AD-A100 636 WALTER REED ARMY MEDICAL CENTER WASHINGTON DC F/G 6/5
ANNUAL PROGRESS REPORT (FY-80) DEPARTMENT OF CLINICAL INVESTIGA--ETC(U)
SEP 80 T M BOEHM

UNCLASSIFIED NL

1 OF 8
AD A100636

AD A100636

# ANNUAL PROGRESS REPORT

FY 80

DTIC
SELECTE
S

# DISCLAIMER NOTICE

THIS DOCUMENT IS BEST QUALITY PRACTICABLE. THE COPY FURNISHED TO DTIC CONTAINED A SIGNIFICANT NUMBER OF PAGES WHICH DO NOT REPRODUCE LEGIBLY.

SECURITY CLASSIFICATION OF THIS PAGE *(When Data Entered)*

## REPORT DOCUMENTATION PAGE

READ INSTRUCTIONS BEFORE COMPLETING FORM

| | |
|---|---|
| 1. REPORT NUMBER: MED-300 | 2. GOVT ACCESSION NO.: AD-100636 |
| 3. RECIPIENT'S CATALOG NUMBER: | |
| 4. TITLE *(and Subtitle)*: Annual Progress Report (FY-80) Department of Clinical Investigation Walter Reed Army Medical Center | 5. TYPE OF REPORT & PERIOD COVERED: 1 Oct 79 - 30 Sep 80 |
| | 6. PERFORMING ORG. REPORT NUMBER: |
| 7. AUTHOR(s): TIMOTHY M. BOEHM, LTC MC Chief, Department of Clinical Investigation | 8. CONTRACT OR GRANT NUMBER(s): 7725 |
| 9. PERFORMING ORGANIZATION NAME AND ADDRESS: Department of Clinical Investigation Walter Reed Army Medical Center Washington, D.C. 20012 | 10. PROGRAM ELEMENT, PROJECT, TASK AREA & WORK UNIT NUMBERS: |
| 11. CONTROLLING OFFICE NAME AND ADDRESS: Headquarters, Walter Reed Army Medical Center Washington, D.C. 20012 | 12. REPORT DATE: FY-80 |
| | 13. NUMBER OF PAGES: 694 |
| 14. MONITORING AGENCY NAME & ADDRESS *(If different from Controlling Office)*: Commander, U.S. Army Health Services Command ATTN: HSPA-I Fort Sam Houston, Texas 78234 | 15. SECURITY CLASS. *(of this report)*: Non-Sensitive |
| | 15a. DECLASSIFICATION/DOWNGRADING SCHEDULE: |

16. DISTRIBUTION STATEMENT *(of this Report)*

DISTRIBUTION STATEMENT A
Approved for public release;
Distribution Unlimited

JUN 22 1981

17. DISTRIBUTION STATEMENT *(of the abstract entered in Block 20, if different from Report)*

18. SUPPLEMENTARY NOTES

The findings in this report are not to be construed as an official Department of the Army position unless so designated by other authorized documents.

19. KEY WORDS *(Continue on reverse side if necessary and identify by block number)*

20. ABSTRACT *(Continue on reverse side if necessary and identify by block number)*

Subject report identifies the approved clinical research activities conducted at WRAMC (during FY-80) that have been approved and annually reviewed by the Clinical Investigation and Human Use Committees. An annual progress report is enclosed for each protocol active during FY-80. Also, enclosed is a list of publications and presentations during FY-80 that reflect work accomplished in conjunction with approved clinical investigation protocols.

DD FORM 1 JAN 73 1473 EDITION OF 1 NOV 65 IS OBSOLETE

SECURITY CLASSIFICATION OF THIS PAGE *(When Data Entered)*

REPORTS CONTROL SYMBOL MED-300

# ANNUAL PROGRESS REPORT (FY-80)

DEPARTMENT OF CLINICAL INVESTIGATION

WALTER REED ARMY MEDICAL CENTER

WASHINGTON, D.C. 20012

This report covers the period (1 October 1979 thru 30 September 1980).

APPROVED FOR PUBLIC RELEASE: DISTRIBUTION UNLIMITED

# FOREWORD

The enclosed annual progress reports constitute documentation of continuing review by the WRAMC Institutional Review Board (Clinical Investigation and Human Use Committees) of ongoing research at WRAMC, which is required by DHHS, FDA, DOD, DA, HSC, and WRAMC regulations.

Requests for annual progress reports are sent to investigators in August, and annual progress reports are due 15 October.

When the annual progress reports are received by DCI, they are checked for accuracy and randomly sent to a institutional review board member who either will recommend approval of the annual progress report, request additional information, or propose scrutiny of the annual progress report by the entire board. The process of requesting additional information from the investigator and resubmittal of the information to the IRB member, in particular, is time-consuming but results in approval of the majority of the annual progress reports leaving few for review by the entire committee. All the individual annual progress reports in the current report have been approved by the committee and therefore represent the culmination of the review process for ongoing research.

Please note that there are several blank pages in the report. Blanks represent annual progress reports still in process of review by the WRAMC Institutional Review Board. A supplement containing these yet unapproved annual progress reports will be published later.

The compilation of this report and review of over 350 ongoing projects could not have been accomplished without the perseverance, patience, and proficience of Mrs. Ethel Ervin.

Accession For
NTIS GRA&I
DTIC TAB
Unannounced
Justification
By
Distribution/
Availability Codes
Dist Avail and/or Special
A-1

## Department of Clinical Investigation

During FY 80 the Clinical Investigation Program at Walter Reed Army Medical Center, already easily the largest in Health Services Command, continued to expand. At the beginning of the fiscal year there were 232 active work units, over 137 new research protocols were approved during the course of the fiscal year. There were more than 78 publications related to approved clinical investigation projects. Despite the increasing workload, the Department of Clinical Investigation provided improved support to the Clinical Investigation and Human Use Committees at Walter Reed Army Medical Center by refining the protocol approval process.

Primary and secondary review of research protocols, editorilization of consent forms and refusal to process protocols not reviewed by department chiefs were among the innovations that allowed the Walter Reed Army Medical Center Clinical Investigation Committee and Human Use Committee to subject Walter Reed Army Medical Center research to the highest standards of review for both scientific merit and adequacy of protection of human subjects.

The designation of a full time editorial assistant, Mrs. Iris Hepburn, played an integral role in the improvement in the protocol processing mechanism.

In FY 80 DCI was able to expand the type of support it could provide investigators. Thanks to the dedicated efforts of Mr. Mack Burton, the admininstrative officer, DCI was able to obtain additional space in outlying buildings, which have now become the Animal Research Facility and Gastroenterology Research Lab, finally providing support in two areas that historically had not had adequate facilities.

As FY 80 ended, DCI's first two allied health scientists, Major Lauren Reed and CPT Rudolfo Bongiovanni were approaching the end of their assignments at WRAMC. Both individuals have made substantial contributions to the clinical investigation program at WRAMC and are evidence that the allied health scientist can play a very important role working in conjunction with the MD investigator.

DCI continues to be fortunate to have outstanding command support, both from Major General Baker and his successor Major General Mittemeyer. Despite relatively austere resources, DCI has enjoyed an adequate budget for supplies and contractural services. The Commander, WRAMC approved the move of DCI to more spacious facilities on Ward 61, which DCI has been occupying since 1/80.

The Clinical Investigation Program at WRAMC has also been very considerably strengthened by the members of the CIC and HUC each of whom have unrelated busy duty assignments but nevertheless dedicate several hours of time monthly to the critical review of protocols, counselling investigators with regard to possible improvements in protocols, and protection of human research subjects at WRAMC.

The future of DCI holds challenges and excitement. From the current rate of protocol submittal, it is estimated that we will close FY 81 with over 500 active protocols. DCI has been tasked with supporting the Vietnam Head Injury Study, a four year recall study of head-injured Vietnam veterans funded by a 1.8 million dollar VA grant. It is clear that the Oncology program at WRAMC requires more personnel in order to fulfill all its responsibilities in clinical research. The Neurology Service wishes to enter the arena of Phase II evaluation of antiepileptic drugs. Finally, the new final DHHS and FDA regulations on clinical investigation will need to be implemented.

DEPARTMENT OF CLINICAL INVESTIGATION

TABLE OF CONTENTS


| | | PAGE |
|---|---|---|
| Unit Summary Sheet | | 1 |
| Table of publications and presentations, FY-80 | | 5 |
| Work Unit Numbers and Protocol Titles by Departments | | 13 |


WORK UNIT NUMBERS AND PROTOCOL TITLES BY DEPARTMENTS

DEPARTMENT OF MEDICINE

General Medicine


| | | |
|---|---|---|
| 1004 | Stress Ulceration in a Medical ICU: Incidence and Possible Prevention with Cimetidine. (FY-77 I) | 13 |
| 1005 | Efficacy Trail Using Hydroxyurea (HU) in Thrombocytosis. PVSG Protocol 12. (FY-80 I) | 14 |
| 1006 | Efficacy Trial Using Hydroxyurea (HU) in Polycythemia Vera Study Group. Protocol 8. (FY-80)I | 16 |


Nephrology and Renal Dialysis Service


| | | |
|---|---|---|
| 1121 | Combination Prednisone and Cytoxan Therapy Coupled with Plasma Exchange in the Treatment of Anti-Glomerular Antibody Membrane Mediated Renal Disease. (FY-76 IP) | 18 |
| 1124 | The Effect of Hyperuricemia on Chronic Renal Failure. (FY-78 I) | 20 |
| 1125 | State of Potassium Balance in the Adult Acute Leukemic Patient. (FY-78 F) | 22 |
| 1127 | Characterization and Response to Therapy in Mild Essential Hypertension. (FY-79 I) | 24 |
| 1128 | Evaluation of the Rehabilitation of End-State Renal Disease Patients by Hemodialysis and Kidney Transplantation Using Activity Recordings. (FY-79 I) | 26 |
| 1129 | Comparison of the Cardiopulmonary Variables in Patients Dialyzed Against Acetate or Bicarbonate Buffer. (FY-79 I) | 28 |
| 1130 | The Role of Hyperuricosuria in the Nephrotoxicity of Radiocontrast Agents. (FY-79 I) | 31 |
| 1131 | [illegible] Anticoagulation Therapy with Coumadine. (FY-80 I) | 33 |

DEPARTMENT OF MEDICINE continued


| | | PAGE |
|---|---|---|
| **Cardiology Service** | | |
| 1215 | Double Blind Evaluation of Lopressor Vs Placebo in the Treatment of Angina Pectoria. (FY-80 I) | 35 |
| **Endocrinology-Metabolism Service** | | |
| 1308 | Inderal Kinetics in Hyperthyroidism. (FY-74 T) | 38 |
| 1310 | TRH in Patients with Hypothalamic-Pituitary Thyroid Disease. (FY-72 P I) | 39 |
| 1311 | Treatment of Thyroid Storm with Anion-Exchange Resin. (FY-74 I) | 43 |
| 1334 | The Regulation of Extrathyroidal Conversion of Thyroxine (T4) to Triiodothyronine (T3). (FY-75 I) | 45 |
| 1340 | Use of Fluorescent Thyroid Scanning to Evaluate Iodine Kinetics during Prophylthiouracil Therapy of Graves' Disease. (FY-76 P I) | 48 |
| 1346 | Thyroid Function Tests in Cord Blood, Maternal Sera and Amniotic Fluid. (FY-76 P I) | 50 |
| 1347 | Investigations into the Physiology of L-Reverse T-3 (rT3) and -3-3 Diiodothyronine (3-3 T2). (FY-76 P I) | 52 |
| 1353 | The Regulation of T4 Conversion. A Grant Proposal. (FY-77 SP I) | 54 |
| 1354 | Purification of Testosteroneestradiol Binding Globulin. A Grant Proposal. (FY-77 I) | 56 |
| 1355 | The Effect of Short-Term High-Dose Steroid upon Thyroidal Release in Thyrotoxicosis. (FY-77 F) | 58 |
| 1357 | Effect of T3 and rT3 on Extracellular Cyclic Nucleotide Levels in Humans. (FY-77 F) | 59 |
| 1358 | The Effect of Obesity and Fasting on T3 Receptors in Circulating Mononuclear Cells. (FY-77 P I) | 60 |
| 1359 | The Effect of Reverse T3 and 3, 3 T2 on Thyroid Gland Secretion, T4 Degradation, and Iodide Leak in Thyrotoxic Patients. (FY-77 F) | 62 |
| 1360 | Investigations Concerning T3 Production Rates. (FY-77 I) | 63 |
| 1361 | Postoperative Changes in Free Testosterone and Sex-Hormone-Binding Globulin. (FY-77 T) | 65 |

DEPARTMENT OF MEDCINE continued

Endocrinology-Metabolism Service continued


| | | PAGE |
|---|---|---|
| 1362 | Medical Treatment of Amenorrhea-Galactorrhea Syndrome with Vitamin $B_6$ (Pyridoxine). (FY-77 SP I) | 66 |
| 1363 | Effect of T3 and rT3 on Plasma Cyclic Nucleotide Levels in Sheep. (FY-77 P I) | 68 |
| 1364 | Effect of L-Tryptophan on LSH and FSH Dynamics in Women. (FY-77 I) | 70 |
| 1365 | Insulin Resistance in Diabetes: Relative Effect of Glucose and Amino Acids. (FY-77 SP P I) | 72 |
| 1366 | The Effect of Glucagon on Thyroidal Economy. (FY-77 F) | 74 |
| 1367 | Effect of Methyldopa on Serum LH and Testosterone in Hypertensive Men. (FY-77 I) | 75 |
| 1368 | Effect of Dietary Phosphate on Serum Levels of Vitamin D Metabolites in Hypoparathyroidism. (FY-77 I) | 77 |
| 1370 | Sex Steroid Receptors in the Human Thyroid Gland. (FY-77 I) | 79 |
| 1371 | Glucose Regulation of Peripheral Thyroidal Economy in Fasted Subjects. (FY-77 P I) | 81 |
| 1372 | Alterations in the Thyrotropin (TSH) Response to Thyrotropin-Releasing Hormone (TRH) Stimulation in Obesity and Fasting.(FY-77 P F) | 82 |
| 1374 | Evaluation of Testosterone Reserve in Infertile Men.(FY-77 SP P I) | 83 |
| 1376 | Effect of Amitriptyline and Amantadine on Growth Hormone Dynamics in Normoglycemia. (FY-77 P I) | |
| 1377 | Effect of Dietary Trytophan Content on Food Intake in Obese Subjects. (FY-77 I) | 87 |
| 1379 | Effect of Post-Weaning Undernutrition on Reproductive Hormones in Rats. (FY-77 SP P I) | 89 |
| 1380 | Effect of Thyroid Status on the Hormonally-Induced Cyclic AMP Responses of the Kidney. (FY-77 P I) | 91 |
| 1381 | Estradiol ($E_2$) Receptors in Rat Thyroid Glands. (FY-77 I) | 93 |
| 1382 | Measurement of Steroids in Fluid Obtained by Micropuncture from Rat Seminiferous Tubules and Epididymes. (FY-77 I) | 95 |
| 1383 | Measurement of Hemoglobin $A_{1-C}$ in the Assessment of the Efficacy of Diabetic Treatment. (FY-77 F) | 97 |

DEPARTMENT OF MEDICINE continued


| Endocrinology-Metabolism Service | | PAGE |
|---|---|---|
| 1385 | Serial Changes in Free Testosterone during Pregnancy Correlation with HCG Levels and Fetal Sex. (FY-78 SP I) | 98 |
| 1386 | The Effect of $\Delta^1$-Testolactone (Teslac) in Male Infertility. (FY-78 P I) | 100 |
| 1387 | Acute Response to Estrogen in Men with Prostate Carcinoma (FY-80 I) | 102 |
| 1388 | The Development of a Radioimmunoassay for Thyronine and 3,5-T2. (FY-78 T) | |
| 1389 | The Effect of Dietary Carbohydrates on T3 Receptor Kinetics. (FY-78 P) | 104 |
| 1390 | Investigations Concerning the Physiology of Iodothyronines during Fasting (FY-78 P I) | 106 |
| 1391 | Regulation of the Initiation of Thyroid Hormone Action.(FY-78 SPI) | 108 |
| 1392 | Steroid Transfer across the Blood-Cerebrospinal Fluid Barrier in the Rhesus Monkey. (FY-78 T) | 110 |
| 1393 | T3 Receptors in Normal and Fasting Rats. (FY-78 I) | 111 |
| 1395 | $T_4$ and $T_3$ Conversion: Effect of Modulation of Glucose Metabolism. (FY-78 I) | 113 |
| 1396 | $T_4$ to $T_3$ Conversion: Effect of Somatostatin Administration. (FY-78 I) | 115 |
| 1397 | The Effect of Free Fatty Acids on Serum Reverse T3 and T3 Levels. (FY-78 P I) | 117 |
| 1398 | Studies on the Pathogenesis of Hypocalcemia in Tumor Associated with Osteoblastic Metabolism. (FY-78 SP I) | 119 |
| 1399 | An Assessment of Parathyroid Hormone (PTH) Levels in Normal Subjects and in Patients with Disorders of Calcium Metabolism. (FY-78 I) | 121 |
| 1300-78 | The Development of a Radioimmunoassay for 3-Monoiodothyronine (3-T1). (FY-78 P I) | 123 |
| 1301-78 | The Effect of $\Delta^1$-Testolactone (Teslac) on 5 Reductase in Rats. (FY-78 P I) | 125 |

DEPARTMENT OF MEDICINE continued

Endocrinology-Metabolism Service continued


| | | PAGE |
|---|---|---|
| 1303-78 | Studies on the Alterations in Drug Metabolism in Hyperthyroidism. (FY-78 I) | 127 |
| 1304-78 | Radionuclide Assessment of Cardiac Function in Patients with Acromegaly. (FY-78 P I) | 129 |
| 1305-78 | Breast Carcinoma and Thyroid Hormone Receptors. (FY-78 P I) | 131 |
| 1307-78 | The Effect of Fasting upon TSH Response to TRH. (FY-79 P I) | 133 |
| 1300-79 | Measurement of Serum Iodothyronines by High Pressure Liquid Chromatography (HPLC). (FY-79 I) | 135 |
| 1301-79 | The Effect of Various Metabolic Conditions on T3 Receptors in Circulating Mononuclear Cells. (FY-79 I) | 137 |
| 1302-79 | WRAMC #7810, Prevention of Gonadal Damage in Men Treated with Combination Chemotherapy for Hodgkin's Disease and Histiocytic Lymphomas. (FY-79 I) | 139 |
| 1304-79 | Thyroid Hormone in Cerebrospinal Fluid (CSF). (FY-79 SP I) | 142 |
| 1305-79 | Thyroid Function in Liver Disease. (FY-79 F) | 144 |
| 1306-79 | Thyroid Status in Ob/Ob Mice. (FY-79 T) | |
| 1307-79 | Effects of High Dose Dexamethasone on Subhuman Primates.(FY-79 PI) | 146 |
| 1308-79 | Stress-Induced Amenorrhea in Military Cadets. (FY-79 I) | 148 |
| 1309-79 | The Anti-Estrogenic Effect of Testolactone (Teslac). (FY-79 I) | 150 |
| 1310-79 | Pilot Investigation for the Treatment of Hirsutism with Oral Cimetidine. (FY-79 P I) | 152 |
| 1311-79 | Assessment of Thyroid Function and the Intrathyroidal Biosynthesis of Thyroid Hormone during the Acute Recovery Phases of Subacute Thyroiditis. (FY-79 I) | 154 |
| 1312-79 | The Effect of Long-Term High Fiber Diets in the Outpatient Management of Insulin Dependent Diabetes Mellitus. (FY-79 I) | 156 |
| 1313-79 | A Radioimmunoassay (RIA) for Human Thyroid Stimulating Hormone (TSH). (FY-79 I) | 157 |
| 1314-79 | Examination of the Effect of Ipodate (Oragrafin) on Thyroid Function. (FY-79 I) | 159 |
| 1315-80 | Sex-Steroid Receptors in the Mouse Thymus. (FY-80 P I) | 61 |

DEPARTMENT OF MEDICINE continued


| | | PAGE |
|---|---|---|
| **Encocrinology-Metabolism Service continued** | | |
| 1316-80 | T3 Receptors in Human White Cells and Liver. (FY-80 I) | 163 |
| 1317-80 | Investigation of the Etiology of Idiopathic Hirsuitism.(FY-80 P I) | 165 |
| 1318-80 | Development of Fluorescent Immunoassay Procedures. (FY-80 I) | 167 |
| 1319-80 | Does Thyroid Hormone Administration Decrease the Size of Cystic Masses in the Thyroid Gland. (FY-80 I) | 169 |
| 1320-80 | Cyclic AMP Response to Glucagon in Bed and Fasting. (FY-80 I) | 171 |
| 1321-80 | Thyrotropin (TSH) Receptors in Physiologic States. (FY-80 I) | 173 |
| 1322-80 | The Relationship between Calcitonin, Nitroprusside and T3. (FY-80 I) | 175 |
| 1323-80 | Thyrotropin (TSH) Receptors in Human Thyroid Tissue. (FY-80 I) | 177 |
| **Gastroenterology Service** | | |
| 1415 | Esophageal Clearing: Quantitated by Radioisotope Scan (FY-77 P I) | 180 |
| 1416 | Esophageal Emptying in Achalasia: Quantitated by a Radioisotope Method. (FY-77 P I) | 182 |
| 1417 | Plasma Ligandin in Liver Disease. (FY-77 I) | 185 |
| 1419 | Cricopharyngeal Bar: A Video Manometric Study. (FY-77 I) | 187 |
| 1420 | Adenyl Cyclase and Guanyl Cyclase and Guanyl Cyclase in the Cat Esophagus. (FY-78 I) | 188 |
| 1422 | The Sequential Staging of the Liver in Hodgkin's Disease with Laparoscopy and Laparotomy. (FY-78 I) | 189 |
| 1423 | A Study of Trifluoroisopropyl Cyanoacrylate Polymer in the Control of Bleeding Peptic Ulcers of the Stomach and Duodenum. (FY-78 F) | 191 |
| 1424 | A Double Blind Study of Long Term Maintenance Cimetidine Therapy on Gastroesophageal Reflux Disease. (FY-78 F) | 194 |
| 1425 | Pulmonary Aspiration from Gastroesophageal Reflux Defined by Pulmonary Aspiration from Gastroesophageal Reflux Defined by Pulmonary Scintiscan and Overnight Intraesophageal pH Monitoring. (FY-78 P I) | 195 |
| 1426 | The Effect of Inodmethacin on Experimentally Induced Acid Stricture on the Cat Esophagus. (FY-78 I) | 197 |

DEPARTMENT OF MEDICINE continued


| | | PAGE |
|---|---|---|
| Gastroenterology Service continued | | |
| 1427 | Nitroglycerine, Terbutaline and Aminophylline in the Treatment of Achalasis (FY-80 SP I) | 199 |
| 1428 | Maximal Rate of Urea Synthesis in Rats as a Determinant of Functional Hepatic Mass. (FY-80 SP I) | 200 |
| 1429 | Colchicine Therapy of Alcoholic Liver Disease - A Multicenter Randomized Controlled Trial. (FY-80 I) | 202 |
| 1430 | Investigation of the Potential of Various Pills to Induce Local Esophagitis. (FY-80 F) | 203 |
| Hematology-Oncology Service | | |
| 1516 | CALGB #7291, Role of Post Operative Radiotherapy, and Combinations of Dactinomycin, Vincristine, Cyclophosphamide and Adriamycin in Childhood Rhabdomyosarcoma. (FY-73 | 204 |
| 1520 | CALGB #7411, Combination Chemotherapy in Induction for Standard Risk and Combination Chemotherapy Plus Crainial Irradiation Plus Daunorubicin for Increased Risk Followed by Maintenance with Continuous Versus Intermitten 6-MP Plus Methotrexate Reinforcement and Subsequent Immunotherapy. (FY-74 I) | 205 |
| 1528 | CALGB #7391, Clinical Trial of Radiotherapy and Chemotherapy in Managing Non-Metastatic Ewing's Sarcoma. (FY-73 | 206 |
| 1532 | CALGB #7451, Combination Radiotherapy and Chemotherapy of Stage III Hodgkin s Disease (Phase III) (FY-75 P I) | 207 |
| 1534 | CALGB #7521, A Comparative Study of the Value of Immunotherapy with MER as Adjuvant to Induction in Two Maintenance Chemotherapy Programs in Acute Myelocytic Leukemia. (FY-76 P I) | 208 |
| 1535 | CALGB #7351, Long Term Surgical Adjuvant Systemic Chemotherapy with or without Adjuvant Immunotherapy in Mammary Carcinoma: C Comparative Study of Cytoxan, Vincristine, Methotrexate, 5-Fluorouracil Versus Cytoxan, Prednisone Versus Cytoxan, Methotrexate and 5-Fluorouracil and MER. A Phase III Study. (FY-76 I) | 209 |
| 1537 | CALGB #7551, Combination Chemotherapy and Radiotherapy for Stage IV Hodgkin's Disease. (FY-76 P I) | 211 |

DEPARTMENT OF MEDICINE continued

Hematology-Oncology Service continued — PAGE

1536 CALGB #7552, Combination Chemotherapy and Immunotherapy for Previously Treated Stage IIIB and IV Hodgkin's Disease. (FY-76 P I) 212

1539 CALGB #7541, Combination Chemotherapy and Immunotherapy in Previously Untreated Stage III and IV Neuroblastoma. A Phase III Study. (FY-76 I) 213

1541 CALGB #7542, Treatment of Non-Hodgkin's Lymphomas in Children. Methotrexate, Vincristine, Dexamethasone, Cyclophosphamide, 6-Mercaptopurine Plus Radiation Therapy to Involved Areas. A Phase III Study. (FY-76 F) 214

1542 CALGB #7584, Adjuvant Chemotherapy in Osteogenic Sarcoma. Adriamycin Versus Sequential Adriamycin - Cyclophosphamide. (FY-76 215

1543 CALGB #7651, Combination Chemotherapy of Stage III and IV Lymphocytic Lumphoma (Lymphosarcoma) in Adults with or without Radiotherapy Consolidation. (FY-76 I) 216

1544 CALGB #7652, A Phase III Study. Combination Chemotherapy of Stage III and IV Histiocytic Lymphoma (Reticulum Cell Sarcoma) in Adults with or without Radiotherapy or Adriamycin Consolidation Induction: Vincristine, Streptonigrin, Prednisone Consolidation. Adriamycin Maintenance: Cyclophosphamide. (FY-76 P F) 217

1546 CALGB #7611, Treatment of Primary Untreated Acute Lymphocytic Leukemia in Patients under 20 Years of Age. (FY-77 SP I) 218

1547 CALGB #7682, Combination Chemotherapy or Chemoimmunotherapy for Metastatic Recurrent or Inoperable Carcinoma of the Breast. (FY-77 I) 219

1548 CALGB #7681, Investigation of the Effects of Adriamycin with and without Added MER in Soft Tissue Sacromas. (FY-77 221

1551 CALGB #7612, Therapy of Acute Lymphocytic Leukemia in Adults: A Comparison of Vincristine, Prednisone and L-Asparaginase. (FY-77 P I) 222

