from WRAMC have been enrolled in the study protocol to date. The collaborative study has enrolled 519 patients. The relatively small primary care outpatient population is responsible for the small number enrolled; however, attempts will be made to raise the consciousness of the staff and housestaff about this protocol.

CONCLUSIONS
A preliminary summary of findings is being written and will be submitted for publication. No difference between ceftriaxone and augmentin has been found; however, approximately 600 more patients are needed to confidently accept the null hypothesis.

REPORT DATE: 05/22/92 WORK UNIT # 6231

DETAIL SUMMARY SHEET

TITLE: Advanced Airway Management Skill Station Using Cats

KEYWORDS: endotracheal, intubation, cats

PRINCIPAL INVESTIGATOR: Restuccia, Robert LTC MC
ASSOCIATES: Bley, John Jr. MAJ VC

DEPARTMENT: Department of Pediatrics

STATUS: Ongoing
APPROVAL DATE: Feb 1989

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

STUDY OBJECTIVE

To teach orotracheal intubation to pediatricians and pediatric nurses attending the Pediatric Advanced Life Support Course at Walter Reed Army Medical Center. Using live cats enables the students to practice on a model which simulates intubation of infants and children.

TECHNICAL APPROACH

Cats are anesthetized with ketamine and acetylpromazine in order to permit orotracheal intubation while maintaining spontaneous respiration. If needed, the cats receive topical lidocaine on their vocal cords to diminish laryngospasm and intramuscular atropine to reduce airway secretions. Each cat is limited to five attempted orotracheal intubations, after which it is returned to the holding cage and monitored until it recovers from anesthesia.

PRIOR AND CURRENT PROGRESS

This protocol has provided the means by which we teach live orotracheal intubation to pediatricians, other physicians, nurses, and ancillary health care providers involved in pediatrics. We have conducted 10 courses at WRAMC since April 1989, and have taught over 220 providers. We anticipate an increase in the number of Pediatric Advanced Life Support Courses at WRAMC in the future (from three to six courses per annum), which would mean a doubling of the intubation laboratory as well. We have not lost any of the 144 cats used during these intubation exercises. Thus, the funds have been used primarily for the maintenance of the animals as well as expendable supplies.

CONCLUSIONS

We would like to add the ferret as another animal model for intubation since it is smaller than the cat and thus mimicks human premature size better. Additional funding of $300/year would be used to procure and maintain these animals. An addendum has been submitted.

REPORT DATE: 05/28/92 WORK UNIT # 6240

DETAIL SUMMARY SHEET

TITLE: A Prospective Study of Short Vs. Long Course Antibiotic Therapy for Central Venous Catheter Infections in Pediatric Patients

KEYWORDS: infection, antibiotic therapy, central venous catheter

PRINCIPAL INVESTIGATOR: Zawadsky, Peter COL MC

DEPARTMENT: Department of Pediatrics STATUS: Completed
APPROVAL DATE: Apr 1989

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

STUDY OBJECTIVE
To compare two durations of therapy for central venous catheter (CVC) infections, with short-term outcome and relapse as study endpoints.

TECHNICAL APPROACH
Patients are eligible for the study if they have documented systemic (i.e., blood) or local (i.e., exit wound) infection and have a long-term, in-dwelling central venous catheter. The systemic and local groups are randomized independently to long or short therapy. Endpoints include failure to clear infection at specified duration of therapy and relapse.

PRIOR AND CURRENT PROGRESS
Six patients have been enrolled. Most of the patient's parents have not been willing to accept 3 weeks of therapy, and therefore, their children have not been enrolled.

CONCLUSIONS
This protocol should be closed. There are not enough patients to enroll to achieve a statistically significant sample.

REPORT DATE: 08/15/92 WORK UNIT # 6245

DETAIL SUMMARY SHEET

TITLE: The Effect of Asphyxia on the Susceptibility of the Suckling Rat Pup to Group B Streptococcal Infection

KEYWORDS: group B streptococcal, asphyxia, neonate

PRINCIPAL INVESTIGATOR: Beachy, Joanna MAJ MC

DEPARTMENT: Department of Pediatrics STATUS: Completed
APPROVAL DATE: Jun 1989

FUNDING: Current FY: $ 0 Previous FYs: $ 1,878 Total: $ 1,878

STUDY OBJECTIVE
To determine if asphyxia affects bacteremia and mortality of group B streptococcal (GBS) infected suckling rats and if the mechanism is mediated via neutrophil number or function. To determine if asphyxia affects bacteremia in the adult rat, and if so, whether the mechanism is mediated via neutrophil number or function.

TECHNICAL APPROACH
Previously established laboratory techniques will be used to evaluate the question in the suckling rat. Specifically, a suckling rat model of GBS sepsis will be used to evaluate bacteremia and mortality following infection with and without asphyxia. Asphyxial methods have been worked out on previous protocols. Previously reported methods of neutrophil number and function will be used to evaluate the affect of asphyxia in vitro. Adult animal model will be developed to evaluate the similar question addressed in neonatal rats.

PRIOR AND CURRENT PROGRESS
All laboratory work and analysis has been completed. The first publication has been submitted, and the second is in preparation. No animals were used this past year. There have been no serious or unexpected adverse reactions or findings.

CONCLUSIONS
Asphyxia affects bacteremia and survival of GBS infected suckling rats and appears to be mediated, in part, by abnormal neutrophil function in both suckling and adult rats. Neonates or adults with asphyxia may be at increased risk of infection.

REPORT DATE: 03/27/92 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: $ 1,241 Previous FYs: $ 67 Total: $ 1,308

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
Initially, our principal effort has been to define effects of TNF on the gonad of the rat. This has been quite successful and will ultimately be useful in this protocol. The technique for culture of pituicytes has been validated in our lab.

CONCLUSIONS
Study is feasible when gonadol effects of cytokines are well delineated.

REPORT DATE: 03/27/92 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: $10,898 Previous FYs: $ 8,681 Total: $ 19,579

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
In our lab, TNF has been shown not to have direct effects on Leydig cell function. Other labs, however, have shown it to decrease testosterone production in sexually mature animals and in porcine systems. We believe the latter observation may be due to small percentage macrophage contamination of their Leydig cell preparations, as we have now shown macrophages to produce a factor which has mwt 16,500 daltons that is acid stable and heat labile. This factor inhibits testosterone production in our system, and the effect is not reproduced by TNF, IL1, IL2, IL6, CRF, or alpha-IFN.

CONCLUSIONS
A macrophage product not previously described inhibits testosterone production. This factor works distal to cAMP production by a mechanism which we are now attempting to define.

REPORT DATE: 03/27/92 WORK UNIT # 6258

DETAIL SUMMARY SHEET

TITLE: Polymorphism of Prolactin in Neonatal Cord Blood

KEYWORDS: prolactic, neonatal

PRINCIPAL INVESTIGATOR: Francis, Gary LTC MC

DEPARTMENT: Department of Pediatrics STATUS: Ongoing
APPROVAL DATE: Jan 1990

FUNDING: Current FY: $ 1,667 Previous FYs: $ 0 Total: $ 1,667

STUDY OBJECTIVE
To determine if prolactin (PRL) exists in multiple species in human cord blood, and, if so, whether or not these different species have different biological activity.

TECHNICAL APPROACH
Cord blood is to be collected from the placenta after delivery of the infant and after detachment from the mother. Serum will be separated and frozen for analysis over G-100 sephadex column chromatography. PRL will be identified by radioimmunoassay (RIA), and biological activity will be assessed by NB2 rat node lymphoma cell bioassay.

PRIOR AND CURRENT PROGRESS
I have discussed this protocol with COL Thomas Klein, Chief, Department of Obstetrics and Gynecology, who agrees with its merit. Although we were previously unable to implement this study due to the absence of the Chief of the OB Service, COL Klein has suggested that new incoming residents in OB-GYN may be interested and, therefore, I will pursue this protocol with them.

CONCLUSIONS
This protocol has merit but has not been implemented due to the absence of the Chief of the OB Service. Attempts will be made to reinstitute this study with new incoming residents.

REPORT DATE: 05/27/92 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.

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
During this review period, four new patients were entered on the study for a total of seven registrants. There were no unexpected toxicities and no toxic deaths. Responses at the 60 day evaluation are: four complete responses, one stable disease, and two progressive disease. Of the four complete responses, two have relapsed, but all are alive. The one patient who had stable disease had a marked clinical improvement. Both patients with progressive disease have died.

CONCLUSIONS
Study should remain open.

REPORT DATE: 06/23/92 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: $ 0 Previous FYs: $ 0 Total: $ 0

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
There were two registrants to this study since the last report; for a total of 13 subjects enrolled to date. Samples have been collected; however, the original principal investigator, Dr. Moore, has not reported back with information to allow continuation of study. Currently, another hematology-oncology fellow (pediatrics) is being identified to complete this protocol.

CONCLUSIONS
Study should remain open.

REPORT DATE: 01/20/92 WORK UNIT # 6274

DETAIL SUMMARY SHEET

TITLE: Assessment of Meconium Suction Techniques in the Piglet Trachea

KEYWORDS: meconium, suction, efficacy

PRINCIPAL INVESTIGATOR: Bent, Rebecca MAJ MC

DEPARTMENT: Department of Pediatrics

STATUS: Ongoing
APPROVAL DATE: Oct 1990

FUNDING: Current FY: $ 165 Previous FYs: $ 0 Total: $ 165

STUDY OBJECTIVE
To compare the efficacy of techniques for removing meconium from an in vitro piglet trachea model; and to evalaute the histopathologic effect on the airway of effective suction techniques; specifically, whether suction pressure, pattern, or presence of meconium impacts histopathologic changes.

TECHNICAL APPROACH
Fourteen suction techniues were tested in each of 14 in vitro piglet trachea. Three efficacious techniques were selected for in vivo comparison. Twenty-four piglets were randomized to one of the three efficacious treatments, either with or without meconium having been instilled into the trachea. After 24 hours, the airways were harvested for blinded histopathological assessment.

PRIOR AND CURRENT PROGRESS
Phase one has been completed, and the results have been presented at the Society for Pediatric Research meeting in May 1991 and to the American Academy of Pediatrics meeting in October 1991. A manuscript has been submitted for publication. Phase two animal work has been completed. Histopathologic assessment has been completed by one blinded pathologist. An abstract has been submitted to the Society for Pediatric Research, and further analysis of the data is underway. There have been no unexpected or adverse reactions or findings, except one piglet developed malignant hyperthermia, a known idiosyncratic reaction to anesthesia.

CONCLUSIONS
There are significant differences in efficacy among meconium suctioning techniques. No clinically significant histopathologic change in the airway occurs as a result of effective suction techniques. Most injury is appreciated proximally, regardless of pressure, pattern, or meconium presence.

REPORT DATE: 02/01/92 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: Ongoing
APPROVAL DATE: Oct 1990

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

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
To date, four patients have been entered and completed the study. The shelf-life of the drug expired and the study has been temporarily halted pending arrival of new drug (about March 1992). There have been no serious or unexpected adverse reactions. One patient was withdrawn from the study by the parent after 4 days. No reason was given.

CONCLUSIONS
None yet.

REPORT DATE: 03/10/92 WORK UNIT # 6277

DETAIL SUMMARY SHEET

TITLE: The Meconium Aspiration Syndrome: Unanswered Questions

KEYWORDS: meconium, newborn infant

PRINCIPAL INVESTIGATOR: Wiswell, Thomas LTC MC
ASSOCIATES: Henley, Mark CAPT MC

DEPARTMENT: Department of Pediatrics

STATUS: Completed
APPROVAL DATE: Dec 1990

FUNDING: Current FY: $ 232 Previous FYs: $ 0 Total: $ 232

STUDY OBJECTIVE
To investigate the incidence of infection among children with meconium aspiration syndrome and meconium stained amniotic fluid. To study the incidence of the disorder among children who have and have not been intubated and suctioned in the delivery room.

TECHNICAL APPROACH
Review the medical records of all infants born at WRAMC who subsequently developed the meconium aspiration syndrome. A review sheet was used which itemized multiple characteristics regarding their delivery room care as well as their subsequent hospital course.

PRIOR AND CURRENT PROGRESS
Study is completed. It has been presented at two national meetings. The paper was published in February 1992.

CONCLUSIONS
Infants born through meconium-stained fluid, who are not intubated and suctioned in the delivery room, may be at higher risk for adverse sequelae; such as, need for mechanical ventilation, prolonged respiratory support, and air leaks. Infants born through meconium-stained fluid are not at any higher risk for systemic infection.

REPORT DATE: 05/18/92 WORK UNIT # 6283

DETAIL SUMMARY SHEET

TITLE: Retrospective Followup of Infant Fever Outcome

KEYWORDS: fever, infant

PRINCIPAL INVESTIGATOR: Zawadsky, Peter COL MC

DEPARTMENT: Department of Pediatrics STATUS: Completed
APPROVAL DATE: Feb 1991

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

STUDY OBJECTIVE
To determine the outcome of infants who develop fever during their first 8-10 weeks of life.

TECHNICAL APPROACH
Infants will be identified who meet specific criteria. They will be followed by medical record review to collect clinical data and to determine the specific outcomes.

PRIOR AND CURRENT PROGRESS
232 records meeting the eligibility criteria were reviewed.

CONCLUSIONS
The incidence of serious bacterial infections was 4.3%. The presence of well recognized viral signs in the absence of irritability and poor feeding may indicate a lower risk of serious bacterial infection.

REPORT DATE: 05/28/92 WORK UNIT # 6286

DETAIL SUMMARY SHEET

TITLE: Retrospective Analysis of Patients with Stomatococcus Mucilaginosus Bacteremia

KEYWORDS: stomatococcus

PRINCIPAL INVESTIGATOR: Zawadsky, Peter COL MC

DEPARTMENT: Department of Pediatrics STATUS: Completed
APPROVAL DATE: Apr 1991

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

STUDY OBJECTIVE
To report on a series of cases of infections due to the bacterium stomatococcus mucilaginosus.

TECHNICAL APPROACH
Retrospective record review of 10 cases.

PRIOR AND CURRENT PROGRESS
The findings have been published in the journal Reviews of Infectious Diseases, November-December 1991.

CONCLUSIONS
Stomatococcus mucilaginosus is an organism of low virulence, but it appears to be an emerging pathogen. Infection due to S. mucilaginosus is likely to be under-reported because the organism may be easily misidentified, and information on it is not included in the data bases of many automated microbiologic identification systems.

REPORT DATE: 06/24/92 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: Hachey, Wayne CPT MC

DEPARTMENT: Department of Pediatrics STATUS: Ongoing
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
To date, only 20% of the necessary preterm patients have been enrolled in the study. There have been no serious or unexpected adverse reactions or patients withdrawn from the study. There have been no direct benefit to those entered into the study.

CONCLUSIONS
Due to the limited data available, no conclusions regarding the usefulness of foot length in the determination of neonatal gestational age can be made.

REPORT DATE: 07/01/92 WORK UNIT # 6291

DETAIL SUMMARY SHEET

TITLE: Effect of Growth Hormone on the Development of Diabetic Nephropathy in the Rat

KEYWORDS: growth hormone, diabetes, nephropathy

PRINCIPAL INVESTIGATOR: Nickels, David MAJ MC
ASSOCIATES: Poth, Merrily MD

DEPARTMENT: Department of Pediatrics

STATUS: Ongoing
APPROVAL DATE: Jul 1991

FUNDING: Current FY: $ 7,615 Previous FYs: $ 0 Total: $ 7,615

STUDY OBJECTIVE
To prospectively evaluate the possible deleterious effects of growth hormone on the development and progression of diabetic nephropathy in the rat.

TECHNICAL APPROACH
Growth hormone (GH) 0.25mg will be administered daily to diabetic and control rats. Groups of rats will be euthanized at 2 days, 4 days, and 19 weeks to assess the effects of GH at various time intervals. Acute effect of GH at day 2 and day 4 will be determined by analysis of overall kidney hypertrophy and also by analysis of kidney insulin-like growth factor-1 content, as measured by RIA after acid extraction of tissue homogenate. Chronic effects of GH after 19 weeks will be analyzed by measurement of 24 hour urinary albumin excretion by ELISA and by evaluation of kidney histology by light microscopy and electron-microscopy.

PRIOR AND CURRENT PROGRESS
Analyses to date show the following: a) Acute effects of GH in the 2-day and 4-day groups: no difference in kidney hypertrophy or intra-renal IGF-1 content was found between the GH treated diabetics and the non-treated diabetic rats. Both diabetic groups showed an equivalent amount of kidney hypertrophy acutely. b) Long-term (19 weeks) groups have just recently been euthanized. Analysis of urinary albumin excretion, kidney histology, and electron-microscropy is orgoing.

CONCLUSIONS
Short-term administration of growth hormone, over 2-4 days, to diabetic rats does not worsen the early kidney hypertrophy seen with diabetes, nor does it change the intra-renal IGF-1 content. Effects of longer term administration of GH on diabetic nephropathy are still being analyzed.

REPORT DATE: 08/26/92 WORK UNIT # 6295

DETAIL SUMMARY SHEET

TITLE: Comparison of Intravenous and Endotracheal Tolazoline Effects on Hypoxia-Induced Pulmonary Hypertension in Newborn Lambs

KEYWORDS: endotracheal, tolazoline, pulmonary hypertension

PRINCIPAL INVESTIGATOR: Curtis, Jerri LCDR MC
ASSOCIATES: Pettett, Phillip COL MC; Payne, Matthew CPT MS

DEPARTMENT: Department of Pediatrics

STATUS: Ongoing
APPROVAL DATE: Aug 1991

FUNDING: Current FY: $16,392 Previous FYs: $ 0 Total: $ 16,392

STUDY OBJECTIVE

To determine whether the endotracheal administration of tolazoline reduces pulmonary vascular resistance in the acutely hypoxic newborn lamb; to compare the effects of endotracheally and intravenously administered tolazoline on systemic vascular resistance during acute hypoxia; and to correlate the clinical effects of endotracheally administered tolazoline with plasma concentrations of tolazoline.

TECHNICAL APPROACH

Using hypoxia as a stimulus for pulmonary arterial vasoconstriction, newborn lambs will be randomized to receive either intravenous or endotracheal administered tolazoline or to serve as a control (receive endotracheal saline). The following cardiovascular parameters will be measured and compared between routes: mean artery pressure, mean pulmonary artery pressure, cardiac output, and pulmonary and systemic vascular resistances. Plasma for tolazoline levels will be obtained at specified time points.

PRIOR AND CURRENT PROGRESS

To date, 10 animals have been studied in each group. Endotracheal tolazoline produced a significant reduction in pulmonary artery pressure and in pulmonary vascular resistance with less severe systemic vascular effects than intravenous tolazoline. Intravenous tolazoline produced a significant reduction in pulmonary and systemic arterial pressures and pulmonary and systemic vascular resistances as anticipated. Plasma tolazoline levels are presently being analyzed. There have been no unexpected adverse reactions or findings.

CONCLUSIONS

When tolazoline is administered endotracheally, it appears to offer advantages over the intravenous route of delivery Specifically, a more selective vasodilation of the pulmonary vasculature over the systemic vasculature. This was an acute set of experiments; therefore, before recommendations for the clinical setting can be made, further investigation is needed in this area.

REPORT DATE: 08/28/92 WORK UNIT # 6298

DETAIL SUMMARY SHEET

TITLE: In-Vitro Comparison of Three Rapid Latex Agglutination Tests for the Detection of H. Influenzae Type b Antigenuria from Four H. Influenzae Conjugate Vaccines

KEYWORDS: conjugated Hib saccharide, latex agglutination tests

PRINCIPAL INVESTIGATOR: Pierce, John COL MC

DEPARTMENT: Department of Pediatrics STATUS: Ongoing
APPROVAL DATE: Sep 1991

FUNDING: Current FY: $ 400 Previous FYs: $ 0 Total: $ 400

STUDY OBJECTIVE
To determine if there is variation in the ability of latex agglutination tests to detect the conjugated Hib saccharide of four conjugated Hib vaccines.

TECHNICAL APPROACH
All vaccines were diluted in urine to 2 ug/ml. Serial 10 and two dilutions of each vaccine were tested for the presence of Hib antigen.

PRIOR AND CURRENT PROGRESS
Data collection and analysis are complete. The abstract and paper are in the final stages of preparation.

CONCLUSIONS
There is greater than 3 log fold variability in the ability to detect conjugated Hib saccharide in urine depending upon which combination of vaccine and latex agglutination test kit is used.

REPORT DATE: 09/04/92 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: Phillips-Dawkins, Terri CPT MC
ASSOCIATES: Weisman, Leonard COL MC

DEPARTMENT: Department of Pediatrics

STATUS: Ongoing
APPROVAL DATE: Sep 1991

FUNDING: Current FY: $ 3,482 Previous FYs: $ 0 Total: $ 3,482

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

The LD50 for S epi in the neonatal rat pup has been determined to be in the dose range of 10^6 - 10^8. Animals receiving lipid in doses ranging from 0.5 to 12 g/kg of lipid demonstrate no significant differences in serum TG levels except at 2 hours post injection when given 12 g/kg. To date, there is no significant difference in mortality when animals are injected with constant concentrations of S epi and given varying doses of intralipid. In vitro assays of neutrophil function are currently being standardized on rat dams.

CONCLUSIONS

A neonatal animal model for S epi sepsis independent of lipid has been established. Lipid given in physiologic doses does not significantly effect mortality or bacteremia in this animal model. Subsequent in vitro assays may help to determine whether lipid has any effect on the ability of the neutrophil to ingest or kill S epi.

REPORT DATE: 04/10/92 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
Through December 1991, there have been 282 cases reviewed and accepted into the registry. All cases have been submitted with slides and have been reviewed. There have been no cases submitted by WRAMC in the reporting year.

CONCLUSIONS
Study should remain open.

REPORT DATE: 04/10/92 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: Feb 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 sen to coordinator to evaluate effects of the cancer and its treatment.

PRIOR AND CURRENT PROGRESS
There have been a total of 2831 eligible National Wilms' Tumor Study patients (those registered, randomized, and now at least 5 years post diagnosis). There are 25 WRAMC patients who are eligible for this study (3 since last Annual Progress Report). The study coordinator was awarded a grant to improve data collection, which will allow this study to remain open for another 5 years.

CONCLUSIONS
Study should remain open.

REPORT DATE: 06/25/92 WORK UNIT # 6148

DETAIL SUMMARY SHEET

TITLE: POG 8104 Comprehensive Care of the Child with Neuroblastoma: A Stage and Age Oriented Study, Phase III

KEYWORDS: neuroblastoma, Stage IV-S, cis-platinum

PRINCIPAL INVESTIGATOR: Maybee, David COL MC

DEPARTMENT: Department of Pediatrics STATUS: Completed
SERVICE: Pediatric Hematology-Oncology Service APPROVAL DATE: May 1982

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

STUDY OBJECTIVE
To prospectively evaluate the prognostic import of stage, using a pathological staging system, in children with neuroblastoma.

TECHNICAL APPROACH
Patients are treated with a variety of therapies according to their age and the stage of their disease.

PRIOR AND CURRENT PROGRESS
No new data has been presented by the study coordinators. Within the past two Annual Progress Report (APR) cycles, there have been no new patients registered. There is no new data to report on the WRAMC registrants.

CONCLUSIONS
Study should be closed.

REPORT DATE: 03/31/92 WORK UNIT # 6162

DETAIL SUMMARY SHEET

TITLE: POG 8451 Intergroup Rhabdomyosarcoma III

KEYWORDS: rhabdomyosarcoma, cis-platinum, radiotherapy

PRINCIPAL INVESTIGATOR: Maybee, David COL MC

DEPARTMENT: Department of Pediatrics STATUS: Completed
SERVICE: Pediatric Hematology-Oncology Service APPROVAL DATE: Dec 1984

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

STUDY OBJECTIVE
a) To compare the effectiveness of various drug therapies in each clinical group, including the use of salvage chemotherapy, to evaluate prognostic factors; b) To determine if second and third look surgery will improve local disease control; and c) To attempt to devise a preoperative staging classification.

TECHNICAL APPROACH
Following complete surgical and medical staging and histologic subclassification, patients will be randomized to receive a specific chemo/radiation regimen, including salvage chemotherapy for advanced stages. Second and third look surgery will be used in some cases.

PRIOR AND CURRENT PROGRESS
This study closed to patient accrual in October 1991, but remained in an ongoing status to report on results. In summation, there were 1,065 patients groupwide; none from WRAMC. Study coordinators report the major accomplishments of this study are: 1) overall survival was improved in IRS III over IRS II; 2) special pelvic sites showed improved survival and bladder salvage; 3) major improvements in clinical group III survival, with a role for second look surgery in successful treatment; and 4) parameningeal patients had improved survival with decreased volumes of radiotherapy. There were no changes in the protocol as a result of toxicities. This is the only information released in relation to toxicity from the study coordinators.

CONCLUSIONS
There are no patients on this study from WRAMC, and no local investigators are acting as study coordinators. This study has closed to patient accrual, and should be closed at WRAMC.

REPORT DATE: 04/14/92 WORK UNIT # 6175

DETAIL SUMMARY SHEET

TITLE: POG 8532 Treatment of Intracranial Ependymomas, A Pediatric Oncology Group Phase III Study

KEYWORDS: ependymomas, chemotherapy, tumors

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 1986

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

STUDY OBJECTIVE

To estimate the occurrence of seeding of IVth ventricular ependymomas in the CNS after surgery and irradiation to study survival and relapse patterns.

TECHNICAL APPROACH

Careful testing to assess extent of disease after surgery (CT, myelogram, psychological testing, etc.). Testing is repeated after radiation and at 4 to 6 month intervals for 2 years.

PRIOR AND CURRENT PROGRESS

Study has not accrued any patients since its closure in November 1990 (there were no WRAMC registrants). There were a total of 53 registrants: 37 remain progression-free (free of progressive disease), 4 are alive with disease, and 11 are dead of disease. One patient died of infection 1 month after surgery. There was no excessive or unusual toxicity on this study.

CONCLUSIONS

In the Annual Progress Report for FY-91, we reported that we wish to keep this study open one more cycle to report data. However, the study coordinators have not yet completed analysis of response data, so we conclude this study should remain open one more year.

REPORT DATE: 06/25/92 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
SERVICE: Pediatric Hematology-Oncology Service

STATUS: Ongoing
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

Protocol was closed to further accrual in January 1991. Overall complete response rate is about 97%. Early event-free survival reveals no significant differences in any planned treatment questions. The only statistically significant comparison that approaches a p-value of .05 is within the Pre-B, poor prognosis phenotype -- Arm C appears to be marginally superior to Arm B (results are still very early). The status of the 19 WRAMC registrants is as follows: 8 are alive off treatment, 7 have died off treatment, and 4 are on therapy (data reported in 1991 Annual Progress Report was in error -- 4, not 3, were on therapy.

CONCLUSIONS

Study should remain ongoing at WRAMC to allow reporting on remaining patients. There will be no further patient accrual on this protocol.

REPORT DATE: 06/25/92 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
There have been 213 patients entered on study (4 from WRAMC), all of whom are off therapy and alive. Laparotomy has resulted in clinical upstaging in 13% of the registrants. There has been a 17% discrepancy rate between local and central pathology review (local for each POG institution, not just WRAMC). Chemotherapy is generally well tolerated; however, dose reductions for side effects, especially for ABVD, are common. Five registrants have gone on to the progressive disease protocol (8626). The complete response rate is 96% for patients without mediastinal disease, 94% for patients with medium amount of mediastinal disease, and 68% for patients with large amount of mediastinal disease. Overall, the disease-free survival rate is 91%. Late effects noted so far include restrictive lung disease, cardiac dysfunction, hypothyroidism, skeletel abnormality, and thyroid nodule.

CONCLUSIONS
Study should remain open.

REPORT DATE: 08/24/92 WORK UNIT # 6184

DETAIL SUMMARY SHEET

TITLE: POG 8653 Study of Childhood Soft Tissue Sarcomas Other than Rhabdomyosarcoma and Its Variants, A POG Phase III Study

KEYWORDS: soft tissue sarcoma, synovial cell sarcoma

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: Aug 1986

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

STUDY OBJECTIVE
To collect data on tissue sarcomas other than rhabdomyosarcoma and Ewing's; and to treat with surgery, chemotherapy, and radiation.