1552 CALGB #7632, Chemotherapy in Indolent Chronic Lymphocytic Leukemia. (FY-77 I) 223

DEPARTMENT OF MEDICINE continued

Hematology-Oncology Service continued

| | | PAGE |
|---|---|---|
| 1554 | CALGB #7691, Comparison of Involved Field Radiotherapy with Involved Field Radiotherapy with Adjuvant MOPP Chemotherapy and Extended Field Radiotherapy in the Treatment of Stage I and II Hodgkin s Disease in Children. (FY-77 F) | 224 |
| 1555 | CALGB Pilot Study #0702, Evaluation of Galactitol 1,2:5,6-Dianhydro in the Treatment of Advanced Carcinoma of the Lung and Melanoma. A Phase III Study. (FY-77 F) | 225 |
| 1556 | CALGB #7721, A Comparative Study of Adriamycin Versus Daunorubicin at Two Dose Levels for Induction and of 4-Week Cycle Versus 8-Week Cycle for Maintenance Chemotherapy in Acute Myelocytic Leukemis. (FY-77 F) | 226 |
| 1558 | CALGB #7761, A Study to Determine the Effectiveness of Single Versus Multiple Alkylating Agents with or without Adriamycin in the Primary Treatment of Multiple Myeloma. (FY-78 I) | 227 |
| 1559 | CALGB #7781, Small Cell Carcinoma of the Lung: Localized Disease. A Phase III Study. Combination Chemotherapy Versus Alternating Chemotherapy Plus Radiotherapy with or without Immunotherapy. (FY-78 SP I) | 228 |
| 1560 | CALGB #7782, Small Cell Carcinoma of the Lung. Extensive Disease. A Phase III Study. (FY-78 I) | 229 |
| 1562 | CALGB #7802, The Treatment of Advanced Non Small Cell Bronchogenic Carcinoma with Cytoxan, CCNU, Hexamethylmelamine, and Methotrexate. (FY-78 F) | 230 |
| 1563 | CALGB #7751, The Comparative Effectiveness of Combination Chemotherapy Alone and with Radiation Therapy by Involved Field or Extended Field in Poor Risk Patients with Stage I or II Hodgkin s Disease. (FY-78 I) | 231 |
| 1564 | CALGB #7772, Phase II Study of Chlorozotocin. (FY-78 I) | 232 |
| 1565 | CALGB #7804, Cyclophosphamide, Adriamycin, Vincristine, Prednisone in Combination with Low Dose 5-Day Infusion Bleomycin in the Treatment of Poor Histology Lymphomas and Modular Poorly Differentiated Lymphocytic Lymphomas. (FY-79 F) | 233 |

DEPARTMENT OF MEDICINE continued

Hematology-Oncology Service continued PAGE

1566 CALGB #7811, Remission Induction and T-COAP Versus T-MOP Maintenance for the Treatment of Recurrent Childhood ALL. (FY-79 F) 234

1567 CALGB #0703, Cis-Platinum Diamminedichloride in Advanced Malignant Lymphomas. (FY-79 P F) 235

1568 CALGB #7892, Multimodal Therapy for the Management of Primary, Nonmetastatic Ewing's Sarcoma of Pelvic and Sacral Bones. (FY-79 236

1569 CALGB #7893, Multimodal Therapy for the Management of Primary, Nonmetastatic Ewing's Sarcoma of Bone, Pelvic and Sacral Sites Excluded. (FY-79 237

1570 CALGB #7851, Treatment of Advanced Diffuse Histiocytic Lymphoma. (FY-79 I) 238

1571 CALGB #7891, Intergroup Rhabdomyosarcoma Study II. (FY-79 239

1572 CALGB #7971, Phase II Study of M-AMSA. Treatment for Melanoma, Ovarian Carcinoma, Breast Carcinoma, Hypernephroma and Hepatoma. (FY-80 I) 240

1573 CALGB #7911, Treatment of Primary Untreated Acute Lymphocytic Leukemia in Patients under 20 Years. (F-79 F) 241

1575 CALGB #7972, A Phase II Trial of AMSA for Refractory Hodgkin's Disease, Diffuse Histiocytic Lymphoma and Diffuse Poorly Differentiated Lymphocytic Lymphoma. (FY-80 I) 243

1576 CALGB #7982, Chemotherapy of Advanced Pancreatic Cancer. A Comparative Phase II Study. (FY-80 I) 244

1577 CALGB #7921, A Comparative Study of Three Remission Induction Regimens and Two Maintenance Regimens for Acute Myelocytic Leukemia. (FY-80 I) 245

1578 CALGB #8081, A Randomized Study Comparing the Combination of Hormonal Therapy and Chemotherapy with Chemotherapy Alone for the Treatment of Advanced Breast Cancer in Postmenopausal Women. (FY-80 I) 246

1579 CALGB #7983, Surgical Adjuvant Systemic Chemotherapy with 5-Fluorouracil, Adriamycin and Mitromycin-C Versus Observation only in Gastric Adenocarcinoma. (FY-80 I) 247

| | | PAGE |
|---|---|---|
| | Hematology-Oncology Service continued | |
| 1603 | WRAMC #7205, The Use of Methyl-CCNU 1(2-Chloroethyl)-3-(4-Methylcyclohexyl)-1-Nitrosourea in the Treatment of Brain Tumors. (FY-75 F) | 248 |
| 1604 | WRAMC #7295, Phase II, Combination Chemotherapy with Dimethyl Triazeno Imidazole Carboxamide and Adriamycin in Soft Tissue and Bone Sarcoma. (FY-75 F) | 249 |
| 1610 | WRAMC #7307, Phase I-II Evaluation of Dibromodulcitol in Previously Treated Patients with Metastatic Carcinoma of the Breast. (FY-73 F) | 250 |
| 1626 | WRAMC #7405, Treatment of Advanced Renal Cell Carcinoma with a Combination 1-(Chlorethyl)-3-Cyclohexy-1-Nitrosourea (CCNU) and Bleomycin. (FY-77 P F) | 251 |
| 1627 | WRAMC #7404, Immunological Evaluation and Immunotherapy of Patients with Carcinoma of the Lung. (FY-75 I) | 252 |
| 1628 | WRAMC #7406, Chemoimmunotherapy of Carcinoma of the Large Bowel. (FY-75 I) | 253 |
| 1629 | WRAMC #7407, Chemoimmunotherapy of Malignant Melanoma. (FY-75 F) | 254 |
| 1630 | WRAMC #7408, Comparative Trial of Tamoxifen and Fluoxymestrone Plus Tamoxifen in Metastatic Breast Cancer. (FY-75 I) | 255 |
| 1643 | The Use of Auto-Factor IX Concentrate (Human) Dried in the in the Treatment of Patients with Bleeding Due to Factor IX Inhibitors. (FY-76 F) | 256 |
| 1644 | WRAMC #7501, Evaluation of Adriamycin and Cis-Platinum Chemotherapy in Treatment of Malignant Disease. A Phase II Study. (FY-75 | 257 |
| 1649 | WRAMC #7602, Chemoimmunotherapy of Prostatic Carcinoma. (FY-76 | 258 |
| 1651 | WRAMC #7504, Combination Chemotherapy for the Treatment of Advanced Gastric Carcinoma with Either 1-(Tetra-hydro-2-Furanyl)-5-Fluorouracil (Ftorafur), Adriamycin and Mitomycin-C Versus 5-Flurouracil, Adriamycin and Mitomycin-C. (FY-76 F) | 259 |
| 1654 | WRAMC #7601-A, The Treatment of Unresectable Bronchogenic Carcinoma with CCNU 2 (2-Chlorethyl)-3-Cyclohexyl-1-Nitrosourea, Cyclophosphamide, Adriamycin, Procarbazine, Hexamethylemalamine, Methotrexate and Irradiation. (FY-77 F) | 260 |

DEPARTMENT OF MEDICINE continued

Hematology-Oncology Service


| | | PAGE |
|---|---|---|
| 1655 | WRAMC #7607, Chemoimmunotherapy of Carcinoma of the Lung using High-Dose Methotrexate and Citrovorum Factor with or without BCG. (FY-77 F) | 261 |
| 1657 | WRAMC #7701, Velban, Bleomycin and Cis-Platinum in the Treatment of Head and Neck Malignancies. (FY-77 F) | 262 |
| 1658 | WRAMC #7702, Adjuvant Chemotherapy of Prostatic Carcinoma with Adriamycin and Cis-Diamminedichloroplatinum II. (FY-78 | 264 |
| 1661 | Polycythemia Vera Study Group Protocols 5,6,7 and 8. The Treatment of Thrombosis in Patients with Polycythemia Vera. (FY-78 I) | 265 |
| 1664 | WRAMC #7705, Metastatic Colo-Rectal Carcinoma. (FY-78 F) | 267 |
| 1665 | WRAMC #7706, Treatment of Refractory Gastrointestinal Tumors with Chlorambucil and Methotrexate. (FY-78 I) | 268 |
| 1666 | WRAMC #7801, Immunological Evaluation and Phase I Immunotherapy Trial of Patients with Various Carcinomas. (FY-78 | 269 |
| 1667 | WRAMC #7803, Metastatic Breast Carcinoma. (FY-78 I) | 270 |
| 1668 | WRAMC #7807, Effect of N-Acetyl-Cysteine on Adriamycin-Induced Acute Cardiac Damage. (FY-79 I) | 271 |
| 1669 | WRAMC #7806, Chemotherapy of Carcinoma of the Urinary Bladder. (FY-79 F) | 272 |
| 1670 | WRAMC #7902, Clinical Trial in Bronchogenic Carcinoma of Specific Immunotherapy as an Adjuvant to Surgery. (FY-79 F) | 273 |
| 1671 | WRAMC #7901, Adjuvant Antiplatelet for Dukes "$B_2$" or "C" Cancer of the Colon. (FY-79 I) | 274 |
| 1672 | Tumor Tissue for Extract Preparation. (FY-79 I) | 275 |
| 1673 | TC 179, Treatment of Stage I/II Testicular Carcinoma with Vinblastine, Actinomycin-D, Cyclophosphamide, Bleomycin and Cis-Platinum. (Testicular Cancer Intergroup Study) (FY-79 I) | 276 |
| 1674 | WRAMC #7807A, Effect of Indocyanine Green Clearance on Plasma Levels of Adriamycin. (FY-79 I) | 277 |
| 1675 | WRAMC #7903, Hepatic Artery Adriamycin Infusion -- A Clinical and Pharmacokinetic Study. (FY-79 I) | 278 |

DEPARTMENT OF MEDICINE continued

Hematology-Oncology Service continued

| | | PAGE |
|---|---|---|
| 1677 | WRAMC #7905, Treatment of Acute Leukemia with Low Dose Adriamycin Infusion. (FY-79 I) | 279 |
| 1678 | WRAMC #7914, Metastatic Colo-Rectal Cancer. (FY-79 I) | 280 |
| 1679 | WRAMC #7907, Use of Methyl CCNU in the Treatment of Melanoma, Colon and Gastric Carcinoma (Group C Drug). (FY-80 I) | 281 |
| 1680 | WRAMC #7908, Use of Streptozotocin in the Treatment of Metastatic Islet Cell Carcinoma (Group C Drug). (FY-80 I) | 282 |
| 1681 | WRAMC #7909, Use of Daunomycin in the Treatment of ALL, AML and Other Leukemias in Adults and Children (Group C Drug). (FY-80 I) | 283 |
| 1682 | WRAMC #7910, Use of 5-Azacytidine in the Treatment of Acute Granulocytic Leukemia in Adults and Children (Group C Drug). (FY-80 I) | 284 |
| 1683 | WRAMC #7911, Use of L-Asparaginase in the Treatment of Acute Lymphoblastic Leukemia in Adults and Children (Group C Drug).(FY-80 I) | 285 |
| 1684 | WRAMC #7912, Use of Hexamethylmelamine in the Treatment of Ovarian Cancer (Group C Drug). (FY-80 I) | 286 |
| 1685 | WRAMC #7911, Use of VP-16 in the Treatment of Small Cell Carcinoma of the Lung (Group C Drug). (FY-80 I) | 287 |
| 1686 | WRAMC #7915, Prevention of Gonadal Damage in Women Treated with Combination Chemotherapy or Radiotherapy below the Diaphragm. (FY-80 I) | 288 |
| 1687 | WRAMC #8002, Phase II Evaluation of Methyl Glyoxal Bis-Guanyl Hydrazone (Methyl-GAG) in Advanced Esophageal Carcinoma, Head and Neck and Cervix. (FY-80 I) | 289 |
| 1688 | WRAMC #8001, Feasibility Study of the Multidisciplinary Approach to Inoperable Lung Cancer Patients. (FY-80 I) | 290 |

Pulmonary Service

| | | |
|---|---|---|
| 1700 | Sleep Apnea in Hypothyroid Patients. (FY-80 SP I) | 291 |

DEPARTMENT OF MEDICINE continued


| | | PAGE |
|---|---|---|
| **Dermatology Service** | | |
| 1601 | Direct Immunofluorescence in Mixed Connective Tissue Disease. (FY-77 T) | |
| **Infectious Disease Service** | | |
| 1903 | Persistence of T Pallidum in Neurosyphillis. (FY-75 P I) | 293 |
| 1905 | Local Immune Response to Neisseria Gonorrhoeae in Humans.(FY-77 I) | 295 |
| 1906 | The Limulus Lysate Assay for the Determination of Gram Negative Meningitis Septic Arthritis and Contamination of Intravenous Fluids. (FY-78 F) | 310 |
| 1908 | Evaluation of Sodium Stibogluconate (Pentostam®) in the Treatment of Cutaneous Leishmaniasis. (FY-78 I) | 312 |
| 1909 | Immunological Evaluation of Patients with Cutaneous Leishmaniasis. (FY-78 I) | 314 |
| 1911 | In Vitro Inhibitory Activity of a Series of 2-Acetylpryridine Thiosemicarbazones toward a Group of Clinically Significant Bacterial Genera. (FY-79 I) | 316 |
| 1912 | Determination of Vancomycin Levels in Clinical Samples using High Press Liquid Chromatography. (FY-79 F) | 318 |
| 1913 | Laboratory Investigation of New Antibiotics. (FY-80 P I) | 320 |
| **DEPARTMENT OF SURGERY** | | |
| **Anesthesiology and General Surgery** | | |
| 2000 | The Effects of Gastric Surgery on the Release of Pancreatic Polypeptide. (FY-78 I) | 322 |
| 2003 | Use of Copolymer as a Lattice for the Growth of Neogut. (FY-80 I P) | 324 |

Peripheral Vascular Service

| | | PAGE |
|---|---|---|
| 2104 | Evaluation of the Efficacy of Suppressing Platelet Activity in Patients with Intermittent Claudication. (FY-77 T) | |
| 2105 | Rapid Screening for Coagulation Abnormalities. (FY-78 T) | |
| 2106 | Management of the Hemodynamically Significant, Asymptomatic Carotid Bruit. (FY-79 I) | 326 |
| 2107 | Perioperative Thrombosis Prophylaxis in Patients with Peripheral Vascular Disease. (FY-79 T) | |
| 2108 | Platelet Aggregation after Carotid Endarterectomy. (FY-79 T) | |
| 2109 | Etiologic Factors for Recurrent Carotid Stenosis. (FY-80 I) | 328 |
| 2110 | Participation of the Reticulo-Endothelial System in Shortening Platelet Survival. (FY-80 T) | 330 |

Ophthalmology Service

| | | |
|---|---|---|
| 2306 | Clinical Quantification of Intraocular Malignant Melanoma Volume. (FY-76 P F) | 331 |
| 2308 | Scleral Buckling for Retinal Detachment 1973 1976. A Retrospective View. (FY-78 F) | 333 |
| 2309 | A Study of Eye Trauma Treatment in the Military. (FY-78 I) | 334 |
| 2310 | Intraocular Lens. (FY-78 I) | 335 |
| 2312 | Corneal Endothelial Cell Loss Following Various Cataract Extraction Techniques. (FY-79 F) | 336 |

Otolaryngology Service

| | | |
|---|---|---|
| 2516 | The Effect of Amplification on Limited High-Frequency Hearing Loss. (FY-77 F P) | 337 |
| 2517 | Evaluation of a Specialized Technique for Training Audiovisual Integration in Hard-of-Hearing Patients. (FY-78 I SP) | 342 |
| 2523 | The Relationship between Electroacoustic Parameters and Perceived Sound Quality of Hearing Aids. (FY-78 I P SP) | 344 |
| 2525 | Generation and Evaluation of Synthetic Facial Images for Studying and Training Lipreading. (FY-78 I P) | 346 |

DEPARTMENT OF SURGERY continued

Otolaryngology Service continued


| | | PAGE |
|---|---|---|
| 2526 | Development of Communication of Self-Assessment Inventory of the Hearing Impaired Soldier. (FY-79 I) | 348 |
| 2527 | Assessing Laryngeal Function Via Residue Inverse Filtering. (FY-79 I) | 351 |
| 2528 | The Effects of Chronic Low Doses of Quinine in Tonic Water on the Electronystamogram (ENG) in Humans. (FY-80 P F) | 353 |
| 2529 | Effect of High Frequency Sensorineural Hearing Loss on the Latency of the Brain Stem Response. (FY-80 I) | 355 |
| 2530 | Test of the Assumptions Underlying the Comparative Hearing Aid Evaluation. (FY-80 I) | 357 |
| 2531 | Maintenance of Speech Fluency Following an Intensive Stuttering Therapy Program. (FY-80 I) | 360 |
| 2532 | The Effects of Age and Brain Damage on Fluid Intelligence in Aphasic Adults with Lesions in Dominant Hemisphere. (FY-80 F) | 362 |


Organ Transplantation Service


| | | |
|---|---|---|
| 2610 | Antilymphocyte Globulin (ALG) and Kidney Transplantation. A Controlled Double Blind Study. (FY-73 I SP) | 364 |
| 2615 | Immunological Monitoring of the Transplant Recipient. (FY-78 F) | 367 |
| 2616 | Obviating the Graft Versus Host Reaction. (FY-78 F) | 368 |
| 2618 | Intentional Donor Specific Pretransplant Transfusion. (FY-80 I) | 369 |
| 2619 | Histocompatibility Antigens and Interstitial Cystitis. (FY-80 I) | 371 |


Urology Service


| | | |
|---|---|---|
| 2805 | Biochemistry Studies of Urinary Polyamines in Human Genitorumiary Carcinoma. (FY-76 T) | |

DEPARTMENT OF SURGERY continued


| | | PAGE |
|---|---|---|
| **Urology Service** continued | | |
| 2809 | Relationships between Prostatic Cancer and excretion of Urinary Cholesterol. (FY-78 I) | 375 |
| 2810 | Comparative Study of High (5000 RADS) Versus Low Dose (2000 RADS) Preoperative Radiation to Radical Cystectomy for Control of Transitional Cell Carcinoma of the Bladder. (FY-78 T) | |
| 2811 | The Value of Excretory Urography, Cystography and Cystoscopy in the Evaluation of Adult Women with Urinary Infection. (FY-80 F) | 376 |
| 2812 | Human Chorionic Gonadotropin (HCG) Producing Cells in Seminomatous Germ Cell Tumors of the Testis: A Prospective and Retrospective Correlation with Tumor Histology and Response to Therapy. (FY-80 I) | 377 |
| 2813 | Alpha Fetoprotein (AFP) and Human Chorionic Gonadotropin (HCG) Producing Cells in Nonseminatous Germ Cell Tumors of the Testis: A Prospective and Retrospective Correlation with Serum AFP and HCG Levels, Tumor Histology and Response to Therapy. (FY-80 F) | 378 |
| 2815 | An Epidemiologic Investigation of Testicular Cancer. (FY-80 I) | 379 |
| **Plastic Surgery Service** | | |
| 2901 | Survival and Critical Perfusion of Microvascular Free Flaps following Occulusions of Pedicle Vessels at Specific Time Intervals. (FY-80 I) | 380 |
| **Allery and Clinical Rheumatology Service** | | |
| 3138 | Immunologic Mechanisms of Cutaneous Reactions to Inhalant Allergens. (FY-76 F P) | 382 |
| 3144 | Neurophysiologic, Immunologic and Biochemical Aspects of Bronchial Asthma. (FY-77 1 P) | 384 |
| 3146 | Immunotherapy Kit Potency Persistance. (FY-77 I) | 387 |
| 3147 | Hymenoptera Venom Safety and Efficacy Evaluation as Allergen Immunotherapy in Insect Sting Allergy Patients. (FY-77 SP P F) | 389 |
| 3149 | Investigation of Immunologic Imbalance in Atopic Dermatitis. (FY-78 F) | 392 |
| 3151 | *Allergic Disease Center Study of Hymenoptera* Insect Venom as an Agent for Diagnosis. (FY-78 F) | 394 |
| 3152 | Factors Affecting the Theophylline Half Life. (FY-78 F) | 395 |

ALLERGY AND CLINICAL RHEUMATOLOGY SERVICE continued PAGE

3154 WRAMC #7802, Evaluation of Prostaglandin Secreting Suppressor Cells in Cancer Patients. (FY-78 I SP) 396

3155 Evaluation of Suppressor Immunoregulatory Cells in the Pathogenesis of Immunodeficiency Disease. (FY-78 I) 398

3158 Evaluation of the Immunopathologic Mechanisms Operative in Dermal Reactions to Insulin in Diabetic Patients. (FY-79 P I) 400

3159R In Vivo Removal of Circulating Antibodies and Immune Complexes. (FY-79 I) 401

3160R Study of Rheumatoid Arthritis and Sjorgen's Principitins in Rheumatoid Arthritis. (FY-79 I P) 412

3161 Evaluation of Immediate Hypersensitivity Skin Tests in Uremic Patients. (FY-79 I) 415

3162R Serial Study of Serological Parameters in Systemic Lupus Erythematosus. (FY-79 I P SP) 417

3163R Histocompatibility Antigens in Acute Anterior Uveitis (AAU). FY-79 I P SP) 432

3164 The Comparison of Zaditen and Theophylline in the Prophylaxis of Bronchial Asthma. (FY-79 I) 435

3165 Clinical Trial of Skin Testing with Major and Minor Pencillin Derivatives in Hospitalized Adults. (FY-80 I) 436

3166 An Evaluation of Local Anesthetic Skin Testing and Progressive Challenge in Patients with a History of an Adverse Reaction to Local Anesthetics. (FY-80 I) 438

DEPARTMENT OF OBSTETRICS AND GYNECOLOGY

4113 Cooperative Gynecologic Oncology Group. (FY-74 I) 440

4116 The Evaluation of Fetal Systolic Time Intervals and Beat to Beat Interval Variations in Fetal Heart Rate as Early Indicators of Fetal Maturity and Fetal Distress. (FY-75 I) 441

4124 Fetal Intensive Care Monitoring in a Long-Range Continuing Project (FY-73 I) 442

| | | PAGE |
|---|---|---|
| 4129 | Antepartum Fetal Evaluation of Noise Evolved Heart Rate Response an an Indicator of Fetal Well-Being. (FY-76 I) | 443 |
| 4134 | Treatment of Women with Cervical Cancer Stage IIB, IIIB, IVA Confined to the Pelvis and/or Para-Aortic Nodes with Radiotherapy Alone Versus Radiotherapy Plus Immunotherapy (Intravenous C-Parvum) (Phase II). (FY-77 I) | 444 |
| 4135 | A Randomized Comparison of Melphalan Alone Versus Adriamycin and Cyclophosphamide Versus Hexamethylmelamine and Melphalan in Patients with Ovarian Adenocarcinoma: Suboptimal Stage II, Stage IV and Recurrent, Equivalent to Stage III and IV (Phase III). (FY-77 I) | 445 |
| 4136 | A Randomized Comparison of Melphalan Alone Versus Melphalan Therapy Plus Immunotherapy (Corynebacterium Parvum in the Treatment of Women with Stage III (Optimal) Epithelial Carcinoma of the Ovary (Phase II). (FY-77 I) | 446 |
| 4137 | A Randomized Comparison of Pelvic and Abdominal Radiation Therapy Versus Pelvic Radiation and Melphalan Versus Melphalan Alone in Stage II Carcinoma of the Ovary (Phase III). (FY-77 I) | 447 |
| 4139 | A Randomized Comparison of Melphalan, 5-Fluorouracil and Megace Versus Adriamycin, Cytoxan, 5-Fluorouracil and Megace in the Treatment of Patients with Primary Stage III, Primary Stage IV, Recurrent or Residual Endometrial Carcinoma (Phase III). (FY-77 I) | 448 |
| 4140 | A Clinical-Pathologic Study of Stage I and Stage II Carcinoma of the Endometrium. (FY-78 I) | 449 |
| 4141 | A Randomized Study of Adriamycin as an Adjuvant after Surgery and Radiation Therapy in Patients with High Risk Endometrial Carcinoma Stage I and Occult Stage II. (FY-78 I) | 450 |
| 4142 | A Phase II Trial ICRF in Patients with Advanced Pelvic Malignancies. (FY-78 I) | 451 |
| 4143 | A Randomized Comparison of Local Excision Versus Cryosurgery in Patients with Limited Grade 1,2, or 3 Cervical Intraepithelial Neoplasia (CIN). (FY-78 I) | 452 |

| | | |
|---|---|---|
| 4144 | A Randomized Comparison of Surgical Conization Versus Cryosurgery in Patients with Extensive Grade 3 Cervical Intraepithelial Neoplasis (CIN). (FY-78 I) | 453 |
| 4145 | A Randomized Comparison of Melphalan Versus No Treatment in the Treatment of Patients with Selected Stage IAi to IBi Ovarian Cancer (Well and Moderately Differentiated). (FY-78 I) | 454 |
| 4146 | A Randomized Comparison of Melphalan Versus Radioisotopes in the Treatment of Patients with No Microscopic Residual Disease Having All Stages IC and II (A,B, and C) and Selected Stage IAii and IBii Ovarian Cancer. (FY-78 I) | 455 |
| 4147 | GOG #7711, Surgical-Pathologic Study of Women with Squamous Cell Carcinoma of the Vulva. (FY-79 I) | 456 |
| 4148 | GOG #7712, A Randomized Study of Radiation Therapy Versus Pelvic Node Resection for Patients with Invasive Squamous Cell Carcinoma of the Vulva Having Positive Groin Nodes. (FY-79 I) | 457 |
| 4149 | Automated Detection of Fetal Heart Pattern Abnormalities. (FY-79 I) | 458 |
| 4150 | On-Line Interpretation of Labor Curve Abnormalities. (FY-79 I) | 459 |
| 4151 | Early Reliable Detection of Fetal Heart Rate Variability by Adaptive Digital Filtering. (FY-79 I) | 460 |
| 4152 | GOG #26H. A Phase II Trial of Maytansine in Patients with Advanced Pelvic Malignancies. (FY-79 I) | 461 |
| 4153 | GOG #26, A Phase II Trial of "Baker's Antifol" in Patients with Advanced Pelvic Malignancies. (FY-79 I) | 462 |
| 4154 | GOG #7831, A Randomized Comparison of Cis-Platinum, 50 mg/m$^2$, IV, Every Three Weeks Versus Cis-Platinum, 100 mg/m$^2$, IV, Daily for Five Days Every Three Weeks Versus Cis-Platinum, 20 mg/m$^2$, IV, Daily for Five Days Every Three Weeks in the Treatment of Patients with Advanced Carcinoma of the Cervix. (Phase III). (FY-79 I) | 463 |
| 4155 | GOG #7863, Evaluation of Adjuvant Vincristine, Dactinomycin, and Cyclophosphamide Therapy in Malignant Germ Cell Tumors of the Ovary after Resection of All Gross Tumor (Phase III). (FY-79 I) | 464 |
| 4156 | GOG #7864, Evaluation of Vinblastine, Bleomycin and Cis-Platinum in Stage III and IV and Recurrent Malignant Germ Cell Tumors of the Ovary (Phase III). (FY-79 I) | 465 |
| 4157 | Prophylactic Antibodies in Abdominal Hysterectomy. (FY-79 I) | 466 |
| 4158 | Prophylactic Antibodies in Elective Cesarean Section.(FY-79 F SP) | 467 |

DEPARTMENT OF OBSTETRICS AND GYNECOLOGY continued PAGE

4159 GOG #42, Treatment of Recurrent or Advanced Uterine Sarcoma. A Randomized Comparison of Adriamycin Versus Adriamycin and Cyclophosphamide (Phase III). (FY-79 I) 468

4160 GOG #7841, A Clinical-Pathologic Study of Stage I and II Uterine Sarcomas. (FY-79 I) 469

4161 GOG #7861, Surgical Staging of Ovarian Carcinoma. (FY-79 I) 470

4162 GOG #7862, A Randomized Comparison of Melphalan Versus Intraperitoneal Chromic Phosphate in the Treatment of Women with Stage I Exclusive of Stage IAi, GI, and IBi, GI) Epithelial Carcinoma of the Ovary (Phase III). (FY-79 I) 471

4163 GOG #26, A Phase II Trial of Cis-Platinum (II) Diamminedichloride. (FY-79 I) 472

4164 Study of Ovarian Cancer in Greater Washington, D.C. (FY-79 I)

4165 GOG #26-I, A Phase II Trial of AMSA in Patients with Advanced Pelvic Malignancies. (FY-79 I) 473

4166 GOG #26-J. A Phase II Trial of Yoshi 864 in Patients with Advanced Pelvic Malignancies. (FY-79 I) 474

4167 GOG #7961, A Phase III Randomized Study of Adriamycin Plus Cyclophosphamide Versus Adriamycin Plus Cyclophosphamide Plus Cis-Platinum in Patients with Advanced Ovarian Adenocarcinoma. Suboptimal Stage III, Stage IV and Recurrent. (FY-79 I) 475

4168 Comparison of Two Antibotic Regimens for the Treatment of Soft Tissue Pelvic Infections. (FY-79 I) 477

4169 Effectiveness of Heat Lamps and Surgigators in Promoting Comfort and Healing of Median Episiotomies. (FY-79 I) 480

4170 A Phase II Trial of Chlorozotocin in Patients with Advanced Pelvic Malignancies. (FY-80 I) 483

4171 GOG #48, A Study of Progestin Therapy and a Randomized Comparison of Adriamycin Versus Adriamycin Plus Cyclophosphamide in Patients with Advanced Endometrial Carcinoma after Hormonal Failure. (FY-80 F) 484

DEPARTMENT OF RADIOLOGY

PAGE

Nuclear Medicine Service

4501 Clinical Evaluation of Fluorescence Scanning of the Thyroid with an Americium 241 Source. (FY-73 T)

4514 Clinical Evaluation of Indium-DTPA. (FY-75 I) 485

4521 Technetium-99m-pyridoxylideneglutamate (99mTc-PG) for Diagnosis of Hepatobilary Disease. (FY-79 I) 490

4522 Determination in Humans of the Effective Half-Life of Botulism, Immune Plasma (Human) Administered Intravenously. (FY-80 I) 493

4523 Determination of Glomerular Filtration Rate using Radiotracer Techniques. (FY-80 I) 495

Radiation Therapy Service

4601 Participation in the National Cooperative Study of Early Hodgkin's Disease. (FY-69 I)(transferred to Hematology-Oncology Service) 496

Diagnostic Radiology Service

4700 Eye Tracking in Radiologists. (FY-[illegible] I) 498

4701 Comparison of Test Chest Phantoms with Human Subjects on Radiographic Chest Unit. (FY-[illegible] I) 499

4702 Video Transmissions, Storage and Diagnostic Evaluation. (FY-[illegible] I) 501

DEPARTMENT OF PATHOLOGY

Blood Bank

5501 Identification of Secretor Status in Group A Individuals by Immunodiffusion. (FY-80 I)

Department of Pediatrics

5701 Newborn Host Defenses: I. Developmental Aspects of Newborn Neutrophil Chemotaxis. (FY-77 [illegible] P) 502

5702 The role of Luteinizing Hormone Releasing (LHRH) in Evaluation of the Hypothalamic Pituitary Gonadal Axis in Children. (FY-7[illegible]) 504

5703 Newborn Host Defenses II. Studies on the Newborn Neutrophil [illegible]-Bromosuccinic Acetic Ester Molecular Probes. (FY-7[illegible] I) 506

5704 Newborn Host Defenses III. Pharmacokinetics and Efficacy of Gentamicin [illegible]. (FY-7[illegible] I) 508

DEPARTMENT OF PEDIATRICS continued

| | | PAGE |
|---|---|---|
| 6025 | Role of Surface Tension Measurement of Amniotic Fluid Lipid Extract in Prediction of RDS in the Newborn. (FY-78 I) | 510 |
| 6026 | Tracheal Aspirate Surface Tension as a Prognostic Indicator in Infants with Respiratory Distress Syndrome (RDS) (FY-78 I) | 513 |
| 6027 | WRAMC #7808, Combined Modality Therapy of Brain Tumors in Childhood. (FY-78 F) | 514 |
| 6028 | Application of Hemoglobin $A_{1C}$ as an Indicator of Juvenile Diabetic Control. (FY-79 F P) | 515 |
| 6029 | Newborn Host Defenses III. Studies of Newborn Neutrophil-Neutrophil Interaction. (FY-79 I P SP) | 516 |
| 6030 | Studies of Adult and Newborn Neutrophil Chemotaxis under Agarose. (FY-79 I) | 518 |
| 6101 | SWOG #7834, Second Induction and Maintenance in Acute Lymphocytic Leukemia, Phase III. (FY-79 I) | 520 |
| 6102 | SWOG #7703, Radiation Therapy in Combination with BCNU, DTIC, or Procarbazine in Patients with Malignant Gliomas of the Brain. Phase III. (FY-79 I) | 522 |
| 6103 | SWOG #7919, Evaluation of m-AMSA in Children with Acute Leukemia and Non Hodgkin's Lymphoma in Relapse. Phase II. (FY-79 I) | 523 |
| 6104 | SWOG #7818, Evaluation of Rubidazone in Children with Acute Lymphoblastic Leukemia and Acute Myelogenous Leukemia. (FY-79 I) | 524 |
| 6105 | SWOG #7607B, Evaluation of Lithium Carbonate in the Amelioration of Hematopoietic Toxicity following Cancer Chemotherapy in Children with Solid Tumors being Treated AD-CON-FU, Phase II. (FY-79 I) | 525 |
| 6106 | SWOG #7604, Evaluation of Galactitol in Patients with Advanced Cancer, Phase II. (FY-79 F) | 526 |
| 6107 | SWOG #7810, Evaluation of Anguidine in Children with Acute Lymphoblastic and Non-Lymphoblastic and Non-Lymphoblastic Leukemia in Relapse, Phase II. (FY-79 I) | 527 |
| 6108 | SWOG #7621, MOPP Versus OPP in the Treatment of Children with Recurrent Brain Tumors, Phase III. (FY-79 I) | 528 |
| 6109 | SWOG #7709, Evaluation of Compliance in Children with Malignant Disease Treated with Prednisone. (FY-79 F) | 529 |
| 6110 | SWOG #7865, Acute Lymphoblastic Leukemia Classification Portion of Alinc 13. (FY-79 I) | 530 |

DEPARTMENT OF PEDIATRICS continued

| | | PAGE |
|---|---|---|
| 6111 | SWOG #7812, Evaluation of Anguidine in the Treatment of Central Nervous System Tumors, Phase II. (FY-79 I) | 531 |
| 6112 | SWOG #7843, Evaluation of Rubidazone in the Treatment of Children with Solid Tumors. (FY-79 I) | 532 |
| 6113 | SWOG #7617, Combination Chemotherapy with Vinblastine Sulfate and Bleomycin Infusion in Children with Metastatic Solid Tumors, Phase II. (FY-79 I) | 533 |
| 6114 | SWOG #7831, Evaluation of Neocarzinostatin in Children with Acute Lymphoblastic and Acute Non-Lymphoblastic Leukemia in Relapse, Phase II. (FY-79 F) | 534 |
| 6115 | SWOG #7376, Evaluation of the Natural History of Histiocytosis X. (FY-79 I) | 535 |
| 6116 | SWOG 7612, MOPP Plus Bleo and A-COP with IF Radiation Therapy in Stage III Hodgkin's Disease in Children. (FY-79 I) | 536 |
| 6117 | SWOG #7712, Comparison of Treatment Regimens for the First CNS Relapse in Children with Acute Lymphocytic Leukemia. (FY-79 I) | 537 |
| 6118 | SWOG #7905, A-COP Plus for Non-Hodgkin's Lymphoma in Children. (FY-79 I) | 538 |
| 6119 | SWOG #7796, Adjuvant Chemotherapy for Localized Unilateral Retinoblastoma, Reese-Ellsworth Group 5, Phase III. (FY-79 I) | 539 |
| 6120 | SWOG #7837, Evaluation of Systemic Therapy for Children with T Cell Acute Lymphatic Leukemia. (FY-79 I) | 540 |
| 6121 | SWOG #7799, Rare Tumor Registry. (FY-79 I) | 541 |
| 6122 | SWOG #7829, A Comparison of Two Dose Regimens of Intrathecal Methotrexate for Treatment of CNS Leukemia, Phase II. (FY-79 I) | 542 |
| 6123 | SWOG #7623, Evaluation of Systemic Regimens in the Treatment of Acute Leukemia of Childhood. Phase III. (FY-79 I) | 543 |
| 6124 | SWOG #8000, The National Wilms Tumor Study - 3 (FY-79 I) | 544 |
| 6125 | SWOG #7909, Evaluation of MOPP Adjuvant Chemotherapy in the Treatment of Localized Medulloblastoma and Ependymoma, Phase III. (FY-79 I) | 545 |
| 6126 | SWOG #7994, Therapy for Extraocular Retinoblastoma with Cyclophosphamide, Vincristine, Adriamycin and Irradiation. (FY-79 I) | 546 |

DEPARTMENT OF PEDIATRICS continued

PAGE

6127 SWOG #7721, Evaluation of Induction, Remission Maintenance with and without Periodic Reinforcement, and CNS Prophylaxis in Acute Non-Lymphocytic Leukemia, Phase III. (FY-79 I) 547

6128 SWOG #7901, Rescue Therapy for Non-CNS Extra-Medullary Disease in Children with Acute Lymphoblastic Leukemia, Phase III. (FY-79 I) 548

6129 SWOG #7906, Multidrug Adjuvant Chemotherapy in Non-Metastatic Osteosarcoma, Comparison of Conpadri-I with Compadri-V, Phase III. (FY-80 I) 549

6130 SWOG #8002, Combination Chemotherapy with Adriamycin, Cis-Diamminedichloroplatinum, Vincristine and Cytoxan in Children with Metastatic Neuroblastoma. Stage IV. (FY-80 I) 550

6131 SWOG #8075, Circulating Immune Complexes in Pediatric Malignancies. (FY-80 I) 551

DEPARTMENT OF NEUROLOGY

7111 Interruption of Maintenance Neuroleptic Therapy. (FY-77 F) 552

7115 Investigation of the Value of Brain Stem Auditory Evoked Response Test in Posterior Fossa Lesions. (FY-80 T)

DEPARTMENT OF PSYCHIATRY

7214 Pre- and Post-Discharge Assessment of Psychiatric Patients. (FY-77 F) 554

7217 Management of Impairment of Accomodations Secondary to Psychotropic Medication. (FY-78 F) 556

7218 Physotigmine Infusion and Lithium Responsitivity. (FY-79 I) 558

7219 Reliability of Serum Tricyclic Antidepressant Levels. (FY-79 F) 560

7220 The Developmental Significance of Transitional Objects. (FY-80 F) 562

7221 The Effect of Hypnotic Intervention on the Electroencephalogram of Low, Medium and High Hypnotic Capacity Patients. (FY-80 I) 563

| Psychology | | PAGE |
|---|---|---|
| 7300 | LSD Follow-Up Study (Establishment of Normal Controls for Neuropsychological Examination). (FY-79 I) | 564 |
| 7301 | Baseline MMPI Profile for an Active Duty Military Population. (FY-79 I) | 566 |
| DIVISION OF HEMATOLOGY, WRAIR | | |
| 9010 | Vitamin $B_6$ Metabolism in the Hematopoietic System of Patients Receiving Isoniazid and Patients with Sideroblastic Anemia. (FY-75 I) | 568 |
| 9012 | The Effect of Infectious Hepatitis on Erythroid Colony Formation by the Plasma Clot Culture Method. (FY-77 T) | 570 |
| 9013 | The Carbohydrate Dependence of Platelet Surface Interactions in Hypercoagulable Stress. (FY-77 T) | |
| 9016 | Investigation of Pyridoxine as a Treatment for Sickle Hemoglobinopthies. (FY-78 PI) | 571 |
| 9019 | Antisickling Agents: Alteration of Hemoglobin Oxygen Affinity. (FY-79 PI) | 573 |
| 9020 | The Effects of $B_6$ Aldehydes on Red Cell Oxygen Affinity. (FY-79 PI) | 577 |
| 9021 | Human-Marrow-in-Mouse Chimera. (FY-80 I) | 579 |
| 9022 | Iron Tolerance Test (ITT). (FY-80 I) | 580 |
| 9024 | The Effect of Microwave Exposure on Immune Regulatory Function. (FY-80 F) | 581 |
| GASTROENTEROLOGY SERVICE, WRAIR | | |
| 9025-A | Functional Characterization of Human Intestinal Lymphocytes in Gastrointestinal Disorders. (FY-77 T) | |
| DIVISION OF SURGERY, WRAIR | | |
| 9030 | Circulating Serum Isoenzymes in Mesenteric Infarction. (FY-77 I) | 582 |
| 9031 | Study of Control Mechanisms for Human Gastric Parietal Cells. (FY-80 I) | 587 |
| 9032 | In Vitro Analysis of Human Colon Ion Transport Mechanisms. (FY-80 I) | 588 |

| AFIP | | PAGE |
|---|---|---|
| 9035 | Effects of Altitude, Mood and Dietary Habits on Performance of Choice-Reaction Time Task. (FY-77 I) | 589 |
| 9036 | Urease and Deaminases in Chemistry and Medicine. (FY-77 I) | 590 |
| 9037 | Localization of Lymphocyte Antigenic Markers in Fixed Paraffin-Embedded Sections. (FY-79 F) | 593 |

DEPARTMENT OF NURSING, WRAMC

| | | |
|---|---|---|
| 9036A | The Educational and Psychological Need Specific to Human Sexuality of Middle Aged Males Post Uncomplicated Myocardial Infarction. (FY-79 I) | 591 |
| 90393 | Nurse Controlled Factors that Influence the Development of Diarrhea in Tube-Fed Patients. (FY-79 I) | 594 |
| 90403 | Reducing Discomfort from Intramuscular Injections in the Dorso-guteal Muscle by Proper Body Positions. (FY-79 I) | 596 |
| 90413 | Attitudes of Health Care Workers toward the Occurrence of Violence in Close Realtionships. (FY-79 I) | 601 |

PROTOCOLS FROM OTHER MEDDAC FACILITIES

| | | |
|---|---|---|
| 9080 | Coronary Artery Disease and Coronary-Prone Behavior. (FY-79 PI) | 603 |
| 9082 | Prevention, Treatment and Rehabilitation of Knee Injury at the U.S. Military Academy, West Point, N.Y. (FY-79 I) | 607 |
| 9086 | The Physical Fitness of Military Women Employed in Health Care Occupations. (FY-80 F) | 609 |
| 9088 | A Comparison of the Use of Cognitive Therapy and Hypnosis in a Group Setting for Treating Obesity. (USUHS & NNMC) (FY-80 I) | 611 |

OTHER DEPARTMENTS, WRAIR

| | | |
|---|---|---|
| 9100 | Evaluation of Computer Assisted Drug-Drug Interaction Monitoring. (FY-80 I) | 612 |

WRAMC Regulation 70-1, Clinical Investigation Program 614

Author Index 652


Code: I = Interim Report F = Final Report P = Publications
SP = Submitted Publications T = Terminated (a report had not been received by the time this report was collated, but a supplementary report will be forthcoming.

Unit Summary Sheet

Department of Clinical Investigation

Walter Reed Army Medical Center

This Annual Progress Report is for the Fiscal Year 1980.

1. Mission Changes

a. Expansion. During FY-80, the Department of Clinical Investigation implemented a new Gastroenterology Research Laboratory in Bldg. T-2. With the help of a Veterinary Officer who is a collaborative investigator, this laboratory is already in full operation and has produced abstracts and publications to date.

b. Currently there are thirteen (13) Clinical Investigation laboratories at WRAMC with all but three (3) located in the new hospital.

c. An animal procedures laboratory, formerly part of the Organ Transplant Service located at Forest Glen, and moved to Bldg #1 on main post in FY 79 is now in Bldg 7. Two portable containment systems for housing rodent size animals are on order thus providing us the ability to kennel rodents within our department. Surgical procedures and radio-isotope injections are now carried out in this area. We continue to depend on WRAIR for kenneling and care of animals larger than rats.

d. Through a $1.8 million grant from the Veterans Administration, DCI WRAMC is supporting a study of Vietnam era veterans with projectile head wounds. The study, now in the data collection phase, will last approximately four years and will eventually accession about 1200 veterans which have been followed medically since their injury as early as 1967. CAT scanning will be used for the first time in a study of such size and scope. The project entitled, "Anatomical and Functional Sequelae of Head Injuries Incurred in Vietnam," was guided from its inception by Dr. William F. Caveness, M.D. until his death in January 1981. MAJ J.D. Dillon, MC, US Army, a neurosurgeon, has taken over as project manager and principal investigator. Term appointments for approximately ten people to conduct the project have been approved by HSC with hiring to proceed as soon as possible after the Presidential hiring freeze is lifted or further defined. We hope to begin accessioning patients in April 1981.

e. Reference Interim change to HSC Reg 10-1, dtd 24 June 1980. The interim change establishes a Department of Clinical Investigation at WRAMC since WRAMC's activity consists of ten (10) or more personnel. The interim change also deletes the Clinical Investigation Service for such activities consiting of ten (10) or more personnel. The interim changes is effective until superseded by a formal printed change to HSC Reg 10-1; and as an interim measure, issued in other than page-for-page format.

2. Personnel Actions, Current Strength

a. Personnel hired on temporary appointment to provide support to investigative projects.

| | | |
|---|---|---|
| Alston, Stephanie | GS-02 | 0699 |
| Wang, Elizabeth | GS-13 | 0180 |

b. Current Manpower

| Description | Grade | MOS | Br | Actual | Name |
|---|---|---|---|---|---|
| C, Clin Invest Dept. | 05 | 61F9C | MC | 1 | Boehm |
| Asst C, Clin Invest Dept. | 04 | 61F9B | MC | 1 | Schuster |
| Lab Officer (Admin) | 04 | 68F9D | MSC | 1 | Reed |
| Biochemist | 03 | 68C00 | MSC | 1 | Bongiovanni |
| Dietitian | 03 | 3420 | AMS | 1 | Douglas |
| Med Lab NCO | E7 | 92B | AMED | 1 | Moody |
| Med Lab SP | E5 | 92B | AMED | 1 | Lambert |
| Med Lab SP | E4 | 92B | AMED | 1 | Morgan |
| Science & Eng | E6 | 01H30 | | 1 | Shelton |
| Supv Rsch Chemist | 14 | 1320 | GS | 1 | Bruton |
| Microbiologist | 12 | 0403 | GS | 1 | Dobek |
| Microbiologist | 12 | 0403 | GS | 1 | Ciak |
| Admin Officer | 11 | 0341 | GS | 1 | Burton |
| Physiologist | 11 | 0413 | GS | 1 | Wright |
| Physiologist | 11 | 0413 | GS | 1 | Lukes |
| Bio Lab Tech | 09 | 0404 | GS | 2 | Dickson<br>Butler |
| Med Tech | 09 | 0644 | GS | 2 | Armstrong<br>Burgess |
| Chemist | 11 | 1320 | GS | 2 | Dawson<br>Rice |
| Chemist | 09 | 1320 | GS | 1 | Maydonovitch |
| Med Tech | 09 | 0645 | GS | 1 | Barnes |
| Bio Lab Tech | 08 | 0404 | GS | 1 | Coleman |
| Med Tech | 07 | 0644 | GS | 2 | Bongiovanni<br>Londono |
| Secy Steno | 07 | 0318 | GS | 1 | Ervin |
| Edit Asst | 07 | 1087 | GS | 1 | Hepburn |
| Supply Tech | 06 | | GS | 2 | Laster<br>Kuffler |

| | | | | | |
|---|---|---|---|---|---|
| Clk, DMT | 04 | 0316 | GS | 2 | McAnnally |
| Bio Lab Tech | 05 | 0404 | GS | 1 | Martin |

3. Investigation Program Summary

| | |
|---|---|
| Number of Active Protocols | 269 |
| Number of Completed Protocols | 66 |
| Number of Terminated Protocols | 32 |

4. Incentive

The Bailey K. Ashford Award medallion presented annually to the staff member at Walter Reed Army Medical Center whose research project was voted the most outstanding contribution to the WRAMC investigative program was Major Thomas G. Brewer, MC, Gastroenterology Service, for his paper entitled, "Maximal Rate of Urea Synthesis Reflects Hepatic Cell Mass in Rats"; and Major Louis N. Pangaro, MC, on the metabolism of the thyroid hormones in health and disease.

5. Funding, FY-80:

| | |
|---|---|
| Civilian Personnel | $536,214.18 |
| Military Personnel | $327,094.34 |
| Travel | $ 21,500.00 |
| Contracts | $115,000.00 |
| Supplies | $472,800.00 |
| MEDCASE | $ 68,101.00 |
| Total | $1,540,709.52 |

TABLE PUBLICATIONS AND PRESENTATIONS, FY-80

DEPARTMENT OF MEDICINE

Johnson JP, et al. "The Role of Plasmaphoresis in Anti-GBM Mediated Renal Disease". Controversies in Nephrology - 1979, Winchester and Schriener, eds., 19[illegible].

Pangaro L. Burman KD and Wartofsky L, et al, Thyroid Function Tests in Cord Blood Maternal Serum Fluid. JCEM 50:1075, 1980.

Pangaro L, Burman KD. and Wartofsky L. Investigations into the Physiology of $RT_3$ and 3,3'T2. JCEM 50:1075, 1980.

Burman KD, et al The Effect of Obesity and Fasting on T3 Receptors in Mononuclear Cells. JCEM 51:106, 1980.

Wray HL. Effect of $T_3$ and $rT_3$ on Plasma Cyclic Nucleotide Levels on Sheep. Endocrinology 107:130-136, 1980.

Glass AR. Insulin Resistance in Diabetes: Relative Effect on Glucose and Amino Acids. Presented at the American Diabetes Association Meeting and at the International Symposium, 1980. (Abstract)

Pangaro L, et al. Glucose Regulation, Peripheral Thyroid Hormone Economy in Fasted Subjects. JCEM 50:1075, 1980.

Burman KD, et al. Alterations in TRH Stimulation in Obesity and Fasting. Metabolism 29:46, 1980.

Wray HL. Effect of Thyroid Status on the Hormonally-Induced Cyclic AMP Response of the Kidney. Endocrionlogy 106 (Suppl):122, 1980.

Vigersky RA and Glass AR. "Effect of Delta-1-Testolactone (Teslac) in Oligospermic Men". J. Andrology 1:67, 1980.

Wray HL, Burman KD, et al. Investigations Concerning the Physiology of Iodothyronines. JCEM 107:130, 1980.

Pangaro LP, Burman KD, et al. The Development of a Radioimmunoassay of Triiodothyronine. JCEM 50:130, 1980.

Vigersky RA, Mozingo D, Eil E, Purohit V, and Bruton J. "Anti-Androgenic Properties of Delta-1-Testolactone (Teslac). Presented at the Endocrine Society June 1980.

Smallridge RC. Radioactive Assessment of Cardiac Function in Patients with Acromegaly. Clinical Research 28:198A, 1980.

Smallridge RC. Breast Carcinoma and Thyroid Hormone Receptors. Clinical Research 28:421A, 1980.

Burman KD, et al. The Effect of Fasting Upon TSH Response to TRH. Metabolism 29:46, 1980.



PRECEDING PAGE BLANK-NOT FILMED

DEPARTMENT OF MEDICINE (continued)

Smith C, Mehlman T, and Vigersky RA. "Treatment of Hirsutism with Cimetidine". Presented at the 62nd Annual Meeting of the Endocrine Society, June 1980.

Raveche E, Vigersky RA, Tjio JH, and Steinberg A. "Murine Thymic Androgen Receptors". Presented at the Amer. Rheumat. Assoc., May 1980.

Brewer TG, Dunn MA, Berry WR and Harmon JW. Urea Synthesis Reflects Hepatic Mass in Rats. Gastroenterology 79 1980.

Tramont EC. Treponema Pallidum (Syphilis) in Principles and Practice of Infectious Disease. Chapter 180, 1979, Mandell, Bennett and Douglas, McGraw Hill, eds), New York.

Dobek A, Klayman J, Dickson E Jr., Scovill J, and Tramont EC. Inhibition of Clinically Significant Bacterial Organisms In Vitro by 2-Acetylpyridine Thiosemicarbazone. Antimicrobial Agents and Chemotherapy. 13 (1):27-36, 1980.

Tramont EC, Ciak J, McChesney D, Boslego JW, and Brinton CC. Cross Reactivity of Gonococcal Pili as Determined by Inhibition of Epithelial Cell Attachment. Presented at the ICCAC, Boston, Mass, 1979. (Abstract)

Tramont EC, Boslego JW, Sadoff J, Zollinger W, Lolik A, Bryan J, and Brinton CC. Safety and Immunogenicity Study of Gonococcal Pilus Vaccine. Presented at the ICCAC, Boston, Mass, 1979. (Abstract)

Tramont EC, Ciak J, Boslego JW, McChesney DG, Brinton CC, and Zollinger W. Anti-Genic Specificity of Antibodies in Vaginal Secretions During Infection with Neisseria Gonorrhoeae. J Infect. Dis. 142:23-31, 1980.

Tramont EC. Role of Adhesion of Neisseria Gonorrhoeae in Disease. Presented at the Ciba Foundation Symposium London, UK, 1980.

Boslego JW, McChesney DG, Sadoff J, Ciak J, and Tramont EC. Human Genital Antibody Response to a Gonococcal Pilus Vaccine. Presented at the ICCAC, New Orleans, 1980. (Abstract)

Burman KD, et al. The Effect of Glucagon on Thyroidal Economy. JCEM, In Press.

Burman KD, et al. Regulations if the Initiation of Thyroid Hormone Action. Hormone Metab. Res: In Press.