TECHNICAL APPROACH
To use adjuvant chemotherapy with vincristine, Adriamycin, cyclophosphamide, and actinomycin D (VACA) plus DTIC, when available from manufacturer, after surgery with or without postoperative radiation (POG 8653). DTIC will be given by a randomized decision (when available).

PRIOR AND CURRENT PROGRESS
There have been 90 registrants entered on study (none from WRAMC). Out of 49 registrants evaluable for response there are: 11 registrants with unknown response, 13 with complete response, 5 with partial response, 4 with marginal response, and 16 with no response. Toxicity continues to be acceptable, with no new developments reported. Disease-free survival after 1 year is 42.3% and at the end of 4 years, 30.1%. The protocol was modified in the reporting year, as the drug DTIC became unavailable from the manufacturer. However, it became available again in May 1992.

CONCLUSIONS
Study should remain open.

REPORT DATE: 02/03/92 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; Edwards, E. Glenn MAJ 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
There were two WRAMC patients since the last APR; both are still on therapy. One of the eight registrants reported in the past has relapsed. Groupwide, there have been 1,597 registrants. Although response is masked at this time, there are no statistical differences between treatment arms. Toxicity is also equal between arms. There have been 13 deaths on treatment since the study opened in 1986 (no WRAMC registrants) that could be attributed to toxicity or treatment complications. Study progress regarding accrual is as expected and should be completed in about 3 years.

CONCLUSIONS
Study should remain open.

REPORT DATE: 04/10/92 WORK UNIT # 6191

DETAIL SUMMARY SHEET

TITLE: POG 8616 Intensive Chemotherapies for Stage III Diffuse Undifferentiated Lymphoma (DU NHL Burkitt and Non-Burkitt), A Randomized Phase III Study

KEYWORDS: lymphoma, diffuse, undifferentiated

PRINCIPAL INVESTIGATOR: Maybee, David COL MC

DEPARTMENT: Department of Pediatrics STATUS: Ongoing
SERVICE: Pediatric Hematology-Oncology Group APPROVAL DATE: Jan 1987

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

STUDY OBJECTIVE
a) To achieve chemotherapeutic cure in a majority of patients with Stage III DU-NHL; b) To compare two regimens for efficacy and toxicity; and c) To study correlation between treatment/response and lactate dehydrogenase (LDH).

TECHNICAL APPROACH
Registrants must be 21 years old or less, previously untreated, and Stage III. Randomization is at diagnosis, between "Total B" regimen and a high dose Cytoxan/methotrexate regimen.

PRIOR AND CURRENT PROGRESS
There have been 135 registrants entered on this study groupwide; 4 from WRAMC that have been reported in previous Annual Progress Reports. Study was closed to further accrual in November 1991 due to completion of accrual goals. Treatment results have been unmasked and show that arm A had 85% remission induction rate, and arm B had a 96% remission induction rate (p=.032). Treatment arm B also appears to be slightly favorable for disease-free survival, with 77.6% disease-free survival rate over the 63.5% rate reported for arm A. However, these results are not yet considered statistically significant. Disease-free survival rates are reported at 12 months post therapy, as no registrant has relapsed beyond that date post therapy. Toxicity data was not provided in the study coordinator report; however, as there were no revisions made to therapy in the last reporting year, we assume it remained acceptable.

CONCLUSIONS
Study should remain open.

REPORT DATE: 04/07/92 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 Group

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 have been no WRAMC registrants in the past reporting year. The one WRAMC registrant remains well. Groupwide, there have been 89 registrants, of whom 76 are evaluable for toxicity: 58% had neutropenia, 51% had elevated liver functions tests (LFT's), 43% had mucositis/stomatitis, 30% had thrombocytopenia, and 18% had leukopenia. Response remains masked. Disease-free survival is 80% during the first year off therapy and 71% during the second year.

CONCLUSIONS

Study should remain open.

REPORT DATE: 04/23/92 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 STATUS: Ongoing
SERVICE: Pediatric Hematology-Oncology Group 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 r gimens; 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.

PRIOR AND CURRENT PROGRESS

There are a total of 134 registrants groupwide, 1 from WRAMC. The complete response rate is 92% for the ACOP+ regimen and 96% for the APO regimen (this is not yet considered a statistically significant difference). Toxicity concerns about Adriamycin (long term cardiac problems) have caused the study coordinators to place all new patients as of December 1991 on the APO arm, which will allow analysis of Adriamycin without the possible factor of Cytoxan in this question. As both arms show similar complete response rates and long-term disease-free survival rates (about 75% after 1 year), assignment to the APO regimen will not cause a decrease in a patient's likelihood of survival. There was no unexpected toxicity. One severe toxicity was reported (cardiac, during Adriamycin therapy), which resulted in the registrant being removed from the study in remission. The WRAMC patient remains well.

CONCLUSIONS

Study should remain open.

REPORT DATE: 04/21/92 WORK UNIT # 6194

DETAIL SUMMARY SHEET

TITLE: POG 8617/8618 Therapy for B-Cell Acute Lymphoblastic Leukemia and Advanced Diffuse Undifferentiated Lymphomas, A Phase II Study

KEYWORDS: B-cell leukemia, 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: Feb 1987

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

STUDY OBJECTIVE

a) To estimate CR rate and disease-free survival in patients with Stage IV diffuse undifferentiated (DU) NHL and B-ALL; and b) To estimate reinduction rate and disease-free survival (DFS) for patients in relapse with NHL.

TECHNICAL APPROACH

For POG 8617, children with untreated B-ALL, Stage IV DU-NHL, or diffuse lymphoma, non-lymphoblastic histology, in first relapse are eligible. For POG 8618, CNS relapse for NHL with non-lymphoblastic NHL, and isolated CNS relapse of 8617 registrants. Regimen involves initial vincristine/Cytoxan/Adriamycin with intrathecal chemotherapy, followed by IV MTX-Ara-C. POG 8618 (closed 1988) was designed to investigate therapy for patients who relapsed in the central nervous system on this protocol, but closed due to lack of accrual.

PRIOR AND CURRENT PROGRESS

There have been 38 new registrants in the past reporting year (none from WRAMC); 125 since this study opened. The study was amended to include Stage III DU-NHL in November 1991 (the study report cutoff date). G-CSF was added to the drug regimen in July 1991, and preliminary results show this drug is effective in reducing severity and duration of the toxicity associated with this study. The complete response rate is 90% for B-ALL and 92% for Stage IV DU-NHL. Long-term survival is approximately 66% for B-ALL and 72% for Stage IV DU-NHL after 2 years (this remains stable).

CONCLUSIONS

Study should remain open.

REPORT DATE: 05/18/92 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

This study was closed to further accrual in April 1990, with a total of 206 patients (4 from WRAMC, as reported in previous Annual Progress Reports). Overall response to chemotherapy ranged from 0-60% depending on brain tumor morphology, extent of initial resection, and presence of metastatic disease at diagnosis. Among the 13 patients who had measurable disease post surgery and complete response to chemotherapy, there was improved survival. Toxicity was mostly hematologic with infectious complications arising in several patients. Study results suggest that this therapy is feasible in select children less than 3 years old with central nervous system malignancy.

CONCLUSIONS

Three WRAMC registrants have died of progressive disease. Although the study has been closed by POG, this study remains ongoing at WRAMC to follow the one registrant who has stable disease after completion of therapy on study.

REPORT DATE: 05/27/92 WORK UNIT # 6196

DETAIL SUMMARY SHEET

TITLE: POG 8741/8742 Treatment of Stage D Neuroblastoma in Children Greater than 365 Days at Diagnosis, A POG Phase II/III Study

KEYWORDS: neuroblastoma, ifosfamide, metastatic neuroblastoma

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: Apr 1987

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

STUDY OBJECTIVE

Phase II: To evaluate response rates in poor prognosis neuroblastoma with Phase II chemotherapy prior to conventional therapy.
Phase III: To evaluate the effectiveness of two chemotherapy regimens in a randomized trial: cisplatin/etoposide/cyclophosphamide/Adriamycin vs. high-dose cisplatin/etoposide/cyclophosphamide/Adriamycin. Data will also be collected to review the effect that tumor resectability has on remission rate and duration.

TECHNICAL APPROACH

Phase II: Cycles of Phase II drugs will be given to evaluate their potential use against neuroblastoma. The first drug is ifosfamide. The response will be evaluated, then conventional chemotherapy will be given.
Phase III: Newly diagnosed patients 365 days old and older who were treated on POG 8741 (Phase II) and failed, or newly diagnosed patients (Stage C and D) who have received no Phase II therapy, are treated with combination chemotherapy and, when possible, surgical removal of tumor.

PRIOR AND CURRENT PROGRESS

Phase II remains closed and there is no change in response data reported in the previous Annual Progress Report. There have been 316 patients accrued in Phase II, which was closed in November of 1991. Response was slightly better for stage C patients than for stage D. Arm-specific results were unmasked: 55% complete response with the high dose cisplatin regimen; 51% complete response for the regimen without high dose cisplatin. Stage C patients had a complete response rate of 60%. Survival differences between the two regimens have not been statistically significant. There are no new findings reported on the toxicity of these two chemotherapy regimens. At this time, study coordinators have not analyzed toxicity data to compare risk of toxicity between the two arms. There is one WRAMC registrant who is still being followed; he remains well off therapy.

CONCLUSIONS

Study should remain open to report follow-up on the WRAMC registrant who is still being followed.

REPORT DATE: 06/25/92 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 STATUS: Ongoing
SERVICE: Pediatric Hematology-Oncology Service 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 was closed to patient accrual in January 1992, with a final accrual of 557 patients. There were four WRAMC patients, two of whom are still on therapy. The other two were reported on previously. The induction rate was 97% in T-ALL and 96% in T-NHL. Unmasking of the treatment arms will be done in the 1992 Fall POG report. Event-free survival appears promising. Therapy is generally well tolerated; however, considerable toxicity has occurred which has been largely reversible.

CONCLUSIONS
Study should remain open at WRAMC to follow patients currently on therapy. There will be no further patient accrual on this protocol.

REPORT DATE: 07/01/92 WORK UNIT # 6202

DETAIL SUMMARY SHEET

TITLE: POG 8739: Evaluation of Alpha Interferon in the Treatment of Recurrent Brain Tumors in Children, A POG Phase II Study

KEYWORDS: interferon, brain tumors

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 the efficacy of alpha-interferon (<-IFN) in children with brain tumors resistant to standard therapy in regard to response rate with different histologic subtypes and duration of response to <-IFN.

TECHNICAL APPROACH

Registrants are less than 21 years old with measurable tumors, and have not received chemotherapy in the preceding 2 weeks or radiation therapy in the preceding 3 months. Ten mega units of <-IFN are given IV 5 days/week for 4 weeks, and if responsive, subjects receive subsequent 4 week courses. Evaluation of response is at 4 weeks, or every other subsequent course.

PRIOR AND CURRENT PROGRESS

This study was closed to accrual (all strata) on May 15, 1992. Final accrual was 30 patients. Study coordinator reports that 2/3 of the response data is not yet evaluated; however, results so far appear disappointing overall. Toxicity remains acceptable. There were no WRAMC registrants on this study.

CONCLUSIONS

This study should be closed at WRAMC.

REPORT DATE: 07/01/92 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: Ongoing
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 designed to sustain MTX levels of 0.5 micromolar for more than 36 hours per pulse.

PRIOR AND CURRENT PROGRESS

There have been 32 patients registered to this study as of March 1992 (none from WRAMC). Twelve patients have received methotrexate plus leucovorin (31 courses); 18 patients have received methotrexate without leucovorin (74 courses). Toxicity (hematologic, mucositis) of this therapy is lessened with leucovorin. Methotrexate levels have been greater than 0.5 micromolar in 34/39 courses evaluable for methotrexate levels. Median has been 1.0, with a range from 0.2 - 3.1 micromolar. Response and disease-free survival remain masked.

CONCLUSIONS

This study should remain open.

REPORT DATE: 08/24/92 WORK UNIT # 6205

DETAIL SUMMARY SHEET

TITLE: POG 8759: The Effectiveness of Phase II Agents in Untreated Metastatic Osteosarcoma or Unresectable Primary Osteosarcoma Vs. Previously Treated Recurrent Osteosarcoma, POG Phase II/III Study

KEYWORDS: osteosarcoma, recurrent, primary

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: Aug 1987

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

STUDY OBJECTIVE

a) To study the response rate to ifosfamide in newly diagnosed metastatic unresectable osteosarcoma or in osteosarcoma presenting as a second malignancy and to study the addition of the agent to a standard treatment regimen for effectivenes and toxicity; and b) To gain biologic information about the tumor.

TECHNICAL APPROACH

Eligible new patients (biopsy proven) will be treated with two courses of ifosfamide upfront, evaluated for response (including biopsy and a surgical excision), and then continued on standard chemotherapy and ifosfamide. Those registrants having recurrence will continue, if responsive, on ifosfamide only.

PRIOR AND CURRENT PROGRESS

This study was closed to new registrants in October 1990, with a final accrual of 72 patients (1 from WRAMC). The WRAMC registrant remains well and has completed therapy. Study coordinators are providing yearly updates on disease-free survival and survival. As of February 1992, the estimated disease-free survival was 60.8 (first year), 44.4 (second year), and 38.8 (third year). Survival was estimated to be 76.5 (first year), 63.2 (second year), and 46.8 (third year).

CONCLUSIONS

Study should remain open at WRAMC to allow reporting of registrants' disease-free survival and survival.

REPORT DATE: 08/24/92 WORK UNIT # 6206

DETAIL SUMMARY SHEET

TITLE: POG 8763: Evaluation of Response and Toxicity of Ifosfamide and VP-16-213 in Children with Resistant Malignant Tumors, A POG Phase II Study

KEYWORDS: solid tumors, ifosfamide/VP-16

PRINCIPAL INVESTIGATOR: Maybee, David COL MC

DEPARTMENT: Department of Pediatrics STATUS: Completed
SERVICE: Pediatric Hematology-Oncology Service APPROVAL DATE: Aug 1987

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

STUDY OBJECTIVE
To determine the antitumor activity and toxicity of ifosfamide (IFX) plus VP-16 against a spectrum of childhood malignant solid tumors resistant to conventional chemotherapy.

TECHNICAL APPROACH
Registrants must be less than 21 years, with confirmed and measurable solid tumor, and be off therapy. VP-16 and IFX are given in 3 day courses, 3 weeks apart, for 18 months if response occurs.

PRIOR AND CURRENT PROGRESS
Last fiscal year's report requested to keep this study open to report further data from study coordinators. They are no longer reporting on this study bi-annually through the Pediatric Oncology Group but are publishing results through medical journals. The only registrant remaining alive is expected to continue to do well off therapy.

CONCLUSIONS
Study should be closed at WRAMC.

REPORT DATE: 09/16/92 WORK UNIT # 6207

DETAIL SUMMARY SHEET

TITLE: POG 8719: Trial of Shortened Therapy without Maintenance for the Treatment of Localized Non-Hodgkin's Lymphoma, A POG Phase III Study

KEYWORDS: non-Hodgkin's lymphoma, localized

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 1987

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

STUDY OBJECTIVE

a) To compare the survival and disease-free survival in patients receiving 9 weeks of induction/consolidation versus patients receiving similar 9 weeks + 24 weeks of maintenance; and b) To continue cancer biopsy studies of POG #8315.

TECHNICAL APPROACH

Children under 21 years with no prior therapy are eligible. Induction/ consolidation therapy is with Cytoxan/Adriamycin/vincristine and prednisone, with intrathecal medications for head and neck primaries only. Maintenance therapy uses oral 6MP/MTX.

PRIOR AND CURRENT PROGRESS

Study was closed to further registration on December 9, 1991. There were 201 registrants groupwide; 2 from WRAMC who are both alive off therapy. Response has been very good for both arms (92-94%, not a statistically significant difference at this time), as has overall survival without relapse (90% in the first year, 85% in the third through ninth years). Findings of the study so far are summarized: 1) efficacy of maintenance therapy and/or XRT are inconclusive, 2) Stages I/II have an outstanding outcome without maintenance therapy, 3) lymphoblastic lymphoma has a poorer response rate and should be treated with maintenance therapy, and 4) no significant difference in toxicity was noted between the two arms.

CONCLUSIONS

Study should remain open to report follow-up of WRAMC patients.

REPORT DATE: 09/11/92 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: Ongoing
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; 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

There have been no WRAMC registrants on this study. Groupwide, 26 patients have been registered; 21 of whom are evaluable for toxicity. Ninety percent had grade 4 white blood cell count suppression, 81% had grade 4 platelet suppression (the remaining 19% experienced grade 3 platelet suppression), 24% had grade 4 hypotension, and 24% had grade 3 anemia. Deaths on study (3) were judged to be acceptable due to factors not explained in the report forwarded to the POG. However, this was acceptable to the POG for the agenda report, and these deaths did not result in an amendment to the treatment regimen.

CONCLUSIONS

Study should remain open.

REPORT DATE: 02/03/92 WORK UNIT # 6211

DETAIL SUMMARY SHEET

TITLE: POG 8731: A Phase II Study of Low-Dose "Continuous" Oral Methotrexate in the Treatment of Children with Progressive or Recurrent Brain Tumors

KEYWORDS: methotrexate, brain tumors

PRINCIPAL INVESTIGATOR: Maybee, David COL MC

DEPARTMENT: Department of Pediatrics STATUS: Completed
SERVICE: Pediatric Hematology-Oncology Service APPROVAL DATE: Oct 1987

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

STUDY OBJECTIVE
To determine the effectiveness of this regimen and evaluate toxicity.

TECHNICAL APPROACH
Eligibility criteria include age less than 21-years-old with recurrent or progressive brain tumor, no more than one previous phase I1 agent for treatment, and measurable residual tumor.

PRIOR AND CURRENT PROGRESS
Study coordinator reported that there have been 80 patients accrued to this study (latest available report was from May 1991, to be updated this April). The one WRAMC registrant was reported on previously (died of tumor progression), and no new patients have been registered from WRAMC. Study was partially closed May 1991 due to completion of accrual goals for several strata. Study was fully closed in November 1991 due to lack of sufficient accrual on remaining open strata and due to concerns about MTX toxicity noted in one patient out of the 80 registrants. Otherwise, toxicity of this treatment is congruent with the experience of treating cancer with MTX in other pediatric patients. There was one complete response, 13 having stable disease, 5 had no measurable response, 31 had progressive disease, and 16 were not evaluable (too early or early death from disease progression).

CONCLUSIONS
Study should be considered completed at WRAMC, as data submission on the one WRAMC registrant has been completed, and there will be no further registrations at WRAMC. No WRAMC personnel are coordinators on this protocol, so it is not likely that any publications citing WRAMC staff will result from this study.

REPORT DATE: 02/03/92 WORK UNIT # 6212

DETAIL SUMMARY SHEET

TITLE: POG 8764: Chemotherapy Regimen for Early and Initial Induction Failures in Childhood Acute Lymphoblastic Leukemia, A POG Phase II Study

KEYWORDS: leukemia, lymphoblastic

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: Oct 1987

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

STUDY OBJECTIVE
To use a continuous infusion Ara-C/VM-26 induction regimen to assess remission rate and 1 year disease-free survival (DFS); and to use CDNA and oncogene probes for characterizing the unique subpopulation.

TECHNICAL APPROACH
Eligible patients must have residual disease following conventional induction therapy or have relapsed within 6 weeks after initial remission induction.

PRIOR AND CURRENT PROGRESS
There have been no registrants on this protocol from WRAMC. Groupwide, there have been 20 patients accrued. Response and disease-free survival are still masked. Toxicities were mostly hematologic, as expected: 68% of 19 evaluable patients had severe neutropenia, 79% had severe thrombocytopenia, and about 75% experienced mild to moderate anemia. Study was closed as of June 1991.

CONCLUSIONS
Study should be closed at WRAMC.

REPORT DATE: 03/31/92 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: $ 315 Previous FYs: $ 11,961 Total: $ 12,276

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

There have been 32 ACML registrants and 12 JCML registrants (none from WRAMC). There were 12 registrants on this study since the last report. The JCML stratum was closed due to completion of accrual goals with no responses and two early deaths that are currently under review. ACML resistrant toxicities are mostly mild and manageable with dose manipulation. Since the last report, there was one possible severe clinical cardiotoxicity in the face of IFN-associated autoimmune hemolytic anemia and a viral illness (these all have been resolved). Response and survival data for ACML registrants remains masked.

CONCLUSIONS

Study should remain open.

REPORT DATE: 06/25/92 WORK UNIT # 6216

DETAIL SUMMARY SHEET

TITLE: POG 8710: Protocol for Second Induction and Maintenance in Childhood Acute Lymphoblastic Leukemia (SIMAL #5), A POG Phase III Study

KEYWORDS: lymphoblastic leukemia

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: Completed
APPROVAL DATE: May 1988

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

STUDY OBJECTIVE

a) To compare disease-free survival (DFS) of regimen including MTX/VM-26 with a control; b) To compare DFS of regimen including IFN with a control; c) To estimate and compare remission duration and toxicity in patients receiving either MTX/VM-26 or IFN as continuous therapy components; d) To determine prognostic value of clinical and biological features at relapse, including immunophenotyping and cytogenetics, all patients; IFN receptors and oncogene profile, INF patients.

TECHNICAL APPROACH

Patients are 21 years or younger and diagnosed with non-T, non-B acute lymphoblastic or undifferentiated leukemia on initial classification or non-Hodgkin's lymphoma with first marrow relapse (more than 25% blasts), first hematologic relapse, or first overt extramedullary relapse (CNS disease excluded) while receiving chemotherapy, or within 6 months of stopping therapy. Patients are not eligible for higher priority protocol. Induction is given over 4 weeks (PBDA/TTT); then patient's treatment is randomized between the three arms described in the above objective.

PRIOR AND CURRENT PROGRESS

Study was closed to accrual on May 15, 1991, with a total of 291 registrants. WRAMC registered two patients, both of whom died of progressive disease off study. The overall induction rate was 74% complete response, 5% partial response, 17% no response, and 3% increasing disease, early death, or not evaluable for analysis. Arm-specific response will remain masked until Spring of 1993. Overall, disease-free survival was 41.3% at 0-6 months, 30% at 6-12 months, and 26% at 18-24 months. By analysis of strata, patients with isolated extramedullary relapse had a better prognosis, with a disease-free rate of 84.5% at 18-24 months. Toxicity has been as expected and acceptable; mostly hematologic with associated infectious complications, transaminase elevations, and allergic reactions.

CONCLUSIONS

WRAMC patients are no longer being followed on study. Study is completed at WRAMC.

REPORT DATE: 07/01/92 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

There have been 168 patients enrolled (5 from WRAMC), 1 in this reporting year). All WRAMC patients are alive and off therapy. One has relapsed and is being treated with radiation. Protocol coordinator reports that the remission rate upon completing all eight cycles of chemotherapy is 90% (data from 118 evaluable patients). It is too early to report data on response to radiotherapy. Toxicity has been acceptable, mostly hematologic as expected, and has resulted in dose delays and dose reductions or omissions. This study completed accrual goals in March 1992. The drug DTIC became unavailable in September 1991; however, this did not affect any WRAMC registrants (drug shortage due to manufacturer's problem). It is not expected that DTIC adds significantly to treatment success based on early analysis of this and other therapy using this drug.

CONCLUSIONS

Study should remain open to allow follow up reporting of WRAMC patients. There will be no further patient accrual on this protocol.

REPORT DATE: 09/16/92 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 Group

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

There have been 482 registrants groupwide (163 since last APR); 1 from WRAMC this reporting year who is on therapy and is currently in complete remission. There has been no change in status for any of the five WRAMC registrants reported previously. Accrual is at a higher than projected rate, but there is concern about registrants assigned to BMT crossing over to the chemotherapy-only arm (shortage of BMT beds, funds, etc.), which may limit strength of comparison between the two arms. Toxicity has continued to be considerable, but is acceptable to study coordinators at POG and NCI. Toxic deaths have been due mostly to sepsis or hemorrhage during periods of myelosuppression. Response rate for 361 evaluable registrants is 85% overall. The engraftment rate for the BMT arm is 79%. There were no revisions in the treatment plan during the reporting year. Study should finish accrual in late 1992 or early 1993.

CONCLUSIONS

Study should remain open.

REPORT DATE: 02/18/92 WORK UNIT # 6224

DETAIL SUMMARY SHEET

TITLE: POG 8827: Treatment of Children with Hodgkin's Disease in Relapse, A POG Phase II Study

KEYWORDS: Hodgkin's disease, childhood, 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: Ongoing
APPROVAL DATE: Nov 1988

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

STUDY OBJECTIVE

To evaluate overall effectiveness of cytosine arabinoside, cisplatin, and VP-16 in children with Hodgkin's disease in relapse.

TECHNICAL APPROACH

Patients are under 21 yrs at diagnosis and have failed MOPP/ABVD or equivalent treatment. Hodgkin's disease must have progressed beyond consideration that radiation alone might be curative. Separate Ara-C, cisplatin, and VP-16 bolus, with IV infusion of Ara-C in between. One cycle takes 12 hrs, with a total of three injections per cycle. This is repeated every 4 wks for a total of eight cycles, with the option to add two cycles for patients who obtain a CR or PR late in therapy. Radiation therapy following CR or PR is offered on this protocol. In August 1991, the consent form was revised (and IRB approved) to include the increased risk of developing acute myelogenous leukemia after receiving the drug VP-16.

PRIOR AND CURRENT PROGRESS

Since the last annual review, there have been six patients registered on this study (total of 25 registrants); none from WRAMC. Accrual goals should be met by the end of 1992. Response to treatment remains masked, as does survival. There were 54 incidences of moderate to severe toxicities on this protocol, most of which were neutropenia and thrombocytopenia. As there have been no registrants from WRAMC, the amendment did not affect WRAMC patients (who would have received VP-16 on this study).

CONCLUSIONS

Study should remain open.

REPORT DATE: 04/17/92 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

There have been 72 patients registered groupwide; none are from WRAMC. Accrual has been slower than expected. Sixty-three registrants were evaluable for response: 67% achieved complete remission, 14% achieved a partial remission, 13% had no response, 3% had increasing disease, and 3% had early deaths on study due to disease progression. Leukopenia, thrombocytopenia, and neutropenia are the most common severe side effects experienced by 63 registrants evaluable for toxicity. Because of the nature of the treatment and the disease, these toxicities are as expected.

CONCLUSIONS

Study should remain open.

REPORT DATE: 04/10/92 WORK UNIT # 6228

DETAIL SUMMARY SHEET

TITLE: POG 8866: Polyethylene Glycol-Conjugated L-Asparaginase Vs. Native L-Asparaginase in Combination with Standard Agents as Second Line Induction Therapy for Children with Acute Lymphocytic Leukemia in Bone Marrow Relapse, Phase II Randomized Trial

KEYWORDS: PEG L-asparaginase, relapsed ALL, 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: Jan 1989

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

STUDY OBJECTIVE

To compare in a randomized trial, the efficacy, toxicity, and feasibility of administration of PEG L-asparaginase (L-asp) to native L-asp as part of chemotherapy for acute lymphatic leukemia (ALL) in second relapse; and to determine serum half life and duration.

TECHNICAL APPROACH

Patients 21 years old and younger with ALL in second marrow relapse are randomized to receive induction therapy with either PEG L-asp or with native L-asp, plus the drugs vincristine, VP-16, prednisone, ifosfamide, and intrathecal Ara-C, methotrexate, and hydrocortisone. The protocol consent form was revised in August 1991 to include the potential risk of developing acute myelogenous leukemia following treatment with VP-16 and was approved by the WRAMC HUC/IRB the same month.

PRIOR AND CURRENT PROGRESS

There have been 73 registrants accrued as of February 1992. There are no registrants from WRAMC. Response and disease-free survival remain masked. There are 67 registrants evaluable for toxicity: the most common toxicity is SGOT/PT, which occurred in 55% of the evaluable registrants, followed by fibrinogen toxicity - 28% and drug fever - 16%. In contrast to other induction regimens, this seems to be much less myelosuppressive.