Smallridge RC and Wray HL. Studies on the Pathogenesis of Hypocalcemia in Tumors Associated with Osteoblastic Metastases. Amer J Med, In Press.

Glass AR, Dahms WT, and Swerdloff RS. Body Fat at Puberty in Rats: Alterations by Changes in Diet. Pediat Res 13:7-9, 1979

DEPARTMENT OF MEDICINE (continued)

Glass AR, Mellitt R, Vigersky RA, and Swerdloff RS. Hypoandrogenism and Abnormal Regulation of Gonadotropin Secretion in Rats Fed a Low Protein Diet. Endocrinology 104:438-442, 1979.

Glass AR, Schaaf, and Dimond RC. Absent Growth Hormone Response to L-tryptophan in Acromegaly. J Clin Endocrinol Metab 48:664-666, 1979.

Glass AR, and Smith CE. Stress-Induced Cortisol Release in Hypothalamic Hypoadrenalism. J.A.M.A 241:1612-1613, 1979

Kidd GS, Glass AR, and Vigersky RA. The Hypothalamic-Pituitary-Testicular Axis in Thyrotoxicosis. J Clin Endocrinol Metab 43: 798-802, 1979.

Glass AR, and Berenberg J. Gynecomastia after Chemotherapy for Lymphoma. Arch Int Med 139:1048-1049, 1979.

Glass AR, Schaaf M, and Dimond RC. Amitriptyline-Induced Suppression of Growth Hormone in Acromegaly. Psychoneuroendocrinology: 5:81-86, 1980.

Glass AR, and Swerdloff RS. Nutritional Influences on Sexual Maturation in the Rat. Fed Proc 39:2360-2364, 1980.

Raum WJ, Glass AR, and Swerdloff RS. Changes in Hypothalamic Catecholamine Neurotransmitters and Pituitary Gonadotropins in the Immature Female Rat: Relationships to the Gonadostat Theory of Puberty Onset. Endocrinology 106:1253-1258, 1980.

Glass AR, and Vigersky RA. Correlation Between Acute and Chronic Increases in Serum Gonadal Steroid Levels After HCG Administration. Fertil Steril: 34:41-45, 1980.

Glass AR, and Vigersky RA. Leydig Cell Function in Idiopathic Oligospermia. Fertil Steril 34:144-148, 1980.

Glass AR, Smallridge RC, Schaaf M, and Dimond RC. Absent Prolactin Response to L-tryptophan in Normal and Acromegalic Subject. Psychoneuroendocrinology 5:261-265, 1980.

Vigersky RA, Mehlman I, Glass AR, and Smith CE. Treatment of Hirsute Women with Cimetidine: A Preliminary Report. N Engl J Med: In Press.

Glass AR, and Vigersky RA. Regulation of Testosterone Production in Man After HCG-Induced Desensitization. J Clin Endocrinol Metab: In Press.

Glass AR, Burman KD, Dahms WT, and Boehm TM. Endocrine Function in Human Obesity. Metabolism: In Press.

DEPARTMENT OF MEDICINE (continued)

Latham KR, Tseng YL, and Glass AR. Nuclear Thyroid Hormone Receptors in ob/ob Mice. Clin Res 27:256A, 1979. (Abstract)

Glass AR, Schaaf M, and Dimond RC. Amitriptyline-Induced Suppression of Growth Hormone in Acromegaly. Physiologist 22:70, 1979. (Abstract)

Glass AR. HCG-Induced Block in Testosterone Production in Man. Proc. Endo. Soc. 61st Ann Mtg, 1979, Abstract 832.

Vigersky RA, and Glass AR. Effect of Testolactone (Teslac) in Oligospermic Men. J Andrology 1:67, 1980. (Abstract)

Tseng YL, Glass AR, and Latham KR. Thyronine Metabolism in Fat and Liver Homogenated from Rats and Genetically Obese Mice. Presented at the Endocrine Society 62nd Annual Meeting, 1980, Abstract 94.

Smallridge RC, Glass AR, Wartofsky L, Ward KE, and Burman KD. Investigations into the Etiology of Elevated Serum Tri-iodothyronine (T3) Levels in Protein Malnourished Rats. Presented at the Endocrine Society 62nd Annual Meeting, 1980, Abstract 596.

Glass AR, Bongiovanni R, and Boehm M. Insulin Resistance in Obesity: Differential Effect on Glucose and Amino Acid Disposal. Diabetes 29 (Supp2): 20A, 1980.

Burman KD, Smallridge RC, Osburne R, Dimond RC, Whorton NE, Kesler P, and Wartofsky L. Nature of Suppressed TSH Secretion During Undernutrition: Effect of Fasting on TSH Responses to Prolonged TRH Infusion. Metabolism 29:46-52, 1980.

Smallridge RC, Wartofsky L, and Dimond RC. Inappropriate Secretion of TSH: Discordance Between the Suppressive Effects of Corticosteroids and Thyroid Hormone. J Clin Endocrinol Metab 48:700-705, 1979.

Chernow B, Johnson LF, Janowitz WR, and Castell DO. Pulmonary Aspiration as a Consequence of Gastroesophageal Reflux - A Diagnostic Approach. Dig Dis & Sci 24:839-844, 1979.

DEPARTMENT OF SURGERY

Harmon JW. Use of Copolymer as a Lattice for the Growth of Neogut. Surgical Forum 30:365-366, 1979.

Kramer KK. Ultrasonographic Measurement of Chorodial Melanoma. Presented at the Annual Association in Research and Vision in Opthamology Meeting May, 1980. Orlando, Florida. (Abstract)

Schwartz DM, and Surr RK. Three Experiments on the California Consonant Test. J. Speech Hear. Dis. February, 1979.

Schwartz DM, Surr RK, et al. Performance of High Frequency Impaired Listeners with Conventional and Extended High Frequency Amplification. Audiology 18, 1979.

Schwartz DM, and Surr RK. High-Pass and Conventional High Frequency Hearing Aids for Listeners with High Frequency Sensorineural Hearing Loss. Auditory and Hearing Prosthetic Research, Larson VD, Egolf D, and Kirlin L eds,.) Grune and Stratton 1979.

Punch JL, Montgomery AA, Schwartz DM, Walden BE, et al. Multidimensional Scaling of Quality Judgments of Speech Stimuls Processed by Hearing Aids. J. Acoust. Soc. Am. 68, 2, 458-465, 1980.

Montgomery AA. "Coarticulation and Lipreading: Comparison of Synthetic and Real Stimuli". Presented at the ASHA Convention, November 1979. (Abstract)

Light JA. ALG Reverses Irreversible Rejection. Presented at the Transpl. Society July 1980. (Abstract)

ALLERGY AND RHEUMATOLOGY SERVICES

deShazo RD, Levinson HI, Dvorak HM, and Davis RW. Late Phase Skin Reaction. J. Immunol. 122:692, 1979.

Smith JA, Mansfield LE, deShazo RD, and Nelson HS. An Evaluation of the Pharmacologic Inhibition of the Immediate and Late Cutaneous Reaction to Allergen. J Allergy Clin Immunol 65:119, 1980.

Smith L, Kaliner M, Davis P, Shelhamer J, and Hubbard V. Autonomic Nervous System Dysfunction in Patients with Cystic Fibrosis. J Allergy Clin. Immunol. 65:217, 1980.

Shelhamer JH, Metcalfe DD, Smith LJ, and Kaliner M. Abnormal Adrenergic Responsiveness in Allergic Subjects: Analysis of Isopro-Terenol-Induced Cardiovascular and Plasma Cystic AMP Responses. J Allergy Clin. Immunol. 66:52-61 1980.

Boehm TM, Kuma[illegible] and Galloway JH. Persistent [illegible] to Insulin. Evidence for Three Immunologic Mechanisms. Presented at the American Academy of Allergy Meeting, 1980. (Abstract)

Floyd M and Tesar JT. The Role of IgM Rheumatoid Factor in Experimental Vasculitis. Clin. Exp. Immunol. 36:165, 1979.

Berne BH, and Lawless OJ. Re-evaluation of Anti-DNA Antibody Levels Detected by the Farr Technique and FIAX Immunofluorescence Assay. Clinical Chemistry 26:1072, 1980.

Ramirez DA and Evans R III. The Diagnosis of Hymenoptera Hypersensitivity. J. Allergy Clinical Immunol. In Press 1980.

DEPARTMENT OF PEDIATRICS

Mease AD, Fischer GW, Hunter KW, and Ruymann FB. Decreased Phytohemagg-Lutinin-Induced Aggregation and C5a-Induced Chemotaxis of Human Newborn Neutrophils. Pediatr. Res. 14:142-146, 1980.

Mease AD, Burgess DP, and Thomas PJ. Differences Between Neonatal and Adult Complement-Induced Neutrophil Aggregation and Cellular Augmentation of Neutrophil Chemotaxis. Pediatr. Res. 14:549

DEPARTMENT OF PSYCHIATRY

Hunter JG. The Developmental Significance of Transitional Objects. Presented to the Annual Department of Psychiatry Research Symposium, June 1980.

DEPARTMENT OF HEMATOLOGY, WRAIR

Kark JA and Lessin LS. Sickle Cell Disease and Variants in Hematology and Oncology M. Lichtman, eds,.) Grune and Stratton, Inc., New York, NY, pp. 89-97, 1980.

Kark JA, Hannah JS, Hicks CU, Borgiovanni R, Lessin LS, and Hayes K. Vitamin $B_6$ Aldehydes as Potential Antisickling Agents. Presented at the Fifth International Red Cell Conference, September 1980, Ann Arbor, Michigan.

Kark JA, Hicks CU, and Borgiovanni R. Inhibition of Erythrocyte Sickling by Pyridoxal Phosphate. Clin. Res. 28:315A, 1980.

USUHS

Krantz DS, Schaeffer M, Davia JE, Dembroski TM, MacDougall JM, and Shaffer RT. Investigation of Extent of Coronary Atherosclerosis, Type A Behavior and Cardiovascular Response to Social Interaction. Presented at the Society for Psychophysiological Research, Vancouver BC, October 1980.

Krantz DS, Glass DC, Schaeffer M, and Davia JE. Behavior Patterns and Coronary Disease: A Critical Evaluation. J.T. Cacioppo and R.E. Petty eds.,) Focus on Cardiovascular Psychophysiology, New York: Gulford, In Press.

PROTOCOL #1004

TITLE: Stress Ulceration in a Medical ICU: Incidence and Possible Prevention with Cimetidine

INVESTIGATORS:

Principal Investigator: Dr. Lawrence F. Johnson
Dr. Michael T. Keegan

DATE COMPLETION: Estimated January 1982

OBJECTIVE: To prove in a double blind randomized fashion if Cimetidine is effective in decreasing the incidence of stress induced gastrointestinal hemorrhage in the Medical Intensive Care Unit.

TECHNICAL APPROACH: See Protocol

PROGRESS and RESULTS: Since the last report, 2 patients have been added to the study. The double blind code has not been broken, so it is impossible to determine at this time the efficacy of Cimetidine vs placebo. Interim evaluation of the submitted data to Smith, Klein, French on 38 patients seems to indicate that there is some trend, but they are not willing to say that there is any significant difference between the two groups at this time. In patients studied so far, there have been no untoward side effects that could be related to the study drug or the protocol. Of note is that accession of patients to the study has been hampered somewhat by the wide spread use of Cimetidine in this hospital and outlying referral hospitals.

CONCLUSIONS: Forty patients have been studied to date under the protocol. Because it is a blinded coded protocol and the code has not been broken and no results are available at this time, it is anticipated that adequate data can be obtained with a total pool of 50 patients. It is asked that the study be continued until at least 10 more patients are accessed.

FUNDS UTILIZED: None

FUNDS REQUESTED, FY 80: Same as original protocol

PUBLICATIONS TO DATE: None

TYPE OF REPORT: Interim

ADDENDUM:

Forty patients have been studied under the protocol and there have been no untoward side effects noted that could be definitely related to the drug or to the protocol. On site inspection and drug inventory has been carried out as prescribed by FDA regulations by Smith, Klein, French Company on a regular basis.



PRECEDING PAGE BLANK-NOT FILMED

| Date: 1 December 1980 | Protocol No: 1005 | Status: Interim X<br>Final |
|---|---|---|

Title of Project:
Polycythemia Vera Study Group #12, Efficacy Trial using Hydroxyurea (HU) in the Treatment of Primary Thrombocytosis.

| Starting Date: 22 January 1980 | Estimated Completion Date: Within the next fiscal year. |
|---|---|

Principal Investigator: Daniel B. Kimball, Jr., COL, MC

| Associate Investigators:<br>Staff and Fellows of the Hematology-Oncology Service | Facility: WRAMC<br>Dept/Svc Department of Medicine |
|---|---|

Key Words:

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: |
|---|---|---|

| FY-80 MEDCASE Cost: | Periodic Review Results:<br>(to be filled in by DCI) |
|---|---|

Study Objective:
To study the usefulness of Hydroxyurea in the treatment of primary thrombocytosis in an attempt to find an acceptable nonalkalating chemotherapy agent to reduce the risk of acute leukemia.

Technical Approach:

Progress during FY-80:
No patients from Walter Reed Army Medical Center have been entered on this national protocol. Nationally 43 patients have been accrued to this study of whom 26 have been evaluated for periods of longer than 3 months. Of the evaluable patients 12 achieved

Number of subjects to be studied before completion of study: (over)

Serious/unexpected side effects in subjects participating in project:

Conclusions: Protocol 12 continues to be open for patient accrual and it is anticipated that 12 more patients acquired nationally would provide for complete accrual to the protocol.

Publications or Abstracts, FY-80: None.

Progress during FY80 (Continued):
a complete remission as defined by a platelet count of less than 450,000. An additional 9 patients have had good partial responses with platelet counts being maintained in the normal range or less than 600,000 for periods of greater than one year in 12 of 21 patients. Only 2 patients have had no response to Hydroxyurea. Toxicity has been mild and consisted mostly of leukopenia. One patient has had pharyngitis and rash secondary to the Hydroxyurea. Three deaths on the study have occurred. One patient died after being in complete remission for a period of more than one year and after Hydroxyurea therapy was discontinued and the patient then relapsed. The Hydroxyurea was restarted in an inappropriately high dose, the patient developed pancytopenia and subsequently died of Candida septicemia. One patient with a history of a previous polycythemia vera developed herpes zoster infection and then went on to develop peripheral blasts and acute leukemia and died of pneumonia. The third death was an elderly patient who died in a nursing home of cardiac causes.

| Date: 1 December 1980 | Protocol No: 1006 | Status: Interim X / Final |
|---|---|---|

Title of Project:
Polycythemia Vera Study Group Protocol #8, Efficacy Trial Using Hydroxyurea (HU) in Polycythemia Vera

| Starting Date: 22 January 1980 | Estimated Completion Date: It is anticipated that the protocol will be closed nationally within the next year. |
|---|---|

Principal Investigator: Daniel B. Kimball, Jr., COL, MC

| Associate Investigators: | Facility: WRAMC |
|---|---|
| Staff and Fellows of the Hematology-Oncology Service | Dept/Svc Department of Medicine |

Key Words:

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: |
|---|---|---|
| FY-80 MEDCASE Cost: | Periodic Review Results: (to be filled in by DCI) | |

Study Objective:
To develop an efficacious nonalkalating form of chemotherapy for the treatment of polycythemia rubra vera in an attempt to reduce the incidence of leukemia.

Technical Approach:

Progress during FY-80: No patients from the Walter Reed Army Medical Center have been randomized to this protocol. Nationally 65 patients have been entered into this study. The study to date has indicated that 100% of all patients treated have had an initial response. The duration of the response, however, varied from brief

Number of subjects to be studied before completion of study: (over)

Serious/unexpected side effects in subjects participating in project:

Conclusions: The study remains open for patient accrual and shows that Hydroxyurea is an effective agent for the initial control of newly diagnosed polycythemia rubra vera. It will take further time to decide whether the leukemia risk is as great with this agent as it is with ionizing radiation or an alkylating agent.

Publications or Abstracts, FY-80:
None

Progress during FY80: (Continued)
to greater than one year. With regard to toxicity slightly more than 50% of the patients had significant toxicity with thrombocytopenia being the most common and leukopenia the next most common as would be expected. Despite the frequency of leukopenia, no patient had a significant infection and evidence of clinical bleeding was rare despite marked thrombocytopenia in some patients. Anemia was of no clinical significance. Twenty-one of 46 patients achieved excellent control without need for any further phlebotomy. Eleven per cent had a satisfactory response with only one occasion per year where the patient was considered to be out of control, that is a hematocrit greater than 50% or a platelet count greater than 1,000,000. Forty-four per cent of the patients failed to achieve adequate control by the criteria mentioned above. Clinically, however, many of these patients who were categorized as failures did very well. There were two deaths in patients in the study which occurred relatively early, but they were not due to inadequate management. There were also two major hemorrhagic episodes, one case of Mallory-Weiss Syndrome which was thought possibly to be secondary to gastrointestinal upset resulting from the Hydroxyurea therapy and there was one episode of gastrointestinal bleeding. An analysis by a group of the failure of the Hydroxyurea regimen suggested the following contributing causes: (1) incorrect doses, (2) inadequate doses despite lack of toxicity, (3) reduction in dosage of Hydroxyurea to inadequate levels after an initial episode of toxicity, (4) inadequate phlebotomy before the patient was started on Hydroxyurea therapy, (5) excessive early iron replacement therapy, and (6) patient unreliability. One patient on the study has developed acute leukemia and the patient had a complete remission following its treatment. Recommendations to investigators within the group included that the patients be phlebotomized adequately before starting Hydroxyurea therapy in order to avoid inadequate hematocrit control in the face of white cell or platelet toxicity. In previously untreated patients, excellent control has been obtained with Hydroxyurea in greater than 75% of the cases, however, in patients who have previously been treated the incidence of excellent control is only 35%. Iron replacement as indicated by serum iron and per cent saturation does occur in patients treated with Hydroxyurea and seems to parallel the increase in mean corpuscular volume. Patients on the Hydroxyurea do not need to be phlebotomized unless the hematocrit is greater than or equal to 50%. A subcommittee has been appointed in order to plan a second generation protocol to succeed this current study.

| Date: 25 September 1980 | Protocol No: 1121 | Status: Interim X / Final |
|---|---|---|

Title of Project: "Combines Prednisone and Cytoxan Therapy Coupled with Plasma Exchange in the Treatment of Anti-glomerular Basement Membrane (Anti-GBM) Antibody Induced Disease"

| Starting Date: November 1975 | Estimated Completion Date: December 1981 |
|---|---|

Principal Investigator: John P. Johnson, MD, LTC, MC, Division of Nephrology, WRAIR

| Associate Investigators: | Facility: WRAIR and WRAMC |
|---|---|
| Jack Moore, Jr., MD, MAJ, MC | Dept/Svc Nephrology Service |

Key Words: Anti-GBM Disease, Good-pasture's Sundrome, Plasma Exchange, Cytoxic Therapy

| Accumulative MEDCASE Cost: 0 | Accumulative Contract Cost: 0 | Accumulative Supply Cost: 0 |
|---|---|---|

| FY-80 MEDCASE Cost: 0 | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective: To compare the effect of Cytoxan and Prednisone alone and in combination with plasma exchange on the rate of disappearance of circulatory anti-glomerular basement membrane antibody and the effect of this in modifying disease course.

Technical Approach: Patients are randomized based on last SS# digit to receive Cytoxan-Prednisons vs. Cytoxan, Prednisone + 4 liter plasma exchange three times weekly plasma exchange require the use of the Blood Bank for plasma exchange use and fresh frozen plasma. Serum samples are serially gathered and analyzed for anti-GBM activity gratis by Curtis Wilson, MD, Chief, Immuno-Pathology , Scripps Research Clinic, La Jolla, California.

Progress during FY-80: Two patients have been enrolled in the protocol during FY 80. One patient is now stable iwtht he nephrotic syndrome and serum creatinine of 2.2 and is off protocol, having completed the regimen. The second patient is currently on the protocol, is undergoing plasma exchange, and is stable with a serum creatinine of 1.6.

Number of subjects to be studied before completion of study: 6 Additional (Total of 20)

Serious/unexpected side effects in subjects participating in project: One patient developed HbSag negative nephritis which necessitated removal of the patient from the protocol The relationship between the hepatitis and plasma exchange remains unclear, but his hepatitis has completely resolved.

Conclusions: Only tentative conclusions can be reached at this time. The rate of disappearance of anti-GBM antibody appears to be similar between the two groups, but the numbers studied are too small to reach definite conclusions.

Publications or Abstracts, FY-80: Johnson, J.P. et al: "The Role of Plasmaphoresis in Anti-GBM Mediated Renal Disease" Controversies in Nephrology, 1979, Winchester and Schreiner (eds.), 1980.

Work Unit No.: 1121

Funds Utilized, FY-80: None

Funding Requirements, FY-81:

Personnel: John P. Johnson, MD, LTC, MC, Department of Nephrology, WRAIR
Jack Moore, Jr., MD, MAJ, MC, Nephrology Service, WRAMC

Funds: None

Equipment: None

Funds: None

Supplies: None

Funds: None

Travel: Presentation at National Meetings

Funds: $600.00

Other: Reprint Expense

Funds: $300.00

Total Funds Requested, FY-81: $900.00

| Date: 13 October 1980 | Protocol No: 1124 | Status: Interim X<br>Final |
|---|---|---|

Title of Project: "The Effect of Hyperuricemia on Chronic Renal Failure"

| Starting Date: December 1977 | Estimated Completion Date: Undetermined |
|---|---|

**Principal Investigator:** Daniel A. Nash, Jr., MD, LTC, MC

| **Associate Investigators:**<br>None | **Facility:** WRAMC Nephrology Service<br>**Dept/Svc** Department of Medicine/ Nephrology Service |
|---|---|

**Key Words:** Hyperuricemia, Chronic Renal Failure

| Accumulative MEDCASE Cost:_____ | Accumulative Contract Cost:_____ | Accumulative Supply Cost:_____ |
|---|---|---|

| FY-80 MEDCASE Cost:_____ | Periodic Review Results:_____<br>(to be filled in by DCI) |
|---|---|

**Study Objective:** To determine if hyperuricemia occurring in patients with chronic renal failure from other causes is a deleterious factor in the progression of their renal failure.

**Technical Approach:** Patients with progressive chronic renal failure and significant hyperuricemia will be prospectively followed until they are entered into a program of hemodialysis or kidney transplantation. Such patients will be randomized into groups whose hyperuricemia is untreated or into groups where the hyperuricemia is normalized with the use of Allopurinol. The course of their renal failure will be plotted using the reciprocal of the creatinine to obtain a linear relationship that can be used for comparison between the two groups.

**Progress during FY-80:** One additional patient was found with a suitable degree hyperuricemia and chronic renal failure to be entered into the protocol. This individual has been followed prospectively for approximately eight months. There have now been a total of 4 entries into this protocol observation.

Number of subjects to be studied before completion of study: 20

**Serious/unexpected side effects in subjects participating in project:** NONE

Conclusions: NONE

Publications or Abstracts, FY-80: NONE

Work Unit No.: 1124

Funds Utilized, FY-80: NONE

Funding Requirements, FY-81:

Personnel: None

Equipment: None

Supplies: None

Travel: $600.00

Other: None

| Date: 13 October 1980 | Protocol No: 1125 | Status: Interim |
|---|---|---|
| | | Final X |

Title of Project: "State of Potassium Balance in the Adult Acute Leukemic Patient"

| Starting Date: June 1978 | Estimated Completion Date: Project Discontinued |
|---|---|

Principal Investigator: Suzanne M. Bergman, MD, MAJ, MC

| Associate Investigators: | Facility: WRAMC Nephrology Service, WRAIR Neohrology Service |
|---|---|
| James D. Fitz, MD, CPT, MC<br>Donald E. Butkus, MD, COL, MC<br>Daniel A. Nash, Jr., MD, LTC, MC | Dept/Svc: Department of Medicine Nephrology Service |

Key Words: Total Body Potassium, Acute Leukemia

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: 0 |
|---|---|---|

| FY-80 MEDCASE Cost: | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective: The objective was to determine the frequency of total body potassium depletion in patients with untreated leukemia, and to assess the effects of therapy on known modulators of potassium homeostasis.

Technical Approach: 15-20 patients with newly diagnosed acute leukemia would be studied for total body potassium, red cell potassium, and serum potassium. This will be performed prior to and after treatment as indicated by standard therapeutic methods.

Progress during FY-80: Because of loss of key personnel, project had to be discontinued.

Number of subjects to be studied before completion of study: Project discontinued

Serious/unexpected side effects in subjects participating in project: None

Conclusions: None

Publications or Abstracts, FY-80: None

Work Unit No.: #1125

Funds Utilized, FY-80:

Funding Requirements, FY-81:

Personnel: Project discontinued, no funding requested

Equipment: None

Supplies: None

Travel: None

Other: None

| Date: 13 October 1980 | Protocol No: 1127 | Status: Interim X / Final |
|---|---|---|

Title of Project: "Characterization and Response to Therapy in Mild Essential Hypertension"

| Starting Date: June 1979 | Estimated Completion Date: June 1984 |
|---|---|

Principal Investigator: Daniel A. Nash, Jr., MD, LTC, MC
Betty Watkins, RN, CPT, ANC

| Associate Investigators: Michael Dugar, Laboratory Technician | Facility: WRAMC Nephrology Service; Medical Outpatient Clinic; Nephrology Laboratory |
|---|---|
| | Dept/Svc: Department of Medicine/ Nephrology Service |

Key Words: Mild Essential Hypertension, Borderline Hypertension, Characterization and Follow-up

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: |
|---|---|---|
| FY-80 MEDCASE Cost: | Periodic Review Results: (to be filled in by DCI) | |

Study Objective: To study patients with borderline hypertension to determine the nature of their essential hypertension within the constraints of standard office techniques. To determine which ongoing therapy has an impact on the development of fixed hypertension in patients with such labile hypertension.

Technical Approach: Patients with borderline hypertension will receive a complete medical evaluation to include renin activity. Blood pressure response to positional changes and to isometric exercise wil be determined. Patients will be treated with diet, sodium restriction, and medications in accord with standard practice. Such patients will be followed prospectively for the development of fixed hypertension. These factors at their preliminary presentation compared for relevance to the frequency and rate of development of fixed hypertension.

Progress during FY-80: Nineteen patients have been entered and evaluated and are under ongoing follow-up.

Number of subjects to be studied before completion of study: 20-40

Serious/unexpected side effects in subjects participating in project: NONE

Conclusions: Long-term follow-up is required in this study (5 year intervals) for conclusions.