CONCLUSIONS

Study should remain open.

REPORT DATE: 04/10/92 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: Ongoing
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 or less will be randomized to receive the standard chemotherapy (vincristine, Adriamycin, and cyclophosphamide) or the standard along with ifosfamide and etoposide.

PRIOR AND CURRENT PROGRESS
There have been 166 registrants entered on this study groupwide; 1 from WRAMC this past reporting year. The WRAMC registrant was transferred to another hospital shortly after beginning treatment. Response and disease-free survival remain masked. Neutropenia, which was moderate to severe in 19% of 135 subjects with evaluable toxicity data, was the most common side effect. There were no toxic deaths. This protocol was revised in October 1991, to include the recently discovered increased risk to patients after treatment with chemotherapy regimens that contain VP-16 of developing malignancy (acute myelogenous leukemia). This amendment is currently being reviewed by the WRAMC IRB. Copies of both the revised and the original consent form are attached (change is circled).

CONCLUSIONS
Study should remain open.

REPORT DATE: 04/14/92 WORK UNIT # 6230

DETAIL SUMMARY SHEET

TITLE: POG 8832: Pre-irradiation Combination Chemotherapy with Cisplatin and Ara-C for Children with Incompletely Resected Supratentorial Malignant Tumors: A Phase II Study

KEYWORDS: cisplatin, Ara-C, supratentorial malignancy

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Blaney, Sussan MAJ MC; Mosijczuk, Askold COL 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 determine toxicities of cisplatin and Ara-C given before cranial irradiation. To estimate efficacy of 15 weeks of therapy with this chemotherapy, and to establish the feasibility and completeness of second surgical resection for incompletely-resected supratentorial tumors after this initial chemotherapy.

TECHNICAL APPROACH
Patients between 3 and 21 years of age will receive 15 weeks of combination chemotherapy after initial surgical resection, followed by second surgery (if needed), and 6 weeks of radiation therapy.

PRIOR AND CURRENT PROGRESS
Accrual on this study was completed in August 1991, and the protocol closed with 68 registrants; 5 of whom are evaluable for response. Complete and partial response rates are given by histologic group; anaplastic ependymoma - 25% (CR+PR), other glial neoplasms - 12%, PNET - 36%, germ cell - 67%. There is no statistical difference between groups for survival. Survival was approximately 85% at 1 year, 45% at 18 months, and 32% at 2 years. There were no WRAMC patients registered on this protocol.

CONCLUSIONS
Study should be considered completed at WRAMC, as there were no WRAMC patients on this study, and it has closed to further accrual.

REPORT DATE: 04/21/92 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: Ongoing
APPROVAL DATE: Feb 1989

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

STUDY OBJECTIVE

1) 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). 2) To determine duration of remission using pulses of induction regimen as continuation therapy. 3) To study the relative toxicities of the two regimens.

TECHNICAL APPROACH

Pediatric patients who have failed induction or relapsed on frontline therapy. 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 is this therapy repeated at 4 week intervals. Az regimen includes this drug for 2 days of the cycle.

PRIOR AND CURRENT PROGRESS

There has been a total of 138 patients registered on this study (62 since last report). There are no new WRAMC registrants. The complete response rate is 37 out of 107 registrants evaluable for response (58 had no response, and 12 died of disease before an evaluable amount of therapy could be administered). Toxicity is significant on both regimens, mostly consisting of grades 3 and 4 thrombocytopenia, neutropenia, and infections. There has been one death on study due to infection. Survival drops rapidly during the first year post-therapy and has not been documented yet for 18 months post therapy. The consent form is in the process of being revised to include the risk that VP-16 has been reported to cause acute myelogenous leukemia in patients who have completed treatment with chemotherapeutic regimens containing this drug.

CONCLUSIONS

Study should remain open.

REPORT DATE: 05/18/92 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

There have been 314 registrants enrolled on study, 6 from WRAMC. Interviews of 258 patients/parents have been completed, and 159 of the case-control interviews have been completed. Study is progressing as planned.

CONCLUSIONS

Study should remain open.

REPORT DATE: 05/18/92 WORK UNIT # 6238

DETAIL SUMMARY SHEET

TITLE: POG 8889 Intergroup Rhabdomyosarcoma Study-IV: Pilot Study for Clinical Group IV Disease

KEYWORDS: rhabdomyosarcoma, chemotherapy

PRINCIPAL INVESTIGATOR: Maybee, David COL MC

DEPARTMENT: Department of Pediatrics STATUS: Completed
SERVICE: Pediatric Hematology-Oncology Service APPROVAL DATE: Apr 1989

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

STUDY OBJECTIVE
To determine feasibility/toxicity of ifosfamide and doxorubicin (ID) as induction chemotherapy and, subsequently, in combination with vincristine, actinomycin-D, and cyclophosphamide (VAC) as maintenance chemotherapy, to treat rhabdomyosarcoma and its variants. This regimen is to be piloted for its possible incorporation into the three-arm IRS-IV study to follow.

TECHNICAL APPROACH
Patients, ages 21 years and younger, with no prior treatment of clinical group IV rhabdomyosarcoma, extraosseous Ewing's, or undifferentiated sarcoma will be given the chemotherapy described above.

PRIOR AND CURRENT PROGRESS
There have been a total of 155 eligible patients registered on this study; none from WRAMC. Study was closed in October 1991. The overall response rate is 64%, which is comparable to previous intergroup rhabdomyosarcoma studies for this clinical group. Toxicity has been considerable, with dose changes being required for nephrotoxicity in a significant number of patients. Myelosuppression was the most common toxicity seen; it occurred in 82% of the study registrants. There were infectious complications in 35 patients that were fatal in 4 patients.

CONCLUSIONS
The study is completed. There were no WRAMC patients registered.

REPORT DATE: 06/23/92 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
SERVICE: Pediatric Hematology-Oncology Service

STATUS: Ongoing
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 three years.

PRIOR AND CURRENT PROGRESS

In the last reporting year, there have been no new WRAMC patients accrued. There are a total of 212 registrants groupwide (7 from WRAMC). Ninety-seven are on POG 8625, and 115 are on POG 8725. Of the 121 patients who were on one of these therapeutic studies prior to this study's opening, only 21 are registered. Of the 260 total patients registered on those therapeutic studies after that date, 191 (73%) are in POG 8828. Although this study will not achieve its original accrual goals, it still has the potential to yield important data on the late effects of Hodgkin's disease and its treatment.

CONCLUSIONS

Study should remain open.

REPORT DATE: 06/23/92 WORK UNIT # 6243

DETAIL SUMMARY SHEET

TITLE: POG 8863 High Dose Cytosine Arabinoside in the Treatment of Advanced Childhood Tumors Resistant to Conventional Therapy, Phase II

KEYWORDS: recurrent/refractory, solid tumors, cytosine arabinoside

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Blaney, Susan MAJ; Edwards, E. Glenn MAJ MC

DEPARTMENT: Department of Pediatrics
SERVICE: Pediatric Hematology-Oncology Service

STATUS: Ongoing
APPROVAL DATE: May 1989

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

STUDY OBJECTIVE

To determine efficacy and toxicity of various advanced refractory solid tumors to high-dose Ara-C (HDAC).

TECHNICAL APPROACH

Patients are 21 years and younger at diagnosis with biopsy-proven, measurable, malignant solid tumor, life expectancy greater than six weeks, adequate nutritional status, blood counts, renal and hepatic function, and no previous HDAC. HDAC is given over 3 days, with about 3 weeks in between cycles.

PRIOR AND CURRENT PROGRESS

There have been 47 patients registered on study, which closed December 9, 1991, due to completion of accrual goals. All patients had previous treatment; 24 had prior XRT, and 3 had received bone marrow transplants. Short-term clinically detectable side effects of HDAC in this group have been: myelosuppression, most likely exaggerated by lower than normal bone marrow reserves due to prior prescription; nausea/vomiting; elevated transaminases (mild); and stomatitis. There was one case of central nervous system toxicity rated as severe; however, it occurred in a patient with severe sodium loss. No WRAMC patients were registered on this study.

CONCLUSIONS

Study should remain open for one more year to report response data.

REPORT DATE: 06/23/92 WORK UNIT # 6244

DETAIL SUMMARY SHEET

TITLE: POG 8865 Recombinant Alpha Interferon in Relapsed T-Cell Disease: A Phase II Study

KEYWORDS: interferon, T-cell, malignancy

PRINCIPAL INVESTIGATOR: Maybee, David COL MC
ASSOCIATES: Blaney, Susan MAJ MC; Mosijczuk, Askold COL MC

DEPARTMENT: Department of Pediatrics STATUS: Ongoing
SERVICE: Pediatric Hematology-Oncology Group APPROVAL DATE: May 1989

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

STUDY OBJECTIVE
To assess response rate of T-cell malignancy to alpha-IFN (<-IFN) who have failed standard therapy. To correlate response rate to presence of IFN receptors, oncogene receptors, modulation of oncogene expression, modulation of oncogene expression by IFN, DNA content, and antiproliferative effect of IFN in-vitro on T-cell lymphoblasts.

TECHNICAL APPROACH
Patients 21 years and younger with refractory T-cell disease in second marrow relapse, meeting entry requirements concerning previous therapy, and with no evidence of serious uncontrolled infection are eligible for this study. Induction of triple intrathecal methotrexate, high-dose cytoxan, and Ara-C is given and continued with pulse maintenance therapy. Induction IFN is given for 5 days x 2 weeks, followed by 3 x week maintenance course.

PRIOR AND CURRENT PROGRESS
There are no WRAMC patients registered on this study. Groupwide, there have been 19 patients registered as of May 1991 (last study coordinator report). Toxicity reports remain the same as last APR. Most commonly seen are infections, nausea, vomiting, transaminase elevations, diarrhea, and decreased coagulation factors. Response data remain masked.

CONCLUSIONS
Study should remain open.

REPORT DATE: 06/25/92 WORK UNIT # 6249

DETAIL SUMMARY SHEET

TITLE: POG 8788: Intergroup Rhabdomyosarcoma Study IV: A Pilot Study for Clinical Group III Disease

KEYWORDS: childhood, rhabdomyosarcoma

PRINCIPAL INVESTIGATOR: Maybee, David COL MC

DEPARTMENT: Department of Pediatrics STATUS: Completed
SERVICE: Pediatric Hematology-Oncology Service APPROVAL DATE: Jun 1989

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

STUDY OBJECTIVE
Pilot study comparing feasibility and toxicity of vincristine/Adriamycin/cytoxan (VAC), or vincristine/Adriamycin/ifosfamide (VAI), or vincristine/ifosfamide/VP-16 (VIE) used with hyperfractionated radiation therapy.

TECHNICAL APPROACH
Patients 21 years old or younger, with clinical group III RMS or extraosseous Ewing's sarcoma, are assigned a treatment regimen according to the institution's assigned regimen (WRAMC uses VAI) randomized between the above mentioned three-drug regimens. Favorable histology head/neck or genitourinary tumors that would be eligible for IRS III are ineligible for this study, as are patients who had prior radiation or chemotherapy. Induction therapy is 16 weeks of chemotherapy and radiation, with continuation therapy of 20-99 weeks of chemotherapy.

PRIOR AND CURRENT PROGRESS
This study was closed in August 1991. There were 319 registrants, none from WRAMC. Results from this pilot study have been incorporated into the current Intergroup Rhabdomyosarcoma Study. The VIE regimen had a 98% response rate, the VAI regimen had a 85% response rate, and the VAC regimen had a 59-89% response rate (depending on cyclophosphamide dose-escalation group). There have been 135 evaluable registrants who have received the radiation portion of the treatment plan. It appears that there is significant myelosuppression following completion of radiation therapy, which has delayed the administration of maintenance chemotherapy that was planned to be given directly following radiation. There were 10 toxic deaths on study, mostly due to infections during periods of myelosuppression.

CONCLUSIONS
Study should be closed at WRAMC.

REPORT DATE: 07/01/92 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: Ongoing
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. 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

There have been 44 patients enrolled on this study groupwide (none from WRAMC). Accrual rate is now 16 subjects per year, somewhat behind the projected 20 per year. There have been seven patients who have had disease and have gone on to be treated on POG 8936. Fifteen of the registrants enrolled with progressive disease went on immediately to receive therapy on POG 8936.

CONCLUSIONS

Study should remain open.

REPORT DATE: 07/01/92 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
SERVICE: Pediatric Hematology-Oncology Service

STATUS: Ongoing
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

There have been 18 patients enrolled on this study. It is too early to report response data on this group. Therapy has been well tolerated. The worst toxicity that has occurred is thrombocytopenia. There have been no WRAMC registrants.

CONCLUSIONS

Study should remain open.

REPORT DATE: 02/18/92 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: Ongoing
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

There are 82 registrants on this study (none from WRAMC), 67 of whom were registered since the last annual review. Out of 36 patients evaluable for response (treatment-specific response is masked), there were 19 complete responses, 6 partial responses, 2 without a response, 7 with progressive disease, and 2 who died of progressive disease before response was measurable. Toxicities have been as expected and none of the three treatment regimens on this protocol have needed to be modified to lessen toxicity.

CONCLUSIONS

Study should remain open.

REPORT DATE: 04/07/92 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: Blaney, Susan MAJ MC; Edwards, E. Glenn MAJ 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
Since the last report, there have been no WRAMC registrants. Groupwide, there have been 70 tissue samples submitted for this study (45 since last report), of which 12 have been registered for use of this protocol. This study requires that the tissue be that of a POG front-line therapeutic study patient. Study coordinators otherwise would not be able to correlate cytogenetics with therapeutic outcome.

CONCLUSIONS
Study should remain open.

REPORT DATE: 04/23/92 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

There have been 116 registrants groupwide; 5 from WRAMC. Accrual is expected to be completed in 2 years. Cases are now being characterized for loss of several chromosomes. Tumors are also being assayed for expression WT1, the putative Wilms' tumor gene. Correlations between these molecular characteristics and relapse-free survival will be carried out when the first 125 cases have a mean follow-up of 1 year post diagnosis, in the event that significant differences emerge prior to full accrual.

CONCLUSIONS

Study should remain open.

REPORT DATE: 04/22/92 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
There have been 297 registrants entered on this study groupwide; 1 from WRAMC. Cytogenetic studies are underway; however, an analysis of overall results has not been done yet.

CONCLUSIONS
Study should remain open.

REPORT DATE: 05/05/92 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 STATUS: Ongoing
SERVICE: Pediatric Hematology-Oncology Service 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
There have been 94 registrants entered on this study so far; one from WRAMC. The WRAMC patient completed therapy and remains in remission. Response and disease-free survival data remain masked. Toxicity has been as expected for these drugs: out of 90 patients evaluable for toxicity, 21% have had neutropenia, 7% have had nausea, and 6% have had hearing loss.

CONCLUSIONS
Study should remain open.

REPORT DATE: 05/27/92 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
ASSOCIATES: McFarland, Janetta MAJ AN

DEPARTMENT: Department of Pediatrics
SERVICE: Pediatric Hematology-Oncology Service

STATUS: Ongoing
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

There have been 716 registrants accrued. Since last Annual Progress Report, five WRAMC registrants have been accrued. A total of 15 families have registered and completed the questionnaire. No further data is reported at this time.

CONCLUSIONS

Study should remain open.

REPORT DATE: 06/23/92 WORK UNIT # 6269

DETAIL SUMMARY SHEET

TITLE: POG 9060 Intensive QOD Ifosfamide for the Treatment of Children with Recurrent or Progressive CNS Tumors, Phase II

KEYWORDS: ifosfamide, recurrent brain 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: Ongoing
APPROVAL DATE: May 1990

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

STUDY OBJECTIVE

To determine the activity of ifosfamide delivered QOD (i.e., M,W,F) in the treatment of children with recurrent/progressive CNS tumors, to evaluate toxicity of this regimen, especially neurotoxicity for patients with (1) no prior cisplatin therapy, (2) prior cisplatin with a total dose less than 300 mg/M2, and (3) prior cisplatin with a total dose greater than 300 mg/M2.

TECHNICAL APPROACH

Patients 21 years old and less with primary intracranial tumor are given ifosfamide three times a week every 21 days as long as the patient continues to demonstrate at least stable disease.

PRIOR AND CURRENT PROGRESS

There have been no WRAMC patients registered on this study. Groupwide, 69 registrants have been enrolled. Toxicity data is available for 59 patients. Response remains masked in this Phase II trial. Hematologic toxicity has been as expected, with about a 21 day (+/- 5 days) recovery time for blood counts. One heavily pretreated registrant became pancytopenic after the first cycle, never recovering blood counts, and died of sepsis. Other toxicities have been acceptable and as expected.

CONCLUSIONS

Study should remain open.

REPORT DATE: 06/25/92 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 STATUS: Ongoing
SERVICE: Pediatric Hematology-Oncology Service 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
There have been 51 registrants entered on study (none from WRAMC). Toxicity has been acceptable with no major toxic events. Both response and disease-free survival are masked in this study.

CONCLUSIONS
Study should remain open.

REPORT DATE: 06/25/92 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
There have been 41 patients enrolled on study (1 from WRAMC, still on therapy). All patients have entered complete response, and there have been two subsequent relapses. Toxicity during consolidation has been significant, and G-CSF was added to the protocol in December 1991. It is too early to report whether this has shortened periods of neutropenia. Significant myelotoxicity has also been seen following craniospinal irradiation, resulting in delays in starting maintenance therapy. There was one death on study due to an infection during a period of neutropenia (which led to the addition of G-CSF to the protocol). To date, the IV 6-MP infusion is being given over 40 hours, which has changed the time listed on the consent form for this drug administration (amendment submitted to IRB on June 12, 1992).

CONCLUSIONS
Study should remain open.

REPORT DATE: 07/01/92 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.

PRIOR AND CURRENT PROGRESS

There have been 52 registrants enrolled on this study. One patient from WRAMC has been enrolled and is currently on therapy and doing well. Treatment is generally well tolerated. The severe toxicities that have occurred are neutropenia and thrombocytopenia. Response is masked. Progression-free survival for 0-6 months is 93.8%.

CONCLUSIONS

Study should remain open.

REPORT DATE: 04/10/92 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
SERVICE: Pediatric Hematology-Oncology Service

STATUS: Ongoing
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 children 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 628 registrants groupwide as of November 1991. WRAMC has registered six patients. There have been 48 cases in which this protocol uncovered possible problems with disease classification.

CONCLUSIONS

Study should remain open.

REPORT DATE: 04/10/92 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.

PRIOR AND CURRENT PROGRESS

There have been 291 registrants groupwide, 3 from WRAMC. Accrual rates are faster than predicted, allowing the third regimens to be activated (currently pending IRB approval at WRAMC). Treatment response has been between 96%-100%, depending on stratum. Two of the WRAMC patients were transferred to other hospitals before response could be evaluated, and the other WRAMC registrant is still in remission on therapy. Study coordinators report that it is too early to evaluate disease-free survival and to report on toxicity data.

CONCLUSIONS

Study should remain open.

REPORT DATE: 04/10/92 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 Fronnt 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 STATUS: Ongoing
SERVICE: Pediatric Hematology-Oncology Service 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 151 registrants to date, 3 from WRAMC. Accrual is at a faster rate than expected and an amendment to the statistical section of this protocol is currently being submitted to the NCI to allow better analysis. Response has been good -- between 75%-100%, depending on the stratum. It is too early in the study to report event-free survival and toxicity. Two of the WRAMC patients are still on this therapy and remain in complete remission, and one patient relapsed on therapy and has been taken off this study.

CONCLUSIONS

Study should remain open.

REPORT DATE: 05/06/92 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 STATUS: Ongoing
SERVICE: Pediatric Hematology-Oncology Service 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).

PRIOR AND CURRENT PROGRESS

There have been 19 patients entered on this study; 1 from WRAMC. The WRAMC registrant died of progressive disease. Five registrants received regimen 1, with objective responses seen in all. This regimen closed May 1991 due to excessive kidney toxicity (failure requiring dialysis). Response to other regimens are masked. No toxic deaths have been observed. Study coordinators reported that the three regimen 1 patients who had kidney toxicity had been pre-treated with cisplatin. Accrual is currently on regimen 3.

CONCLUSIONS

Study should remain open.

REPORT DATE: 05/05/92 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: Ongoing
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, 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 have received 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.

PRIOR AND CURRENT PROGRESS
There have been 17 registrants enrolled on this study (none from WRAMC). In 9 registrants evaluable for response, there have been 8 complete responses. One patient was declared ineligible for the study. Toxicity has been acceptable, mostly hematologic, with infectious complications in several registrants. One registrant died of infection on study. The protocol coordinators are in the process of adding the drug GM-CSF to the treatment regimen to explore its role in reducing toxicity.

CONCLUSIONS
Study should remain open.

REPORT DATE: 05/27/92 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 STATUS: Ongoing
SERVICE: Pediatric Hematology-Oncology Service 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.

PRIOR AND CURRENT PROGRESS
There have been 13 patients registered on this study, to date (none from WRAMC). Study coordinator reports that there have been no unexpected adverse reactions to therapy offered on this study. Response has been good, with only one registrant relapsing.

CONCLUSIONS
Study should remain open.

REPORT DATE: 06/25/92 WORK UNIT # 6288

DETAIL SUMMARY SHEET

TITLE: POG 9110: SIMAL #6: Rotational Drug Therapy After First Marrow Relapse of Non-T, Non-B ALL: Pediatric Oncology Group Pilot Study for a Phase III Trial

KEYWORDS: second induction, chemotherapy, leukemia

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: Jun 1991

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

STUDY OBJECTIVE
To determine feasibility and toxicity of continuous infusion doxorubicin when given as a single agent for ALL in first relapse; to assess feasibility and toxicity of a rotating weekly parenteral drug regimen for continuing remission; and to estimate the leukemic cell kill of continuous infusion doxorubicin.

TECHNICAL APPROACH
Patients 21 years of age and less at the time of initial diagnosis with ALL, in first marrow relapse while receiving chemotherapy or after cessation of therapy, will be given continuous infusion doxorubicin to induce remission, followed by 105 weeks of continuation therapy with standard anti-leukemia drugs.

PRIOR AND CURRENT PROGRESS
There have been 72 patients registered on this study as of February 1992 (2 from WRAMC). The response rate has been 89% complete response and 11% no response. Toxicity has been acceptable; mostly hematologic with associated infections. Both WRAMC patients are off therapy. One has died of progressive disease, and one was removed from protocol to receive autologous bone marrow transplant therapy after having complete response to induction therapy on protocol.

CONCLUSIONS
Study should remain open.

REPORT DATE: 06/25/92 WORK UNIT # 6289

DETAIL SUMMARY SHEET

TITLE: POG 9139: A Dose-Escalating Study of Cisplaltin Used Concomitantly with Hyperfractionated Irradiation in the Treatment of Children with Newly Diagnosed Brain Stem Glioma Cancer: A Phase I Study

KEYWORDS: cisplatin, childhood, brain stem glioma

PRINCIPAL INVESTIGATOR: Maybee, David COL MC

DEPARTMENT: Department of Pediatrics STATUS: Completed
SERVICE: Pediatric Hematology-Oncology Service APPROVAL DATE: Jun 1991

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

STUDY OBJECTIVE
To determine the acute and subacute toxicities associated with continuous infusion cisplatin to be used as a radiosensitizer simultaneously with hyperfractionated radiotherapy; and to establish the cisplatin dose level for this treatment plan.

TECHNICAL APPROACH
Patients between the ages of 3 and 21 years of age with newly diagnosed glial tumor will be given continuous infusion cisplatin with hyperfractionated radiation therapy. Dose escalations will be done when at least three patients have been evaluated at the starting dose and will continue until the maximum tolerated dose is reached (no more than three dose escalations are to be done). Dose limiting toxicities are defined as: serum creatine greater than twice baseline, neutropenia (less than 200 ANC), and grade 4 thrombocytopenia. As this is a poor prognosis group, ototoxicity will not be used as a dose-limiting toxicity.

PRIOR AND CURRENT PROGRESS
As of February 1992, there were 16/17 patients who had completed planned therapy. The third dose level had been reached. One patient on dose level three died on therapy due to a hemorrhage within the tumor, and one patient on dose level three had a grade 4 neutropenia after the second course of cisplatin. Otherwise, no excessive hematologic, renal, audiologic, or other toxicities were reported. Study was completed in May 1992. The maximum tolerated dose was incorporated into a Phase III trial which randomizes between hyperfractionated and conventional schedule radiotherapy. This protocol is currently being reviewed by the WRAMC IRB (POG 9239). There were no WRAMC patients enrolled on this Phase II trial.

CONCLUSIONS
Study should be closed.

REPORT DATE: 07/01/92 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
SERVICE: Pediatric Hematology-Oncology Service

STATUS: Ongoing
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).

PRIOR AND CURRENT PROGRESS

There have been five registrants entered as of February 1991, plus one WRAMC registrant who was enrolled at the end of May. The WRAMC patient is currently on therapy. It is too early to report other data.

CONCLUSIONS

Study should remain open.

REPORT DATE: 07/01/92 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 9035, the pre-radiation chemotherapy protocol.

PRIOR AND CURRENT PROGRESS

There has been one patient registered on this study groupwide, which is expected. The WRAMC patient on the chemotherapy study (POG 9035), which precedes radiation therapy on this study, has not yet reached a point in therapy where this protocol can be offered.

CONCLUSIONS

Study should remain open.

REPORT DATE: 07/01/92 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: Ongoing
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.

PRIOR AND CURRENT PROGRESS
There have been 17 patients enrolled on this study groupwide; none from WRAMC. There has been no incidence of serious or unexpected adverse reactions reported, to date, by the POG. It is too early to report further data.

CONCLUSIONS
Study should remain open.

REPORT DATE: 08/24/92 WORK UNIT # 6296

DETAIL SUMMARY SHEET

TITLE: POG 9150 Intergroup Rhabdomyosarcoma Study IV: STAGE 1 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.

PRIOR AND CURRENT PROGRESS

There have been no WRAMC registrants on this study in the reporting year. Study coordinators report that it is too early to provide data on this study.

CONCLUSIONS

Study should remain open.

REPORT DATE: 08/24/92 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 STATUS: Ongoing
SERVICE: Pediatric Hematology-Oncology Service 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.

PRIOR AND CURRENT PROGRESS
There have been no WRAMC registrants. Study coordinators have not provided a report to date -- one is expected in October of 1992.

CONCLUSIONS
Study should remain open.

REPORT DATE: 03/04/92 WORK UNIT # 3600

DETAIL SUMMARY SHEET

TITLE: Determination of Noncompliance in Prescription Pickup

KEYWORDS: non-compliance, prescription

PRINCIPAL INVESTIGATOR: Nelson, Bruce COL MS
ASSOCIATES: Buchanan, Terry MAJ MS

SERVICE: Pharmacy Service STATUS: Ongoing
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
While some progress has been made on part one of the study, part two of the study has been suspended due to the transfer of the original principal investigator. We request that the study remain in the "ongoing" status while we decide when and who will proceed with the study.

CONCLUSIONS
No conclusions have been made.

REPORT DATE: 06/15/92 WORK UNIT # 3601

DETAIL SUMMARY SHEET

TITLE: Evaluation of the Effect of Clinical Pharmacists on Inpatient Health Care Outcomes

KEYWORDS: clinical pharmacist, intervention, mortality

PRINCIPAL INVESTIGATOR: Bjornson, Darrell LTC MS
ASSOCIATES: Hiner, William COL MS; Potyk, Roger LTC MS

SERVICE: Pharmacy Service STATUS: Completed
APPROVAL DATE: May 1990

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

STUDY OBJECTIVE
To estimate the effect of clinical pharmacist intervention on patient length of stay, patient drug cost per admission, and mortality in the medical and surgical inpatient population.

TECHNICAL APPROACH
This will be an experimental study comparing patients followed by medical care teams with clinical pharmacists (two general medicine and one general surgery team) with concurrent, non-randomized control groups of patients who will be followed by medical care teams without clinical pharmacists (three general medicine and two general surgery teams). Three clinical pharmacists will be randomly assigned to each of two teams on the general medicine wards and one team on the general surgery ward. The clinical pharmacist in the Hematology/Oncology area will continue to function in that area, and data on his patients will be compared with regional norms.

PRIOR AND CURRENT PROGRESS
The study began in October 1990 and will continue through January 1992, with 3,638 patients followed. Analysis and interpretation of the data will occur following the application of the severity of illness level to each patient. This is presently being done with a civilian contractor and the Patient Administration Systems and Biostatistical Activity (PASBA) at Ft. Sam Houston, TX. There have been three presentations on the progress of the study to the American Society of Hospital Pharmacists (ASHP) Advisory Committee (Dec 90, Apr 91, Dec 91). The methodology was presented at the Federation of International Pharmacy Meeting (Sep 91) and ASHP Clinical Midyear Meeting (Dec 91). Final results will be presented at the ASHP Midyear Clinical Meeting in December 1992.

CONCLUSIONS
No conclusions can be drawn from the data until the patient severity of illness level is applied. Data analysis will proceed in the Fall. Final results will be presented in December 1992, at which time the study will be completed.

REPORT DATE: 07/24/91 WORK UNIT # 3602

DETAIL SUMMARY SHEET

TITLE: Demographic Evaluation of Prescription Utilization and Expenditures in a Military Health Facility

KEYWORDS: prescription, expenditures (costs), utilization

PRINCIPAL INVESTIGATOR: Davies, William MAJ MS

SERVICE: Pharmacy Service STATUS: Completed
APPROVAL DATE: Apr 1991

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

STUDY OBJECTIVE

To quantitatively describe drug utilization and costs for patients using a military medical facility, according to their age and sex; to demonstrate the impact of demographic considerations in budgeting and allocating funds for pharmacy services at military medical facilities; and to compare utilization and costs within a military health care facility for patients receiving their prescriptions exclusively from civilian physicians versus military prescribers.

TECHNICAL APPROACH

A restrospective analysis of randomly sampled ambulatory medication profiles of members of the Kimbrough Army Community Hospital, Tri-Service Microcomputer Pharmacy System (TMPS), 1 July 1989 through 30 June 1990. One hundred patients, 50 male and 50 female, were selected for 10 different age groups; <6, 6-18, 19-24, 25-44, 45-54, 55-64, 65-69, 70-74, 75-79, >80 years. Entire samples were used if the groups contained <50 patients. Exclusion criteria included any patient who received prescriptions from the WRAMC Pharmacy. The number of prescriptions, number of different drugs, total prescription costs, patient age, and sex were entered into a data base for statistical analysis.

PRIOR AND CURRENT PROGRESS

There were 984 medication profiles reviewed; 174 patients were excluded. Only 34 women met criteria for females >80 years. Prescription use/cost increased with age, with significant variations among age groups based on Tukey's test. A significant difference in use/cost between the sexes was found, but no clear pattern could be verified. Prescription costs doubled over three consecutive age groups (25-44, 45-54, 55-64), from $52.99+/-$104.68 to $181.82+/-$299.61. Patients in the age groups >45 years who presented prescriptions only from civilian physicians had significantly lower use/costs than patients of military prescribers, although average costs were slightly higher for some age groups.

CONCLUSIONS

Demographic variables are important in the military health system with planned active duty force reduction, and growth and aging of retired military population. Computer programs capable of monitoring, analyzing, and reporting use/costs of ambulatory prescription services based on demographics could be used for budget analysis and forecasting. More research is needed to find reason for differences between use/costs generated by military vs. civilian prescribers.

REPORT DATE: 01/22/92 WORK UNIT # 9609

DETAIL SUMMARY SHEET

TITLE: Radial Nerve F Wave Study

KEYWORDS: F wave response, radial nerve, extensor indicus proprius

PRINCIPAL INVESTIGATOR: Bryant, Philip MAJ MC
ASSOCIATES: Robinson, Michael CPT MC; Fujimoto, Ronald MAJ MC

SERVICE: Physical Medicine and Rehabilitation Service STATUS: Ongoing
APPROVAL DATE: Nov 1988

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

STUDY OBJECTIVE
To obtain a normal latency value for the radial nerve F wave.

TECHNICAL APPROACH
A mean latency value (in milliseconds) will be determined for the F response of the extensor indicus proprius (EIP) muscle, innervated by the radial nerve. Values will be standardized by height. A technique of surface stimulation with cathode placement lateral to the biceps tendon at the flexion crease of the antecubital fossa and surface recording over the EIP muscle will be employed. A Disa 1500 electrodiagnostic machine will be used to provide the stimulation and recording of the F response.

PRIOR AND CURRENT PROGRESS
This study has been delayed by the departure of the principal investigator from the military. Upon reevaluation, it was determined by the statistical consultants in DCI that a minimum of 51 subjects would be necessary to provide statistical significance. Radial F wave response studies were performed on 41 subjects, bilaterally. Ten further studies are planned and should be completed within the next month. No serious or unexpected adverse reactions have occurred as a result of this study. Healthy subjects, no patients, were involved in this study. Statistical analysis will be completed upon accrual of the 10 outstanding subjects.

CONCLUSIONS
Pending statistical analysis of the results.

REPORT DATE: 02/19/92 WORK UNIT # 9612

DETAIL SUMMARY SHEET

TITLE: Epidemiology of Injuries Requiring Physical Therapy During Operation Desert Shield

KEYWORDS: Desert Shield, injuries, physical therapy

PRINCIPAL INVESTIGATOR: Sweeney, Jane COL SP

SERVICE: Physical Medicine and Rehabilitation Service STATUS: Ongoing
APPROVAL DATE: Nov 1990

FUNDING: Current FY: $ 2,058 Previous FYs: $ 0 Total: $ 2,058

STUDY OBJECTIVE
To describe characteristics of injuries requiring physical therapy in mobilized personnel during Operation Desert Shield/Storm in Southwest Asia; to relate injury data to soldier demographics; and to survey workload, work hours, military duties, and professional activities during deployment.

TECHNICAL APPROACH
Injury characteristics, recovery patterns, and patient demographic data will be collected on all new patients evaluated by Army physical therapists from three units in Southwest Asia (47th Field Hospital, 300th Field Hospital and 50th General Hospital) and from three evacuation units in Germany (98th, 97th, and 2nd General Hospitals).

PRIOR AND CURRENT PROGRESS
Preliminary data from 233 Physical Therapy subjects at the 47th Field Hospital (Bahrain) during October-December 1990 revealed the following trends: a) patient profile: male (87%), Caucasian (65%), 28 years of age, 7.1 years in the military, injured 9.9 weeks after deployment; b) musculoskeletal injuries located in legs (52%), spine (41%), arms (7%); c) 90% returned to duty after average treatment duration of 8.3 days; and d) 23% were deployed with pre-existing musculoskeletal disorders.

CONCLUSIONS
Early physical therapy management in a field environment was instrumental in returning and maintaining mobilized service members at duty after sustaining musculoskeletal injuries.

REPORT DATE: 01/13/92 WORK UNIT # 9613

DETAIL SUMMARY SHEET

TITLE: The Effects of a Clinical Reasoning Development Program on Documentation and Staff Morale: A Multi-site Study for Program Evaluation

KEYWORDS: clinical reasoning, morale, burnout

PRINCIPAL INVESTIGATOR: Sinnott, Melissa MAJ SP

SERVICE: Physical Medicine and Rehabilitation Service STATUS: Completed
APPROVAL DATE: Nov 1990

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

STUDY OBJECTIVE
To evaluate the effects of a clinical reasoning development program on the morale of occupational therapists and the content of their documentation.

TECHNICAL APPROACH
Intervention will include both didactic presentation of material related to clinical reasoning and an experiential component, with analysis of videotaped treatment sessions. Tests include personality and burnout inventories and a work environment scale. Documents to be coded and analyzed include OT discharge summaries and case narratives generated by the study participants.

PRIOR AND CURRENT PROGRESS
Data has been collected at all three data points. For last data point, all instruments were administered per protocol, and case narratives were collected. Currently awaiting inpatient records from patients recently discharged to obtain OT discharge summaries.

CONCLUSIONS
Document coding and data analysis are ongoing. Incomplete conclusions at this time.

REPORT DATE: 01/2[illegible] 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 CPT MC

SERVICE: Physical Medicine and Rehabilitation Service STATUS: Ongoing
APPROVAL DATE: Feb 1991

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

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
The study has progressed well. We have collected data at five major Army medical centers on 227 subjects. There have been no adverse effects, as this was survey information. There have been no benefits derived for the current patient population.

CONCLUSIONS
The casualties referred to physical medicine services primarily were referred from Orthopaedic Service, and the primary reasons for referral were musculoskeletal injuries and electrodiagnostic evaluations. Peripheral nerve injuries were a common cause of functional deficit. Functional impairments were common, with ambulation problems being the most common.

PEPORT DATE: 04/06/92 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, reflex

PRINCIPAL INVESTIGATOR: Marin, Raul CPT MC
ASSOCIATES: Kishbaugh, David MAJ MC; Kirk, Kevin LTC MC

SERVICE: Physical Medicine and Rehabilitation Service STATUS: Ongoing
APPROVAL DATE: Mar 1991

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

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, as well as 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
The total number of subjects required in the protocol was 50 normals and 20 L5 radicular patients. So far, 70 subjects have been evaluated. Of these, 51 are defined as normals, 12 as L5 radiculopathies, 6 as S1 radiculopathies, and 1 as L4 radiculopathy. Of the 51 normals, 6 have been retested; 1 was retested by two examiners. There are still seven additional subjects that have been evaluated in a blind fashion, but whose diagnosis has not been supplied by the Neurosurgery Service. Only six more normal subjects and eight L5 radiculopathy subjects remain to be recruited. These latter ones may be found within the seven subjects not yet identified by Neurosurgery. No subjects have had any adverse side effects requiring withdrawal from the study. No patients have personally benefited from this study.

CONCLUSIONS
So far, even though the data has not been fully analyzed, it appears that the EDB deep tendon reflex is not a sensitive measure of L5 radiculopathy. The specificity of the test still needs to be defined.

REPORT DATE: 07/02/92 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: Ongoing
APPROVAL DATE: Jun 1991

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

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 he 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
Questionnaires (58) were distributed to the 1991-92 Intern Class at all four intervals, and data collection is complete. There was a 100% response rate for the first two intervals and approximately a 25% response rate for each of the latter two. Similarly, questionnaires (45) were distributed to the 1992-93 Intern Class pre- and post-orientation, with a 100% return rate. Analysis of data will begin in July.

CONCLUSIONS
Conclusions are pending data analysis.

REPORT DATE: 08/14/92 WORK UNIT # 1326-90

DETAIL SUMMARY SHEET

TITLE: Predictors of Thyroid Dysfunction in Patients Treated with Lithium

KEYWORDS: lithium, thyroid, predictors

PRINCIPAL INVESTIGATOR: Joslin, Scott CPT MC
ASSOCIATES: Burman, Kenneth COL MC; Wartofsky, Leonard COL MC

DEPARTMENT: Department of Psychiatry

STATUS: Completed
APPROVAL DATE: Sep 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 34 Total: $ 34

STUDY OBJECTIVE
To prospectively determine the incidence of anatomical or functional thyroid disease in patients treated with lithium (Li) over the course of 1 year. To determine what factors by history, biochemical status, autoimmune status, and functional status may predict the course of dysfunction over the course of 1 year. To evaluate changes in iodine content of the thyroid in Li patients.

TECHNICAL APPROACH
Evaluation of 100 patients who are being treated for the first time with Li with thyroid function testing, TSI, TBII, physical examination, ultrasound, fluorescent iodine scanning, and serial Li level analysis at the initiation of Li treatment, and again after 2 months, 6 months, and 1 year.

PRIOR AND CURRENT PROGRESS
The fluorescent iodine scanner went out of service approximately 1 year ago and has been determined not serviceable. With the relocation of the Kyle Metabolic Unit, the storage area for the machine and testing was also lost. No patients have been enrolled; the study has been terminated.

CONCLUSIONS
None.

REPORT DATE: 07/14/92 WORK UNIT # 7239

DETAIL SUMMARY SHEET

TITLE: Visual Information Processing in Psychiatric Patients

KEYWORDS: vision, acuity, schizophrenia

PRINCIPAL INVESTIGATOR: Blair, Sidney CAPT MC

DEPARTMENT: Department of Psychiatry STATUS: Ongoing
APPROVAL DATE: Jul 1988

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

STUDY OBJECTIVE
To compare vernier visual acuity in normal subjects and in psychiatric patients.

TECHNICAL APPROACH
Subjects attempt to discriminate computer-generated vernier stimuli. Responses are tallied and analyzed by computer.

PRIOR AND CURRENT PROGRESS
Prior work evaluated visual stimulus parameters and interaction patterns of visual and auditory stimuli. Current work is directed at instrumentation for presentation of auditory stimuli of varying parameters for the purpose of defining tonal difference thresholds and temporal interference patterns. No new subjects were enrolled in the last year; total enrollment to date is 16. There were no serious or unexpected reactions or subjects withdrawn from the study. There were no benefits to subjects.

CONCLUSIONS
Preliminary work with tonal difference thresholds, as evaluated by computer-generated stimuli, is in good agreement with the results obtained with classical instrumentation.

REPORT DATE: 03/30/92 WORK UNIT # 7240

DETAIL SUMMARY SHEET

TITLE: Cerebral Dysfunction in Schizophrenic Subtypes

KEYWORDS: schizophrenia, neuropsychology, electrophysiology

PRINCIPAL INVESTIGATOR: Warden, Debra MD
ASSOCIATES: Anderson, Milton CPT MC; Coats, Michael MD

DEPARTMENT: Department of Psychiatry

STATUS: Ongoing
APPROVAL DATE: Dec 1989

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

STUDY OBJECTIVE
To determine if clinically identified subtypes of schizophrenic patients exhibit findings on neuropsychological and neurophysiological testing consistent with predominantly left hemisphere, right hemisphere, or bilateral frontal lobe dysfunction.

TECHNICAL APPROACH
To identify positive and negative symptom patients by a Positive and Negative Symptom Scale (PANSS) after a semistructured interview. The Schedule for Affective Disorders and Schizophrenia (SADS) will be utilized to confirm the diagnosis of schizophrenia, according to Research Diagnostic Criteria (RDC). Patients will then receive evoked potential testing, EEG with brainmapping, neuropsychological testing, and neurological exam.

PRIOR AND CURRENT PROGRESS
Human resources have been diverted temporarily from this project to the Traumatic Brain Injury (TBI) project. No additional patients have been enrolled since the 1991 report. Testing of schizophrenia patients should resume in the near future. Even with limited resources, the plan is to resume collaboration with NINDS (also on the TBI project) to continue neuropsychological testing of the patients. Because both schizophrenia patients and TBI patients have evidence of frontal lobe dysfunction, testing both populations is important.

CONCLUSIONS
With limited resources, the priority will be to facilitate collaboration with Dr. Grafman, NINDS, to continue neuropsychological evaluation of schizophrenia patients.

REPORT DATE: 07/01/92 WORK UNIT # 7241

DETAIL SUMMARY SHEET

TITLE: The Relationship Between Hypnotic Capacity and Dissociative Experience

KEYWORDS: hypnosis, dissociation

PRINCIPAL INVESTIGATOR: Wain, Harold PhD
ASSOCIATES: Sandman, Les CPT MC; Radcliffe, Elizabeth MA

DEPARTMENT: Department of Psychiatry

STATUS: Terminated
APPROVAL DATE: Feb 1990

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

STUDY OBJECTIVE
To determine the relationship between hypnotic capacity, as measured by the Hypnotic Induction Profile (HIP) and dissociative experience, as measured by the Dissociative Experience Scale (DES).

TECHNICAL APPROACH
Seventy-five competent, adult psychiatric outpatients new to WRAMC's Department of Psychiatry will be given the DES questionnaire at the same time that they are asked to fill out other data to initiate their evaluation. The DES will have a cover letter asking for the patient's involvement in the study and indicating their treatment at WRAMC will not change by participation. After the patient has been seen by a psychiatrist, he will be asked to participate in the administration of the HIP.

PRIOR AND CURRENT PROGRESS
This research protocol has been administratively terminated.

CONCLUSIONS
This research protocol has been administratively terminated.

REPORT DATE: 07/30/92 WORK UNIT # 7244

DETAIL SUMMARY SHEET

TITLE: Visual-Auditory Masking

KEYWORDS:

PRINCIPAL INVESTIGATOR: Weir, Linda LTC MC

DEPARTMENT: Department of Psychiatry STATUS: Terminated
APPROVAL DATE: Apr 1991

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

STUDY OBJECTIVE
This research protocol has been administratively terminated.

TECHNICAL APPROACH
This research protocol has been administratively terminated.

PRIOR AND CURRENT PROGRESS
This research protocol has been administratively terminated.

CONCLUSIONS
This research protocol has been administratively terminated.

REPORT DATE: 06/11/92 WORK UNIT # 7245

DETAIL SUMMARY SHEET

TITLE: Investigation of Ultradian Rhythms of Mood in Depression

KEYWORDS: ultradian rhythms, depression

PRINCIPAL INVESTIGATOR: Hall, Donald CPT MC

DEPARTMENT: Department of Psychiatry STATUS: Ongoing
APPROVAL DATE: May 1991

FUNDING: Current FY: $ 163 Previous FYs: $ 0 Total: $ 163

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
There have been 43 subjects entered into this protocol. There have been no adverse reactions.

CONCLUSIONS
Ultradian cycles have been identified in most subjects. The plan is to study 10 more subjects.

REPORT DATE: 08/11/92 WORK UNIT # 7246

DETAIL SUMMARY SHEET

TITLE: A Randomized Concentration-Controlled Trial of Fluoxetine in the Treatment of Major Despresive 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: $ 7,854 Previous FYs: $ 0 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. 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. There were no untoward effects of the drug or other aspects of the study protocol in any of the volunteer subjects.

CONCLUSIONS
The one subject who finished the protocol allowed us to demonstrate 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 problem facing this study is recruiting enough subjects to achieve a large enough n for statistical analysis.

REPORT DATE: 06/22/92 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: Compton, Alan COL MC

DEPARTMENT: Department of Psychiatry

STATUS: Ongoing
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
Analysis partially completed. No adverse results from this chart review. No new developments.

CONCLUSIONS
Island and New York Puerto Ricans appear similar to each other and distinct from Blacks and Caucasians (non-Hispanic) in demographic and clinical features.

REPORT DATE: 04/03/92 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: Ongoing
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 an NDA.

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 and 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 this report period, 2 studies were performed, for a total of 28 patients studied to date. 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: 04/02/92 WORK UNIT # 4527

DETAIL SUMMARY SHEET

TITLE: Technetium (Tc99m) Antimony Trisulfide Colloid - A Lymphoscintigraphic Agent

KEYWORDS: lymphoscintigraphy, antimony trisulfide, colloid

PRINCIPAL INVESTIGATOR: Anderson, Jay COL MC

DEPARTMENT: Department of Radiology STATUS: Ongoing
APPROVAL DATE: Nov 1981

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

STUDY OBJECTIVE
To clinically evaluate technetium (Tc99m) antimony trisulfide colloid (a Phase III IND radiopharmaceutical) in the evaluation of lymph nodes, lymphatics, and/or bone marrow distribution. Although these agents have been valuable in the evaluation of patients, radiopharmaceutical companies do not find it commercially profitable to seek an NDA. As a result, in order to offer this diagnostic modality to the patients we serve, we must have a protocol.

TECHNICAL APPROACH
The study is unchanged. The pharmaceutical is obtained from Cadema Company and labeled with the routine technetium 99m pertechnetate within our clinic. The exam is only performed on those patients for whom the primary clinical physician believes potential clinical information for the patient may be obtained. Any side effect is recorded on data sheets which are forwarded to the primary commercial company.

PRIOR AND CURRENT PROGRESS
This radiopharmaceutical remains a valuable diagnostic imaging tool. Sixteen studies were performed during this reporting period; for a total of 450 studies since the protocol started in 1981. The number of studies reported to be effective during this report period was 16. No untoward effects have been observed.

CONCLUSIONS
None.

REPORT DATE: 09/22/92 WORK UNIT # 4531

DETAIL SUMMARY SHEET

TITLE: Diagnostic Imaging of Adrenal Medulla (Pheochromocytoma, Paragangliomas, and Neuroblastomas) with I-131 MIBG (Metaiodobenzylguanidine Sulfate)

KEYWORDS: pheochromocytoma, I-131 MIBG

PRINCIPAL INVESTIGATOR: Anderson, Jay COL MC

DEPARTMENT: Department of Radiology STATUS: Ongoing
APPROVAL DATE: Sep 1984

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

STUDY OBJECTIVE
To evaluate the use of I-131 metaiodobenzylguanidine sulfate (I-131 MIBG) as an aid in the diagnosis, evaluation, and localization of pheochromocytomas, paragangliomas, neuroblastomas, and/or adrenal medullary hyperplasia. This radiopharmaceutical has already been proven useful in the evaluation of disease noted above. Because no commercial company pursues approval by the FDA, it remains in an IND status. To reduce cost, an IND was obtained from the FDA to offer this scan.

TECHNICAL APPROACH
This protocol will offer a diagnostic exam for the patient rather than implement a scientific study; no experimental design compilation of data, etc., will be done. All side effects will be reported to the FDA. There is no modification to the original protocol.

PRIOR AND CURRENT PROGRESS
During the current reporting period, five (5) patients have had I-131 MIBG studies performed. This makes a total of 77 patients since the protocol started in 1984. There have been no adverse reactions, and no patients have withdrawn. Of the five patients injected during this report period, all five studies were 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 saves WRAMC money because the patients are not referred to a civilian hospital to obtain the same exam.

REPORT DATE: 10/14/92 WORK UNIT # 4535

DETAIL SUMMARY SHEET

TITLE: Pharyngeal and Esophageal Manifestations of Rheumatoid Arthritis

KEYWORDS: rheumatoid arthritis, esophagus

PRINCIPAL INVESTIGATOR: Kohanski, Phillip CPT MC
ASSOCIATES: Dachman, Abraham MD

DEPARTMENT: Department of Radiology

STATUS: Ongoing
APPROVAL DATE: Aug 1988

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

STUDY OBJECTIVE
To ascertain if there is a relationship between rheumatoid arthritis and esophageal disease. Similar diseases, such as scleroderma, are believed to have esophageal disease associated with them.

TECHNICAL APPROACH
Questionnaires, brief histories, and physicals are performed to see if a patient has rheumatoid arthritis. Barium swallows are performed to see if the patient has esophageal disease. These two sets of data are then compared.

PRIOR AND CURRENT PROGRESS
A total of 20 patients and 25 controls were enrolled in this study since its approval. There was no incidence of serious or unexpected adverse reactions. The study is complete, and a paper will be written within the year.

CONCLUSIONS
None.

REPORT DATE: 09/20/92 WORK UNIT # 4538

DETAIL SUMMARY SHEET

TITLE: Ultrasound Guided Laser Ablation of Tumors

KEYWORDS: laser, liver, ultrasound

PRINCIPAL INVESTIGATOR: Dachman, Abraham MD

DEPARTMENT: Department of Radiology STATUS: Ongoing
APPROVAL DATE: Sep 1989

FUNDING: Current FY: $ 500 Previous FYs: $ 0 Total: $ 500

STUDY OBJECTIVE
To employ an experimental technique to treat colorectal metastases limited to the liver. This is to be considered a palliative procedure that avoids the need for surgery or general anesthesia.

TECHNICAL APPROACH
Patients with limited colorectal carcinoma metastases to the liver, and not candidates for surgery, are staged using CT and ultrasound. Under ultrasound guidance, a needle is placed into the tumor and the laser fiber is placed through the needle into the tumor. An Nd:YAG laser is used at 1 to 3 watts for about 6 minutes. Sequential placement of the laser fiber in various portions of the tumor are used to attempt to totally destroy the tumor.

PRIOR AND CURRENT PROGRESS
One patient was enrolled in this project last year; this is the total to date. This patient has been treated 15 times over two hospital admissions. This has been accomplished without any significant complications. The follow-up to date (10 month) indicates that the treated tumors have not grown. The patient has had interim chemotherapy, however. Thus, benefits attributable to the laser procedure are uncertain. The technique has been improved based on this experience.

CONCLUSIONS
This limited experience indicates the general feasibility and relative safety of the procedure. The Surgical Service has requested that this protocol be extended for intraoperative use. This might apply when unexpected intraoperative findings preclude excision (i.e., proximity to the inferior vena cava).

REPORT DATE: 05/01/92 WORK UNIT # 2023A

DETAIL SUMMARY SHEET

TITLE: In Vitro Determination of the Response of Skeletal Muscle to Halothane, Caffeine and Halothane Plus Caffeine

KEYWORDS: skeletal muscle, halothane/caffeine, malignant hyperthermia

PRINCIPAL INVESTIGATOR: Karan, Steven MAJ MC
ASSOCIATES: Muldoon, Sheila MD

DEPARTMENT: Department of Surgery
SERVICE: Anesthesia-Operative Service

STATUS: Completed
APPROVAL DATE: Dec 1985

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

STUDY OBJECTIVE

To determine the effect of halothane, caffeine, and halothane plus caffeine on skeletal muscle exposed to known concentrations of these agents and electrically stimulated. These tests will form the basis of normal controls for the Malignant Hyperthermia (MH) Testing Laboratory at USUHS, Department of Anesthesiology.

TECHNICAL APPROACH

A small piece of skeletal muscle is removed from the paraspinal muscles in a patient undergoing lumbar laminectomy. This muscle is suspended in a Krebs-Ringer's solution and is exposed to different concentrations of halothane, caffeine, and halothane plus caffeine. The response to electrical stimulation is noted, and the results compared to patients with the clinical diagnosis of malignant hyperthermia. The protocol was amended in FY90 to include patients undergoing knee surgery, cardiac bypass surgery, and abdominal surgery for skeletal muscle from the vastus lateralis, vastus medialis, and rectus, respectively.

PRIOR AND CURRENT PROGRESS

In accordance with the memorandum for clinical investigation researchers dated February 1990, new research protocols are required if the project is ongoing for more than 5 years. In compliance with this memorandum, the protocol is closed.

CONCLUSIONS

Since periodic control data is necessary for continued disgnostic malignant hyperthermia testing, the formation of a new protocol is underway and will be submitted for approval in the near future (May-June 1992).

REPORT DATE: 09/28/92 WORK UNIT # 2032A

DETAIL SUMMARY SHEET

TITLE: Pain Control After Thoracotomy and Its Effect on Pulmonary Function

KEYWORDS: pain, thoracotomy, pulmonary function

PRINCIPAL INVESTIGATOR: Lupkas, Raymond CPT MC

DEPARTMENT: Department of Surgery STATUS: Ongoing
SERVICE: Anesthesia-Operative Service APPROVAL DATE: Sep 1988

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

STUDY OBJECTIVE
To compare three different methods of pain control after thoracotomy and to evaluate the effects on pulmonary function.

TECHNICAL APPROACH
Patients are randomized to receive epidural morphine, intercostal nerve blocks, or interpleural local anesthetic for postoperative pain control. Patients are visited daily for 3 days and asked to perform a bedside pulmonary function test and to quantitate their pain using a visual analog pain scale. The original protocol has been modified to eliminate the interpleural local anesthetic group because it was found that this group did not receive adequate pain control.

PRIOR AND CURRENT PROGRESS
There have been 42 patients enrolled thus far; 20 to epidural morphine and 22 to intercostal nerve blocks. The study has been halted at this time because of severe difficulties in obtaining a spirometer and other commitments to the OR.

CONCLUSIONS
The data is now being reviewed to see if the information already gained is statistically significant.

REPORT DATE: 04/29/92 WORK UNIT # 2038A

DETAIL SUMMARY SHEET

TITLE: Prevention of Spinal Headaches after Incidental Dural Puncture during Epidural Catheter Placement

KEYWORDS: headache, dural puncture, epidural catheter

PRINCIPAL INVESTIGATOR: Stamatos, John CPT MC
ASSOCIATES: Karan, Steven MAJ MC

DEPARTMENT: Department of Surgery STATUS: Completed
SERVICE: Anesthesia-Operative Service APPROVAL DATE: Apr 1989

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

STUDY OBJECTIVE
To assess prophylactic therapy for the prevention of spinal headaches after incidental dural puncture with an epidural needle.