Publications or Abstracts, FY-80: NONE

Work Unit No.: 1127

Funds Utilized, FY-80:

Funding Requirements, FY-81:

Personnel: None

Equipment: None

Supplies: None

Travel: $600.00

Other: None

In response to the Annual Report Review Committee question asking about the cost of adding more patients versus continuing with the current group, the following is applicable in reference to Protocol Work Unit #1127. A population demographic study of only nineteen patients is much too small a number, considering the variability of the questions being asked - e.g. incidence of morbidity, benefit of weight reduction, etc. At this point, there is no cost to speak of as all patients are simply being followed by the investigators as part of the ongoing particular patient population.

| Date: 15 October 1980 | Protocol No: 1128 | Status: Interim X<br>Final |
|---|---|---|

Title of Project: "Evaluation of the Rehabilitation of End-Stage Renal Disease Patients by Hemodialysis and Kidney Transplantation Using Activity Recording"

| Starting Date: June 1979 | Estimated Completion Date: June 1982 |
|---|---|

Principal Investigator: Daniel A. Nash, Jr., MD, LTC, MC

| Associate Investigators: | Facility: WRAMC Nephrology and Organ Transplant Svc<br>WRAIR Neuropsychiatry Division |
|---|---|
| Gregory Belenky, MAJ, MC<br>Jimmy Light, MD, COL, MC | Dept/Svc: WRAMC Department of Medicine<br>Nephrology Service |

Key Words: Rehabilitation with End-Stage Renal Disease; Hemodialysis versus Kidney Transplantation; Activity Monitoring

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: 0 |
|---|---|---|

| FY-80 MEDCASE Cost: | Periodic Review Results:<br>(to be filled in by DCI) |
|---|---|

Study Objective: To monitor the activity of patients with end-stage renal disease prior to and after being treated with conventional hemodialysis or receiving kidney org transplantation. Thereby determining if rehabilitation by one of these ESRD treat modalities is clearly superior to the other.

Technical Approach: A movement monitor (actograph) will be placed on patients who develop evidence of uremia as a consequence of end-stage renal disease and are in imminant need of hemodialysis or kidney transplantation. This baseline activity will be compared to repeat determination of activity after institution of either hemodialysis or transplantation. The differences in the activity with each therapeutic modality will be compared to baseline, and will also be compared between treatment modalities. In this way, profiles of patient rehabilitation will be developed for comparison.

Progress during FY-80: Four patients were entered and had baseline activities recorded and repeat studies performed after hemodialysis was initiated in each. From such initial studies important steps were taken to improve the sensitivity and reproducibility of the activity monitoring device. A new and improved monitor has been developed.

Number of subjects to be studied before completion of study: 40-60

Serious/unexpected side effects in subjects participating in project: NONE

Conclusions: NONE

Publications or Abstracts, FY-80: NONE

Work Unit No.: 1128

Funds Utilized, FY-80:

Funding Requirements, FY-81:

Personnel: None

Equipment: None

Supplies: None

Travel: $600.00

Other: $1,800.00 - Computer rental time for deprograming activity monitor)

| Date: 27 August 1980 | Protocol No: 1129 | Status: Interim X<br>Final |
|---|---|---|

Title of Project: "COMPARISON OF THE CARDIOPULMONARY VARIABLES OF PATIENTS DIALYZED AGAINST ACETATE OR BICARBONATE BUFFER"

| Starting Date: November 1979 | Estimated Completion Date: June 1981 |
|---|---|

Principal Investigator: Suzanne M. Bergman, MD; Jack Moore, Jr., MD

| Associate Investigators: | Facility: Dialysis Unit, WRAMC<br>Medical, Cardiac, Surgical, Thoracic ICU |
|---|---|
| Mitchell M. Mutter, MD<br>Barbara Smith, RN | Dept/Svc Medicine/Nephrology |

Key Words: Acetate Dialysate, Bicarbonate Dialysate, Cardiac Output, Peripheral Resistance

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: |
|---|---|---|

| FY-80 MEDCASE Cost: | Periodic Review Results:<br>(to be filled in by DCI) |
|---|---|

Study Objective: To determine if there is a difference in cardiopulmonary function when the buffer in the dialysate used for hemodialysis is changed from acetate to bicarbonate, and to provide physiologic data on which to base a rational choice of dialysate buffers.

Technical Approach: Swan-Ganz catheters and radial arterial lines were placed and used in determining cardiac outputs by thermo dilution and in monitoring arterial pressure. Hemodialysis was performed twice; once using the standard acetate dialysate and once using a bicarbonate buffered dialysate. Cardiac output, heart rate, right atrial pressure, arterial pressures, plasma renin activity, catecholamines, osmolality and blood gases were determined every hour.

Progress during FY-80. Six patients were fully studied on the protocol. One patient died in between the dialysis periods and did not complete the study.

Number of subjects to be studied before completion of study: 15

Serious/unexpected side effects in subjects participating in project: None

Conclusions:

Publications or presentations, FY-80:

Work Unit No.: 1129

Funds Utilized, FY-80:

Funding Requirements, FY-81:

Personnel: None

Equipment: Balloon flotation catheters - $1,000.00

Supplies: $600.00

Travel: $600.00

Other: $150.00

# DISPOSITION FORM

For use of this form, see AR 340-15; the proponent agency is The Adjutant General's Office.

| REFERENCE OR OFFICE SYMBOL | SUBJECT |
|---|---|
| HSNP-MN | Investigational Drug Progress Report - Para 7 AR 40-7 |

TO C, Clinical Investigation Svc (ATTN: Timothy M. Boehm, MD) FROM Suzanne M. Bergman, MD DATE 26 August 80 CMT 1

1. Annual Progress Report on the Clinical Investigation Program, Work Unit #1129, Comparison of the Cardiopulmonary Variables in Patients Dialyzed Against Acetate and Bicarbonate Buffer. Investigators: Suzanne M. Bergman, MD, MAJ, MC; Jack Moore, Jr., MD, MAJ, MC;

2. The hemodialysis and hemodynamic monitoring are performed in the Dialysis Unit or the Medical, Cardiac, Thoracic, or Surgical Intensive Care Units located on the fourth floor of the Walter Reed Army Medical Center.

3. Seven critically ill patients were entered on the protocol and six survived to finish the study. One patient expired during the interim period between dialyses.

4. Maintenance of arterial blood gases and acid-base balances were not different with either dialysate. A small improvement in cardiac output and vascular resistance was noted with the bicarbonate containing dialysate in some patients. A statistical analysis has not yet been made. Determinations of plasma renin activity and catecholamines will be done at the end of the study period as a group.

The preparation of a bicarbonate dialysate is a laborious procedure. Dialysis with a bicarbonate containing dialysate is a safe procedure as long as dialysate pH is checked every hour and adjusted as necessary.

5. Additional information gained in conjunction with the hemodynamic monitoring are changes in endogenous vasoactive substances such as plasma renin and catecholamines. Future studies as an appendum to this protocol may include the measurement of opioid peptides (not available one year ago) and increasing the $Na^+$ concentration of the dialysate (decreasing osmotic water shifts).

6. There have been no significant observations using a bicarbonate dialysate

Suzanne M. Bergman

SUZANNE M. BERGMAN, MD
MAJ, MC
Asst. Chief, Nephrology Service
Walter Reed Army Medical Center

DA FORM 1 FEB 82 2496 REPLACES DD FORM 96, EXISTING SUPPLIES OF WHICH WILL BE ISSUED [illegible]

| Date: 11 August 1980 | Protocol No: 1130 | Status: Interim X / Final |
|---|---|---|

Title of Project: THE ROLE OF HYPERURICOSURIA IN THE NEPHROTOXICITY OF RADIOCONTRAST AGENTS

| Starting Date: 8 April 1980 | Estimated Completion Date: July 1982 |
|---|---|

Principal Investigator: Jack Moore, Jr., MD, MAJ, MC, Staff, Nephrology Service

| Associate Investigators: | Facility: Walter Reed Army Medical Center |
|---|---|
| Daniel A. Nash, Jr., MD, LTC (P), Chief, Nephrology Service<br>Anthony Henry, MD, CPT, MC, Fellow<br>James Hasbargen, MD, CPT, MC, Fellow | Dept/Svc: Department of Medicine, Nephrology Service |

Key Words: NEPHROTOXICITY, RADIOCONTRAST AGENTS, URIC ACID

| Accumulative MEDCASE Cost: 0 | Accumulative Contract Cost: 0 | Accumulative Supply Cost: 0 |
|---|---|---|

| FY-80 MEDCASE Cost: | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective: To determine if the incidence of, or severity of, radiocontrast-induced acute renal failure (ARF) can be attenuated by pre-contrast exposure therapy with isotonic solutions, and if so, does bicarbonate solution add to the attenuation of ARF by increasing the solubility of uric acid in the urine.

Technical Approach: All patients accepted for the study must meet "high risk" for contrast requirements. They are then sequentially randomized to one of three arms: 1.) Dextrose infusion, 2.) Normal saline infusion, or 3.) Isotonic bicarbonate infusion, followed by oral carbonic anhydrase inhibitors. Sequential blood renal function tests and urines for creatinine and uric acid are collected.

Progress during FY-80:

So far (11 August 1980) 4 patients have been studied. No conclusions can be reached as yet.

Number of subjects to be studied before completion of study:

Serious/unexpected side effects in subjects participating in project:

Conclusions: No conclusions can be reached as yet. This protocol has only been operative since 8 April 1980.

Publications or Abstracts, FY-80: None

Work Unit No.: 1130

Funds Utilized, FY-80: 0

Funding Requirements, FY-81:

Personnel: Jack Moore, Jr., MD, MAJ, MC, Principal Investigator
Daniel A. Nash, Jr., MD, LTC (P), MC, Chief, Nephrology Service
Anthony Henry, MD, CPT, MC
James Hasbargen, MD, CPT, MC

Funds: 0

Equipment: None

Funds: 0

Supplies: None

Funds: 0

Travel: For presentation at National Meetings

Funds: $600.00

Other: Reprint Costs

Funds: $300.00

Total Funds Requested, FY-81: $900.00

| Date: 13 October 1980 | Protocol No: 1131 | Status: Interim x<br>Final |
|---|---|---|

Title of Project: "Hematuria During Anticoagulation Therapy With Coumadin"

| Starting Date: November 1979 | Estimated Completion Date: November 1981 |
|---|---|

Principal Investigator: Daniel A. Nash, Jr., MD, LTC, MC

| Associate Investigators: | Facility: Nephrology Service, Laboratory and Clinic Area |
|---|---|
| James Hasbargen, MD, CPT, MC<br>Anthony Henry, MD, CPT, MC<br>Brian Copley, MD, MAJ, MC | Dept/Svc: Department of Medicine/ Nephrology Service |

Key Words: Coumadin Therapy, Hematuria, Urine Urokinase Activity

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: 125.85 |
|---|---|---|

| FY-80 MEDCASE Cost: | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective: To determine the incidence of microscopic hematuria in patients receiving standard Coumadin therapy. To determine the etiology of hematuria when it occurs in such patients. To determine if urine urokinase is abnormal in such patients with hematuria.

Technical Approach: Patients receiving Coumadin for standard indications and standard dosages will be screed for the presence of microscopic hematuria. Those determined to have hematuria on repeat examination and in the absence of Coumadin over anticoagulation will be further evaluated. This evaluation will include urological and hematological evaluation for causes of hematuria. Further, urine urokinase activity will be determined to see if this urine anticoagulant factor is abnormal in such patients.

Progress during FY-80: 84 patients have been screened for microscopic hematuria. Four patients found to have microscopic hematuria underwent urological and hematological evaluations. Urines have been stored for urine urokinase activity. The urine urokinase assay is under development.

Number of subjects to be studied before completion of study: 1-200 more patients

Serious/unexpected side effects in subjects participating in project: NONE

Conclusions: NONE

Publications or Abstracts, FY-80: NONE

In response to the Annual Report Review Committee question asking about the cost of adding more patients versus continuing at the present group level, the following is applicable in reference to Protocol Work Unit #1131. No more patients are being added to the study until those currently entered complete their evaluation (urine urokinase) and the data are analyzed. Depending on the results of these data, additional patients may at that time be considered in the interest of attaining statistical significance.

Work Unit No.: 1131

Funds Utilized, FY -80:

Funding Requirements, FY-81:

Personnel: None

Equipment: None

Supplies: $800.00

Travel: $600.00

Other: $150.00

| Date: 5 September 1980 | Protocol No: 1215 | Status: Interim / Final |
|---|---|---|

Title of Project: Double Blind Evaluation of Lopressor Vensus Placebo in the Treatment of Angina Pectoris

| Starting Date: 2 May 1980 | Estimated Completion Date: June 1981 |
|---|---|

Principal Investigator: Patrick K.C. Chun, M.D., MAJ, MC

| Associate Investigators: | Facility: Walter Reed Army Medical Center |
|---|---|
| Fayaz Shawl, M.D., CPT, MC<br>Clarion Johnson, M.D., CPT, MC<br>James E. Davis, M.D., COL, MC | Dept/Svc: Cardiology |

Key Words: Lopressor, Double Blind, Angina

| Accumulative MEDCASE Cost: 0 | Accumulative Contract Cost: 0 | Accumulative Supply Cost: 0 |
|---|---|---|

| FY-80 MEDCASE Cost: 0 | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective: To document beneficial effects of a selective Beta Blocking Drug Lopressor for angina in 16 patients.

Technical Approach: 16 patients enrolled in study, treated in double blind fashion at increasing doses and followed with history and physicals and graded exercise treadmills.

Progress During FY-80: 6 to 16 patients have already completed the study. Study is progressing well without complications. We are at the same rate as the other centers participating.

Number of subjects to be studied before completion of study: 16

Serious/unexpected side effects in subjects participating in project: None

Conclusions: Study proceeding on schedule with beneficial effects of Lopressor demonstrated.

Publications or Abstracts, FY-80: None

# DISPOSITION FORM

For use of this form, see AR 340-15, the proponent agency is TAGCEN.

| REFERENCE OR OFFICE SYMBOL | SUBJECT |
|---|---|
| HSWP-ME | Protocol |

TO Clinical Investigation Svc FROM Kenneth D. Burman, MD DATE 2 Sep 80 CMT 1

K.D. Burman/ej/61416

1. Please allow protocols #1308, 1329,1331,1359,1366,1372, and 1389 to terminate.

2. Please keep the following protocols active for two (2) more years as explained below:

1311 - We require the use of this protocol because if a patient does enter the hospital in thyroid storm this protocol could be life saving.

1334 - We have made great progress on this protocol but would like it to stay active so that we could isolate and purify the enzyme responsible for T4 to T3 conversion.

1346 - We have developed new assays especially by HPLC for the measurement of thyronenes and would like this protocol to stay active so that we could measure these thyronenes in cord blood and amniotic fluid.

1347 - We have not yet finished this protocol and would like to have its time period extended so that we could finish our studies investigating extrathyroid deiodenation.

1353 - We would like to finish this project by isolating and characterizing the T3 receptor.

1360 - Dr. Smallridge and I have sent one paper to be published comparing T2 production rates and would like to have this protocol open so that if the referees need more studies we could perform them.

1390 - We would like to measure thyronens by HPLC.

1391 - We would like to continue to measure phosphatase activity in various conditions.

1388 - We are still in the process of developing a thyronine assay.

Ken Burman

KENNETH D. BURMAN, MD
LTC, MC
Assistant Chief, Endocrine-Metabolic Svc
and Kyle Metabolic Unit

DA FORM 2496 REPLACES DD FORM 95, WHICH IS OBSOLETE.

# DISPOSITION FORM

For use of this form, see AR 340-15, the proponent agency is TAGCEN.

| REFERENCE OR OFFICE SYMBOL | SUBJECT |
|---|---|
| HSWP-ME | Response to Comments by Dr. Evans on Protocol 1308, 1311, 1359, and 1360 |

TO Clinical Investigation Svc FROM Kenneth D. Burman, MD DATE 4 Dec 80 CMT 1
Asst Ch, Endo-Metab Svc Burman/eds/61416

1. 1308 - As noted on detail summary sheet, this report is a final report. There are no abstracts on this protocol because Dr. Lowenthal left the service and there is no one to measure Inderal levels.

2. 1311 - It is mandatory and important that this be renewed so that this life threatening disease can be adequately treated when and if such a patient enters the hospital.

3. 1359 - Dr. Boehm is presently writing up this manuscript.

4. 1360 - The first paper emanating from this protocol was so interesting and important it was rapidly accepted for publication (in press JCEM) and further, opened up new important questions relative to other iodothyronines. In short, we are the first to show that iodothyronine clearance rates can be performed with unlabelled hormones. This is an important contribution with wide spread implications.

KENNETH D. BURMAN, MD
LTC, MC
Asst Ch, Endocrine-Metabolic Service

| Date: | Protocol No: 1308 | Status: Interim / X Final |
|---|---|---|

Title of Project:

Inderal Kinetics in Hyperthyroidism

| Starting Date: 3-29-74 | Estimated Completion Date: 8-80 |
|---|---|

Principal Investigator: KENNETH D. BURMAN, MD, LTC, MC

| Associate Investigators: | Facility: WRAMC |
|---|---|
| Leonard Wartofsky, MD, COL, MC | Dept/Svc Medicine |

Key Words: Inderal/hyperthyroidism

| Accumulative MEDCASE Cost: 0 | Accumulative Contract Cost: 0 | Accumulative Supply Cost: 500 |
|---|---|---|

| FY-80 MEDCASE Cost: | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective.

To determine Inderal levels in patients with thyrotoxicosis.

Technical Approach:

Serum Inderal is measured by ultraviolet absorption

Progress during FY-80:

None

Number of subjects to be studied before completion of study:

Serious/unexpected side effects in subjects participating in project: None

Conclusions: Inderal levels do not correlate with T4 levels.

Publications or Abstracts, FY-80: None

Work Unit No.: 1310

Title of Project: TRH in Patients with Hypothalamic Pituitary Thyroid Disease

Investigators:

Principal: Leonard Wartofsky, COL, MC

Associates: K. D. Burman, LTC, MC, R.C. Dimond, LTC, MC, M. Schaaf, M.D.

Objectives: To assess the response to synthetic TRH (Thyrotropin releasing hormone) in various suspected endocrine disorders.

Technical Approach: Patients are studied on the metabolic ward. Blood samples are drawn for measurement of thyrotropin, prolactin, and other hormones, before and after this bolus injection or infusion of 100-500 mcg of synthetic TRH. Until Dec 1976, the latter agent was an investigational drug but has since been released for clinical use.

Progress & Results: Approximately 610 such studies have been completed in approximately 405 subjects. Although some data continues to accumulate with time and is yet to be analyzed, much already has appeared in the publications listed below. It is anticipated that additional studies on elucidation of abnormalities of the hypothalamic-pituitary-thyroid axis employing TRH as a probe will continue to be highly productive.

Conclusions: TRH has been found to be a useful agent for the assessment of disorders of the hypothalamic-pituitary-thyroid axis, with minimal or negligible side effects or problems associated with its use; and has also proved to be a valuable research tool.

Funds Utilized FY-80

| | | |
|---|---|---|
| 1100 | Personnel | - |
| 2100 | Travel | - |
| 2319 | Rental | - |
| 2400 | Print & Repro. | - |
| 2572 | Contractual Svcs | - |
| 2600 | Cons. Supplies | 3700 |
| 3100 | Non-Exp. Equip. | - |
| | Total | 3700 |

Funds Requested FY-81

| | | |
|---|---|---|
| 1100 | Personnel | 2000 |
| 2600 | Cons. Supplies | 3000 |
| 2100 | Travel | 600 |
| 2400 | Print & Repro. | 400 |
| 2572 | Contractual Svcs | 800 |
| | Total | 6800 |

Publications: (1) Noel, G., R.C. Dimond, L. Wartofsky, J.M. Earll, and A.G. Frantz. Continuous Infusion of TRH in Man. J. Clin. Endocrinol. 38:6-17, 1974.

(2) Wartofsky, L., R.C. Dimond, G.L. Noel, R.A. Adler, A.G. Frantz, and J.M. Earll. Effect of Water Loading on TSH and PRL Responses to TRH. J. Clin. Endocrinol. & Metab., 41:784-787, 1975.

(3) Wartofsky, L., et al., Failure of Propranolol to alter TSH and PRL Responses to TRH in Thyrotoxicosis, J. Clin. Endocrinol. Metab., 41:489-490, 1975.

(4) Wartofsky, L., et al, Estimates of Pituitary Stores of TSH and PRL in Normal and Hypothyroid Subjects by Use of Continuous TRH Infusion, Advances in Thyroid Research, Excerpta Medica, pp. 268-271, 1976.

(5) Wartofsky, L., et al, Effect of Acute Increases in Serum T3 on TSH and PRL Responses to TRH, J Clin Endocrinol & Metab, 42:451-466, 1976.

(6) Wartofsky, L., et al, Nature of Thyroidal Suppression and TSH and PRL Responses to TRH during Experimental Malaria in Man, J Clin Endocrinol & Metab, 44:85-90, 1977.

(7) Burman, K.D., R.C. Dimond, F.D. Wright, J.M. Earll, J. Bruton, and L. Wartofsky, A Radioimmunoassay for 3,3'5'-Triiodothyronine (Reverse T3): Assessment of Thyroid Gland Content, Serum Measurements in Conditions of Normal and Altered Thyroidal Economy, and Serum Concentrations following Administration of TRH and TSH, J Clin Endocrinol & Metab 44:660-672, 1977.

(8) Corrigan, D.F., K.D. Burman, R.C. Dimond, M. Schaaf, J.M. Earll, J.E. Rogers, F.D. Wright, and L. Wartofsky, Parameters of Thyroid Function in Patients with Active Acromegaly, Metabolism 27:209-216, 1978.

(9) Burman, K.D., R.C. Dimond, Y-Y Djuh, J. Bruton, T.B. Washburn, F.D. Wright, and L. Wartofsky, Failure of 3,3'-T2 Administration to Alter TSH and Prolactin Responses to TRH Stimulation, Metabolism 27:677-683, 1978.

(10) Burman, K.D., R.C. Smallridge, R. Osburne, R.C. Dimond, N.E. Whorton, P. Kesler, and L. Wartofsky, Nature of Suppressed TSH Secretion During Undernutrition: Effect of Fasting on TSH Responses to Prolonged TRH Infusion, Metabolism 29:46-52, 1980.

(11) Smallridge, R.C., L. Wartofsky, and R.C. Dimond, Inappropriate Secretion of TSH: Discordance Between the Suppressive Effects of Corticosteroids and Thyroid Hormone, J Clin Endocrinol Metab 48:700-705, 1979.

(12) Corrigan, D.F., K.D. Burman, R.C. Dimond, M. Schaaf, J.M. Earll, J.E. Rogers, F.D. Wright, and L. Wartofsky, Parameters of Thyroid Function in Patients with Active Acromegaly, Metabolism 27:209-216, 1978.

(13) Burman et al: Failure of 3,3'-T2 to Alter Prolactin & TSH Responses to TRH Stimulation, Metabolism 27:677-683, 1978.

(14) Boehm, T.M., R.C. Dimond, and L. Wartofsky, Isolated Thyrotropin Deficiency with TRH-induced TSH Secretion and Thyroidal Release, J Clin Endocrinol Metab 43:1041-1045, 1976.

(15) Burman, K.D., R.C. Dimond, G.S. Noel, J.M. Earll, A.G. Frantz, and L. Wartofsky, Klinefelter's Syndrome: Examination of Thyroid Function, and the TSH and PRL Responses to TRH Prior To and After Testosterone Administration, J Clin Endocrinol Metab 41:1161-1166, 1976.

(16) Burman, K.D., R.C. Dimond, F.D. Wright, J.M. Earll, J. Bruton, and L. Wartofsky, A Radioimmunoassay for 3,3',5'-Triiodothyronine (Reverse T3): Assessment of Thyroid Gland Content, Serum Measurements in Conditions of Normal and Altered Thyroidal Economy, and Serum Concentrations following Administration of TRH and TSH, J Clin Endocrinol Metab 44:660-672, 1977.

Type of Report: Interim

Estimated Date of Completion: Two Years

# DISPOSITION FORM

For use of this form, see AR 340-15, the proponent agency is TAGCEN.

| REFERENCE OR OFFICE SYMBOL | SUBJECT |
|---|---|
| HSWP-ME | Renewal of Protocols Previously Funded for Three Years |

TO: C, Dep Clin Invest | FROM: C, Endo-Metab Svc | DATE: 28 Jan 81 | CMT 1

Wartofsky/bak/6-1416

1. The attached progress reports are submitted as addenda to maintain and renew protocols #1310 and #1340 for an additional 2-3 years.

2. Protocol #1340 has been inactive since 1979 due to the departure of the former principal investigator, Dr. Charles Smith. These data have been reviewed and have considerable promise for publication but additional patients will be required. No modification to the prior protocol is anticipated.

3. Protocol #1310 is the umbrella protocol for the authorized investigative use of TRH in a variety of circumstances. Since it is anticipated that evaluation of the pituitary-thyroid axis will continue to be a relevant and important aspect of numerous related endocrine clinical studies, renewal is requested in order to facilitate such evaluation. It should be noted that this has been a highly productive protocol with 16 publications listed which involved TRH studies. Relative to the annual budget, this represents an unparalleled cost/efficiency ratio.

L. WARTOFSKY, M.D.
COL, MC
Chief, Endocrine-Metabolic Service
and Kyle Metabolic Unit

DA FORM 2496 REPLACES DD FORM 96, WHICH IS OBSOLETE.

| Date: | Protocol No: 1311 | Status: Interim X<br>Final |
|---|---|---|

**Title of Project:**

Treatment of thyroid storm with anion Exchange Resin

| Starting Date: 3-29-74 | Estimated Completion Date: 8 82 |
|---|---|

**Principal Investigator:** KENNETH D. BURMAN, MD, LTC, MC

| Associate Investigators: | Facility: WRAMC |
|---|---|
| LEONARD WARTOFSKY, MD, LTC, MC | Dept/Svc Med/Endo |

**Key Words:** Resin/thyroid storm.

| Accumulative MEDCASE Cost: 0 | Accumulative Contract Cost: 0 | Accumulative Supply Cost: 0 |
|---|---|---|

| FY-80 MEDCASE Cost: | Periodic Review Results: (to be filled in by DCI) |
|---|---|

**Study Objective:** To have available a treatment for thyroid storm when needed.

**Technical Approach:**

Anion exchange resin removes circulating thyronines.

**Progress during FY-80:**

no patient has entered hospital

Number of subjects to be studied before completion of study: 1-3

Serious/unexpected side effects in subjects participating in project: None

**Conclusions:** None yet

**Publications or Abstracts, FY-80:** None

Work Unit No.: 1311

Funds utilized, FY-80: $23,182

Funding requirements, FY-81:

Supplies: $2,000

Other: $400

| Date: 22 Oct 80 | Protocol No: 1334 | Status: Interim |
|---|---|---|

Title of Project: The regulation of $T_4$ to $T_3$ conversion

| Starting Date: 1 Aug 75 | Estimated Completion Date: 1 Aug 82 |
|---|---|

Principal Investigator: Kenneth D. Burman, LTC, MC

| Associate Investigators: | Facility: WRAMC |
|---|---|
| Robert C. Smallridge, LTC, MC | Dept/Svc Kyle Metabolic Unit |

Key Words: $T_4$, $T_3$

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: |
|---|---|---|

| FY-80 MEDCASE Cost: | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective: To isolate the enzyme responsible for $T_4$ to $T_3$ conversion.