TECHNICAL APPROACH
Patients are assigned randomly to one of the following three groups: (1) A catheter is placed through the puncture site for the anesthetic and is removed 12 hours after the procedure. (2) A catheter is placed one interspace above the puncture site with no anesthetic administered and remains in place for 12 hours after the procedure. (3) A catheter is placed one interspace above the puncture site and remains in place for 12 hours after the procedure, and saline is injected at the end of the procedure before the catheter is removed.

PRIOR AND CURRENT PROGRESS
Another center completed the study before this study could be initiated at WRAMC.

CONCLUSIONS
None.

REPORT DATE: 03/12/92 WORK UNIT # 2045A

DETAIL SUMMARY SHEET

TITLE: Multicenter Study of the Davol Intraspinal Port

KEYWORDS: epidural, narcotics, cancer pain

PRINCIPAL INVESTIGATOR: Hahn, Marc CPT MC
ASSOCIATES: Stamatos, John CPT MC

DEPARTMENT: Department of Surgery STATUS: Ongoing
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
There was no progress on this study during the past fiscal year. The company is presently modifying the catheter as a result of a high incidence of infection (15%). The study will continue after the changes are complete. There are a total of 11 patients in the study. There have been no serious problems or adverse reactions.

CONCLUSIONS
None at this time.

REPORT DATE: 07/13/92 WORK UNIT # 2050A

DETAIL SUMMARY SHEET

TITLE: Intraoperative Use of Patient Controlled Anxiolysis

KEYWORDS: patient-controlled, analgesia, stress response

PRINCIPAL INVESTIGATOR: Hahn, Marc MAJ MC
ASSOCIATES: Furukawa, Kenneth MAJ MC; Baum, Andrew PhD

DEPARTMENT: Department of Surgery
SERVICE: Anesthesia-Operative Service

STATUS: Ongoing
APPROVAL DATE: Feb 1990

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

STUDY OBJECTIVE
To determine the effect of intraoperative use of a patient-controlled analgesia device for anxiolysis, provided the patient has adequate analgesia for the operation with a subarachnoid block. Is there a difference compared to standard anesthetist-administered anxiolysis?

TECHNICAL APPROACH
All patients will be given a subarachnoid anesthetic for comparable operative procedures; inguinal herniorrhapies or knee arthroscopies. Preoperative evaluation includes psychometric testing, blood and urine samples for fentanyl and cortisol, repetitive fine motor testing, and extensive counselling. Intraoperative evaluation includes all of the above before skin incision and at skin closure. Postoperative visits repeat the preoperative measures. Analysis of questionnaires and laboratory samples is performed at the Uniformed Services University of the Health Sciences.

PRIOR AND CURRENT PROGRESS
This study has been on hold for the last 6 months due to lack of availability of psychology personnel for administration for psychometric tests and due to inability to obtain a PCA pump for study purposes. At this point, data from the first 20 patients has been reviewed by the Psychology Department for initial analysis for an abstract to be presented at a forum this August. Dr. Hahn has left the Army, and Dr. Furukawa will assume responsibility for the study as principal investigator. Due to pressures for operative time in the main operating room, the study will utilize patients from the Ambulatory Surgery Center, pending review by the ASC staff.

CONCLUSIONS
No conclusive evidence for efficacy or a difference has been demonstrated. The initial data interpretation by the Psychology Department is not available at this time.

REPORT DATE: 09/11/92 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: Kline, Mark CPT MC
ASSOCIATES: Guzzi, Louis MAJ MC; Stoltzfus, Daniel MAJ MC

DEPARTMENT: Department of Surgery
SERVICE: Anesthesia-Operative Service

STATUS: Ongoing
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 we will compare intraoperative hemodynamics as well as episodes of postoperative ischemia, as documented by Holter monitoring, EKG's recorded, and cardioenzymes drawn each postoperative day for a maximum of 3 days.

PRIOR AND CURRENT PROGRESS

To date, 32 patients have completed the study; 17 of these were enrolled during the last year. Twenty-seven patients completed the entire 72 hours of Holter monitoring. Statistical analysis of the data reveal no significant difference between the PTCA and CABG groups for intraoperative hemodynamics and ischemia or postoperative hemodynamics. For postoperative ischemia, however, the PTCA group had significantly more ST segment depression on postoperative day 2 than did the CABG group. These results were summarized in an abstract accepted for presentation at the American Society of Anesthesiologists 1992 Annual Meeting in October.

CONCLUSIONS

A small increase in levels of postoperative ischemia for the PTCA group has been detected. Although this difference is statistically significant, the level of clinical significance is not known. Enrollment of approximately 30 additional patients will be required to complete the study.

REPORT DATE: 10/31/91 WORK UNIT # 2052A

DETAIL SUMMARY SHEET

TITLE: Preanesthetic Management in Children: A Combination of Intramuscular Midazolam and Ketamine as Compared to Each Medication Separately

KEYWORDS: preoperative, pediatric, midazolam

PRINCIPAL INVESTIGATOR: Stamatos, John CPT MC

DEPARTMENT: Department of Surgery STATUS: Completed
SERVICE: Anesthesia-Operative Service APPROVAL DATE: May 1990

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

STUDY OBJECTIVE

To determine the optimal induction agent for children about to undergo surgery; it should be easily administered, have a quick onset, provide adequate amnesia and sedation without respiratory depression or hemodynamic compromise, and be eliminated quickly. In the absence of a single agent that meets these criteria, this study will try to determine if a combination of midazolam and ketamine might more closely approximate the ideal agent.

TECHNICAL APPROACH

ASA 1 and 2 patients ages 3-6 years old will be entered into the study. Each unpremedicated child will be randomly assigned to receive 10 mcg/kg glycopyrrolate and either 0.3 mg/kg midazolam (Gp 1), 0.15 mg/kg midazolam + 1.5 mg/kg ketamine (Gp 2), or 3 mg/kg ketamine (Gp 3) in a single intramuscular injection. The time from injection until the child can be easily separated from his parents will be recorded using a mask acceptance technique. Each child will be evaluated 1 day postop and 1 week postop for any lasting effects.

PRIOR AND CURRENT PROGRESS

To date, 30 children have been entered into the study. Presently, the data is being reviewed for publication.

CONCLUSIONS

The combination of midazolam and ketamine has a faster onset than either drug separately.

REPORT DATE: 08/26/92 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: Condon, Brian COL MC

DEPARTMENT: Department of Surgery STATUS: Ongoing
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
At present, a sample of 52 patients has been achieved. Since 100 patients was identified as the desired sample size, data collection is still in progress.

CONCLUSIONS
Study is still in progress. Data collection and analysis is not complete.

REPORT DATE: 05/15/92 WORK UNIT # 2055A

DETAIL SUMMARY SHEET

TITLE: The Comparison of Propofol/Sufentanil and Midazolam/Sufentanil as Conscious Sedatives for Extracorporeal Shock Wave Lithotripsy

KEYWORDS: propofol, lithotripsy, conscious sedatives

PRINCIPAL INVESTIGATOR: Crowl, Frank MAJ MC

DEPARTMENT: Department of Surgery
SERVICE: Anesthesia-Operative Service

STATUS: Completed
APPROVAL DATE: Apr 1991

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

STUDY OBJECTIVE
To determine if propofol provides significant reduction in pain and nausea during conscious sedation for lithotripsy when compared to other hypnotic/sedative compounds.

TECHNICAL APPROACH
Pain and nausea scores were elicited during the procedure and immediately after the procedure and then compared to a randomized control.

PRIOR AND CURRENT PROGRESS
A total of 50 patients were enrolled in the study, which is the total number approved. Data analysis is in progress.

CONCLUSIONS
There was no significant difference in pain or nausea scores between groups. Both drug regimens provided good to excellent conditions for the procedure and were well received by the patients.

REPORT DATE: 06/05/92 WORK UNIT # 2504

DETAIL SUMMARY SHEET

TITLE: The Effect of Speech Babble on the Speech Recognition Ability of Soldiers with H-3 Physical Profiles

KEYWORDS: hearing-impaired, speech perception, noise

PRINCIPAL INVESTIGATOR: Cord, Mary MA
ASSOCIATES: Atack, Rodney PhD; Walden, Brian PhD

DEPARTMENT: Department of Surgery
SERVICE: Army Audiology and Speech Center

STATUS: Ongoing
APPROVAL DATE: Jun 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 1,119 Total: $ 1,119

STUDY OBJECTIVE

To develop and standardize a measure of speech recognition ability in noise to be administered to soldiers who are being evaluated by the Military Medical Retention Boards (MMRB) for possible administrative action. Such a measure will permit more objective judgements regarding relative communication handicap.

TECHNICAL APPROACH

The study will have two stages. The first experiment is designed to determine the least favorable signal-to-noise ratio (S/N) for monosyllabic words and multi-talker noise at which normal-hearing listeners can just maintain 100% correct recognition of words. In the second experiment, the speech and noise task will be presented to a large sample of H-3 profile soldiers at that S/N to derive normative data for this task.

PRIOR AND CURRENT PROGRESS

Data collection on 15 normal-hearing subjects is complete and a S/N for experiment two has been determined. In the past year, data has been collected on 232 H-3 profile soldiers at 11 Army audiology facilities. At this time, data has been collected on a total of 308 H-3 profile soldiers. Test-retest data has been collected on 19 subjects. There have been no serious or unexpected adverse reactions, and no subjects have withdrawn from the study. There has been no direct benefit to patients.

CONCLUSIONS

Data collection has not yet been completed. However, preliminary data suggests that scores vary considerably from near 100% correct to relatively poor recognition, as was hypothesized. Test-retest data collected thus far suggest this is a reliable measure.

REPORT DATE: 07/15/92 WORK UNIT # 2505

DETAIL SUMMARY SHEET

TITLE: The Use of Temporal and Spectral Cues in the Identification of Vowels by Hearing Impaired Listeners

KEYWORDS: frequency resolution, temporal resolution, hearing-impaired

PRINCIPAL INVESTIGATOR: Summers, W. Van PhD
ASSOCIATES: Leek, Marjorie PhD

DEPARTMENT: Department of Surgery
SERVICE: Army Audiology and Speech Center

STATUS: Completed
APPROVAL DATE: Jul 1990

FUNDING: Current FY: $ 420 Previous FYs: $ 168 Total: $ 588

STUDY OBJECTIVE

To determine whether hearing-impaired listeners' deficits in frequency resolution result in alterations in their reliance on frequency versus temporal information in vowel identification.

TECHNICAL APPROACH

Frequency resolution, temporal resolution, and vowel identification data will be measured for hearing-impaired listeners, normal-hearing listeners, and normal-hearing listeners in noise. Vowel stimuli will contain both temporal and spectral cues to vowel identity. The focus of the study is on whether hearing-impaired listeners with near-normal temporal resolution and impaired frequency resolution rely more on temporal information in making vowel identification decisions than normal-hearing listeners.

PRIOR AND CURRENT PROGRESS

This protocol was completed during this period. A manuscript based on the results was accepted for publication in the Journal of Speech and Hearing Research. A total of 33 subjects participated in the study, including 14 hearing-impaired listeners and 19 normal-hearing listeners. No additional subjects were enrolled during the last year. There have been no adverse reactions from subjects nor has any subject withdrawn from the study. There is no benefit to the subjects.

CONCLUSIONS

Hearing-impaired listeners tended to rely less on formant frequency information in vowel identification than normal-hearing listeners. Vowel duration affected labelling similarly across groups. Frequency and temporal resolution scores were no better predictors of cue reliance than audiometric thresholds. The results suggest group differences in the perceptual weighting of cues to vowel identity.

REPORT DATE: 01/16/92 WORK UNIT # 2507

DETAIL SUMMARY SHEET

TITLE: Acoustic and Perceptual Analysis of Voice Quality Following Laryngotracheoplasty

KEYWORDS: laryngotracheoplasty, voice, acoustics

PRINCIPAL INVESTIGATOR: McClean, Michael PhD
ASSOCIATES: Edmonds, Charles MAJ MC; Gurevich-Uvina, Joyce MA

DEPARTMENT: Department of Surgery
SERVICE: Army Audiology and Speech Center

STATUS: Completed
APPROVAL DATE: Oct 1990

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

STUDY OBJECTIVE

To describe acoustic and perceptual aspects of voice production in a group of individuals who have undergone laryngotracheoplasty, and to evaluate relationships between different vocal parameters and the characteristics of surgical procedure carried out in different patients. This is a pilot study intended to assess the general value of acoustic analysis procedures for assessing the outcome of laryngotracheoplasty.

TECHNICAL APPROACH

High quality audio tape recordings will be obtained from six children and one adult who have undergone laryngotracheoplasty and an age and gender matched group of normal control subjects. Subjects will produce sustained vowels and repeat simple syllables. Audio recordings will be digitized at 20 kHz to an AT-type microcomputer using CSpeech signal analysis software. Physical measures of voice jitter (msec), shimmer (%), signal/noise ratio (dB), and fundamental frequency (Hz) will be made. Perceptual ratings of vocal breathiness, roughness, and strain-strangled quality will also be obtained by three judges.

PRIOR AND CURRENT PROGRESS

The patients showed abnormal acoustic and perceptual aspects in their voices; only one fell within two standard deviations of the normal means for the acoustic parameters. However, this person had an abnormally low fundamental frequency. Perceptual judgements were reliable across the three judges; ratings were consisent with interpretations given to the acoustic data for the different subjects. Generally, abnormal patterns in voice acoustics were highly variable across the patients and are interpretable in relation to the specific structural features of their larynges. Fifteen subjects were recorded this past year (the total for the study). There have been no adverse effects and no benefit to them.

CONCLUSIONS

Observations strongly support continued application of acoustic analysis procedures to assess laryngeal function associated with laryngotracheoplasty. Acoustic analysis of such cases could be better interpreted if supplemented with laryngeal stroboscopic data; this approach will be taken in clinical application.

REPORT DATE: 02/03/92 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 STATUS: Ongoing
SERVICE: Army Audiology and Speech Center APPROVAL DATE: Nov 1990

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

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 was approved by the NIH in June 1991, and funding began July 1991. None of the proposed experiments have been initiated yet. Several pieces of equipment have been purchased, AV speech materials have been gathered or are on order, and computer programming to support this work is underway. The first protocol stemming from this grant has been approved as of September 1991 (Work Unit No. 2514).

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: 04/02/92 WORK UNIT # 2510

DETAIL SUMMARY SHEET

TITLE: Prediction of Stutterig Severity from Physiologic Measures of Speech Motor Systems

KEYWORDS: stuttering, speech kinematics, severity

PRINCIPAL INVESTIGATOR: McClean, Michael PhD

DEPARTMENT: Department of Surgery STATUS: Ongoing
SERVICE: Army Audiology and Speech Center APPROVAL DATE: Jan 1991

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

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
During the past year, the movement recordings system, protocol display computer, signal acquisition, and analysis systems have been fully configured and put in operation for this research. Speech kinematic and stuttering severity data have been obtained on 22 adult stutterer subjects. Analysis of temporal aspects of movement of fluent utterances have been completed on six subjects. There have been no serious or unexpected adverse reactions, and none of the subjects have withdrawn from the study. Physiologic measures obtained during speech disfluencies have been of benefit to a few subjects, in that they have provided the speech-language pathologist with an improved picture of the stuttering patterns shown by these subjects.

CONCLUSIONS
The data analyzed in six subjects indicate a systematic relationship between stuttering severity and duration of inter- and intrastructural timing. More severe stutterers show either extremely long or extremely short event durations. This may reflect compensation strategies required for their production of fluent utterances. This interpretation has implications for how therapy programs are designed for individual stutterers.

REPORT DATE: 05/11/92 WORK UNIT # 2511

DETAIL SUMMARY SHEET

TITLE: The Transmission of Prosodic Information Via Selected Spectural Regions of Speech

KEYWORDS: speech perception, normal-hearing, prosody

PRINCIPAL INVESTIGATOR: Grant, Kenneth PhD
ASSOCIATES: Cord, Mary MS

DEPARTMENT: Department of Surgery
SERVICE: Army Audiology and Speech Center

STATUS: Ongoing
APPROVAL DATE: Apr 1991

FUNDING: Current FY: $ 5,350 Previous FYs: $ 0 Total: $ 5,350

STUDY OBJECTIVE

To determine a) whether prosodic speechy information (e.g., syllable number, syllabic stress, sentence intonation, and phrase juncture) can be equally conveyed by different, but equally intelligible, spectral regions of speech; and b) whether suprasegmental cues are mapped spectrally in the same way as overall speech intelligibility.

TECHNICAL APPROACH

This protocol includes three sub-projects, each with 10 normal-hearing adult subjects. Depending on the sub-project, subjects will listen to filtered words or sentences and will be required to identify either a) the number of syllables and the stress pattern of the word, b) the intonation (rising for a question, falling for a statement) of the sentence, or c) the phrase structure of a sentence. For each sub-project, six filter conditions will be evaluated. The filter conditions chosen will have the same Articulation Index (AI=0.1) according to ANSI Standard S3.5-1969 and the same intelligibility (roughly 35% correct monosyllabic word identification).

PRIOR AND CURRENT PROGRESS

Data collection for the first two sub-projects (the transmission of syllable number and syllabic stress in 1-3 syllable words and the transmission of intonation in sentences) has been completed. Data collection for the third sub-project (the transmission of phrase boundary location in sentences) is approximately half done. To date, 25 normal-hearing subjects have been enrolled. An additional five subjects are required to complete the protocol. There have been no adverse or unexpected reactions from subjects, and no subjects have withdrawn from this study. Aside from general information, there has been no benefit to the subjects participating in this protocol.

CONCLUSIONS

Results indicate that equally intelligible but spectrally distinct regions of speech do not convey prosodic features of speech equally. In particular, cues for intonation are transmitted best through the low frequency bands, whereas cues for syllable number, syllabic stress, and phrase boundary location tend to be more evenly distributed across the spectrum.

REPORT DATE: 07/06/92 WORK UNIT # 2513

DETAIL SUMMARY SHEET

TITLE: Neuromotor Aspects of Speech Disfluency

KEYWORDS: neuromotor, stuttering, orofacial

PRINCIPAL INVESTIGATOR: McClean, Michael PhD

DEPARTMENT: Department of Surgery STATUS: Completed
SERVICE: Army Audiology and Speech Center APPROVAL DATE: Jul 1991

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

STUDY OBJECTIVE
To describe the kinematics of speech disfluencies; to determine whether premovement lip muscle activity levels are associated with speech disfluency; to determine whether speech disfluency is associated with long-term changes in lip muscle reflex amplitude; and to assess whether stutterers show abnormal patterns of lip muscle reflex modulation prior to speech, abnormal fine force control, or abnormal muscle compensation to load perturbation.

TECHNICAL APPROACH
This protocol was approved in association with a grant proposal to the NIH which was not funded. The technical approach involves kinematic and electromyographic recording of lip, jaw, and laryngeal structures during speaker repetitions of simple speech utterances. Mechanical perturbations are applied to the perioral region to elicit reflex and compenstory muscle software. Resulting kinematic and electromyographic measures are analyzed and interpreted in relation to the above objectives.

PRIOR AND CURRENT PROGRESS
This NIH grant proposal was approved but not recommended for funding by the National Deafness and Communication Disorders Advisory Council at its meeting January 1992. It should be noted that some of the proposed work on the grant has been incorporated into other active protocols with DCI: WU #2510, Prediction of Stuttering Severity from Physiologic Measures of Speech Motor Systems, and WU #2518, Prespeech Modulation of Lip Muscle Reflexes in Stutterers and Nonstutterers.

CONCLUSIONS
None.

REPORT DATE: 08/13/92 WORK UNIT # 2514

DETAIL SUMMARY SHEET

TITLE: Evaluating the Articulation Index for Audotory-Visual Consonant Recognition

KEYWORDS: speech perception, normal-hearing, articulation index

PRINCIPAL INVESTIGATOR: Grant, Kenneth Ph.D.
ASSOCIATES: Cord, Mary MS; Clay, John PhD

DEPARTMENT: Department of Surgery
SERVICE: Army Audiology and Speech Center

STATUS: Ongoing
APPROVAL DATE: Aug 1991

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

STUDY OBJECTIVE
To identify the most salient auditory cues in auditory-visual consonant recognition, and to examine the accuracy of the Articulation Index procedure for predicting auditory-visual speech recognition scores from auditory speech recognition scores.

TECHNICAL APPROACH
This protocol includes two sub-projects requiring normal-hearing subjects to identify via speechreading (V), audition (A), and combination of the two (AV), 18 initial consonants distorted by noise (sub-project 1) or filtering (sub-project 2). In sub-project 1, eight different speech-to-noise ratios resulting in A scores between 40-90% correct are evaluated. In sub-project 2, 12 different filter conditions resulting in a similar range of percent correct scores are evaluated.

PRIOR AND CURRENT PROGRESS
Much of the first year's effort was spent developing a computer test facility for the processing and control of audiovisual speech materials. The acquisition of optical and laser video equipment, touch screen terminals, and appropriate test materials, and the programming of these devices was a major accomplishment during this first year. Pilot data collection for the first sub-project has recently begun, as has the recruiting of subjects. Two subjects have been recruited so far. Speech test materials have been digitized and processed for subject testing (e.g., mixed with speech-shaped noise, filtered, normalized, etc.). Formal data collection will begin in September 1992.

CONCLUSIONS
Results from our pilot tests indicate that speech-to-noise ratios between -11 dB to +5 dB are sufficient to produce the desired range of a performance (40-90% correct consonant recognition). Visual alone recognition for these same consonants by one highly experienced speechreader was 43% correct.

REPORT DATE: 08/14/92 WORK UNIT # 2588

DETAIL SUMMARY SHEET

TITLE: Hearing Loss and the Perception of Complex Sounds

KEYWORDS: resolution, harmonics, spectral

PRINCIPAL INVESTIGATOR: Leek, Marjorie PhD

DEPARTMENT: Department of Surgery STATUS: Ongoing
SERVICE: Army Audiology and Speech Center APPROVAL DATE: Aug 1988

FUNDING: Current FY: $ 126 Previous FYs: $ 3,905 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 preliminary data analysis have been in progress on two experiments, and pilot work is underway on two others. Thirty-nine patients have participated in protocols associated with this grant thi_ year, for a total enrollment of 97 subjects. There have been no adverse reactions nor any patients withdrawn from the study. There is no direct benefit to patients.

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: 04/02/92 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: Ongoing
SERVICE: Army Audiology and Speech Center APPROVAL DATE: Jan 1989

FUNDING: Current FY: $ 1,555 Previous FYs: $ 5,005 Total: $ 6,560

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
Using the upgraded cochlear model, vowel stimuli have been modified to reflect abnormal processing based on frequency resolution measurements on one subject. Other forms of speech (e.g., sentences) have been processed through the "impaired" model and recorded to demonstrate some of the degradations to speech understanding experienced by hearing-impaired subjects. Temporal waveforms of vowel stimuli were analyzed through custom-generated software in a preliminary attempt at prediction of confusion due to the abnormal cochlear process. Partial data have been collected from one subject this year, but no new vowel recognition data have been collected to date. Two hearing-impaired subjects had previously participated, for a total of three subjects. There have been no adverse reactions, and no subjects have withdrawn from the study. There is no benefit to subjects.

CONCLUSIONS
Work on this protocol demonstrates that speech processed through an auditory model constrained to have functional damage based on measurement of frequency resolution of one patient provides a realistic indication of the distortions experienced by hearing-impaired listeners. However, the validity of this simulated hearing-loss has yet to be established through the analysis of vowel confusion matrices.

REPORT DATE: 04/21/92 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: Ongoing
APPROVAL DATE: Feb 1989

FUNDING: Current FY: $ 646 Previous FYs: $ 2,139 Total: $ 2,785

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

No new patients have been enrolled in this project since the last report. The total number of subjects enrolled in the project 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. Most of the data analyses are complete, and a manuscript reporting these data is in preparation.

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: 06/26/92 WORK UNIT # 2594

DETAIL SUMMARY SHEET

TITLE: Measurement of Ear Canal Sound Pressure Levels in Infants and Young Children

KEYWORDS: hearing aids, ear canal SPL, infant

PRINCIPAL INVESTIGATOR: MacNeil, Donna MA

DEPARTMENT: Department of Surgery
SERVICE: Army Audiology and Speech Center

STATUS: Ongoing
APPROVAL DATE: May 1989

FUNDING: Current FY: $ 0 Previous FYs: $ 6,220 Total: $ 6,220

STUDY OBJECTIVE

To develop a clinically practical procedure for predicting sound pressure levels (SPL) developed in the ear canal when hearing aids are worn by very young children. Correction factors from test cavities to real-ear measurements in infants and young children will enable hearing aid output levels to be set to a level which will provide maximum gain without overamplification which could cause additional hearing loss.

TECHNICAL APPROACH

Difficulties in enlisting pediatric subjects, and recent data published by Feigin et al. (1989) which casts doubt on the relation between ear canal volume and SPL measures, has prompted us to re-think our original goals and procedure. By examining the relationship between ear canal volume and real-ear SPL for 14 patients who have completed the protocol, as well as in simulated ear volumes, we feel that the sought-after relation can be obtained without the need for additional patients. Both graphical and correlational technique will be used for this purpose.

PRIOR AND CURRENT PROGRESS

Data from these subjects showing the real-ear SPL value for various test frequencies are being plotted with ear canal volume as a paramater. It is expected that subjects with smaller ear canal volume will demonstrate greater SPL values when compared to SPL values measured in a standard 2cc coupler volume. These real-ear data will be compared to data obtained from simulated ear-canal volumes in an effort to demonstrate whether other factors (e.g., middle ear compliance, ear canal length, etc.) may be responsible for the SPL values obtained. There was no incidence of serious or unexpected adverse reactions.

CONCLUSIONS

Preliminary attempts to measure SPL values in simulated adult ear-canal volumes using a modified 2cc coupler have resulted in a close approximation of real-ear SPL values. Plans to evaluate existing data from 14 patients and to expand simulation efforts are in progress.

REPORT DATE: 04/21/92 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: $ 0 Previous FYs: $ 1,995 Total: $ 1,995

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

Data collection was completed on this project during the previous year, with a total of 10 subjects having completed the study. There have been no adverse reactions from subjects, nor has any subject withdrawn from the study. There is no benefit to the subjects. During the past year, two major analyses of these data have been underway. First, extensive software modifications have been undertaken to allow a more precise characterization of the auditory filter under the stimulus conditions specific to this experiment. Second, collaboration has begun with Dr. Walt Jesteadt, Director of Research, Boys Town National Research Hospital, to use these data to examine the additivity of masking in hearing-impaired versus normal-hearing listeners.

CONCLUSIONS

For both normal- and hearing-impaired listeners, bandwidth and asymmetry of auditory filters are related to sensitivity loss at high frequency but not at low frequencies. This suggests that poor frequency resolution is caused by the same pathology that underlies the sensitivity loss. Noise masking also may simulate hearing loss in normal-hearing subjects not only by raising threshold, but also by producing poor frequency resolution demonstrated by hearing-impaired patients.

REPORT DATE: 04/03/92 WORK UNIT # 3006

DETAIL SUMMARY SHEET

TITLE: Validation of the Accuracy and Reliability of the Present System Used in the SICU for Culturing Intravascular Catheter Segments

KEYWORDS: validation, culturing, catheter

PRINCIPAL INVESTIGATOR: Hnatiuk, Oleh MAJ MC

DEPARTMENT: Department of Surgery STATUS: Completed
SERVICE: Critical Care Medicine Service APPROVAL DATE: Feb 1990

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

STUDY OBJECTIVE
To validate the current method of collection and culture of central venous catheters; that is, to determine whether plating of the catheters at the bedside as opposed to the routine submission to the lab would increase the sensitivity of identifying various organisms.

TECHNICAL APPROACH
When a central venous catheter is due to be changed or removed (3 days - MICU, 5 days - SICU) the site will be prepared and the distal 6 cm. of the catheter will be removed using a standardized approach. The segments will be divided according to the unit from which they originated and a portion will be plated on agar at the bedside while the remaining portion will be sent to the lab for processing in a routine fashion. Culture results will then be collected and verified by the PI. Demographic data will be collected and will ultimately be entered into a dBASE programming package.

PRIOR AND CURRENT PROGRESS
Data collection and interpretation are completed. There have been 212 catheters from 95 patients analyzed. There were no serious or adverse reactions. Manuscript preparation is in progress.

CONCLUSIONS
A total of 39 catheter tips were positive for greater than or equal to 15 organisms. Thirteen of these were simultaneously positive at the bedside and in the lab. Cultures were exclusively positive in 22 cases immediately plated at the bedside, whereas laboratory plating resulted in only 4 exclusively positive cases. This discrepancy was statistically significant.

REPORT DATE: 05/13/92 WORK UNIT # 3007

DETAIL SUMMARY SHEET

TITLE: Total Parenteral Nutrition Via Pulmonary Artery Catheter

KEYWORDS: TPN, catheter, infection

PRINCIPAL INVESTIGATOR: Yowler, Charles LTC MC

DEPARTMENT: Department of Surgery STATUS: Completed
SERVICE: Critical Care Medicine Service APPROVAL DATE: Feb 1990

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

STUDY OBJECTIVE
To examine the hypothesis that delivery of total parenteral nutrition (TPN) via pulmonary artery catheter does not increase the risk of catheter infections above that of other multiple lumen catheters.

TECHNICAL APPROACH
Patients with pulmonary artery catheters will have any needed TPN delivered through a dedicated catheter port. Cultures will be obtained from these catheters and compared to cultures from triple lumen catheters being used to deliver TPN. Catheter infection rates will then be compared.

PRIOR AND CURRENT PROGRESS
There has been no further subject accrual in the last year due to a change in clinical practice to more nutrition by the enteral route. Thirty-one patients with 61 catheter lines were entered in 1990-1991, and none have been entered since. Essentially all patients are now receiving either enteral nutrition or nutrition via triple lumen catheter.

CONCLUSIONS
Due to the inability to recruit patients, this study is closed.

REPORT DATE: 04/13/92 WORK UNIT # 3008

DETAIL SUMMARY SHEET

TITLE: The Use of Capnography During the Transport of Intubated Patients

KEYWORDS: capnography, transport, critically ill

PRINCIPAL INVESTIGATOR: Stoltzfus, Daniel MAJ MC
ASSOCIATES: Kuzma, Paul CPT MC

DEPARTMENT: Department of Surgery
SERVICE: Critical Care Medicine Service

STATUS: Ongoing
APPROVAL DATE: Feb 1990

FUNDING: Current FY: $ 963 Previous FYs: $ 4,608 Total: $ 5,571

STUDY OBJECTIVE

To evaluate the information gained from a non-invasive measure of exhaled carbon dioxide while transporting mechanically ventilated, critically ill patients. Also to evaluate if the use of this device would better ensure adequate patient ventilation.

TECHNICAL APPROACH

A baseline measure (prior to transport) of the patient's minute ventilation arterial blood gas, peak airway pressure, and exhaled carbon dioxide concentration will be compared to the values obtained following transport out of the ICU to a second location. During the transport back to the ICU, the nurse or doctor will be instructed to maintain a set number (baseline while on the ventilator) of exhaled CO2. There has been no modification to the original protocol.

PRIOR AND CURRENT PROGRESS

Twelve (12) subjects were enrolled during the last year, bringing the total enrollment to 15. There have been no serious or unexpected adverse reactions and no patients have been withdrawn from the study. There was no directly measurable benefit to the subjects at the time of study. As each subject functioned as his/her own control, we were able to observe any difference in the efficiency of manual ventilation and arterial chemistries when capnography was added during intra-hospital transport. The study was terminated early (before the predicted n=30 was reached) because of an ethical concern for patient safety. As described in the conclusions section, subjects monitored without capnography developed acidemic states which might be harmful.

CONCLUSIONS

The mean decrease in the patients' arterial pH during "blinded transport" was -.10 compared to -.037 with the use of capnography. The mean increase in arterial pCO2 during "blinded transport" was 13.3 mmHg, compared with 5.1 mmHg when capnography was used. These two met statistical significance (.003, .0005, respectively). Patients were manually ventilated in a more efficient and safer fashion when capnography was used to direct medical care.

REPORT DATE: 04/13/92 WORK UNIT # 3009

DETAIL SUMMARY SHEET

TITLE: Effect of Empiric Low Dose Amphotericin B on the Development of Disseminated Candidasis in a Surgical Intensive Care Unit

KEYWORDS: low-dose, amphotericin B, candidiasis

PRINCIPAL INVESTIGATOR: Stoltzfus, Daniel MAJ MC

DEPARTMENT: Department of Surgery STATUS: Ongoing
SERVICE: Critical Care Medicine Service 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
Twelve (12) subjects were enrolled during the last year, bringing the total enrollment to 20. Patients #9, 13, 14, 15, 16, and 18 (n=6/12) died prior to completion for the study data. One (1) patient was removed from the study early to empirically receive a dose of amphotericin B lower than per protocol. No subject had a serious or unexpected adverse reaction except for renal dysfunction. All patients with developing renal dysfunction were evaluated by the Nephrology Service and found to have non-protocol related contributions. Subjects did not receive a definable benefit during the study. These patients are critically ill, and this longitudinal study records data for 25 days following entrance.

CONCLUSIONS
The study will continue until at least 30 subjects have been enrolled (15 in each group). 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: 09/09/92 WORK UNIT # 3010

DETAIL SUMMARY SHEET

TITLE: Comparison of Norepinephrine with Phentolamine to Dopamine Alone and to Norepinephrine with Low Dose Dopamine as Initial Agent for Inotropic/Pressor Support in Normovolemic Patients in Septic Shock

KEYWORDS: septic shock, normovolemic

PRINCIPAL INVESTIGATOR: Bowes, Joan CPT MC

DEPARTMENT: Department of Surgery STATUS: Completed
SERVICE: Critical Care Medicine Service APPROVAL DATE: Jan 1991

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

STUDY OBJECTIVE
To compare norepinephrine with phentolamine, to dopamine alone, and to norepinephrine with low dose dopamine as the initial agent for inotropic support in normovolemic patients in septic shock.

TECHNICAL APPROACH
Normovolemic patients with a diagnosis of septic shock who meet entrance criteria will be assigned to one of three arms (norepinephrine with phentolamine, dopamine alone, or norepinephrine with low dose dopamine) based on the previously stated preference of the attending physician. Serial laboratory data will be obtained and then hemodynamic parameters will be obtained using a pulmonary artery catheter. Approved modifications to the original protocol included waiver of informed consent and the requirement of an arterial line for entrance.

PRIOR AND CURRENT PROGRESS
Two patients were enrolled in the study with insufficient data collected on each. These patients were enrolled from January 1991 to January 1992. Enrollment of patients seems to have been hampered by difficulty identifying patients who meet entrance criteria and difficulty collecting data (as mentioned above). The Critical Care Medicine Research Committee decided that continuance of this study was no longer feasible (14 April 1992). There were no adverse reactions, and no patients were withdrawn from the study. There was no clear benefit to any of the patients.

CONCLUSIONS
No conclusions can be drawn.

REPORT DATE: 04/17/92 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 Surgery
SERVICE: Critical Care Medicine Service

STATUS: Ongoing
APPROVAL DATE: Feb 1991

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

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

Prospective, randomized, double blinded, two-period crossover design. Patients receiving mechanical ventilation will be randomly placed on one of two modes of ventilation. Their oxygen consumption (VO2) will be measured by the metabolic cart. They will then be placed on the other mode and have their VO2 measured. These VO2 values will be compared for the two modes. To ensure that there is no change in nonrespiratory VO2 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

The metabolic cart instrument which measures the VO2 directly has been purchased and was received on location in March 1992. To date, one patient has been enrolled in the study. There have been no adverse effects.

CONCLUSIONS

It is too premature to comment on any study conclusions. Additional time will be necessary to complete the study.

REPORT DATE: 06/08/92 WORK UNIT # 2035

DETAIL SUMMARY SHEET

TITLE: Investigation of the Etiology of Postoperative Hypocalcemia after Thyroidectomy in the Thyrotoxic Patient

KEYWORDS: surgery, thyroid, hypocalcemia

PRINCIPAL INVESTIGATOR: Azarow, Kenneth CPT MC
ASSOCIATES: Beam, Thomas LTC MC; Burman, Kenneth COL MC

DEPARTMENT: Department of Surgery
SERVICE: General Surgery Service

STATUS: Ongoing
APPROVAL DATE: Jan 1989

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

STUDY OBJECTIVE
To determine if the thyrotoxic individual is more susceptible to hypocalcemia following thyroid surgery than is the euthyroid patient.

TECHNICAL APPROACH
Patients are evaluated in clinic preoperatively; blood is drawn for all parameters mentioned in the study. Twenty-four hour urine is obtained. Postoperative blood draws are performed by the surgical team and handled by the Principal Investigator. Patients are followed per normal post-surgical routine by the operating surgeon.

PRIOR AND CURRENT PROGRESS
There were no patients entered in this study this past year. The principal investigator has been reassigned, and a new principal investigator is currently being selected to complete this project. He/she will begin as of July 1992.

CONCLUSIONS
None, as of this report.

REPORT DATE: 07/13/92 WORK UNIT # 2037

DETAIL SUMMARY SHEET

TITLE: The Effect of Cyclooxygenase Inhibition on Mortality and Tumor Necrosis Factor in a Lethal Model of Septic Shock in the Rat

KEYWORDS: septic shock, cyclooxygenase inhibition, tumor necrosis factor

PRINCIPAL INVESTIGATOR: Lane, Brian CPT MC

DEPARTMENT: Department of Surgery STATUS: Terminated
SERVICE: General Surgery Service APPROVAL DATE: Apr 1989

FUNDING: Current FY: $ 0 Previous FYs: $ 1,365 Total: $ 1,365

STUDY OBJECTIVE
To examine the effect of ibuprofen, a cyclooxygenase inhibitor, on mortality and tumor necrosis factor (TNF) in a clinically relevant model of septic shock in the rat.

TECHNICAL APPROACH
Using a lethal model in the rat of septic shock, a statistically relevant number of rats will be allocated to six groups to determine the effect of ibuprofen, a cyclooxygenase inhibitor, on mortality. Levels of TNF will be assayed to examine the time course of this monokine in hypermetabolic and hypometabolic phases of septic shock to determine its role in the pathophysiology of septic shock.

PRIOR AND CURRENT PROGRESS
This research protocol has been administratively terminated.

CONCLUSIONS
This research protocol has been administratively terminated.

REPORT DATE: 07/01/92 WORK UNIT # 2057

DETAIL SUMMARY SHEET

TITLE: Endotoxin and Cytokine Regulation of Contractile Function of Human Vasculature

KEYWORDS:

PRINCIPAL INVESTIGATOR: Jaques, David LTC MC

DEPARTMENT: Department of Surgery STATUS: Terminated
SERVICE: General Surgery Service APPROVAL DATE: Feb 1991

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

STUDY OBJECTIVE
This research protocol has been administratively terminated.

TECHNICAL APPROACH
This research protocol has been administratively terminated.

PRIOR AND CURRENT PROGRESS
This research protocol has been administratively terminated.

CONCLUSIONS
This research protocol has been administratively terminated

REPORT DATE: 06/08/92 WORK UNIT # 2058

DETAIL SUMMARY SHEET

TITLE: Vascular Rings: 35 Years of Treating This Anomaly

KEYWORDS: vascular ring, aortic arch, congenital anomaly

PRINCIPAL INVESTIGATOR: Azarow, Kenneth CPT MC

DEPARTMENT: Department of Surgery STATUS: Completed
SERVICE: General Surgery Service APPROVAL DATE: Jun 1991

FUNDING: Current FY: $ 795 Previous FYs: $ 0 Total: $ 795

STUDY OBJECTIVE
To review the experience at Walter Reed in treating vascular rings over the past 50 years. Specifically, to demonstrate that new imaging modalities can be used in place of invasive angiography.

TECHNICAL APPROACH
To retrospectively review the clinic charts of all patients operated on at Walter Reed who were diagnosed with vascular ring.

PRIOR AND CURRENT PROGRESS
Review completed. A paper was written and was published in the Annals of Thoracic Surgery.

CONCLUSIONS
Magnetic resonance imaging is a preferable alternative to angiography in the assessment of vascular ring.

REPORT DATE: 06/08/92 WORK UNIT # 2059

DETAIL SUMMARY SHEET

TITLE: Perianal Paget's Disease: Laceral Advancement Flaps as an Alternative to Skin Grafts

KEYWORDS: Paget's, perianal

PRINCIPAL INVESTIGATOR: Azarow, Kenneth CPT MC
ASSOCIATES: Solla, Julio MAJ MC; McNeil, Jennifer CPT MC

DEPARTMENT: Department of Surgery
SERVICE: General Surgery Service

STATUS: Completed
APPROVAL DATE: Sep 1991

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

STUDY OBJECTIVE
To describe a new approach to the reconstruction of the perianal region after resection of Paget's disease; and to review the prior experience with this disease at Walter Reed and its management.

TECHNICAL APPROACH
Files of the tumor registry will be reviewed. A recent case of perianal Paget's will be described, along with a new approach in reconstructing the defective left post resection.

PRIOR AND CURRENT PROGRESS
The review of files was completed. A paper was written and was accepted by Surgical Rounds.

CONCLUSIONS
Lateral advancement flaps are an acceptable alternative to skin grafting and have fewer potential complications.

REPORT DATE: 06/18/92 WORK UNIT # 2317

DETAIL SUMMARY SHEET

TITLE: Intraocular Irrigating Solutions: Effect on Corneal Endothelium

KEYWORDS: endothelial cells, cornea, glutathione

PRINCIPAL INVESTIGATOR: Kramer, Kenyon COL MC

DEPARTMENT: Department of Surgery STATUS: Ongoing
SERVICE: Ophthalmology Service APPROVAL DATE: Apr 1983

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

STUDY OBJECTIVE
To determine the relative importance of glutathione in intraocular irrigating solutions to the corneal endothelium during cataract surgery.

TECHNICAL APPROACH
Preoperative cell size measurements and corneal thickness measurements will be made. Subjects will randomly receive intraocular irrigating solutions with glutathione or without. Similar measurements will be made postoperatively and compared.

PRIOR AND CURRENT PROGRESS
An initial 51 patients were studied, and inconclusive results were published. It was determined that additional data would strengthen the findings. Thus, an additional 67 patients have been enrolled. Approximately 20 patients remain to have the postoperative photograph taken. No patients had adverse reactions.

CONCLUSIONS
The value of glutathione in intraocular solution extracapsular cataract surgery remains unproven.

REPORT DATE: 03/17/92 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: $ 0 Previous FYs: $ 0 Total: $ 0

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 fr. gments of the lens will be driven into the eye.

TECHNICAL APPROACH

Fragments of polycarbonate, either with or without dyes, will be placed into the center of the vitreous cavity through a 3 mm incision through the sclera. Two controls will be used: sham operated with no intraocular foreign body (negative control) and iron (positive control). Parameters that will be monitored include fundus appearance, intraocular inflammation, intraocular pressure, and ERG. Animals will be euthanized at 1 week to 6 months and the eyes examined histopathologically.

PRIOR AND CURRENT PROGRESS

Surgical technique has been refined utilizing 10 protocol rabbits. The protocol has been started (six rabbits to date). An interim analysis will be performed at 10 weeks. There have been no serious or unexpected adverse reactions or findings.

CONCLUSIONS

Study in progress.

REPORT DATE: 03/17/92 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: $ 5,946 Previous FYs: $ 3,969 Total: $ 9,915

STUDY OBJECTIVE

To determine whether scleral lacerations can be effectively closed 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 the standard fashion, or closed via the 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. An addendum to evaluate the integrity of CA closed lacerations by increasing IOP (10 rabbits) has been approved.

PRIOR AND CURRENT PROGRESS

On histopathologic examination, a fribrous bridge was noted in all animals by 2 weeks. Prior to this, IOP and dark-adapted ERG a and b wave amplitudes were significantly lower in open eyes compared to those in which wounds were closed using CA or suture.

	OPEN	CA	SUTURED	
IOP (mmHg)	0.0 ± 0.0	7.8 ± 2.5	13.0 ± 3.0	*p=0.0440
a-Wave (mV)	30.9 ± 9.9	72.5 ± 9.0	89.6 ± 8.7	*p=0.0146
b-Wave (mV)	69.3 ± 26.7	179.6 ± 21.2	193.4 ± 14.2	*p=0.0182

*Using Kruskal-Wallis one-way ANOVA; mean ± SEM

A trend toward delayed wound closure was noted on histopathologic analysis of the glued eyes examined within the first 2 weeks. Otherwise, the clinical course of the CA group compared favorably with eyes closed by the standard suture technique. No. of rabbits: 69. There have been no adverse reactions/findings.

CONCLUSIONS

This study supports the efficacy of using cyanoacrylate adhesive as a temporary, battlefield expedient method of closing scleral lacerations. Work is beginning on the addendum.

REPORT DATE: 04/20/92 WORK UNIT # 2320

DETAIL SUMMARY SHEET

TITLE: Mood and Behavior Changes with Topical Ophthalmic Beta-Adrenergic Blockade

KEYWORDS: B-adrenergic, blockers, glaucoma

PRINCIPAL INVESTIGATOR: Cox, Kevin CPT MC

DEPARTMENT: Department of Surgery STATUS: Ongoing
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
Enrollment of patients continues. We have 41 patients enrolled in the study to date; 16 females and 25 males. There have been no serious adverse reactions. Patients have benefited from timely follow-up with continuity of care, and some cases of suspected hypertension have been detected and appropriately referred.

CONCLUSIONS
No firm conclusions are available as yet, but if any effect exists of topical B-blockers on mood it appears to be idiosyncratic.

REPORT DATE: 04/16/92 WORK UNIT # 2630

DETAIL SUMMARY SHEET

TITLE: The Concomittant Use of Azathioprine and Pretransplant Transfusions

KEYWORDS: azathioprine, pretransplant, transfusions

PRINCIPAL INVESTIGATOR: Shaver, Timothy MAJ MC

DEPARTMENT: Department of Surgery STATUS: Completed
SERVICE: Organ Transplant Service APPROVAL DATE: Nov 1983

FUNDING: Current FY: $ 0 Previous FYs: $ 362 Total: $ 362

STUDY OBJECTIVE
To study the effectiveness of pretransplant azathioprine (Imuran) in reducing the incidence of sensitization to pretransplant blood transfusions.

TECHNICAL APPROACH
Potential recipients will be given five pretransplant tranfusions, 2 weeks apart, of stored (2-week-old) packed blood cells. They will be given azathioprine (Imuran) 1mg/kg/day (50 mg/day in children) starting 1 week prior to the first tranfusion and continuing daily for 3 months after the final transfusion. One 7cc clot tube of blood will be examined for reactivity against a panel of random T and B lymphocytes.

PRIOR AND CURRENT PROGRESS
Study was completed 18 months ago, but left open pending publication. There have been no new admissions to this protocol during this time. The study should be closed at this time.

CONCLUSIONS
Pre-transplant transfusions with concomitant Imuran produces a low level of sensitization, (significantly lower than in patients who were transfused without Imuran (8-23%; $p<.05$). However, the Imuran transfusion patients have shown no better transplant success rate (88%, 1 year graft survival) than the non-Imuran patients (91% at 1 year).

REPORT DATE: 10/23/92 WORK UNIT # 2631

DETAIL SUMMARY SHEET

TITLE: Development of an Extracorporeal Liver Support System

KEYWORDS: extracorporeal, liver failure

PRINCIPAL INVESTIGATOR: Fernandez, Carlos LTC MC

DEPARTMENT: Department of Surgery STATUS: Completed
SERVICE: Organ Transplant Service APPROVAL DATE: Jan 1986

FUNDING: Current FY: $ 195 Previous FYs: $ 2,195 Total: $ 2,390

STUDY OBJECTIVE
To test an extracorporeal liver support system (ECLS) and develop SOP's for use in future clinical trials.

TECHNICAL APPROACH
Livers are removed from +10 kg pigs. The liver will be placed in the liver cassette system. The "donated" liver will be connected to a larger 20 kg pig via vascular access for extracorporeal perfusion. The production of bile by the harvested liver will suggest that the system is functional.

PRIOR AND CURRENT PROGRESS
This pilot study has been completed and has resulted in a publication in Military Medicine.

CONCLUSIONS
The initial results are very encouraging; however, additional sophistication needs to be incorporated into the system to provide reproducible and reliable perfusion in order to proceed with the technology into the clinical setting in fulminate hepatic failure.

REPORT DATE: 04/14/92 WORK UNIT # 2632

DETAIL SUMMARY SHEET

TITLE: Treatment with Liver Transplantation and Human Monoclonal Anti-Hepatitis B Virus IgG of a Hepatitis B Virus Carrier who has End Stage Chronic Active Hepatitis

KEYWORDS: antibody, monoclonal, transplantation

PRINCIPAL INVESTIGATOR: Shaver, Timothy MAJ MC
ASSOCIATES: Fernandez, Carlos MD

DEPARTMENT: Department of Surgery
SERVICE: Organ Transplant Service

STATUS: Ongoing
APPROVAL DATE: Jul 1988

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

STUDY OBJECTIVE

To evaluate the effectiveness of a new human monoclonal anti-hepatitis B virus antibody in the prevention of recurrent hepatitis B infection following liver transplantation in chronic hepatitis B virus carriers with end stage chronic active hepatitis.

TECHNICAL APPROACH

Patients are initially entered into the study at the University of Pittsburgh based on the need for liver transplantation secondary to chronic active hepatitis from hepatitis B virus. Once these conditions have been satisfied, the patient is then presented with the above protocol. They are treated preoperatively with injections of the monoclonal antibody, followed by liver transplantation, and then ongoing treatment postoperatively. This postoperative treatment is continued indefinitely based on the demonstrated half-life of the antibody in each patient. Once this is determined, they are then redosed on an every 2 to 4 week basis.

PRIOR AND CURRENT PROGRESS

No new Walter Reed patients have been entered, and no candidates for this study are now awaiting transplantation at the University of Pittsburgh. The patients previously entered at the University of Pittsburgh continue their monthly follow-ups to determine the rate of recurrence of hepatitis B. No new patients are being entered at the University of Pittsburgh due to the development of a mutated strain of hepatitis B which is no longer effected by the monoclonal antibody. The monoclonal antibody is being redeveloped in the lab to determine if this mutation can be prevented or treated with a second monoclonal. As previously reported, no patients with hepatic malignancy are currently being entered as was the case with the original two patients.

CONCLUSIONS

The study appears to show a delay in the recurrence of hepatitis B viremia in patients receiving this antibody. A few patients continue to develop viremia several months to greater than 1 year from transplantation, but no firm data have been generated from this study. An interim publication was expected this fiscal year; however, due to the above new information, this has not reached fruition.

REPORT DATE: 03/23/92 WORK UNIT # 2633

DETAIL SUMMARY SHEET

TITLE: Use of Antilymphocyte Preparations in Solid Organ Transplantation

KEYWORDS: anti-lymphocyte, preparations, transplantation

PRINCIPAL INVESTIGATOR: Bueno, Carlos MD
ASSOCIATES: Shaver, Timothy MAJ MC

DEPARTMENT: Department of Surgery
SERVICE: Organ Transplant Service

STATUS: Ongoing
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 ALG (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

Five additional patients have been added to the study, making a total of 18 that have received MALG prophylactically post transplant; 16 still have functioning allografts (89%). The 1 year actuarial graft survival rate is 88.6% in this group, and this compares favorably to previous prophylactic ALG protocols at this institution: 1) 1980-83, 71%, and 2) 1984-89, 85%. The only reactions to MALG were transient (<1 day) fevers in 10 of the 18 recipients. It should be noted that only one of the two graft losses was due to rejection. The other was a Candida infection around the kidney, as well as a Vitamin K dependent coagulation problem.

CONCLUSIONS

Prophylactic ALG is effective in inducting immunologic tolerance with minimal adverse reactions. Only 3 of the 18 recipients had rejection episodes. Although some of the patients are not 1-year post transplant yet, this rejection rate (0.17/patient) compares favorably to the previous prophylactic ALG protocols: 1) 1980-83, 1.57/patient, and 2) 1984-89, 0.78/patient.

REPORT DATE: 04/22/92 WORK UNIT # 2634

DETAIL SUMMARY SHEET

TITLE: Determination of Epstein-Barr Virus Replication in Lateral Tongue Epithelium of Immunosuppressed Patients

KEYWORDS: tongue epithelium, oral hairy leukoplakia, Epstein-Barr virus

PRINCIPAL INVESTIGATOR: Shaver, Timothy MAJ MC
ASSOCIATES: Childers, Esther MAJ DC; Foss, Robert LT, DC

DEPARTMENT: Department of Surgery
SERVICE: Organ Transplant Service

STATUS: Completed
APPROVAL DATE: Apr 1990

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

STUDY OBJECTIVE

To ascertain the presence of Epstein-Barr Virus (EBV) replication in lateral tongue epithelium of immunosuppressed and healthy individuals in order to clarify the role of Epstein-Barr virus in the etiology of oral hairy leukoplakia (OHL). Oral hairy leukoplakia is considered prognostic of AIDS, and understanding the mechanism of EBV expression could lead to further progress in the unravelling of the complex oral clinical picture of immunosuppression.

TECHNICAL APPROACH

After a brief intraoral examination, the lateral border of the participant's tongue is gently scraped with a microdissecting stainless steel curette to obtain a sample of tongue epithelium. The sample is then fixed in a solution of glutaraldehyde in formalin, and the submitted specimens are then cut, stained, and examined under light and electronmicroscopy. The electronmicroscopic identification of intranuclear EBV replication, as indicated by viral particles in various stages of assembly, is considered a positive result. These positive samples are then tested with a DNA genome probe for EBV.

PRIOR AND CURRENT PROGRESS

Five patients have been entered during the last fiscal year, for a total of 10 patients who have been entered into the study. During the past fiscal year, the exfoliative cytology specimens from the lateral tongue epithelium were examined from healthy individuals from a prior study, which were used as controls. No virus particles were seen in either group. There have been no serious or unexpected adverse reactions, and no patients have been withdrawn from the study.

CONCLUSIONS

The results suggest that clinically normal lateral tongue epithelium is not the reservoir for EBV in this population. No additional conclusions can be made from this study at present.

REPORT DATE: 08/26/92 WORK UNIT # 2401

DETAIL SUMMARY SHEET

TITLE: Evaluation of Porous Coated Total Knee and Hip Prostheses in Achieving a Stable Prosthesis Bone Interface

KEYWORDS: porous, total joint, prosthesis

PRINCIPAL INVESTIGATOR: Hopkinson, William LTC MC

DEPARTMENT: Department of Surgery STATUS: Completed
SERVICE: Orthopaedic Surgery Service APPROVAL DATE: Aug 1983

FUNDING: Current FY: $ 962 Previous FYs: $ 0 Total: $ 962

STUDY OBJECTIVE
Evaluate the long-term results of the use of uncemented hip and knee replacements.

TECHNICAL APPROACH
Ongoing yearly hip and knee rating (clinical) and radiographs, which are the clinical standard with or without research.

PRIOR AND CURRENT PROGRESS
The first 100 consecutive uncemented hip replacements have been followed from 5 to 7 years. This data has been recorded for the patients, and statistical analysis has been completed. The paper has been accepted for publication in the Journal of Bone and Joint Surgery. This patient group will continue annual follow-up with hip ratings and radiographs.

CONCLUSIONS
Limp was found to be related to the surgical approach at 2 years, but was found not to be significant at 5 years. The presence of localized bone loss and some late femoral subsidene has become a clinical concern.