Technical Approach: Affinity chromatography

Progress during FY-80: Have not isolated it yet

Number of subjects to be studied before completion of study:

Serious/unexpected side effects in subjects participating in project:

Conclusions:

Publications or Abstracts, FY-80: None

Work Unit No: 1334

Funds utilized, FY-80: $4,235

Funding requirements, FY-81:

| | |
|---|---|
| Supplies: | $5,000 |
| Other: | 2,000 |

[illegible] MEMORANDUM

[illegible] of [illegible] Department Agency is TASCFA.

| REFERENCE OR OFFICE SYMBOL | SUBJECT |
|---|---|
| HSWP-ME | Renewal of Protocols Previously Funded for Three Years |

TO C, Dep Clin Invest

FROM C, Endo-Metab Svc

DATE 28 Jan 31

CMT 1

Wartofsky/bak/6-1416

1. The attached progress reports are submitted as addenda to maintain and renew protocols #1310 and #1340 for an additional 2-3 years.

2. Protocol #1340 has been inactive since 1979 due to the departure of the former principal investigator, Dr. Charles Smith. These data have been reviewed and have considerable promise for publication but additional patients will be required. No modification to the prior protocol is anticipated.

3. Protocol #1310 is the umbrella protocol for the authorized investigative use of TRH in a variety of circumstances. Since it is anticipated that evaluation of the pituitary-thyroid axis will continue to be a relevant and important aspect of numerous related endocrine clinical studies, renewal is requested in order to facilitate such evaluation. It should be noted that this has been a highly productive protocol with 16 publications listed which involved TRH studies. Relative to the annual budget, this represents an unparalleled cost/efficiency ratio.

Arnold Wartofsky

L. WARTOFSKY, M.D.
COL, MC
Chief, Endocrine-Metabolic Service
and Kyle Metabolic Unit

DA [illegible] REPLACES DD FORM 96, WHICH IS OBSOLETE.

47

Work Unit No.: 1340

Title of Project: Use of Fluorescent Thyroid Scanning to evaluate Iodine Kinetics during Propylthiouracil Therapy of Graves' Disease

Principal Investigator: Leonard Wartofsky, COL, MC

Associate Investigators: Kenneth D. Burman, LTC, MC
Douglas Van Nostrand, MAJ, MC

Objective: To utilize the fluorescent thyroid scanner to quantitate and follow alterations in thyroidal iodine content during antithyroid therapy of Graves' disease.

Technical Approach: 20-24 patients with Graves' disease are to be studied.

The following tests will be performed weekly throughout the study: serum thyroxine (T4), serum triiodothyronine (T3), resin uptake of triiodothyronine (T3RU), serum iodine ($I_s$), thyroidal $^{127}I$ ($I_t$) by fluorescent scan. In addition, two 24 hour urines per week will be collected and 24 hour iodide excretion ($I_u$) determined. At the end of each study period a perchlorate discharge test ($Cl_2$) will be performed.

Basal determinations of entry into study: T4, T3, T3RU, $I_s$, $I_t$, $I_u$, $Cl_2$.

Study period I: Propylthiouracil 150 mg/day weekly: T4, T3, T3RU, $I_s$, $I_t$, $I_u$

Study period ends when weekly studies are stable; $Cl_2$ at end of study period.

Study Period II: Propylthiouracil 450 mg/day.

Study period ends when weekly studies are stable; $Cl_2$ at end of study period.

Study Period III: Propylthiouracil 1200 mg/day.

Study period ends when weekly studies are stable; $Cl_2$ at end of study period.

Study Period IV: Identical to Study Period III except 5 drops SSKI tid.

Study ends at one week.

Progress & Results: 14 patients have been studied to date and the data is presently being re-evaluated. Attempts are being made to resume these studies in 1981 after a lapse in activity prompted by the departure of the former principal investigator.

Conclusions: None as yet

Side Effects/Complications: There were absolutely no unexpected side effects or increased incidence of side effects related to any of the therapeutic manipulations detailed in the study protocol in any patients studied to date.

Funds Utilized FY-80: None

| Funds Requested FY-81 | | |
|---|---|---|
| 1100 | Personnel | 2000 |
| 2100 | Travel | 600 |
| 2319 | Rental | 200 |
| 2400 | Print & Reprod | 300 |
| 2572 | Contract Svcs. | 600 |
| 2600 | Cons. Supplies | 1500 |
| 3100 | Non-Expend Equip. | - |
| | Total | 5200 |

Publications: (1) Thrall J, Corcoran R, Wartofsky L, et al: Quantitative Thyroid Fluorescent Scanning Technique: Clinical Experience, Amer. J. Roentgenol 130.517-522, 1978.

(2) Thrall J, Burman KD, Wartofsky L, et al: Solitary Autonomous Thyroid Nodules: Comparison of Fluorescent and Pertechnetate Imaging, J. Nucl. Med. 18:1064-1068, 1977.

Type of Report: Interim

Estimated Date of Completion: Three Years

| Date: | Protocol No: 1346 | Status: Interim X<br>Final |
|---|---|---|

Title of Project:

Thyroid function tests in Cord Blood Maternal Serum Fluid

| Starting Date: 9-30-75 | Estimated Completion Date: 8-82 |
|---|---|

Principal Investigator: KENNETH D. BURMAN, MD, LTC, MC

| Associate Investigators: | Facility: WRAMC |
|---|---|
| LEONARD WARTOFSKY, MD, COL, MC<br>ROBERT C. SMALLRIDGE, LTC, MC<br>LOUIS PANGARO, MAJ, MC<br>DR. CANNMANN | Dept/Svc Endocrine |

Key Words: Cord blood/Maternal Serum Fluid

| Accumulative MEDCASE Cost: 0 | Accumulative Contract Cost: 0 | Accumulative Supply Cost: 0 |
|---|---|---|

| FY-80 MEDCASE Cost: | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective:

To measure levels of thyronines in cord blood and maternal fluid.

Technical Approach:

Develop radioimmunoassays for various thyronines

Progress during FY-80:

Have developed RIA for T4 et.

Number of subjects to be studied before completion of study: 10-15

Serious/unexpected side effects in subjects participating in project: None

Conclusions: There is deminished extra thyroidal conversion in newborn babies.

Publications or Abstracts, FY-80:

Pangaro, L., Burman, KD, Wartofsky, L et al JCEM 50:1075, 1980

Work Unit No: 1346

Funds utilized, FY-80: $20,000

Funding requirement, FY-81:

Supplies: $5,000

| Date: | Protocol No: 1347 | Status: Interim X<br>Final |
|---|---|---|

Title of Project:

Investigations into the physiology of RT3 and 3,3'T2

| Starting Date: 4-8-76 | Estimated Completion Date: 8-82 |
|---|---|

Principal Investigator: KENNETH D. BURMAN, MD, LTC, MC

| Associate Investigators:<br>LEONARD WARTOFSKY, MD, COL, MC | Facility: WRAMC<br>Dept/Svc Endo |
|---|---|

Key Words:
Reverse T3

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: |
|---|---|---|

| FY-80 MEDCASE Cost: | Periodic Review Results:<br>(to be filled in by DCI) |
|---|---|

Study Objective: To ascertain the factors that later extrathyroidal conversion.

Technical Approach: Develop specific radioimmunoassays and in some cases infuse thyronenes to fed and fasting and patients with thyroidal disease.

Progress during FY-80:

About 10 patients have been infused with 3'5'T2

Number of subjects to be studied before completion of study: 15

Serious/unexpected side effects in subjects participating in project: None

Conclusions: Cadiolabelled and unlabelled thyronenes five the same MCR

Publications or Abstracts, FY-80:

PANGARO, L, BURMAN, KD, WARTOFSKY, L, JCEM 50:1075, 1980

Work Unit No: 1347

Funds utilized, FY-80: $360.00

Funding requirements: FY-81:

| | |
|---|---|
| Supplies: | $1,000 |
| Other: | 1,000 |
| Travel: | 400 |

| Date: | Protocol No: 1353 | Status: Interim x<br>Final |
|---|---|---|

Title of Project:

The regulation of T4 conversion

| Starting Date: 12/30/76 | Estimated Completion Date: 8/82 |
|---|---|

Principal Investigator: KENNETH D. BURMAN

| Associate Investigators: | Facility: WRAMC |
|---|---|
| LEONARD WARTOFSKY, MD, LTC, MC<br>ROBERT C. SMALLRIDGE, LTC, MC<br>Dr. KEITH LATHAM | Dept/Svc Dept of Med/Endocrine |

Key Words:

T4 Conversion

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: |
|---|---|---|
| | | |

| FY-80 MEDCASE Cost: | Periodic Review Results: (to be filled in by DCI) |
|---|---|
| | |

Study Objective:

To ascertain the factors regulating T4 to T3 conversion

Technical Approach:

Develop systems in vivo and in vitro to quantitate conversion.

Progress during FY-80:

Rat studies demonstrated that carbohydrate content of diet increases conversion.

Number of subjects to be studied before completion of study: Rats

Serious/unexpected side effects in subjects participating in project: None

Conclusions: Carbohydrates increase T4 to T3 conversion

Publications or Abstracts, FY-80:

SMALLRIDGE, RC, BURMAN, KD, WARTOFSKY, L et al, JCEM tentatively accepted.

54

Work Unit No: 1353

Funds utilized, FY-80: $20,000

Funds required, FY-81:

Supplies: $5,000

Other: 400

| Date: 15 October 1980 | Protocol No: 1354 | Status: Interim X<br>Final |
|---|---|---|

Title of Project: Purification of Testosterone-estradiol Binding Globulin

| Starting Date: 3 Nov 1976 | Estimated Completion Date: 30 Sept 1982 |
|---|---|

Principal Investigator: Robert A. Vigersky, M.D. MAJ MC

| Associate Investigators: | Facility: WRAMC |
|---|---|
| | Dept/Svc Kyle Metabolic Unit |

Key Words: Testosterone-estradiol binding globulin

| Accumulative MEDCASE Cost: 0 | Accumulative Contract Cost: 0 | Accumulative Supply Cost: 0 |
|---|---|---|

| FY-80 MEDCASE Cost: | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective:

To purify, characterize and develop a radioimmunoassay for testosterone-estradiol binding globulin. This protein is responsible for the transport of sex steroids from their site of production in the gonad to their target tissues. It, thus, controls the availability of sex steroids to breast, skin, prostate, etc. Measurement of this protein is indirect; thus, the aim is to develop methods to directly measure it in biologic fluids.

Technical Approach:

Sequential use of Sephadex G-100 chromatography, Concanavilin A chromatography, temperature-dependent affinity chromatography; and preparative polyacrylamide gel electrophoresis. Qualitative analysis is by analytical polyacrylamide gel electrophoresis and the monitoring of the purification process is by a dextran-coated charcoal assay measuring the total binding of the protein.

Progress during FY-80:

Approximately 6000 fold purification has been reached and we are now accumulating enough purified protein to inject into rabbits to make antibodies and to iodinate.

Number of subjects to be studied before completion of study: N/A

Serious/unexpected side effects in subjects participating in project: N/A

Conclusions: Significant progress has been made over the last year in reaching the first part of the project goal, i.e. purification. The next phase is to develop a radioimmunoassay for TeBG

Publications or Abstracts, FY-80: None

Work Unit No.: 1354

Funds Utilized, FY-80: None

Funding Requirements, FY-81: $4550

Personnel: None

Equipment: None

Supplies: $3000

Travel: $500

Other: (2572) $750; (2400) $300

| Date: 1 October 1980 | Protocol No: 1355 | Final |
|---|---|---|

Title of Project: The Effect of Short-Term, High-Dose Steroid upon Thyroidal Release in Thyrotoxicosis.

| Starting Date: 29 May 1977 | Estimated Completion Date: Uncertain |
|---|---|

Principal Investigator: Timothy M. Boehm, LTC MC

| Associate Investigators:<br>Leonard Wartofsky, COL MC<br>Kenneth D. Burman, LTC MC | Facility: WRAMC<br>Dept/Svc Endo-Metab Svc |
|---|---|

Key Words: $^{131}I$, $^{125}I$, thyroxine, steroid, thyrotoxicosis, thyroidal release.

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: $1,000 |
|---|---|---|
| FY-80 MEDCASE Cost: none | Periodic Review Results: (to be filled in by DCI) | |

Study Objective:

To ascertain whether high dose steroid inhibits thyroidal release in thyrotoxicosis.

*Technical Approach: In brief, a double isotope technique was used to measure thyroidal release and parameters of peripheral thyroid hormone metabolism. There were no modifications to the original protocol, except that some patients received slightly smaller amounts of $^{125}I$ and $^{125}I$-T4 than specified in the original protocol.

Progress during FY-80: No progress -- a very low priority study.

Number of subjects to be studied before completion of study: None

Serious/unexpected side effects in subjects participating in project: None

Conclusions: Study is terminated prior to completion. Other projects have assumed higher priority, and patient recruitment was difficult because of the long inpatient hospitalization required.

Publications or Abstracts, FY-80: None

| Date: 2 Oct 80 | Protocol No: 1357 | Status: ~~Ongoing~~ Final |
|---|---|---|

Title of Project: Effect of $T_3$ and $rT_3$ on Extracellular Cyclic Nucleotide Levels in Humans.

| Starting Date: 6 April 1977 | Estimated Completion Date: 30 Sept 1980 |
|---|---|

Principal Investigator: H. Linton Wray, LTC, MC

| Associate Investigators: | Facility: WRAMC, Washington, D.C. |
|---|---|
| Kenneth D. Furman, LTC, MC<br>Robert C. Smallridge, LTC, MC<br>Leonard Wartofsky, COL, MC | Dept/Svc Kyle Metabolic Unit |

Key Words: Thyroid hormones, cyclic AMP, cyclic GMP

| Accumulative MEDCASE Cost: None | Accumulative Contract Cost: None | Accumulative Supply Cost: $1,286.00 |
|---|---|---|

| FY-80 MEDCASE Cost: None | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective:

To determine if, in humans, urine and plasma levels of cyclic AMP and cyclic GMP are changed by administration of 3,5,3' triiodothyronine ($T_3$) and 3,3',5' triiodothyronine (reverse $T_3$, $rT_3$).

Technical Approach:

Hypothyroid patients will be studied before, during and after taking $T_3$, $rT_3$ or both $T_3$ and $rT_3$. Hyperthyroid patients will be studied only with $rT_3$. Patients will be studied for 12 days; 3 days of baseline, 6 days of treatment and 3 days of post-treatment. Plasma cyclic AMP and cyclic GMP and serum $T_3$, $rT_3$ and $T_4$ will be measured on days 1-5 and 8-12.

Progress during FY-80:

No patients were studied in FY-80.

Number of subjects to be studied before completion of study: N/A

Serious/unexpected side effects in subjects participating in project: None

Conclusions: This project is terminated as of 30 September 1980 because of difficulty in recruiting patients to be studied.

Publications or Abstracts, FY-80: None

| Date: | Protocol No: 1358 | Status: Interim X<br>Final |
|---|---|---|

Title of Project:
The effect of obesity and fasting on T3 receptors in mononuclear cells.

| Starting Date: 4-6-77 | Estimated Completion Date: 8-82 |
|---|---|

Principal Investigator: KENNETH D. BURMAN, MD,LTC,MC

| Associate Investigators: | Facility: WRAMC |
|---|---|
| LEONARD WARTOFSKY,MD,COL,MC | Dept/Svc Dept of Med/Endocrine |

Key Words: Obesity/fasting/T3 receptors

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: |
|---|---|---|

| FY-80 MEDCASE Cost: | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective:
To determine the physiologic factors that alter T3 receptors.

Technical Approach:
Develop a T3 radio receptor assay

Progress during FY-80:
T3 receptors were low in obesity and thyrotoxicosis and increased in fasting. We are now correlating T3/T4 receptors with acetylase activity in the receptor preparation.

Number of subjects to be studied before completion of study: 25

Serious/unexpected side effects in subjects participating in project: None

Conclusions: T3 receptors are physiologically regulated

Publications or Abstracts, FY-80:

BURMAN,KD,et al JCEM 51:.06,80

Work Unit No.: 1358

Funds utilized, FY-80: $38.45

Funding requirements, FY-81: $2,000

Supplies: $2,000

Travel: $400

| Date: | Protocol No: 1359 | Status: Interim / Final X |
|---|---|---|

Title of Project: The effect of reverse T3 on thyroid secretion.

| Starting Date: 4-21-77 | Estimated Completion Date: 8-80 |
|---|---|

Principal Investigator: KD BURMAN, MD, LTC, MC

| Associate Investigators: | Facility: WRAMC |
|---|---|
| Timothy Boehm, MAJ, MC<br>Leonard Wartofsky, COL, MC | Dept/Svc Dept of Med/Endocrine |

Key Words:
Reverse T3/thyroid

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: |
|---|---|---|
| | | |

| FY-80 MEDCASE Cost: | Periodic Review Results: (to be filled in by DCI) |
|---|---|
| | |

Study Objective:
To determine if rT3 influences T4 levels and kinetics.

Technical Approach:
Reverse T3 ingested orally while I4 isotope given

Progress during FY-80:
None

Number of subjects to be studied before completion of study: 10

Serious/unexpected side effects in subjects participating in project: None

Conclusions: RT3 does not affect T4 kinetics

Publications or Abstracts, FY-80: None

| Date: | Protocol No: 1360 | Status: Interim X<br>Final |
|---|---|---|

**Title of Project:** Investigations concerning T3 production rates

| Starting Date: 1977 | Estimated Completion Date: 8-82 |
|---|---|

**Principal Investigator:** KENNETH D. BURMAN, MD,LTC,MC

| Associate Investigators: | Facility: |
|---|---|
| ROBERT SMALLRIDGE<br>CHARLES SMITH<br>LEONARD WARTOFSKY<br>B.J.GREEN | WRAMC<br>Dept/Svc Dept of Med/Endocrine |

Key Words: Thyroid hormone/T3

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: |
|---|---|---|

| FY-80 MEDCASE Cost: | Periodic Review Results: (to be filled in by DCI) |
|---|---|

**Study Objective:** To determine if labelled and unlabelled hormones have identical clearance rates.

**Technical Approach:**
Adminster labelled and unlabelled hormones and calculate kinetics.

**Progress during FY-80:** About 10 patients have had 3,'5'T2 and 3'5'T2 [illegible] infusions with identical clearance rates. We will now extend these infusions to 10-15 other patients with other iodo thyronens.

Number of subjects to be studied before completion of study: about 15

Serious/unexpected side effects in subjects participating in project: none

**Conclusions:** Unlabelled 3'5'T2 can be used for kinetics

**Publications or Abstracts, FY-80:**

SMALLRIDGE,RC, BURMAN KD, ETAL JCEM under consideration

Work Unit No.: 1360

Funds utilized: FY-80: $1,000

Funding requirements, FY-81:

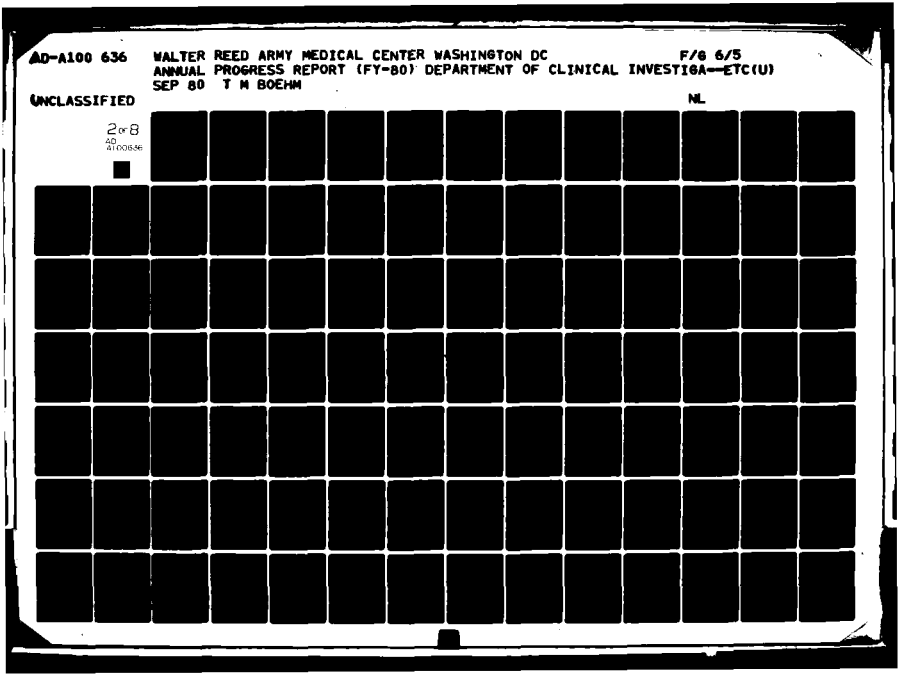
Supplies: $5,000

Other: 400

AD-A100 636 WALTER REED ARMY MEDICAL CENTER WASHINGTON DC F/G 6/5
ANNUAL PROGRESS REPORT (FY-80) DEPARTMENT OF CLINICAL INVESTIGA--ETC(U)
SEP 80 T M BOEHM

UNCLASSIFIED NL

2 of 8
AD
A100636



| Date: 10 Sept 80 | Protocol No: 1361 | Status: Interim<br>Final X |
|---|---|---|

Title of Project:

Postoperative changes in free testosterone and sex-hormone-binding-globulin

| Starting Date: 1977 | Estimated Completion Date: 30 Sept 80 |
|---|---|

Principal Investigator: Allan R. Glass, M.D., MAJ MC

| Associate Investigators: | Facility: WRAMC<br>Dept/Svc Kyle Metabolic Unit |
|---|---|

Key Words: surgery, free testosterone

| Accumulative MEDCASE Cost: 0 | Accumulative Contract Cost: 0 | Accumulative Supply Cost: $2,400 |
|---|---|---|

| FY-80 MEDCASE Cost: 0 | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective:

To assess the changes in serum testosterone and free testosterone occurring after surgery

Technical Approach:

Measurement of testosterone and free testosterone before and after surgery

Progress during FY-80: None. Project was essentially completed during prior fiscal years, with one resulting publication. Project is now terminated.

Number of subjects to be studied before completion of study: none

Serious/unexpected side effects in subjects participating in project:

none

Conclusions:

Both total and free testosterone fall after surgery under general anesthesia.

Publications or Abstracts, FY-80: None.

| Date: 15 October 1980 | Protocol No: 1362 | Status: Interim X / Final |
|---|---|---|

Title of Project: Medical Treatment of Amenorrhea-Galactorrhea Syncromes with Vitamin $B_6$ (Pyridoxine)

| Starting Date: 21 Dec 1976 | Estimated Completion Date: 30 Sept 1981 |
|---|---|

Principal Investigator: Robert A. Vigersky, M.D. MAJ MC

| Associate Investigators: | Facility: WRAMC |
|---|---|
| | Dept/Svc Kyle Metabolic Unit |

Key Words: Amenorrhea-galactorrhea; pyridoxine

| Accumulative MEDCASE Cost: 0 | Accumulative Contract Cost: 0 | Accumulative Supply Cost: 0 |
|---|---|---|
| FY-80 MEDCASE Cost: 0 | Periodic Review Results: (to be filled in by DCI) | |

Study Objective: To treat women with idiopathic amenorrhea-galactorrhea with a co-factor in the synthesis of dopamine which would thereby increase dopamine levels. Since dopamine is a prolactin inhibitory factor, it might be expected that prolactin levels would decrease. This would be an alternative to either bromocriptine therapy or observation in the treatment of these syndromes.

Technical Approach: Pre-treatment and post-treatment testing with provocative (pyridoxine, chlorpromazine, TRH, and LRH) and suppressive (L-Dopa) to determine whether or not chronic treatment with pyridoxine has altered prolactin dynamics or the dynamics of other pituitary trophic hormones.

Progress during FY-80: Methods for the plasma measurement of pyridoxine levels in the blood of women receiving this therapy have been established in collaboration with MAJ R. Bongiovanni. The failure of the women to clinically respond may be due to the failure to reach adequate levels.

Number of subjects to be studied before completion of study: 10

Serious/unexpected side effects in subjects participating in project: None

Conclusions: Pyridoxine has, to date, not been effective in lowering prolactin levels in amenorrhea-galactorrhea syndromes but has caused the resumption of menses in 2 of the 6 women so far treated with this regimen. Pyridoxine levels in plasma are currently being determined as well as those of pyridoxine metabolites.

Publications or Abstracts, FY-80: Kidd, G.S., Dimond, R., and Vigersky, R.A., "Response of Hyperprolactinemic Women to Short Term and Long Term Pyridoxine Therapy," submitted.

Work Unit No.: 1362

Funds Utilized, FY-80: None

Funding Requirements, FY-81: $1200

Personnel: None

Equipment: None

Supplies: $1200

Travel: None

Other: None

| Date: 10 Oct 1980 | Protocol No: 1363 | Status: Interim Final |
|---|---|---|

Title of Project:
Effect of $T_3$ and $rT_3$ on Plasma Cyclic Nucleotide Levels on Sheep

| Starting Date: 21 Dec 1976 | Estimated Completion Date: 30 Sept 1982 |
|---|---|

Principal Investigator: H. Linton Wray, LTC, MC

| Associate Investigators:<br>Kenneth D. Burman, LTC, MC<br>John P. Alfred, CPT, MC<br>Leonard Wartofsky, COL, MC | Facility: WRAMC<br>Dept/Svc Kyle Metabolic Unit |
|---|---|

Key Words: thyroid hormone, cyclic AMP, cyclic GMP

| Accumulative MEDCASE Cost: None | Accumulative Contract Cost: None | Accumulative Supply Cost: $7,413 |
|---|---|---|

| FY-80 MEDCASE Cost: None | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective:
To determine if plasma levels of cyclic AMP and cyclic GMP are changed by administration of 3,5,3' triiodothyronine and 3,3',5' triiodothyronine (reverse $T_3$, $rT_3$).

Technical Approach: The animals were divided into five groups, and each group received one of the following treatments: 1) placebo, 2) low $T_3$ (1.5 µg/kg), 3) high $T_3$ (4.5 µg/kg), 4) high $rT_3$ (4 µg/kg), or 5) low $rT_3$ (2.5 µg/kg) plus low $T_3$ (1.5 µg/kg) in combination. Treatments were administered daily for 7 days and the animals were studied throughout this period. Cyclic nucleotides and iodothyronines were measured by RIA.

Progress during FY-80: The attached paper required extensive revision as well as accumulation and analysis of new data during the last year. The mechanism of the increase in plasma cyclic AMP in response to $T_3$ requires clarification and is the subject of an addendum to protocol.

Number of subjects to be studied before completion of study: 18

Serious/unexpected side effects in subjects participating in project: None

Conclusions: The results indicate that in the sheep 1) $T_3$ markedly increases cAMP and decreases $T_4$ and $rT_3$ levels, whereas $rT_3$ administration is inactive in both of these systems; 2) neither $T_3$ nor $rT_3$ alters plasma cGMP; 3) degradation of $rT_3$ is directed relatively more to 3,3'$T_2$; 4) metabolism of both $T_3$ and $rT_3$ contribute comparably to 3,3'$T_2$ levels; and 5) $T_3$ may enhance the conversion of $rT_3$ to both 3,3'$T_2$ and 3',5$T_2$.