REPORT DATE: 08/25/92 WORK UNIT # 2410

DETAIL SUMMARY SHEET

TITLE: The Use of Arthroscopic Abrasion Chondroplasty in the Treatment of Osteoarthritis of the Knee

KEYWORDS: arthroscopic, chondroplasty, osteoarthritis

PRINCIPAL INVESTIGATOR: Hopkinson, William LTC MC

DEPARTMENT: Department of Surgery STATUS: Ongoing
SERVICE: Orthopaedic Surgery Service APPROVAL DATE: Aug 1987

FUNDING: Current FY: $ 0 Previous FYs: $ 8,439 Total: $ 8,439

STUDY OBJECTIVE
To evaluate the results of abrasion chondroplasty as a treatment for osteoarthritis of the knee.

TECHNICAL APPROACH
Forty patients with osteoarthritis of the knee will be randomized into two treatment groups. One group will have arthroscopy and knee debridement; the other group will have arthroscopy, knee debridement, and abrasion chondroplasty. Annual knee rating, clinical exam, and radiographs will be performed.

PRIOR AND CURRENT PROGRESS
The clinical study is still ongoing; however, there has been great difficulty in randomization. No patients have been enrolled in the study in the past year, and two patients have completed the study. There were no adverse reactions, and both patients have improved clinically.

CONCLUSIONS
None, at this point.

REPORT DATE: 07/10/92 WORK UNIT # 2414

DETAIL SUMMARY SHEET

TITLE: Use of Platelet Derived Growth Factor in Sarcoma Detection

KEYWORDS: PDGF, sarcoma, tumor marker

PRINCIPAL INVESTIGATOR: Berrey, Hudson LTC MC

DEPARTMENT: Department of Surgery STATUS: Terminated
SERVICE: Orthopaedic Surgery Service APPROVAL DATE: Nov 1988

FUNDING: Current FY: $ 0 Previous FYs: $ 196 Total: $ 196

STUDY OBJECTIVE
To determine the specificity of platelet derived growth factor (PDGF) as a sarcoma tumor marker.

TECHNICAL APPROACH
To obtain blood specimens pre- and postoperatively from patients undergoing surgery for suspected tumors. To correlate type and amount of tumor mass to level of serum PDGF.

PRIOR AND CURRENT PROGRESS
This research protocol has been administratively terminated.

CONCLUSIONS
This research protocol has been administratively terminated.

REPORT DATE: 11/09/92 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: Ongoing
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
Patient entry into this protocol has been slow. Starting in December 1992 patient enrollment is expected to increase. No patients have been enrolled this fiscal year; 43 altogether. No adverse or unexpected reactions are noted for this fiscal year. This is a minimal risk study.

CONCLUSIONS
No prospective studies evaluating the relationship between back pain and pregnancy have been published to date. Information gained from this study when it is complete will be valuable to identify the natural history of back pain and pregnancy.

REPORT DATE: 02/07/92 WORK UNIT # 2418

DETAIL SUMMARY SHEET

TITLE: Clinical Investigation of the PWB Spine System

KEYWORDS: PWB spine system, spinal fusion

PRINCIPAL INVESTIGATOR: van Dam, Bruce LTC 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. There is no change in the protocol.

PRIOR AND CURRENT PROGRESS
A total of 13 subjects were enrolled in this study in 1990 and 11 subjects in 1991; the last subject in August 1991. Compared to more conventional pedicle fixation (i.e., Steffee), there has been a higher rate of pseudarthrosis requiring revision surgery; five thus far, and three are scheduled for pseudarthrosis repair (30% overall).

CONCLUSIONS
At least in the hands of the principal investigator, the results of fusion with this instrumentation are inferior to other spinal implants. Therefore, no further enrollment has occurred since August 1991, though follow-up will continue.

REPORT DATE: 03/04/92 WORK UNIT # 2419

DETAIL SUMMARY SHEET

TITLE: The Treatment of Carpal Tunnel Syndrome with Pyridoxine

KEYWORDS: carpal tunnel, pyridoxine, vitamin B6

PRINCIPAL INVESTIGATOR: Smith, Allan COL MC
ASSOCIATES: Bagg, Mark MAJ MC; Wynder, Stephen LTC MC

DEPARTMENT: Department of Surgery
SERVICE: Orthopaedic Surgery Service

STATUS: Ongoing
APPROVAL DATE: Dec 1989

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

STUDY OBJECTIVE
To define the efficacy of pyridoxine in treatment of carpal tunnel syndrome.

TECHNICAL APPROACH
Prospective randomized study of patients with documented carpal tunnel syndome; patients treated with conservative measures versus those treated with conservative measures plus pyridoxine.

PRIOR AND CURRENT PROGRESS
This protocol was not initiated due to the transfer of the original principal investigator. The current PI is reviewing pertinent literature, subsequent to prior approval date, and protocol modifications may be required based on more recent knowledge.

CONCLUSIONS
Protocol will be initiated but may require modification. This is being reviewed.

REPORT DATE: 04/20/92 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: Berrey, Hudson LTC 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 review of four charts will be made of MRI patients who have undergone surgery and radiation therapy for soft tissue sarcomas of the extremities.

PRIOR AND CURRENT PROGRESS
No patients have been completed.

CONCLUSIONS
Project will continue.

REPORT DATE: 04/21/92 WORK UNIT # 2421

DETAIL SUMMARY SHEET

TITLE: The Effect of Methotrexate on Bone Ingrowth in a Rabbit Model

KEYWORDS: methotrexate, bone ingrowth

PRINCIPAL INVESTIGATOR: Kim, Christopher CPT MC

DEPARTMENT: Department of Surgery STATUS: Completed
SERVICE: Orthopaedic Surgery Service APPROVAL DATE: Mar 1990

FUNDING: Current FY: $ 799 Previous FYs: $ 0 Total: $ 799

STUDY OBJECTIVE
To evaluate the effect of methotrexate on bony ingrowth into a porous-coated titanium implant.

TECHNICAL APPROACH
Procedure will be performed unilaterally on the animals.

PRIOR AND CURRENT PROGRESS
This project has been completed.

CONCLUSIONS
Data to be published.

REPORT DATE: 01/28/92 WORK UNIT # 2424

DETAIL SUMMARY SHEET

TITLE: Early Percutaneous Intramedullary Fixation of Long Bone Deformity in Severe Osteogenesis Imperfecta

KEYWORDS: intramedullary fixation, long bone, osteogenesis imperfecta

PRINCIPAL INVESTIGATOR: Tenuta, Joachim CPT MC
ASSOCIATES: McHale, Kathleen LTC MC

DEPARTMENT: Department of Surgery
SERVICE: Orthopaedic Surgery Service

STATUS: Completed
APPROVAL DATE: Nov 1990

FUNDING: Current FY: $ 962 Previous FYs: $ 0 Total: $ 962

STUDY OBJECTIVE

To evaluate the effectiveness of percutaneous pinning of long bones in patients with severe osteogenesis imperfecta. To review the stability and revision rate, as well as to make a comparison with plating of long bones.

TECHNICAL APPROACH

Charts will be reviewed of patients treated in two institutions: WRAMC and Childrens' Hospital National Medical Center, Washington, DC. Data to be collected includes the procedure and type of long bone recorded and complications (to include need for revision, which can be quite frequent in these patients with extremely fragile bones) observed in follow-up visits. The technique will be compared to other types of procedures in order to determine its value.

PRIOR AND CURRENT PROGRESS

Seven patients had 25 long bones stabilized with percutaneous intramedullary pin fixation. These patients sustained no immediate postoperative complications and had a reduced revision rate as compared to other procedures. Plating of long bones was compared. Plating was shown to have more postoperative difficulty but appeared to be technically easier than placement of a telescoping rod. Since this was a chart review, there was no real benefit to the patients studied and there were no adverse effects.

CONCLUSIONS

Early percutaneous intramedullary fixation of long bone deformities in patients with osteogenesis imperfecta provided early stabilization in a simple, reproducible manner.

REPORT DATE: 06/10/92 WORK UNIT # 2425

DETAIL SUMMARY SHEET

TITLE: Treatment of Residual Clubfoot, the Bean Shaped Foot, by Opening Wedge Medial Cuneiform Osteotomy and Closing Wedge Cuboid Osteotomy: Clinical Review and Cadaver Correlation

KEYWORDS: residual clubfoot

PRINCIPAL INVESTIGATOR: McHale, Kathleen LTC MC

DEPARTMENT: Department of Surgery STATUS: Completed
SERVICE: Orthopaedic Surgery Service APPROVAL DATE: Jan 1991

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

STUDY OBJECTIVE
To study the amount of correction obtained by an opening wedge medial cuneiform osteotomy and closing wedge cuboid osteotomy in cadaver feet; and to predict the amount of correction that is obtained by this procedure in patients with residual clubfoot. Present clinical experience will be reviewed.

TECHNICAL APPROACH
Through two short incisions directly over the involved bones, an opening osteotomy and a closing osteotomy will be made on the medial cuneiform and cuboid bones, respectively. Postoperative x-rays will be performed. The procedure will be done on patients with residual clubfoot and repeated on normal cadaver feet.

PRIOR AND CURRENT PROGRESS
Project is complete. Ten feet in 7 patients and 10 cadaver feet were operated on.

CONCLUSIONS
This procedure is simple, effective, and reproducible. It will address not only the residual adductus but the supination in the midfoot.

REPORT DATE: 04/22/92 WORK UNIT # 2426

DETAIL SUMMARY SHEET

TITLE: Chart Review of Infected Diabetic Feet

KEYWORDS: diabetic patients, foot ulcerations

PRINCIPAL INVESTIGATOR: Busey, James CPT MS

DEPARTMENT: Department of Surgery STATUS: Ongoing
SERVICE: Orthopaedic Surgery Service APPROVAL DATE: Jan 1991

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

STUDY OBJECTIVE
To review charts for the effect of possible release of endogenous cytokines during local infection to heal diabetic ulcers; and to review diabetic admissions for foot infections and compare diagnostic procedures, treatment, and patient status.

TECHNICAL APPROACH
Diabetic patients with foot ulcerations will be recruited for study and evaluation of wound size, redness, and drainage; both pre- and post-admission. Charts of patients with diabetic ulcers and infections from the Dysvascular Foot Clinic, as well as inpatient records from Internal Medicine, Surgery, and Orthopaedics will be reviewed.

PRIOR AND CURRENT PROGRESS
Study included examination of medical and surgical treatment of 23 diabetics admitted with foot infections between August 1987 and January 1991. Because this is a chart review only, no patients were withdrawn or suffered any adverse reactions. There were no direct benefits to the patients.

CONCLUSIONS
An infection may stimulate the body in releasing endogenous cytokines to assist in healing. Diabetic cellulitis with no ischemia or gangrene caused amputation after 1987.

REPORT DATE: 04/15/92 WORK UNIT # 2427

DETAIL SUMMARY SHEET

TITLE: The Effects of Intraoperative Blood Loss on Serum Antibodic Level in Patients Undergoing Total Joint Arthroplasty

KEYWORDS: total joint arthroplasty, serum antibiotic levels, blood loss

PRINCIPAL INVESTIGATOR: Tenuta, Joachim CPT MC
ASSOCIATES: Asplund, Lynn RN BSN

DEPARTMENT: Department of Surgery
SERVICE: Orthopaedic Surgery Service

STATUS: Ongoing
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 HPLC. The preoperative and intraoperative serum concentrations will be compared. The data will be interpreted by the pharmacokineticist. An additional blood sample will be drawn at 300 minutes.

PRIOR AND CURRENT PROGRESS

Fifteen subjects have been enrolled in this study since September 1991. There have been no serious or unexpected adverse reactions, and no patient has been withdrawn from the study. There is no benefit to the patient. The blood loss ranges from 600-2400 cc.

CONCLUSIONS

All serum samples have not been run by the DCI Support Lab. Therefore, no results have been interpreted at this time.

REPORT DATE: 06/29/92 WORK UNIT # 2428

DETAIL SUMMARY SHEET

TITLE: Postoperative Fever Associated with Patient Controlled Analgesia in Orthopaedic Patients

KEYWORDS: PCA

PRINCIPAL INVESTIGATOR: Hayda, Roman CPT MC

DEPARTMENT: Department of Surgery STATUS: Completed
SERVICE: Orthopaedic Surgery Service APPROVAL DATE: Jun 1991

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

STUDY OBJECTIVE
To study the incidence of fever in postoperative orthopaedic patients following spine surgery or knee and hip replacement surgery with the use of patient controlled analgesia (PCA) versus traditional intramuscular analgesia.

TECHNICAL APPROACH
Following informed consent, patients will be randomized into two groups for postoperative pain control: PCA or conventional intramuscular analgesia. Data will be collected: demographic and medical information, type of surgery, and fever cure over 3 postoperative days.

PRIOR AND CURRENT PROGRESS
This study has been closed by the principal investigator due to difficulty recruiting patients, time constraints and poor ward recovery room cooperation with protocol.

CONCLUSIONS
Although the question remains to be answered, the study has been closed prior to obtaining sufficient data to analyze.

REPORT DATE: 09/03/92 WORK UNIT # 2429

DETAIL SUMMARY SHEET

TITLE: Evaluation of Somatic Sensory, Auditory, and Motor Evoked Potentials in Idiopathic Scoliosis with Brainstem MRI Correlation

KEYWORDS: scoliosis, MRI, evoked potentials

PRINCIPAL INVESTIGATOR: Stevens, William CPT MC

DEPARTMENT: Department of Surgery STATUS: Completed
SERVICE: Orthopaedic Surgery Service APPROVAL DATE: Jul 1991

FUNDING: Current FY: $ 819 Previous FYs: $ 0 Total: $ 819

STUDY OBJECTIVE
To more accurately quantify previously described brain stem asymmetry in patients with adolescent idopathic scoliosis (AIS) and to correlate these findings with evoked potential measurements.

TECHNICAL APPROACH
Patients will be recruited from the Scoliosis Clinic at WRAMC and will undergo MRI of the posterior fossa and evoked potential measurements. The surface area of the cerebral peduncles will be measured at the level of the mamillary bodies using a digitized scanner. These results will be compared to similar measurements made on a control population without AIS.

PRIOR AND CURRENT PROGRESS
There have been 14 subjects enrolled in this study during the first year. A statistically significant difference in the size of the cerebral peduncles on the left and right sides of the brain was noted in patients with AIS but was not demonstrated in subjects without AIS. This left to right size difference in the cerebral peduncles was not correlated with abnormal findings on evoked potential measurements. Auditory and somatosensory evoked potentials were within normal limits for patients with AIS.

CONCLUSIONS
The findings of brain stem asymmetry in the cerebral peduncles in patients with AIS may be used to direct further research regarding the etiology of this disorder. These findings may represent a pattern of subtle CNS variations in AIS patients or may indicate a defect in fine motor control which is mediated via the cerebral peduncles.

REPORT DATE: 09/10/92 WORK UNIT # 2430

DETAIL SUMMARY SHEET

TITLE: Closed Osteotomy Using Lithotripsy--Cadaver Trials

KEYWORDS: lithotripsy, shockwaves, bone

PRINCIPAL INVESTIGATOR: Brown, Maurice CPT MC

DEPARTMENT: Department of Surgery STATUS: Completed
SERVICE: Orthopaedic Surgery Service APPROVAL DATE: Aug 1991

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

STUDY OBJECTIVE

To determine the ability of extracorporeal shockwaves (ESW) to fracture bone. The ability to perform closed osteotomy would facilitate incision-less surgery in several orthopaedic procedures. Extracorporeal shockwaves have been used successfully to fracture renal stones.

TECHNICAL APPROACH

Shockwaves of maximum power will be applied to cadaveric extremities with the focal point directed at the bone cortex. Fresh frozen cadaveric limbs will be obtained from the Uniformed Services University of the Health Sciences. A Dornier HM4 lithotripter will be used. This device is designed for the treatment of renal lithiasis. Shockwaves will be generated via an underwater electrode. As a spark is generated across the electrode, water is vaporized. The amount of watervaporized, and hence the amplitude of the resulting shockwave, is determined by the voltage delivered across the electrode. The total power delivered is the product of the voltage applied and the total number of shockwaves delivered.

PRIOR AND CURRENT PROGRESS

Radiographic analysis: No radiographic change was noted during the course of treatment in any of the extremities. Gross inspection: In all extremities the skin was intact. There was no ecchymosis or hematoma noted on external examination. However, a slight decrease in skin turgor was noted at the treatment site. During dissection, all tissues were noted to be intact. Cortical bone and intramedullary bone were unchanged.

CONCLUSIONS

It became apparent that even if this method was eventually successful fracturing bone it would be economically unfeasible to treat patients with ESW when the cost of electrodes alone would be several times the cost of current techniques. This is a new application of a relatively new technology. Much work remains to be done. However, these researchers feel confident that eventually ESW will bring changes to orthopaedics of the same magnitude experienced by urology.

REPORT DATE: 09/14/92 WORK UNIT # 2431

DETAIL SUMMARY SHEET

TITLE: Roentgenographic Evaluation of the AML Porous Coated Acetabular Components: A Six-Year Minimum Follow-Up Study

KEYWORDS: uncemented, acetabular components

PRINCIPAL INVESTIGATOR: Beauchesne, Richard MAJ MC

DEPARTMENT: Department of Surgery STATUS: Completed
SERVICE: Orthopaedic Surgery Service APPROVAL DATE: Sep 1991

FUNDING: Current FY: $ 902 Previous FYs: $ 0 Total: $ 902

STUDY OBJECTIVE
To evaluate uncemented acetabular components at long-term follow-up.

TECHNICAL APPROACH
Radiographic and chronicle follow-up at 6 years minimal post-op will be performed. This retrospective review will include 233 cases.

PRIOR AND CURRENT PROGRESS
The review was performed, and a paper was presented to the Annual Meeting of the American Academy of Orthopaedic Surgeons. All data has been gathered in this retrospective analysis.

CONCLUSIONS
Functional result is excellent: 1.7% unstable, 37% optimal interface, 52% suboptimal but stable, and 11% determining. There continues to be concern about osteolysis.

REPORT DATE: 01/17/92 WORK UNIT # 2048

DETAIL SUMMARY SHEET

TITLE: Effect of IL-1 on Glucocorticoid Inhibition of Wound Healing

KEYWORDS: IL-1, wound healing

PRINCIPAL INVESTIGATOR: Schoenfeld, Phil CPT MC

DEPARTMENT: Department of Surgery STATUS: Completed
SERVICE: Otolaryngology-Head & Neck Surgery Svc APPROVAL DATE: Feb 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 15,076 Total: $ 15,076

STUDY OBJECTIVE
To determine if administration of IL-1 reverses the delay in wound healing caused by glucocorticoids. To determine the effect of administration of vitamin A on plasma IL-1 levels.

TECHNICAL APPROACH
Wound healing will be measured in a rat model using a constant speed tensiometer in a control group and in groups given steroids, vitamin A, and IL-1. IL-1 levels will be assayed in a group given steroids and vitamin A, as well as in a group given only steroids and in a control group.

PRIOR AND CURRENT PROGRESS
This project was assumed by a new principal investigator with the best of intentions to complete the work; however, due to the status in which the project was transferred and the time constraints allotted for completion of the project, the new PI was unable to proceed with this study at this time.

CONCLUSIONS
None.

REPORT DATE: 07/07/92 **WORK UNIT #** 2501

DETAIL SUMMARY SHEET

TITLE: Tensile Strength of Wounds Closed Under Increasing Tension in the Pig Model

KEYWORDS: wound closing tension, scar tensile strength, positive relationship

PRINCIPAL INVESTIGATOR: Livermore, George CPT MC

DEPARTMENT: Department of Surgery **STATUS:** Ongoing
SERVICE: Otolaryngology-Head & Neck Surgery Svc **APPROVAL DATE:** Mar 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 5,874 Total: $ 5,874

STUDY OBJECTIVE

To assess the relationship between wound closing tension and scar tensile strength in the pig animal model. A positive relationship has previously been shown in the rat model.

TECHNICAL APPROACH

Ten Hampshire pigs will be subjected to skin excisional wounds of varying degrees. The scars will be harvested at 30 days postop and sent for analysis of tensile strength, histology, and biochemical analysis. The findings will be compared for statistically significant relationships.

PRIOR AND CURRENT PROGRESS

All experimental work and data analysis has been completed. A manuscript is in preparation.

CONCLUSIONS

The relationship between wound closing tension and scar tensile strength observed in the rat has been repeated in the pig. At higher tensions, the relationship is non-linear.

REPORT DATE: 08/04/92 WORK UNIT # 2503

DETAIL SUMMARY SHEET

TITLE: Salicylate Ototoxicity in Humans, A Clinical Study

KEYWORDS: salicylate, aspirin, audiometric testing

PRINCIPAL INVESTIGATOR: Brammer, Robert COL MC

DEPARTMENT: Department of Surgery STATUS: Ongoing
SERVICE: Otolaryngology-Head & Neck Surgery Svc APPROVAL DATE: May 1990

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

STUDY OBJECTIVE
To examine the otologic effect of salicylate (specifically aspirin) in humans with conventional and high frequency audiometry with serum salicylate level correlation.

TECHNICAL APPROACH
Subjects will be accrued and undergo audiometric testing with no salicylate on board for baseline determination. Thereafter, five varying clinical dosage levels of ASA trials, by daily ingestion for a week, will be undertaken with audiometry at the end of each week. A week of rest off ASA will be given to each volunteer participant to allow return to baseline audiometric levels. Data will be collected and correlated with serum levels of ASA taken prior to each audiometric test.

PRIOR AND CURRENT PROGRESS
To date, the Beltone 5000 audiometer for high frequency audiometric testing has not been purchased. Therefore, no subjects have been entered into this study. It was recently discovered by the PI that the proper paperwork has not been completed for purchase of the audiometer. This will be undertaken during the next year.

CONCLUSIONS
None.

REPORT DATE: 06/03/92 WORK UNIT # 2509

DETAIL SUMMARY SHEET

TITLE: Wound Healing: The Effect of Platelet Derived Growth Factor on the Tensile Strength of Wounds Closed Under Tension in Rats

KEYWORDS: tensile strength, rats, wounds

PRINCIPAL INVESTIGATOR: Tzikas, Thomas MAJ MC
ASSOCIATES: Pickett, Bradley MAJ MC; Brammer, Robert COL MC

DEPARTMENT: Department of Surgery
SERVICE: Otolaryngology-Head & Neck Surgery Svc

STATUS: Completed
APPROVAL DATE: Dec 1990

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

STUDY OBJECTIVE
To evaluate the effects of platelet-derived growth factor on the tensile strength of wounds closed under equal tension in rats and on the tensile strength of wounds closed without tension.

TECHNICAL APPROACH
Six groups of 12 rats each were divided into: (1) no tension control; (2) tension control; (3) zyplast collagen-no tension; (4) zyplast collagen-tension; (5) zyplast collagen/platelet-derived growth factor-no tension; or (6) zyplast collagen/platelet-derived growth factor-tension. The animals in each group were euthanized at 5 days, and the excised wounds were evaluated for tensile strength.

PRIOR AND CURRENT PROGRESS
The experimental study is completed. Data is currently being analyzed.

CONCLUSIONS
Pending data analysis.

REPORT DATE: 06/24/92 WORK UNIT # 2512

DETAIL SUMMARY SHEET

TITLE: Analysis of Wounds by a Soft Tissue Hardness Transducer (STHT) System: A Pilot Study

KEYWORDS: STHT system

PRINCIPAL INVESTIGATOR: Hayes, David MAJ MC

DEPARTMENT: Department of Surgery STATUS: Terminated
SERVICE: Otolaryngology-Head & Neck Surgery Svc APPROVAL DATE: May 1991

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

STUDY OBJECTIVE
This research protocol has been administratively terminated.

TECHNICAL APPROACH
This research protocol has been administratively terminated.

PRIOR AND CURRENT PROGRESS
This research protocol has been administratively terminated.

CONCLUSIONS
This research protocol has been administratively terminated.

REPORT DATE: 08/18/92 WORK UNIT # 2585

DETAIL SUMMARY SHEET

TITLE: Incidence of Maxillary Sinusitis in Nasally Intubated Patients

KEYWORDS: maxillary sinusitis, intubated

PRINCIPAL INVESTIGATOR: Callahan, Scott CPT MC
ASSOCIATES: Cukier, Andrew CPT MC

DEPARTMENT: Department of Surgery
SERVICE: Otolaryngology-Head & Neck Surgery Svc

STATUS: Terminated
APPROVAL DATE: Mar 1988

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

STUDY OBJECTIVE
To determine the incidence of maxillary sinusitis in patients with a prolonged period of indwelling nasal tubes of varying sizes and functions.

TECHNICAL APPROACH
Patients in the ICU and on the ward with nasal endotracheal tubes and/or nasogastric tubes for greater than 3 days will be evaluated with weekly sinus x-rays and biweekly sinus ultrasounds for evidence of maxillary sinusitis. If evidence is found, a sinus puncture will be done to determine the causative organism.

PRIOR AND CURRENT PROGRESS
This research protocol has been administratively terminated.

CONCLUSIONS
This research protocol has been administratively terminated.

REPORT DATE: 04/15/92 WORK UNIT # 2597

DETAIL SUMMARY SHEET

TITLE: Wound Healing: Development of Tensile Strength Vs. Time for Wounds Closed Under Tension in Rats

KEYWORDS: wound healing, tension, tensile strength

PRINCIPAL INVESTIGATOR: Pickett, Bradley CPT MC
ASSOCIATES: Burgess, Lawrence MAJ MC; Livermore, George CPT MC

DEPARTMENT: Department of Surgery
SERVICE: Otolaryngology-Head & Neck Surgery Svc

STATUS: Completed
APPROVAL DATE: Nov 1989

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

STUDY OBJECTIVE
To demonstrate the time course of development of tensile strength in wounds closed with and without tension.

TECHNICAL APPROACH
The study will be performed by dividing Sprague-Dawley rats into experimental and control groups. In the experimental group, skin will be removed from the area of the panniculus carnosus and wounds will be closed creating approximately 90 grams of closing tension. Control rats will have transverse incisions closed under minimal tension. Rats will be euthanized at 5, 7, 10, 14 and 21 days. The wounds will then be harvested and subjected to breakload testing.

PRIOR AND CURRENT PROGRESS
The study was completed, and the results show that wounds closed under tension have greater tensile strength than control wounds beginning at 7 days of healing. In both control and tension wounds, the increase in wound tensile strength began to plateau after 21 days. Studying the time course of increase in wound tensile strength, there appears to be two rapid periods of growth that correspond to the proliferative and maturation phases of wound healing. These findings applied to tensile strength curves imply that wounds closed under tension gain tensile strength at a greater rate than control wounds during the proliferative phase of wound healing. During the maturation phase of wound healing, the rates for increase in wound strength are nearly identical for experimental and control wounds.

CONCLUSIONS
This study confirms the findings of a previous study showing greater wound tensile strength in wounds closed under tension. Additionally, the time course for increase in tensile strength demonstrates two periods of rapid growth that correspond to biological events during wound healing. Wounds closed under tension are stronger primarily because of changes that occur during the scar proliferation.

REPORT DATE: 01/17/92 WORK UNIT # 2114

DETAIL SUMMARY SHEET

TITLE: Phase I Study of the Sclerosant Agent Aethoxyskerol in Patients with Varicose Veins of the Lower Extremities

KEYWORDS: Aethoxysklerol, sclerosant, varicose veins

PRINCIPAL INVESTIGATOR: Villavicencio, Leonel MD
ASSOCIATES: Lauer, Carl MD; Gomez, Edward LTC MC

DEPARTMENT: Department of Surgery
SERVICE: Peripheral Vascular Surgery Service

STATUS: Completed
APPROVAL DATE: Oct 1990

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

STUDY OBJECTIVE

To evaluate in a pilot study of 10 carefully monitored patients with varicose veins of the lower extremities, the relative safety of injections of the sclerosing agent, Aethoxysklerol (Polidocanol), given intravenously into the effected varicosities.