Publications or Abstracts, FY-80:
Endocrinology 107: 130-136, 1980

Work Unit No: 1363

Funds utilized, FY-80: $1,461 (2600)

Funding requirements, FY-81:

Personnel: Vincent M. Butler, GS-09

Equipment: Automated RIA System (81 MEDCASE)

Supplies: $6,500

Travel: $1,100

Other: $3,500

| Date: 10 Sept 1980 | Protocol No: 1364 | Status: Interim X<br>Final |
|---|---|---|

Title of Project: Effect of L-tryptophan on LH and FSH dynamics in women

| Starting Date: 1978 | Estimated Completion Date: 1981 |
|---|---|

Principal Investigator: Allan R. Glass, M.D., MAJ MC

| Associate Investigators: | Facility: WRAMC |
|---|---|
| | Dept/Svc Kyle Metabolic Unit |

Key Words: L-tryptophan, LH, FSH

| Accumulative MEDCASE Cost: 0 | Accumulative Contract Cost: 0 | Accumulative Supply Cost: $100 |
|---|---|---|

| FY-80 MEDCASE Cost: 0 | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective:

To determine how L-tryptophan, as a neurotransmitter precursor, interacts with the regulation of LH and FSH in women.

Technical Approach:

Assessment of pituitary gonadotropin reserve by LHRH and estrogen challenge before and after administration of L-tryptophan.

Progress during FY-80: Due to lack of time and personnel as well as difficulty in recruiting volunteers, no subjects were studied under this protocol during FY 80.

Number of subjects to be studied before completion of study: approx 12

Serious/unexpected side effects in subjects participating in project:
none

Conclusions:

Deferred

Publications or Abstracts, FY-80:
none

Work Unit No.: 1364

Funds utilized, FY-80: 0

Funding requirements: FY-81:

Supplies: $2,000

Other: 4,000

| Date: 10 Sept 80 | Protocol No: 1365 | Status: Interim X<br>Final |
|---|---|---|

Title of Project: Insulin resistance in diabetes: relative effect on glucose and amino acids

| Starting Date: 1978 | Estimated Completion Date: 1982 |
|---|---|

Principal Investigator: Allan R. Glass, M.D., MAJ MC

| Associate Investigators: | Facility: WRAMC |
|---|---|
| | Dept/Svc Kyle Metabolic Unit |

Key Words:
L-valine, obesity, diabetes, insulin resistance

| Accumulative MEDCASE Cost: 0 | Accumulative Contract Cost: $13,900 | Accumulative Supply Cost: $2,500 |
|---|---|---|

| FY-80 MEDCASE Cost: | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective:

To determine whether, in states of insulin resistance, the effects of insulin on amino acid metabolism are blunted, as are the effects of insulin on glucose metabolism.

Technical Approach: Administration of IV bolus loads of valine or glucose to normal subjects and to subjects with various disorders in which insulin resistance plays a role.

Progress during FY-80: 35 subjects were studied during FY 80- half normals, half non-diabetic obese subjects. Plan is to extend study to other groups of subjects with insulin resistance in FY 81.

Number of subjects to be studied before completion of study: 30

Serious/unexpected side effects in subjects participating in project:
one syncopal episode probably related to venipuncture (vasovagal)

Conclusions: Valine disposal is normal in obese subjects in whom glucose disposal is impaired.

Publications or Abstracts, FY-80: Abstract presented at Amer Diabetes Assoc meeting, 1980, and also at International Symposium. Paper submitted for publication.

Work Unit No.: 1365

Funds utilized: FY-80: $9,500

Funding requirements, FY-81:

Supplies: $12,000

Travel: $1,000

Other: $4,400

| Date: | Protocol No: 1366 | Status: Interim / Final X |
|---|---|---|

Title of Project:

The effect of glucagon on thyroidal economy

| Starting Date: 1/5/78 | Estimated Completion Date: 8/82 |
|---|---|

Principal Investigator: KENNETH D. BURMAN, MD,LTC,MC

| Associate Investigators: LEONARD WARTOFSKY, JOHN T. O'BRIAN, ROBERT SMALLRIDGE, LINDA JONES | Facility: WRAMC |
|---|---|
| | Dept/Svc Dept of Med/Endocrine |

Key Words: Glucagon/thyroid hormone

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: |
|---|---|---|

| FY-80 MEDCASE Cost: | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective: To ascertain if T3 alters glucagon.

Technical Approach:
Administer small dose T3 during fasting and measure glucagon by RIA

Progress during FY-80:
A total of about 15 patients studied and show that T3 decreases glucagon clearance rate.

Number of subjects to be studied before completion of study: 0

Serious/unexpected side effects in subjects participating in project:
None

Conclusions: T3 regulates glucagon

Publications or Abstracts, FY-80:

BURMAN, KD, Et al JCEM in press

| Date: 10 Sept 1980 | Protocol No: 1367 | Status: Interim x<br>Final |
|---|---|---|

Title of Project: Effect of methyldopa on serum LH and testosterone in hypertensive men.

| Starting Date: not yet begun | Estimated Completion Date: 1982 |
|---|---|

Principal Investigator: Allan R. Glass, MD, MAJ MC

| Associate Investigators:<br>Nabil Gemayel MD CPT MC | Facility: WRAMC<br>Dept/Svc Kyle Metabolic Unit |
|---|---|

Key Words:
clonidine, LH, testosterone

| Accumulative MEDCASE Cost: 0 | Accumulative Contract Cost: 0 | Accumulative Supply Cost: $436 |
|---|---|---|

| FY-80 MEDCASE Cost: | Periodic Review Results:<br>(to be filled in by DCI) |
|---|---|

Study Objective:
To determine whether the drug clonidine produces changes in serum LH or testosterone in hypertensive men.

Technical Approach:

Measurement of serum LH , FSH, and testosterone, as well as responses to LHRH and HCG, before and after clonidine treatment.

Progress during FY-80:

Due to an administrative mixup, the principal investigator never received formal approval to begin work on this protocol, so nothing has been done yet.

Number of subjects to be studied before completion of study: 20

Serious/unexpected side effects in subjects participating in project:
none

Conclusions:

Deferred

Publications or Abstracts, FY-80:
none

Work Unit #: 1367

Funds utilized, FY-80: $436

Funding requirements, FY-81:

| | |
|---|---|
| Supplies: | $4,000 |
| Travel: | $1,000 |
| Other: | $9,300 |

| Date: 10 Oct 1980 | Protocol No: 1368 | Status: Interim |
|---|---|---|

**Title of Project:** Effect of Dietary Phosphate on Serum Levels of Vitamin D metabolites in Hypoparathyroidism.

| Starting Date: 26 April 1977 | Estimated Completion Date: 30 Sept 1982 |
|---|---|

**Principal Investigator:** H. Linton Wray, LTC, MC

| **Associate Investigators:**<br>Joseph Bruton, Ph. D.<br>Ira Mehlman, LTC, MC | **Facility:** WRAMC<br>**Dept/Svc** Kyle Metabolic Unit |
|---|---|

Key Words: Phosphate, Vitamin D metabolism

| Accumulative MEDCASE Cost: None | Accumulative Contract Cost: $200.00 | Accumulative Supply Cost: $ 59,891 |
|---|---|---|

| FY-80 MEDCASE Cost: None | Periodic Review Results: (to be filled in by DCI) |
|---|---|

**Study Objective:** To determine if serum levels of 25-OH-D (25-hydroxy-vitamin D), 24, 25-$(OH)_2$-D (24, 25-dihyrdoxyvitamin D) and 1,25-$(OH)_2$-D (1, 25-dihydroxy-vitamin D) are changed by short-term manipulation of dietary phosphate intake in hypoparathyroid patients.

**Technical Approach:** The 15 day protocol consists of 2 days on normal phosphate intake (1.0 g of phosphorus), 10 days on low phosphate intake (0.5 g of phosphorus) and 3 days on high phosphate intake (1.5 g of phosphorus). During the period of phosphate restriction, phosphate-binding antacids will be given. A patient group of phosphate-replete, antacid-treated will serve as a control group. Serum inorganic phosphate, ionized calcium, total calcium, magnesium and creatinine and plasma 25-OH-D, 24, 25-$(OH)_2$-D and I, 25-$(OH)_2$-D will be determined.

**Progress during FY-80:** NMC personnel have now set-up a chromatography system which appears adequate for the vitamin D assays in human serum. Control samples are now being processed to determine our normal ranges.

Number of subjects to be studied before completion of study: 14

Serious/unexpected side effects in subjects participating in project: None

**Conclusions:** The experimental protocol has been shown to effectively lower urine and serum phosphate in a manner which will provide the appropriate changes to allow correlations with the changes in the vitamin D metabolites.

*Publications or Abstracts, FY-80:* None

Work Unit No.: 1368

Funds utilized, FY-80: $26,400 (2600)

Funding requirements, FY-81:

Personnel: Delbert Dawson (GS-11)
Vincent M. Butler (GS-09)

Equipment: Automated RIA System (FY-81) MEDCASE

Supplies: $25,000

Other: $2,800

| Date: 15 October 1980 | Protocol No: 1370 | Status: Interim X<br>Final |
|---|---|---|

Title of Project: Sex Steroid Receptors in the Human Thyroid Gland

| Starting Date: 24 May 77 | Estimated Completion Date: 30 Sept 1982 |
|---|---|

Principal Investigator: Robert A. Vigersky, M.D. MAJ MC

| Associate Investigators: | Facility: WRAMC |
|---|---|
| | Dept/Svc Kyle Metabolic Unit |

Key Words: Thyroid; Sex steroids; Receptors

| Accumulative MEDCASE Cost: 0 | Accumulative Contract Cost: 0 | Accumulative Supply Cost: $699.15 |
|---|---|---|
| FY-80 MEDCASE Cost: 0 | Periodic Review Results: (to be filled in by DCI) | |

Study Objective: To determine whether the increase incidence in thyroid disease seen in women is due to abnormalities in the receptor for estrogen and/or androgen in their thyroid glands. The additional aim is to characterize these receptors with respect to their physico-chemical identity and to compare them to similar receptors in more classic target tissues for these steroids.

Technical Approach: Measurement of affinity constant and binding capacity by Scatchard analysis of cytosol made from thyroid glands obtained at the time of thyroidectomy. Also, kinectic analysis, size and charge determination, and steroid specificity will be measured and compared to those of other receptors.

Progress during FY-80: Accumulation of tissue for ultimate receptor measurement and the analysis of similar parameters in other non-classic target tissues such as the thymus (human) to compare with the thyroid.

Number of subjects to be studied before completion of study: 10

Serious/unexpected side effects in subjects participating in project: None

Conclusions: Methods have been perfected and other tissues run for comparison to allow appropriate conclusions to be made from the data obtained on the human tissue.

Publications or Abstracts, FY-80: None

Work Unit No.: 1370

Funds Utilized, FY-60: $699.15

Funding Requirements, FY-61: $3700

Personnel: None

Equipment: None

Supplies: $3000

Travel: $500

Other: (2400) $200

| Date: | Protocol No: 1371 | Status: Interim |
|---|---|---|
| | | Final X |

Title of Project: Glucose Regulation, Peripheral Thyroid Hormone Economy in Fasted subjects.

| Starting Date: 1-5-78 | Estimated Completion Date: 8-80 |
|---|---|

Principal Investigator: KENNETH D. BURMAN, MD,LTC,MC

| Associate Investigators: L. WARTOFSKY COL,MC RC SMALLRIDGE,LTC,MC | Facility: WRAMC |
|---|---|
| | Dept/Svc Dept of Med/Endocrine |

Key Words: Glucose/thyroid hormone

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: |
|---|---|---|
| | | |

| FY-80 MEDCASE Cost: | Periodic Review Results: (to be filled in by DCI) |
|---|---|
| | |

Study Objective:

To determine the effect of glucose on T3/rT3 levels.

Technical Approach:

Administer glucose during feeding and fasting and measure T3/rT3 by RIA

Progress during FY-80:

About 30 patients studied

Number of subjects to be studied before completion of study: 0

Serious/unexpected side effects in subjects participating in project: None

Conclusions: Glucose increases T3 and decreases rT3

Publications or Abstracts, FY-80:

PANAGARO, et al JCEM 50:1075,80

| Date: | Protocol No: 1372 | Status: Interim / Final X |
|---|---|---|

Title of Project: Alterations in TRH stimulation in obesity and fasting.

| Starting Date: 12-5-77 | Estimated Completion Date: 8-80 |
|---|---|

Principal Investigator: KENNETH D. BURMAN, MD,LTC,MC

| Associate Investigators: | Facility: WRAMC |
|---|---|
| | Dept/Svc Dept of Med/Endocrine |

Key Words: TRH/Obesity

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: |
|---|---|---|

| FY-80 MEDCASE Cost: | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective:

To quantitate TSH stimulation in fasting.

Technical Approach:

TRH tests in feeding and fasting periods.

Progress during FY-80:

A total of about 20 patients studied by TRH infusions.

Number of subjects to be studied before completion of study: 0

Serious/unexpected side effects in subjects participating in project: None

Conclusions: TSH decreases in fasting

Publications or Abstracts, FY-80

Burman,KD et al, Metabolism 29:46,1980

| Date: 10 Sept 80 | Protocol No: 1374 | Status: Interim X<br>Final |
|---|---|---|

Title of Project: Evaluation of testosterone reserve in infertile men.

| Starting Date: 1978 | Estimated Completion Date: 1982 |
|---|---|

Principal Investigator: Allan R. Class MD MAJ MC

| Associate Investigators: | Facility: WRAMC |
|---|---|
| | Dept/Svc Kyle Metabolic Unit |

Key Words:
testosterone, HCG, infertility

| Accumulative MEDCASE Cost: $1,000 | Accumulative Contract Cost: $73,000 | Accumulative Supply Cost: $13,100 |
|---|---|---|

| FY-80 MEDCASE Cost: $1,000 | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective:
To determine how the testis responds to single and multiple injections of HCG.

Technical Approach:
Measurement of serum levels of gonadal hormones before and after various regimens of HCG administration.

Progress during FY-80: Approx 15 subjects studied during FY 80.

Number of subjects to be studied before completion of study: 20

Serious/unexpected side effects in subjects participating in project:
none

Conclusions:
Resensitization of testosterone production after intial HCG-induced desensitization may be related to a shift in the pathway of testosterone biosynthesis.

Publications or Abstracts, FY-80: Two papers published in FY80, one paper in press, one paper in preparation. One abstract presented at National AFCR meeting.

Work Unit No.: 1374

Funds utilized, FY-80: $44,000

Funding requirements, FY-81:

| | |
|---|---|
| Supplies: | $6,000 |
| Travel: | $1,000 |
| Other: | $18,000 |

| Date: 10 Sept 80 | Protocol No: 1376 | Status: Interim X<br>Final |
|---|---|---|

Title of Project: Effect of amitriptyline and amantadine on growth hormone dynamics in acromegaly.

| Starting Date: 1978 | Estimated Completion Date: 1982 |
|---|---|

Principal Investigator: Allan R. Glass, M.D., MAJ MC

| Associate Investigators: | Facility: WRAMC |
|---|---|
| | Dept/Svc Kyle Metabolic Unit |

Key Words:
L-tryptophan, amitriptyline, acromegaly, growth hormone, prolactin

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: 39,000 |
|---|---|---|

| FY-80 MEDCASE Cost: | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective:
To determine how the drugs amantadine and amitriptyline interact with the pituitary gland in acromegaly.

Technical Approach: Measurement of serum prolactin and growth hormone basally and in response to perturbation tests before and after administration of either amitriptyline or amantadine.

Progress during FY-80: Amitriptyline portion of study completed. Addendum to revise protocol currently pending prior to beginning on amantadine section in FY 81.

Number of subjects to be studied before completion of study: 25

Serious/unexpected side effects in subjects participating in project:
none

Conclusions:
Amitriptyline suppresses growth hormone modestly in acromegaly. L-tryptophan stimulates growth hormone in normals but not in acromegaly, and stimulates prolactin in neither.

Publications or Abstracts, FY-80:
Two papers published during FY 80.

Work Unit No.: 1376

Funds utilized, FY-80: $435

Funding requirements, FY-81:

| | |
|---|---|
| Supplies: | $3,000 |
| Other: | $4,000 |

| Date: 10 Sept 80 | Protocol No: 1377 | Status: Interim X<br>Final |
|---|---|---|

Title of Project: Effect of dietary tryptophan content on food intake in obese subjects

| Starting Date: 1978 | Estimated Completion Date: 1982 |
|---|---|

Principal Investigator: Allan R. Glass, M.D., MAJ MC

| Associate Investigators: | Facility: WRAMC |
|---|---|
| | Dept/Svc Kyle Metabolic Unit |

Key Words: tryptophan, obesity, food intake

| Accumulative MEDCASE Cost: 0 | Accumulative Contract Cost: 0 | Accumulative Suppl; Cost: $20 |
|---|---|---|

| FY-80 MEDCASE Cost: 0 | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective:

To determine whether the proportion of tryptophan in food can directly affect food intake

Technical Approach:

Measurement of food intake in individuals consuming only a liquid formula diet supplemented with various amounts of tryptophan

Progress during FY-80: Due to lack of time and personnel no subjects have been studied under this protocol during FY 80.

Number of subjects to be studied before completion of study: 12

Serious/unexpected side effects in subjects participating in project:

none

Conclusions:

Deferred

Publications or Abstracts, FY-80:

none

Work Unit No.: 1377

Funds utilized, FY-80: none

Funding requirement, FY-81:

| | |
|---|---|
| Supplies: | $1,000 |
| Other: | $3,000 |

| Date: 10 Sept 80 | Protocol No: 1379 | Status: Interim X<br>Final |
|---|---|---|

Title of Project: Effect of post-weaning undernutrition on reproductive hormones in rats

| Starting Date: 1978 | Estimated Completion Date: 1982 |
|---|---|

Principal Investigator: Allan R. Glass MD MAJ MC

| Associate Investigators: | Facility: WRAMC |
|---|---|
| | Dept/Svc Kyle Metabolic Unit |

Key Words:
undernutrition, puberty

| Accumulative MEDCASE Cost: 0 | Accumulative Contract Cost: 0 | Accumulative Supply Cost: $3,800 |
|---|---|---|

| FY-80 MEDCASE Cost: 0 | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective:

To determine how undernutrition affects sexual maturation in rats

Technical Approach:

Determination of the response of the hypothalamic-pituitary-testicular axis to various perturbation tests in normal and underfed rats

Progress during FY-80: @2 experiments were conducted; both were unsuccessful due to technical problems. Shortage of animal space has temporarily precluded additional studies. A major addendum to this protocol is in preparation.

Number of subjects to be studied before completion of study:

Serious/unexpected side effects in subjects participating in project:

Conclusions:

Undernutrition delays puberty in rats by means of gonadotropin deficiency.

Publications or Abstracts, FY-80: One paper published in FY 80, one paper submitted for publication.

Work Unit No.: 1379

Funds utilized: FY-80: $1,862

Funding requirements, FY-81:

| | |
|---|---|
| Supplies: | $5,000 |
| Travel: | $1,000 |
| Other: | $9,000 |

| Date: 10 Oct 1980 | Protocol No: 1380 | Status: Interim |
|---|---|---|

**Title of Project:** Effect of Thyroid Status on the Hormonally-Induced Cyclic AMP Responses of the Kidney

| Starting Date: 19 Oct 1977 | Estimated Completion Date: 30 Sept 1982 |
|---|---|

**Principal Investigator:** H. Linton Wray, LTC, MC

| Associate Investigators: | Facility: WRAMC |
|---|---|
| Wayman W. Cheatham, MAJ, MC | Dept/Svc Kyle Metabolic Unit |

**Key Words:** Thyroid Hormone, cyclic AMP, cyclic GMP

| Accumulative MEDCASE Cost: $1,000 | Accumulative Contract Cost: $ 600 | Accumulative Supply Cost: $17,264 |
|---|---|---|

| FY-80 MEDCASE Cost: None | Periodic Review Results: (to be filled in by DCI) |
|---|---|

**Study Objective:** To determine if the renal hormone receptor - second messenger systems of two unrelated polypeptide hormones are affected by thyroid hormone. By measuring nephrogenous cyclic AMP during parathyroid and antidiuretic hormone infusions in hyper- and hypo- thyroid patients, it can be determined if thyroid hormone influence the renal cyclic AMP responses to these hormones.

**Technical Approach:** Hyperthyroid and hypothyroid patients will be admitted to Ward 47 for a 3 day study protocol and will be similarly studied after becoming euthyroid. During each admission the patient will undergo two 3-hour renal clearance procedures, one with PTH infusion and another with vasopressin infusion.

**Progress during FY-80:** Six patients were studied this year with results simil to those reported in the FY-79 report. In addition, preliminary studies have shown that immunoreactive PTH levels during PTH infusion were higher in hypothyroid patients than in euthyroid patients.

Number of subjects to be studied before completion of study: 30

Serious/unexpected side effects in subjects participating in project: None

**Conclusions:** The delayed water excretion in hypothyroid patients and the decreased fractional excretion of phosphate in hyperthyroid patients are not associated with demonstrated changes in renal responses to vasopressin and parathyroid hormone. An addendum to the protocol has been submitted (attached).

**Publications or Abstracts, FY-80:**

Endocrinology 106(Suppl): 122, 1980.

Work Unit #1380

Funds utilized: FY, 80: $3,061 (2600)

Funding requirements, FY-81:

| | |
|---|---|
| Personnel: | Gerald M. Sheldon SP-6<br>Vincent M. Butler GS-09 |
| Equipment: | Automated RIA System (FY-81 MEDCASE) |
| Supplies: | $8,000 |
| Travel: | $1,100 |
| Other: | $5,000 |

Addendum to protocol, Work Unit #1380

1. This protocol, "Effect of Thyroid Status on the Hormonally -induced Cyclic AMP Responses of the Kidney", has resulted in three abstracts and three papers which are currently in preparation. One aspect of these investigations has demonstrated little effect of thyroid status on the renal responses to infused parathyroid hormone (PTH) when measured by nephrogenous cyclic AMP (NcAMP) and fractional excretion of phosphate ($FE_{PO4}$). However, preliminary studies have shown that immunoreactive PTH levels during PTH infusion were higher in hypothyroid patients than in euthyroid patients yet the measured renal responses were not significantly different (attached abstract). This suggested that hypothyroid patients had a decreased clearance of infused PTH and were in fact hyporesponsive to PTH.

2. We propose to continue to investigate the effect of thyroid status on PTH metabolism and responses by measuring biologically active as well as immunoreactive PTH in addition to NcAMP and $FE_{PO4}$ during PTH infusion. Two bioassays will be employed. A cytochemical assay using rat renal tubules will be performed by Dr. James Posillico of Duke University and a adenylate cyclase assay using canine renal membranes will be performed by Dr. Robert Nissenson of University of California. Six patients with hyperthyroidism and six with hypothyroidism will be studied on a two day protocol which will not include the previously used anti-diuretic hormone infusion. These studies will determine whether biologically active PTH during PTH infusion is affected by thyroid status and will be important in the interpretation of the renal responses to PTH.

| Date: 15 October 1980 | Protocol No: 1381 | Status: Interim X<br>Final |
|---|---|---|

Title of Project: Estradiol Receptors in Rat Thyroid Glands

| Starting Date: 24 May 1977 | Estimated Completion Date: 30 Sept 1982 |
|---|---|

Principal Investigator: Robert A. Vigersky, M.D. MAJ MC

| Associate Investigators: | Facility: WRAMC |
|---|---|
| | Dept/Svc Kyle Metabolic Unit |

Key Words: Estrogen; receptors; thyroid

| Accumulative MEDCASE Cost: 0 | Accumulative Contract Cost: 0 | Accumulative Supply Cost $426.20 |
|---|---|---|

| FY-80 MEDCASE Cost: 0 | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective: To study the nature of the estrogen receptors in the rat thyroid so that these studies can be used as a model for examining similar receptors in the human. Techniques to be developed will be used for these and other non-classic target tissues such as the thymus.

Technical Approach: Determination of the binding capacity and affinity, steroid specificity, net size and charge, sedimentation coefficient, and steady-state kinectics of the receptor as obtained from the cytosol of male and female rats of varying ages.

Progress during FY-80: Progress in these methods has been made using the thymus gland as a model and the already accumulated data has been compared to that in other non-classic as well as classic target tissues for estrogen.

Number of subjects to be studied before completion of study: N/A

Serious/unexpected side effects in subjects participating in project: N/A

Conclusions: Estrogen receptors exist in the thyroid glands of both male and female rats are appear to be similar in their physico-chemical nature to those of other receptors.

Publications or Abstracts, FY-80: None

Work Unit No.: 1381

Funds Utilized, FY-80: $426.20

Funding Requirements, FY-81: $7300

Personnel: None

Equipment: None

Supplies: $6600

Travel: $500

Other: (2400) $200

| Date: 15 October 1980 | Protocol No: 1392 | Status: Interim X / Final |
|---|---|---|

Title of Project: Measurement of Steroids in Fluid Obtained by Micropuncture from Rat Seminiferous Tubules and Epididymes.

Starting Date: 24 May 1977 | Estimated Completion Date: 30 Sept 1983

Principal Investigator: Robert A. Vigersky, M.D. MAJ MC

| Associate Investigators: | Facility: WRAMC |
|---|---|
| | Dept/Svc Kyle Metabolic Unit |

Key Words: Micropuncture; sex steroids.

| Accumulative MEDCASE Cost: 0 | Accumulative Contract Cost: 0 | Accumulative Supply Cost: $2438.96 |
|---|---|---|

| FY-80 MEDCASE Cost: 0 | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective: To study the control of spermatogenesis by sex steroids, particularly estradiol and testosterone. Also to investigate the nature of the blood-testis barrier to these steroids and to other substances.

Technical Approach: Testicular micropuncture using laboratory fabricated glass micropipets in adult male rats. Measurement of steroids by micro-methods of radioimmunoassay. Infusion of various drugs and hormones intravenously and measurement of them as they appear in the seminiferous tubule.

Progress during FY-80: Methods for simultaneous cannulation of the jugular and femoral vein have been developed so that constant infusion and blood sampling can be accomplished. A study of the ability of methotrexate, a commonly used agent in the treatment of malignancies, has been completed showing 100 times lower levels in the testicle.

Number of subjects to be studied before completion of study: N/A

Serious/unexpected side effects in subjects participating in project: N/A

Conclusions: A blood-testis barrier exists for the drug, methotrexate. This may explain the reason that the testis is a frequent site of recurrence of leukemia.

Publications or Abstracts, FY-80: None

Work Unit No.: 1382

Funds Utilized, FY-60: $2438.96

Funding Requirements, FY-61: $6700

Personnel: Susan Barnes, GS-09

Equipment: None

Supplies: $5000

Travel: $500

Other: (2572) $1000; (2400) $300

| Date: 1 October 1980 | Protocol No: 1383 | Status: Interim / Final |
|---|---|---|

Title of Project: Measurement of Hemoglobin A1C in the Assessment of the Efficacy of Diabetic Treatment

| Starting Date: 7/27/77 | Estimated Completion Date: present |
|---|---|

Principal Investigator: Timothy M. Boehm, LTC MC

| Associate Investigators: P. Leapley, R.D. | Facility: WRAMC |
|---|---|
| | Dept/Svc: Department of Clinical Investigation |

Key Words: Glycosylated hemoglobin, diabetes, diabetic diet

| Accumulative MEDCASE Cost: $11,938.00 | Accumulative Contract Cost: | Accumulative Supply Cost: $16,821.53 |
|---|---|---|
| FY-80 MEDCASE Cost: | Periodic Review Reports: (to be filled in by MA) | |

*Study Objective: To evaluate the response of hemoglobin A1C to modifications of diabetic therapy.