TECHNICAL APPROACH

Standard dosage (40 mg) of the sclerosing agent will be administered to each patient. Medical history and physical exam [BP, pulse, respiration, temperature, and lab exams (including liver function tests, CBC, urinalysis), EKG, and pulmonary function tests] will be performed. These routine studies will be completed pre-injection, and 120 min and 7 days post-injection. Color photographs will be taken before injection and after injection at 1 and 2 wk and at 1 and at 2 mo. Elastic stockings will be prescribed after treatment. Immediate reactions (e.g., pain, swelling) and delayed local reactions (e.g., vein thrombosis, ecchymosis) will be noted. Systemic reactions (e.g., dizziness, nausea) will be recorded.

PRIOR AND CURRENT PROGRESS

The study went smoothly. All patients were interested in attending their treatment sessions and were very cooperative. They came punctually to their appointments and were followed carefully. An assigned nurse coordinator assisted in data collection and appointment scheduling. The study ended as planned, and the material was given to the FDA for approval of Phase II-III which will be a multicenter trial of Polidocanol involving 440 patients. Patients' charts contain photos taken at the different intervals and provide an excellent demonstration of the effectiveness and safety of the drug.

CONCLUSIONS

Absence of systemic effects and low response values observed in study are considered indicators of safety. The vital signs and laboratory values did not vary by more than one-half the clinical normal range. All patients were compliant, and very satisfied when treatment ended. There were no complications with the Polidocanol injection. In summary, Polidocanol proved to be a safe substance when utilized as a sclerosing agent for varices of the lower extremities.

REPORT DATE: 08/04/92 WORK UNIT # 2906

DETAIL SUMMARY SHEET

TITLE: Intracellular Studies with Epidermal Growth Factor

KEYWORDS: EGF, processing

PRINCIPAL INVESTIGATOR: Robie, Daniel CPT MC
ASSOCIATES: Schaudies, Paul CPT MS

DEPARTMENT: Department of Surgery
SERVICE: Plastic Surgery Service

STATUS: Terminated
APPROVAL DATE: Mar 1988

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

STUDY OBJECTIVE
a) To determine the effect of epidermal growth factor (EGF) on human breast cancer cell lines; b) To study interactions between growth factor and malignant cells; and c) To measure levels of EGF and receptors in benign and malignant breast disease.

TECHNICAL APPROACH
Attempt to establish malignant cell lines and to assay cells in terms of binding internalization, processing and growth responsiveness to EGF. Lyophilized homogenates of normal and pathologic breast tissue will be measured for content of EGF using a radioimmunoassay. Comparison between benign and malignant breast disease for EGF content and correlation with patient factors (i.e., hormone levels) will be calculated.

PRIOR AND CURRENT PROGRESS
This research protocol has been administratively terminated.

CONCLUSIONS
This research protocol has been administratively terminated.

REPORT DATE: 06/04/92 WORK UNIT # 2909

DETAIL SUMMARY SHEET

TITLE: Analysis of Antibiotic Diffusion Rates and Bacteriocidal Efficacy of Diffused Antibiotics Across a Silicone Breast Implant

KEYWORDS: antibiotic, diffusion, implant

PRINCIPAL INVESTIGATOR: Smith, George COL MC

DEPARTMENT: Department of Surgery STATUS: Completed
SERVICE: Plastic Surgery Service APPROVAL DATE: May 1990

FUNDING: Current FY: $ 0 Previous FYs: $ 1,042 Total: $ 1,042

STUDY OBJECTIVE
To investigate the rate of gentamycin diffusion through a silicone membrane in a double lumen breast implant.

TECHNICAL APPROACH
80 milligrams of gentamycin will be diluted with 50 cc of normal saline. Fluid will then be placed in the lumen of a double saline-gel breast implant. The implant will be incubated at 37 degrees C in a beaker of saline. Samples of the saline bath surrounding the implant will be collected at various times over 2 weeks. Samples will be submitted for antibiotic concentration analysis. On the original study ANCEF was being studied, but in the pilot study the concentration of ANCEF that diffused through the silicone was insufficient for analysis. The study, therefore, has been limited to gentamycin analysis.

PRIOR AND CURRENT PROGRESS
A sample of implants were studied as described. The results were inconsistent and defied statistical analysis due to small sample size and due to inconsistent results from controls. As funds were exhausted, the study was closed.

CONCLUSIONS
The sample size was too small and/or the measurements too imprecise to draw conclusions from this study.

REPORT DATE: 02/05/92 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: Ongoing
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. There will be four treatment groups of six dogs each randomized onto an 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
For the period of March through April 1991, the alveolar clefts were prepared. From April to September 1991, the alveolar cleft and oronasal fistula were allowed to mature in each animal. In September and October 1992, the stents were removed from the fistuli and the inflammation allowed to subside. During the reporting period, 25 animals were utilized (one dog was euthanized due to previous surgery). In January 1992, two additional dogs were euthanized due to non-related causes. The necropsy report is pending.

CONCLUSIONS
The alveolar cleft model in the dog was successfully executed, and we are to begin treatment of the cleft as described.

REPORT DATE: 02/05/92 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: Ongoing
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 operated but 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 pending availability of a recombinant, highly purified BIP, we decided to defer treatment of the non-human primates with the originally planned partially purified protein. Therefore, the 18 non-human primates were turned in, and we are awaiting re-issue of the new NHPS to be treated with the recombinant, highly purified bone inductive protein currently available.

CONCLUSIONS
Awaiting initiation of the protocol.

REPORT DATE: 02/05/92 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 created and either fixed in place or advanced with either semi-rigid fixation (wire fixation) or rigid fixation (plates and screws). The fifth treatment group will consist of the control. At 6 months, three non-human primate species from each treatment group will be euthanized and the skulls evaluated using topographical landmarks and a three SPACE digitizer. The cranial module will be calculated for each specimen. Individual cranial metric measurements will be divided by the individual cranial modules. The remainder of the non-human primate species will be euthanized at 1 year post-treatment, and the skulls evaluated similarly.

PRIOR AND CURRENT PROGRESS

Due to the non-availability of funding during the reporting period, no progress was realized. Subsequently, funding has been made available from the U.S. Army Research and Development Command.

CONCLUSIONS

Awaiting initiation of protocol.

REPORT DATE: 05/26/92 WORK UNIT # 2913

DETAIL SUMMARY SHEET

TITLE: Platelet Derived Growth Factor Formula in the Treatment of Chronic Wounds

KEYWORDS: growth factors, platelets, wound

PRINCIPAL INVESTIGATOR: Antoine, Gregory LTC MC

DEPARTMENT: Department of Surgery STATUS: Ongoing
SERVICE: Plastic Surgery Service APPROVAL DATE: Jan 1991

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

STUDY OBJECTIVE
To determine the effect platelet products have on the healing of diabetic chronic ulcers. This project will also serve as a pilot study of non-diabetic wounds.

TECHNICAL APPROACH
This is a double-blind, crossover, control study. Each patient will be treated for 3 weeks with a salve prepared from their own platelets or with a placebo salve. Following a 2 week washout period, there will be a crossover. After completion of the 8 week study, the patients may enter an open study of platelet formulation for no more than 6 weeks. If the wound is unhealed at that time, the patients will be offered WU# 2113 as an alternative.

PRIOR AND CURRENT PROGRESS
This study has not been initiated as funding has not been approved by USAMRDC.

CONCLUSIONS
None.

REPORT DATE: 07/21/92 WORK UNIT # 2710

DETAIL SUMMARY SHEET

TITLE: Fresh Tissue Procurement for NIH Tissue Culture

KEYWORDS: colon mucosa, bronchial epithelial, pleural fluids

PRINCIPAL INVESTIGATOR: Edwards, Fred LTC MC

DEPARTMENT: Department of Surgery STATUS: Completed
SERVICE: Thoracic Surgery Service APPROVAL DATE: Apr 1987

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

STUDY OBJECTIVE
To study the metabolic activation and deactivation of chemical carcinogens in cultured lung and colon explants. To study the capability of human lung and colon epithelium to metabolize chemical carcinogens to mutagens. To investigate biochemical differences of normal and tumor tissue.

TECHNICAL APPROACH
Lung and colon tissue removed at time of biopsy or resection are transported to NIH where tissue cultures will be established and cytochemical studies performed. These results will be compared to demographic and environmental profiles.

PRIOR AND CURRENT PROGRESS
During the time period of 1 May 1991 to 20 July 1992, 32 patients have been enrolled, with 32 tumor/lung/blood specimens delivered to the National Institutes of Health (NIH) for this study.

CONCLUSIONS
This protocol is offering no educational benefit to the Thoracic Surgery Service, Department of Surgery, and should be closed.

REPORT DATE: 08/27/92 WORK UNIT # 2712

DETAIL SUMMARY SHEET

TITLE: Surgical Implications of Three-dimensional Modeling of the Heart

KEYWORDS: modeling, heart, computer

PRINCIPAL INVESTIGATOR: Edwards, Fred COL MC

DEPARTMENT: Department of Surgery STATUS: Ongoing
SERVICE: Thoracic Surgery Service APPROVAL DATE: Sep 1991

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

STUDY OBJECTIVE
To focus on the creation of an accurate detailed extensive two- and three-dimensional computer graphic model of the normal adult human heart and its integration with an interactive computer-aided interface.

TECHNICAL APPROACH
For this project, a Silicon Graphics 4D/310VGX graphics workstation will be utilized. Incorporating a 33 MHz RISc processor, the system will be capable of 30 MIPS and 5 MFLOPS of performance. The VGX graphics subsystem will provide 40 MFLOPS of performance dedicated to graphics processing and 48 bits of color display. This system is capable of real time manipulation of highly complex rendered 3-dimensional objects. Two commercial software packages will be used to provide the maximum number of possible applications for the 3-dimensional cardiothoracic data set.

PRIOR AND CURRENT PROGRESS
During the past fiscal year, USAMRDC considered this protocol for funding; however, funds were not awarded. This study will be reconsidered by USAMRDC during FY93 for funding.

CONCLUSIONS
None.

REPORT DATE: 04/21/92 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 and 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 study is a multiple group cooperative effort, and accrual of 600 patients is expected. WRAMC randomized 24 patients to the protocol. Two patients are being followed on drug. Three patients are being followed off drug. Eighteen patients have died due to prostate cancer. One patient is lost to follow-up. Study has been closed to patient accrual at WRAMC and remains open for follow-up only.

CONCLUSIONS
It was concluded that in patients with advanced prostate cancer, treatment with leuprolide and flutamide is superior to treatment with leuprolide alone.

REPORT DATE: 01/10/92 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
In patients with locally advanced bladder cancer: (1) To compare the survival of those treated with cystectomy alone to those treated with M-VAC (methotrexate/vinblastine/Adriamycin/cisplatin) followed by cystectomy in a randomized Phase III neoadjuvant trial; and (2) To quantify the "tumor downstaging" effect of neoadjuvant M-VAC.

TECHNICAL APPROACH
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
There are two patients in this study. The first patient was randomized to M-VAC plus radical cystectomy. The second patient was randomized to cystectomy. Both patients are doing very well. No adverse reactions to treatment or toxicities have been noted.

CONCLUSIONS
None.

REPORT DATE: 01/27/92 WORK UNIT # 2847

DETAIL SUMMARY SHEET

TITLE: ECOG EST 5886 A Phase III Trial of Cisplatin Alone or in Combination with Doxorubicin, Vinblastine and Methotrexate in Advanced Bladder Cancer

KEYWORDS: doxorubicin, vinblastine, methotrexate

PRINCIPAL INVESTIGATOR: McLeod, David COL MC

DEPARTMENT: Department of Surgery STATUS: Completed
SERVICE: Urology Service APPROVAL DATE: Oct 1988

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

STUDY OBJECTIVE
To determine if cisplatin in combination with doxorubicin, vinblastine, and methotrexate is more effective than cisplatin alone in the treatment of patients with advanced bladder cancer, in terms of objective response rate, response duration and survival.

TECHNICAL APPROACH
Randomized, multicenter, Phase III trial for patients with histologically proven advanced bladder carcinoma, not curable by surgery or radiation therapy. Patients are randomized to cisplatin alone or methotrexate, vinblastine, Adriamycin, and cisplatin.

PRIOR AND CURRENT PROGRESS
There have been no patients randomized to this protocol from WRAMC. This protocol was terminated by the ECOG in May 1989; however, administrative error has resulted in the study being reported for the first time as closed with this report.

CONCLUSIONS
None.

REPORT DATE: 04/30/92 WORK UNIT # 2850

DETAIL SUMMARY SHEET

TITLE: ECOG EST 3887 Phase III Chemotherapy of Disseminated Advanced Stage Testicular Cancer with Cisplatin Plus Etoposide with Either Bleomycin or Ifosfamide

KEYWORDS: testicular cancer, VIP, BEP

PRINCIPAL INVESTIGATOR: McLeod, David COL MC

DEPARTMENT: Department of Surgery STATUS: Completed
SERVICE: Urology Service APPROVAL DATE: Dec 1988

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

STUDY OBJECTIVE
To determine response rate and duration of remission of BEP compared to VIP combination therapy; to determine the toxicity of VIP compared to BEP combination chemotherapy; and to confirm the efficacy and toxicity of intravenous Mesna.

TECHNICAL APPROACH
Patients are randomized to VIP (cisplatin, ifosfamide, Mesna, etoposide) or BEP (cisplatin, etoposide, bleomycin). Patients are reevaluated after 4 weeks of treatment and are observed/treated based on patient response to randomized therapy.

PRIOR AND CURRENT PROGRESS
There are four (4) patients enrolled on this protocol. All four patients have done well on their individual treatments. Two patients were randomized to treatment Arm A (VIP). Two patients were randomized to treatment Arm B (BEP). All patients will receive G-CSF (granulocyte colony stimulating factor). The patients enrolled will be followed off-study. The Eastern Cooperative Oncology Group closed this study effective April 1992. The study had met its accrual goals.

CONCLUSIONS
None.

REPORT DATE: 04/21/92 WORK UNIT # 2854

DETAIL SUMMARY SHEET

TITLE: ECOG EST 3886 Randomized Phase III Evaluation of Hormonal Therapy Vs. Observation in Patients with Stage D1 Adenocarcinoma of the Prostate Following Pelvic Lymphadenectomy and Radical Prostatectomy

KEYWORDS: zoladex, orchiectomy, adenocarcinoma/prostate

PRINCIPAL INVESTIGATOR: McLeod, David COL MC

DEPARTMENT: Department of Surgery STATUS: Ongoing
SERVICE: Urology Service APPROVAL DATE: Feb 1989

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

STUDY OBJECTIVE
To determine the time to progression and survival in patients with histologically confirmed Stage D1 prostate cancer following radical prostatectomy and pelvic lymphadenectomy treated with no immediate hormonal therapy compared to those treated immediately with hormonal therapy.

TECHNICAL APPROACH
This is a multicenter randomized Phase III trial. Patients can be randomized to hormonal therapy or observation. Those patients randomized to observation may be registered to receive hormonal therapy if their disease progresses. All patients that progress on hormonal therapy will be followed off study drug.

PRIOR AND CURRENT PROGRESS
Throughout the country, 87 patients have been enrolled in this study. No patients have been randomized to this protocol from WRAMC.

CONCLUSIONS
None as yet.

REPORT DATE: 07/19/92 WORK UNIT # 2858

DETAIL SUMMARY SHEET

TITLE: Treatment of Benign Prostatic Enlargement Using Balloon Dilatation

KEYWORDS: BPH, BPH dilator

PRINCIPAL INVESTIGATOR: McLeod, David COL MC

DEPARTMENT: Department of Surgery STATUS: Completed
SERVICE: Urology Service APPROVAL DATE: Jul 1989

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

STUDY OBJECTIVE
(1) Verify the performance of the device; (2) Det rmine the pressures and diameter required to dilate the prostate; (3) Determine that these are not anticipated, adverse responses to this intervention; and (4) Judge the quality of the clinical result.

TECHNICAL APPROACH
Male patients will be chosen, ages 45 and older. Patients will be selected at the investigator's discretion and consistent with standard practice in evaluating patients for prostatic surgery.

PRIOR AND CURRENT PROGRESS
In February 1992 the HUC/IRB was informed that patient accrual to the 90 Fr was closed. Patients, however, were continued to be enrolled to the Fr 120 balloon. A total of nine patients were enrolled from WRAMC to the 40 Fr arm, and one patient was enrolled to the 120 Fr arm. Due to poor patient accrual, this study is being closed.

CONCLUSIONS
None.

REPORT DATE: 09/11/92 WORK UNIT # 2859

DETAI "IMMARY 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: Ongoing
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 28 patients have been randomized to this protocol; 2 this past fiscal year. Ten (10) patients have died due to prostate cancer. The 18 remaining patients are being followed in the Urology Clinic every 3 months or sooner if necessary. Of these patients, nine are being followed on study drug (flutamide vs. placebo), seven are being followed off drug, and two are being followed on open labeled flutamide. There have been no incidence of serious or unexpected adverse reactions.

CONCLUSIONS
None at this time.

REPORT DATE: 05/27/92 WORK UNIT # 2860

DETAIL SUMMARY SHEET

TITLE: Expression of C-ErbB-2 Oncoprotein in Prostatic Carcinoma

KEYWORDS: c-ErbB-2, prostate, cancer

PRINCIPAL INVESTIGATOR: Moul, Judd MAJ MC
ASSOCIATES: Kuhn, Eric MAJ MC; Sesterhenn, Isabel MD

DEPARTMENT: Department of Surgery
SERVICE: Urology Service

STATUS: Ongoing
APPROVAL DATE: Oct 1989

FUNDING: Current FY: $ 482 Previous FYs: $ 0 Total: $ 482

STUDY OBJECTIVE

To determine if the c-erbB-2 oncogene protein is over expressed in prostate cancer. In breast cancer, this oncogene's expression correlates to adverse prognosis, and we seek to determine if a similar association is present for prostate cancer.

TECHNICAL APPROACH

(1) Obtain paraffin archival pathologic material from prostate cancer cases. (2) Immunohistochemistry staining for c-erbB-2 oncoprotein in sections from these cases. (3) Correlation of staining to clinical outcome. (4) Differential polymerase chain reaction (PCR) to assay for c-erbB-2 gene amplification in those cases that exhibited protein expression.

PRIOR AND CURRENT PROGRESS

Data collection has been completed with the following findings: a) Definite positive membranous staining for c-erbB-2 oncoprotein was detected in 18/53 (34%) clinically localized prostatic carcinomas; b) Staining was essentially equally distributed among grades and stages: 6/27 (22%) well differentiated; 8/20 (40%) moderately differentiated; 4/6 (66%) poorly differentiated; 6/18 (33%) pathologic Stage B; 12/23 (36%) pathologic Stage C; c) For the 18 positive staining cases, no gene amplification was detected via differential PCR; and d) At a mean follow-up of 36 months, there was a trend toward a more adverse prognosis for those cases expressing the c-erbB-2 oncoprotein.

CONCLUSIONS

Approximately one-third of clinically localized prostate cancers express the c-erbB-2 oncoprotein via immunohistochemistry using pAB-1 in archival material. Although oncoprotein expression was detected, no cases demonstrated DNA gene amplification. Although results are preliminary, c-erbB-2 might be a prognostic marker for prostate cancer.

REPORT DATE: 05/27/92 WORK UNIT # 2862

DETAIL SUMMARY SHEET

TITLE: Flow Cytometric Proliferative Activity in Stage I Nonseminomatous Testicular Cancer

KEYWORDS: flow cytometry, testicular cancer, Stage I

PRINCIPAL INVESTIGATOR: Moul, Judd MAJ MC
ASSOCIATES: Foley, John MAJ MC; Hitchcock, Charles MAJ MC

DEPARTMENT: Department of Surgery
SERVICE: Urology Service

STATUS: Ongoing
APPROVAL DATE: Apr 1990

FUNDING: Current FY: $ 8,780 Previous FYs: $ 5,109 Total: $ 13,889

STUDY OBJECTIVE

To determine if DNA flow cytometric proliferative index (PI) measurement helps aid more accurate staging of clinically localized testicular cancer. To determine if this flow cytometric measurement (FCM) parameter will discern who is pathologic Stage I vs. occult Stage II.

TECHNICAL APPROACH

The cohort consists of all patients treated at Walter Reed since 1980 who were clinical Stage I preoperatively and then underwent retroperitoneal lymphadenectomy for testicular cancer. From this group, two subgroups were identified: Group 1 were patients without retroperitoneal metastases who were pathologic Stage I; group 2 were patients with occult retroperitoneal metastases discovered and, therefore, upstaged to Stage II. Paraffin archival histological material was obtained on these cases and subjected to FCM.

PRIOR AND CURRENT PROGRESS

Data collection has been completed with the following findings: 47 archival blocks were examined for the 23 Stage I patients and 26 blocks for the 13 Stage II patients. Of the 73 block FCM samples, 50 (69%) were aneuploid, 20 (27%) were multiploid, and 3 (4%) were diploid. The mean DNA index (DI) for Stage I and II was 1.72 and 1.42, respectively; suggesting a loss of genetic material as the tumors progressed. The mean percent-S phase (%S) (all sample cells) was 16.4 vs 17.2 for Stage I and II, respectively, and the mean %S for aneuploid-only cell population was 20.5 vs 31.5 ($p = 0.0254$), respectively. The mean proliferative activity (PI) was 30.7 for the 19 evaluable Stage I cases and 45.4 ($p = 0.0134$) for the 10 evaluable Stage II cases.

CONCLUSIONS

Flow cytometry measurements such as %S-aneuploid and PI may help stratify clinical Stage I nonseminomatous testicular germ tumor (NSGT). Further work is necessary on a larger cohort of patients, as well as subjecting data to multivariate analysis, to determine if FCM may be a clinically useful study for patients with testicular cancer.

REPORT DATE: 01/27/92 WORK UNIT # 2863

DETAIL SUMMARY SHEET

TITLE: A Dose Response Study of the Effect of Flutamide on Benign Prostatic Hypertrophy

KEYWORDS: flutamide, BPH

PRINCIPAL INVESTIGATOR: McLeod, David COL MC

DEPARTMENT: Department of Surgery STATUS: Completed
SERVICE: Urology Service APPROVAL DATE: Jun 1990

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

STUDY OBJECTIVE
To evaluate the dose response of flutamide in patients with benign prostatic hypertrophy as measured by: a) improvement in maximum urinary flow rate, b) reduction in prostate volume, c) improvement in symptom score, and d) reduction in residual urine.

TECHNICAL APPROACH
Patients with symptoms of benign prostatic hypertrophy are randomized to placebo or flutamide. Flutamide dosages: 125 mg BID, 250 mg BID, 250 mg TID, 250 mg QD. All drugs are given over a 24 week span of time. The endpoints of the study are urinary flow rates, prostate size, residual volume, PSA, and subjective symptoms.

PRIOR AND CURRENT PROGRESS
Five patients have entered this protocol. One patient has completed the study. The last patient enrolled suffered a heart attack 59 days after entering study, which was not believed to be related to the study medication. This was reported to the study sponsor. All other patients are alive and well. This study has reached its accrual goals and is, therefore, completed.

CONCLUSIONS
None.

REPORT DATE: 07/10/92 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

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 asse s 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
Three patients have been randomized to this protocol. Two patients have been randomized to radiation and have done well on their treatment. One patient was randomized to observation and is doing well.

CONCLUSIONS
None.

REPORT DATE: 07/21/92 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.

PRIOR AND CURRENT PROGRESS
As of June 1992, the population enrolled into this clinical trial at WRAMC totals 61 subjects: 41 randomized (2 drug, 6 balloon dilation, 8 watchful waiting, and 25 TURP); and 20 non-randomized (2 drug, 0 balloon dilation, 5 watchful waiting, and 13 TURP). The protocol has been closed to enrollment of follow-up and Class II (open prostatectomy vs. TURP) subjects.

CONCLUSIONS
No conclusions to date; data collection is ongoing.

REPORT DATE: 06/20/91 WORK UNIT # 2866

DETAIL SUMMARY SHEET

TITLE: ECOG 1890 A Phase II Study of Taxol in Metastatic Prostate Cancer

KEYWORDS: Taxol, prostate cancer, hormone refractory

PRINCIPAL INVESTIGATOR: McLeod, David COL MC

DEPARTMENT: Department of Surgery STATUS: Completed
SERVICE: Urology Service APPROVAL DATE: Nov 1990

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

STUDY OBJECTIVE
To establish the response rate and duration, survival and toxicity of Taxol in patients with advanced hormone refractory prostate cancer.

TECHNICAL APPROACH
Patients are registered to receive Taxol 135-170mg/M2 by continuous infusion over 21 days for a maximum of 6 cycles. Patients are evaluated, and if progressive disease occurs at any time, the patient is discontinued. Patients are observed as being stable, having complete response, or having partial response.

PRIOR AND CURRENT PROGRESS
This study was approved November 1990. No patients have entered the protocol. Termination notice from the Eastern Cooperative Oncology Group was received May 1991.

CONCLUSIONS
This study has met its accrual goals.

REPORT DATE: 09/02/92 WORK UNIT # 2867

DETAIL SUMMARY SHEET

TITLE: Utilization of Cystoscopically Placed Cobra Catheters for Directed Irrigation of Lower Pole Calyceal Stones During Extracorporeal Shock Wave Lithotripsy (ESWL)

KEYWORDS: ESWL, cobra catheters, calyceal stones

PRINCIPAL INVESTIGATOR: Nicely, Eric MAJ MC

DEPARTMENT: Department of Surgery
SERVICE: Urology Service

STATUS: Completed
APPROVAL DATE: Sep 1991

FUNDING: Current FY: $ 1,517 Previous FYs: $ 0 Total: $ 1,517

STUDY OBJECTIVE

To determine whether directed irrigation through a cobra catheter will improve clearance of lower calyceal stones treated with extracorporeal shock wave lithotripsy (ESWL).

TECHNICAL APPROACH

Record review of patients having lower pole renal stones treated with cobra catheter in place and those treated without ureteral catheterization during the same period of time.

PRIOR AND CURRENT PROGRESS

Records review completed of 42 patients having lower pole renal calculi treated without ureteral catherization and 45 patients treated with cobra catheter irrigation during ESWL procedure. Stone-free rate at 3 months in the first group was 54%. Stone-free rate at 3 months in the cobra catheter group was 73%. The p-value for this difference, using Pearson's Chi square test, is 0.07. There were no serious or unexpected adverse reactions identified. Patients treated with the cobra catheter have benefited by decreasing the chances of requiring additional treatment(s) for their lower pole renal calculi.

CONCLUSIONS

The use of a cobra catheter for directed irrigation of lower calyceal renal calculi during ESWL is effective in improving the stone-free rate at 3 months after the procedure.

REPORT DATE: 09/11/92 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
SERVICE: Urology Service

STATUS: Ongoing
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 seven patients have been enrolled into this protocol. Three patients have been randomized to receive androgen blockage before surgery. One patient has had surgery in this group and has had no adverse side effects from the drug therapy. Four patients have been randomized to prostatectomy alone. Of these four patients, three have had surgery and have done well postoperatively. Groupwide, there has been one adverse reaction reported as exacerbation of chronic CHF, multivessel coronary artery disease, and cardiomyopathy with ectopy. This incident was not considered related to the drug therapy administered as part of this study.

CONCLUSIONS

None as yet.

REPORT DATE: 09/15/92 WORK UNIT # 9801

DETAIL SUMMARY SHEET

TITLE: Production of Positive and Negative Control Slides and Mouse Brain Suspension for Fluorescent Rabies Antibody Test

KEYWORDS: rabies

PRINCIPAL INVESTIGATOR: Mouer, Thomas DAC
ASSOCIATES: Choyce, Richard DAC

SERVICE: Veterinary Service STATUS: Completed
APPROVAL DATE: Dec 1986

FUNDING: Current FY: $ 0 Previous FYs: $ 298 Total: $ 298

STUDY OBJECTIVE
To produce positive and negative control slides and absorbing suspensions for specific rabies antigen identification.

TECHNICAL APPROACH
Brain suspensions of normal and rabies infected mouse brain will be used to identify rabies antigen in suspect brain tissue. Fluorescein labelled anti-rabies globulin will be used for all positive, negative, and suspect tissue.

PRIOR AND CURRENT PROGRESS
FY 92 activity:

positive	9
negative	133
Total FAT	142

CONCLUSIONS
This study is being closed, as a new protocol has been written to continue this study.