*Technical Approach: (See attached abstract.) In brief, an attempt was made to correlate responses to diet therapy with changes in glycosylated hemoglobins.

*Progress during FY-80: None. The dietitian interested in the study departed WRAMC.

| Number of subjects to be studied before completion of study: 0 |
|---|
| Serious/unexpected side effects in subjects participating in project: 0 |

Conclusions: See abstract. In brief, patients may manifest improvement in HighA1C plus glucose in response to diet therapy without losing weight, indicating that diet therapy may be efficacious without promoting weight reduction.

Publications or Abstracts, FY-80: None. Efforts are being made to gather the data for publication.

| Date: 10 Sept 80 | Protocol No: 1385 | Status: Interim X<br>Final |
|---|---|---|

Title of Project:

Serial changes in free testosterone during pregnancy

| Starting Date: 1978 | Estimated Completion Date: 1981 |
|---|---|

Principal Investigator: Allan R. Glass MD MAJ MC

| Associate Investigators: | Facility: WRAMC |
|---|---|
| Thomas Klein MD LTC MC | Dept/Svc Kyle Metabolic Unit/ ObGyn |

Key Words:
free testosterone, pregnancy

| Accumulative MEDCASE Cost: 0 | Accumulative Contract Cost: $8,000 | Accumulative Supply Cost: $1,000 |
|---|---|---|

| FY-80 MEDCASE Cost: 0 | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective:

To determine whether free testosterone levels in serum change during early pregnancy and whether such changes correlate with fetal sex.

Technical Approach:

Measurement of total and free testosterone during pregnancy.

Progress during FY-80:

170 subjects studied. Assays of testosterone, free testosterone, and DHT completed.

Number of subjects to be studied before completion of study: 30

Serious/unexpected side effects in subjects participating in project:
none

Conclusions:
Free testosterone falls modestly with increasing fetal age. Free testosterone is not correlated with fetal sex.

Publications or Abstracts, FY-80:
One paper submitted for publication.

Work Unit No.: 1385

Funds utilized, FY-80: $8,000

Funding requirements, FY-81

| | |
|---|---|
| Supplies: | $3,000 |
| Travel: | $1,000 |
| Other: | $4,400 |

| Date: 15 October 1980 | Protocol No: 1386 | Status: Interim x<br>Final |
|---|---|---|

Title of Project: The Effect of Delta-1-Testolactone (Teslac) in Male Infertility.

| Starting Date: 22 Nov 1977 | Estimated Completion Date: 30 Sept 1983 |
|---|---|

Principal Investigator: Robert A. Vigersky, M.D. MAJ MC

| Associate Investigators: Allan R. Glass, MAJ MC | Facility: WRAMC |
|---|---|
| | Dept/Svc Kyle Metabolic Unit |

Key Words: Infertility, male; Testolactone; Oligospermia

| Accumulative MEDCASE Cost: 0 | Accumulative Contract Cost: $3503 | Accumulative Supply Cost: $7262.20 |
|---|---|---|

| FY-80 MEDCASE Cost: 0 | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective: To improve sperm counts, and thereby fertility, in men with idiopathic oligospermia. To study the mechanism of the oligospermia with repect to hormonal parameters and response to HCG and LRH and to investigate the effect of lowering estrogen levels and blocking estrogen action has on the basal and stimulated levels of the other hormones.

Technical Approach: LRH and HCG testing along with basal semen analyses is performed before beginning on Teslac 1 Gm/day and Tamoxifen 20 mg/day orally. Semen and hormonal parameters are monitored monthly and the HCG and LRH tests are repeated at the time of pregnancy or after 1 year on the medication whichever is first.

Progress during FY-80: Twelve men were entered into the Teslac alone protocol with a 100% increase in sperm counts (11 of 12 responding) and 4 pregnancies. Five men have been begun on the combination of Teslac and Tamoxifen.

Number of subjects to be studied before completion of study: 30

Serious/unexpected side effects in subjects participating in project: None

Conclusions: Blocking estrogen formation with the aromatase inhibitor, Teslac, seems to have been effective in increasing sperm counts and promoting fertility in men with idiopathic oligospermia. Tamoxifen may provide additional benefit.

Publications or Abstracts, FY-80: Vigersky, R.A. and Glass A.R., "Effect of $\Delta^1$-Testolactone (Teslac) in Oligospermic Men," J. Andrology 1:67, 1980.

Work Unit No.: 1386

Funds Utilized, FY-80: $10765.20

Funding Requirements, FY-81: $10,700

Personnel: Temporary hire, GS-07 to be named

Equipment: None

Supplies: $2000

Travel: $500

Other: (2572) $8000; (2400) $300

| Date: 10 Sept 80 | Protocol No: 1387 | Status: Interim X<br>Final |
|---|---|---|

Title of Project: Acute responses to estrogen in men with prostate carcinoma

| Starting Date: 1978 | Estimated Completion Date: 1982 |
|---|---|

Principal Investigator: Allan R Glass MD MAJ MC

| Associate Investigators: | Facility: WRAMC |
|---|---|
| | Dept/Svc Kyle Metabolic Unit |

Key Words:
estrogen, LH, prostate carcinoma

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: 0 | Accumulative Supply Cost: 0 |
|---|---|---|

| FY-80 MEDCASE Cost: 0 | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective:

To determine whether men with prostate carcinoma respond to acute estrogen administration differently from normal men

Technical Approach:

Measurement of serum LH and estrogen after administration of an acute estrogen challenge

Progress during FY-80:
No subjects studied. This study was essentially done by someone else and has recently been published. Protocol is undergoing evaluation to study a different subject group, as per recent addendum.

Number of subjects to be studied before completion of study: 15

Serious/unexpected side effects in subjects participating in project:
none

Conclusions:

Deferred

Work unit no.: 1387

Funds utilized, FY-80: 0

Funding requirements: FY-81:

| | |
|---|---|
| Supplies: | $1,000 |
| Other: | $3,000 |

| Date: | Protocol No: 1389 | Status: Interim / Final XX |
|---|---|---|

Title of Project:

THe effect of Dietary Carbohydrate on T3 Receptors.

| Starting Date: 1978 | Estimated Completion Date: 1980 |
|---|---|

Principal Investigator: KENNETH D. BURMAN, LTC, MC

| Associate Investigators: | Facility: WRAMC |
|---|---|
| L. WARTOFSKY, COL, MC<br>RC SMALLRIDGE, LTC,MC<br>AR GLASS, MAJ,MC<br>YVONNE LUKES | Dept/Svc Dept of Med/Endocrine |

Key Words: Carbohydrate/T3 receptors

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: |
|---|---|---|
| FY-80 MEDCASE Cost: | Periodic Review Results: (to be filled in by DCI) | |

Study Objective:

To ascertain if carbohydrate intake alters T3 receptors levels.

Technical Approach:

Isolate T3 receptors from rat liver and solubilize receptor

Progress during FY-80:

25 rats studied by eating 79% or 64% carbohydrate diet and then receptors isolated.

Number of subjects to be studied before completion of study: rats

Serious/unexpected side effects in subjects participating in project:

None

Conclusions:

Carbohydrates do not alter receptor levels

Work unit no.: 1389

Funds utilized, FY-80: $1,075

Funding requirements, FY-81:

| | |
|---|---|
| Personnel: | Lukes |
| Supplies: | $2,000 |
| Other: | 400 |
| Travel: | 1,000 |

| Date: | Protocol No: 1390 | Status: Interim X<br>Final |
|---|---|---|

Title of Project:

Investigations Concerning the Physiology of Iodothyronines

| Starting Date: 6-78 | Estimated Completion Date: 8-82 |
|---|---|

Principal Investigator: Kenneth D. Burman, LTC, MC

| Associate Investigators: | Facility: WRAMC |
|---|---|
| | Dept/Svc Dept of Med/Endocrine |

Key Words:
Iodothyronines

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: |
|---|---|---|

| FY-80 MEDCASE Cost: | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective:
To quantitate the factors influcing iodothyronine conversions.

Technical Approach:
Serum measurements by RIA in various states.

Progress during FY-80:

Develop RIS for 3,5 T2

Number of subjects to be studied before completion of study: 30

Serious/unexpected side effects in subjects participating in project: None

Conclusions: There is decreased extrathyroidal conversion in fasting.

Publications or Abstracts, FY-80:

Wray HL, Burman, KD, et al JCEM: 107:130, 1980

Work unit no.: 1390

Funds utilized, FY-80: $20,000

Funding requirements: FY-81:

Supplies: $5,000

| Date: | Protocol No: 1391 | Status: Interim x<br>Final |
|---|---|---|

Title of Project:

Regulations if the Initiation of Thyroid Hormone Action

| Starting Date: 1-78 | Estimated Completion Date: 8-81 |
|---|---|

Principal Investigator: Kenneth D. Burman, LTC, MC

| Associate Investigators:<br>Keith Latham<br>Wartofsky, L<br>Yvonne Lukes | Facility: WRAMC<br>Dept/Svc Dept of Med/Endocrine |
|---|---|

Key Words: T3 receptors

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: |
|---|---|---|

| FY-80 MEDCASE Cost: | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective:

To determine how thyroid hormones work.

Technical Approach:

Isolate and purify T3 receptors

Progress during FY-80: Block T3 receptor activity with Ipodate and sulfhydryl oxidizing agents.

Number of subjects to be studied before completion of study: all animals

Serious/unexpected side effects in subjects participating in project: none

Conclusions: THe receptor has acetylase activity and a MW of about 50,000 Daltous

Publications or Abstracts, FY-80:

Burman, KD et al, Hormone Metab Res: In press

Work unit no: 1391

Funds utilized, FY-80: $20,000

Funding requirements, FY-81:

Personnel: Burman and Latham

Supplies: $5,000

| Date: 15 October 1980 | Protocol No: 1392 | Status: Interim / Final x |
|---|---|---|

Title of Project: Steroid Transfer across the Blood-Cerebrospinal Fluid Barrier in the Rhesus Monkey.

| Starting Date: 27 Dec 1977 | Estimated Completion Date: Completed |
|---|---|

Principal Investigator: Robert A. Vigersky, M.D. MAJ MC

| Associate Investigators: | Facility: WRAMC |
|---|---|
| | Dept/Svc Kyle Metabolic Unit |

Key Words: Blood-Cerebrospinal Fluid Barrier

| Accumulative MEDCASE Cost: 0 | Accumulative Contract Cost: 0 | Accumulative Supply Cost: x 0 |
|---|---|---|

| FY-80 MEDCASE Cost: 0 | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective: To determine whether or not different glucocorticoids have varying rates of entry into the CSF from blood.

Technical Approach: Injection of unlabelled dexamethasone, prednisone, and cortisol into a vein and measurement of the levels in peripheral venous blood and CSF via an Ommaya reservoir.

Progress during FY-80: No experiments were performed in FY-80

Number of subjects to be studied before completion of study: N/A

Serious/unexpected side effects in subjects participating in project: N/A

Conclusions: None of the steroids measured had any advantage in the rate of entry into the CSF.

Publications or Abstracts, FY-80: None

| Date: | Protocol No: 1393 | Status: Interim X<br>Final |
|---|---|---|

Title of Project:
T3 Receptors in Normal and Fasting Rats

| Starting Date: 1-78 | Estimated Completion Date: 8-81 |
|---|---|

Principal Investigator: Kenneth D. Burman, LTC, MC

| Associate Investigators: | Facility: WRAMC |
|---|---|
| | Dept/Svc Dept of Med/Endocrine |

Key Words: T3 receptor/Fasting

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: |
|---|---|---|

| FY-80 MEDCASE Cost: | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective:
To measure T3 receptors in rat liver during fasting,

Technical Approach:
Isolate T3 receptors in fed and fasting rat.

Progress during FY-80:
We are in the process of determining why T3 receptors decrease in fasting.

Number of subjects to be studied before completion of study: rats

Serious/unexpected side effects in subjects participating in project:
none

Conclusions:
T3 receptors decrease during fasting

Publications or Abstracts, FY-80: none

Work unit no.: 1393

Funding requirements: FY-81:

Personnel: Lukes, Burman

Supplies: $2,000

| Date: | Protocol No: 1395 | Status: Interim X<br>Final |
|---|---|---|

Title of Project:

T4 to T3 Conversion: Effect of Modulation of Glucose Metabolism

| Starting Date: 78 | Estimated Completion Date: 81 |
|---|---|

Principal Investigator: Kenneth D. Burman, LTC, MC

| Associate Investigators: | Facility: WRAMC |
|---|---|
| | Dept/Svc Dept of Med/Endocrin |

Key Words: Glucose /T4 conversion

| Accumulative MEDCASE Cost:_____ | Accumulative Contract Cost:_____ | Accumulative Supply Cost:_____ |
|---|---|---|

| FY-80 MEDCASE Cost:_____ | Periodic Review Results:_____<br>(to be filled in by DCI) |
|---|---|

Study Objective: To study the mechanism by which glucose increases T4 to T3 conversion in rat liver.

Technical Approach:
Hepatic isolation and quantitation of T4 conversion.

Progress during FY-80:
Have shown that sulfhydyl groups and glucose increase enzyme activity

Number of subjects to be studied before completion of study: rats

Serious/unexpected side effects in subjects participating in project:
None

Conclusions: Glucose enhances T4 and T3 conversion

Publications or Abstracts, FY-80: None

Work unit no.: 1395

Funds utilized, FY-80:

Funding requirements, FY-81:

| | |
|---|---|
| Personnel: | Yvonne Lukes, Kenneth D. Burman |
| Equipment: | |
| Supplies: | $3,000 |
| Travel: | 400 |
| Other: | |

| Date: | Protocol No: 1396 | Status: Interim X<br>Final |
|---|---|---|

Title of Project:

$T_4$ to $T_3$ Conversion: Effect of Somatostatin Administration

| Starting Date: 78 | Estimated Completion Date: 81 |
|---|---|

Principal Investigator: Kenneth D. Burman, LTC, MC

| Associate Investigators: | Facility: WRAMC |
|---|---|
| | Dept/Svc Dept of Med/Endocrine |

Key Words: Somatostation/T4 conversion

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: |
|---|---|---|

| FY-80 MEDCASE Cost: | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective: To determine if somatostation alter T4 conversion and T3 receptors and also to determine if somatostation receptors are altered by thyroid hormone levels.

Technical Approach:

Somatostatin receptor in thyroid and pituitary gland, somatostatin RIA, T3/T4 receptors

Progress during FY-80:

Have developed assay for measuring somatostatin receptors in thyroid and pituitary gland.

Number of subjects to be studied before completion of study: rats

Serious/unexpected side effects in subjects participating in project: None

Conclusions: Thyroid hormone probably alters somatostatin receptor levels

Publications or Abstracts, FY-80: None

Work unit no.: 1396

Funds utilized, FY-80: $1,554.94

Funding requirements, FY-81:

| | |
|---|---|
| Personnel: | Yvonne Lukes |
| Equipment: | |
| Supplies: | $2,000 |
| Travel: | 400 |
| Other: | 1,000 |

| Date: | Protocol No: 1397 | Status: Interim x<br>Final |
|---|---|---|

Title of Project:
The effect of Various Metabolic Conditions on T3 Receptors in Circulating Mononuclear Cells.

| Starting Date: 79 | Estimated Completion Date: 82 |
|---|---|

Principal Investigator: Kenneth D. Burman, LTC, MC

| Associate Investigators: | Facility: WRAMC |
|---|---|
| L. Wartofsky, COL<br>Keith Latham | Dept/Svc Dept of Med/Endocrine |

Key Words: T3 receptors

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: |
|---|---|---|

| FY-80 MEDCASE Cost: | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective: Measure T3 receptors in various illnesses and quantitate and correlate T3 receptor activity.

Technical Approach:
Set up T3 receptor assay and set up acetylase enzyme activity.

Progress during FY-80:
Develop acetylase activity

Number of subjects to be studied before completion of study: 30

Serious/unexpected side effects in subjects participating in project:
None

Conclusions: T3 probably regulates acetylase activity

Publications or Abstracts, FY-80:

Burman, et al JCEM 51:106,80
Maxon, Premachandra NEJM, May 29 1980

Work unit no.: 1397

Funds utilized, FY-80:

Funding requirements, FY-81:

Personnel: Djuh, Latham, and Burman

Equipment:

Supplies: $5,000

Travel:

Other:

| Date: 10 October 1980 | Protocol No: 1398 | Status: Interim |
|---|---|---|

Title of Project: Studies on the pathogenesis of hypocalcemia in tumors associated with osteoblastic metastases

| Starting Date: June 1978 | Estimated Completion Date: 30 Sep 1982 |
|---|---|

Principal Investigator: Robert C. Smallridge, LTC, MC
H. Linton Wray, LTC, MC

| Associate Investigators: | Facility: WRAMC |
|---|---|
| Marcus Schaaf, M.D.<br>John Horton, M.D.<br>Richard C. Dimond, LTC, MC | Dept/Svc Kyle Metabolic Unit |

Key Words: Hypocalcemia, osteoblasts, cancer

| Accumulative MEDCASE Cost: None | Accumulative Contract Cost: None | Accumulative Supply Cost: $2,900 |
|---|---|---|

| FY-80 MEDCASE Cost: None | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective: To determine whether the hypocalcemia seen in some patients with osteoblastic metastases is due to hypoparathyroid, secondary hyperparathyroidism, an abnormality in vitamin D metabolism, or an unidentified humoral substance with osteoblastic activity.

Technical Approach:
(1) 24 hour urines for calcium, phosphate, creatinine
(2) Serum for Ca, PO4, Mg, alkaline phosphatase, parathyroid, vitamin D metabolites.
(3) Calcium and parathormone infusions
(4) Bone marrow biopsies for tissue culture to test in vitro the cells' ability to incorporate $^{3}$H-proline into collagen.

Progress during FY-80: Vitamin D metabolite assays are nearly ready to utilize. The results of our first patient have been reported, on the article accepted for publication.

Number of subjects to be studied before completion of study: 8

Serious/unexpected side effects in subjects participating in project: None

Conclusions: Deferred

Publications or Abstracts, FY-80: Amer J Med (in press)

Work unit no.: 1398

Funds utilized, FY-80: $2,255 (2600)

Funding requirements, FY-81:

| | |
|---|---|
| Personnel: | Delbert Dawson GS-11 |
| | Gerald M. Sheldon SP-6 |
| Equipment: | Automated RIA System (FY-81 MEDCASE) |
| Supplies: | $2,500 |
| Travel: | 500 |
| Other: | 1,000 |

| Date: 10 Oct 1980 | Protocol No: 1399 | Status: Interim ~~Final~~ |
|---|---|---|

Title of Project: An assessment of parathyroid hormone (PTH) levels in normal subjects and in patients with disorders of calcium metabolism

| Starting Date: May 1978 | Estimated Completion Date: 30 Sept 1982 |
|---|---|

Principal Investigator: Robert C. Smallridge, LTC, MC
H. Linton Wray, LTC, MC

| Associate Investigators: | Facility: WRAMC |
|---|---|
| Marcus Schaaf, M.D.<br>Richard C. Dimond, LTC, MC | Dept/Svc Kyle Metabolic Unit |

Key Words: Parathormone

| Accumulative MEDCASE Cost: None | Accumulative Contract Cost: None | Accumulative Supply Cost: $1,200 |
|---|---|---|

| FY-80 MEDCASE Cost: None | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective: To establish the ranges of serum PTH levels in normal subjects and patients with metabolic disorders.

Technical Approach: Venipuncture for blood samples to measure PTH levels.

Progress during FY-80: Although we have a research quality PTH antiserum, the shortage of laboratory personnel has prevented the development of this important radioimmunoassay to date.

Number of subjects to be studied before completion of study: 100

Serious/unexpected side effects in subjects participating in project: None

Conclusions: Deferred

Publications or Abstracts, FY-80: None expected. Reference ranges being established.

Work unit no.: 1399

Funds utilized, FY-80: $1,129 (2600)

Funding requirements, FY-81:

| | |
|---|---|
| Personnel: | Vincent M. Butler, GS-09 |
| Equipment: | |
| Supplies: | $2,500 |
| Travel: | $500 |
| Other: | $1,500 |

| Date: | Protocol No: 1300-78 | Status: Interim X<br>Final |
|---|---|---|

Title of Project:
The Development of a Radioimmunoassay of Triiodothyronine

| Starting Date: 78 | Estimated Completion Date: 81 |
|---|---|

Principal Investigator: Kenneth D. Burman, LTC, MC

| Associate Investigators:<br>L. Wartofsky, COL<br>RC Smallridge, LTC | Facility: WRAMC<br>Dept/Svc Dept of Med/Endocrine |
|---|---|

Key Words: Radioimmunoassay

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: |
|---|---|---|

| FY-80 MEDCASE Cost: | Periodic Review Results:<br>(to be filled in by DCI) |
|---|---|

Study Objective: To develop radioimmunoassay for thyroid hormones

Technical Approach:
Conjugate and inject rabbits and then bleed occasionally and check for antibodies

Progress during FY-80:
Antibody developed for 3,5T2

Number of subjects to be studied before completion of study: rabbits

Serious/unexpected side effects in subjects participating in project:
None

Conclusions: None yet

Publications or Abstracts, FY-80:

Pangaro, LP, Burman, KD, et al JCEM 50:130, 1980

Work unit no.: 1300-78

Funds utilized, FY-80:

Funding requirements, FY-81:

| | |
|---|---|
| Personnel: | Burman |
| Equipment: | |
| Supplies: | $2,000 |
| Travel: | |
| Other: | |

| Date: 15 October 1980 | Protocol No: 1301-78 | Status: Interim X / Final |
|---|---|---|

Title of Project: The Effect of $\Delta^1$-Testolactone (Teslac) on 5-alpha Reductase in Rats.

| Starting Date: 24 Jan 78 | Estimated Completion Date: 30 Sept 81 |
|---|---|

Principal Investigator: Robert A. Vigersky, M.D. MAJ MC

| Associate Investigators: | Facility: WRAMC |
|---|---|
| | Dept/Svc Kyle Metabolic Unit |

Key Words: Teslac; Receptors; 5-aopha Reductase.

| Accumulative MEDCASE Cost: 0 | Accumulative Contract Cost: 0 | Accumulative Supply Cost: $394.40 |
|---|---|---|
| FY-80 MEDCASE Cost: 0 | Periodic Review Results: (to be filled in by DCI) | |

Study Objective: To determine whether or not the anti-androgenic activity of Teslac in vivo is due to its ability to interact with the enzyme that converts testosterone to dihydrotestosterone.

Technical Approach: Measurement of dihydrotestosterone levels in blood obtained from immature castrate rats given either testosterone alone or testosterone plus Teslac. Also, measurement of the in vitro ability of Teslac to prevent the conversion of testosterone to dihydrotestosterone by rat propstate cytosol.

Progress during FY-80: It would appear that Teslac does not have any anti enzyme activity and that its anti-androgenic effect is via its ability to interact with the androgen receptor

Number of subjects to be studied before completion of study: N/A

Serious/unexpected side effects in subjects participating in project: N/A

Conclusions: Teslac is an anti-androgen as well as inhibiting estrogen activity via anti-receptor activity. Further studies are in progress to characterize Teslac's ability to interact with the estrogen receptor.

Publications or Abstracts, FY-80: Vigersky, R.A., Mozingo, D., Eil, E. Purohit, V., and Bruton, J., "Anti-androgenic Properties of Delta-1-Testolactone (Teslac)," Endo. Soc.

Work Unit No.: 1301-78

Funds Utilized, FY-80: $394.40

Funding Requirements, FY-81: $5600

Personnel: None

Equipment: None

Supplies: $3800

Travel: $500

Other: (2572) $1000; (2100) $300

| Date: 15 October 1980 | Protocol No:1303-78 | Status: Interim X<br>Final |
|---|---|---|

Title of Project: Studies on the Alterations in Drug Metabolism in Hyperthyroidism.

| Starting Date: 28 Mar 78 | Estimated Completion Date: 30 Sept 81 |
|---|---|

Principal Investigator: Robert A. Vigersky, M.D. MAJ MC

| Associate Investigators: | Facility: WRAMC |
|---|---|
| | Dept/Svc Kyle Metabolic Unit |

Key Words: Hyperthyroidism; Methimazole, Dexamethasone

| Accumulative MEDCASE Cost: 0 | Accumulative Contract Cost: 0 | Accumulative Supply Cost: 0 |
|---|---|---|

| FY-80 MEDCASE Cost: 0 | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective: To determine if changes in metabolism of drugs used to treat hyperthyroidism are due to the elevated thyroxine levels, themselves, or mediated th rough beta-adrenergic effects.

Technical Approach: The half lives and plasma levels of dexamethasone and methimazole will be measured after intravenous injection while the patients are hyperthyroid and after treatment with beta-adrenergic blockade. They will be studied again after being rendered euthyroid by the appropriate therapy as clinically indicated.

Progress during FY-80: No patients were accrued into this protocol during FY-80 due to the departure of the participating Fellow.

Number of subjects to be studied before completion of study: 10

Serious/unexpected side effects in subjects participating in project: None

Conclusions: The blood awaits analysis and therefore results are currently unavailable.

Publications or Abstracts, FY-80: None

Work Unit No.: 1303-78

Funds Utilized, FY-80: None

Funding Requirements, FY-81: $3000

Personnel: None

Equipment: None

Supplies: $3000

Travel: None

Other: None

| Date: | Protocol No: 1304-78 | Status: Interim |
|---|---|---|

Title of Project: Radioactive assessment of cardiac function in patients with acromegaly

| Starting Date: July 1978 | Estimated Completion Date: 18 months |
|---|---|

Principal Investigator: Robert C. Smallridge, LTC, MC

| Associate Investigators:<br>Marcus Schaaf, M.D.<br>Mitchell Mutter<br>Wm. Oetgen<br>Douglas van Nostrand | Facility: WRAMC<br>Dept/Svc Kyle Metabolic Unit |
|---|---|

Key Words: Acromegaly/cardiac function

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: |
|---|---|---|

| FY-80 MEDCASE Cost: | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective: To determine whether acromegalic patients may have impaired left ventricular (LV) function

Technical Approach: LV function studies using multiplegated acquisition (MU GA) scans, this procedure involves the injection of $^{99m}$Technetium labeled human serum albumin

Progress during FY-80: An additional 15 patients have been studied (total of 38). The data are being compiled now for a manuscript.

Number of subjects to be studied before completion of study: Open ended - all new acromegal

Serious/unexpected side effects in subjects participating in project: None

Conclusions: Many acromegalic patients have abnormal LV function, despite successful therapy for their acromegaly.

Publications or Abstracts, FY-80: Clinical Research 28: 198A, 1980

Work Unit No: 1304-78

Funds Utilized, FY-80:

Funding Requirements, FY-81:

Personnel: $500.00 (McAnally, Kuffler, Bruton, Martin)

Equipment: None

Supplies: $400.00

Travel: $500.00

Other: Reprints $300.00

| Date: | Protocol No: 1305-78 | Status: Interim XXXX |
|---|---|---|

Title of Project: Breast carcinoma and thyroid hormone receptors

| Starting Date: July 1978 | Estimated Completion Date: 1 yr |
|---|---|

Principal Investigator: Robert C. Smallridge, LTC, MC

| Associate Investigators: Keith Latham, Ph. D. | Facility: |
|---|---|
| | Dept/Svc |

Key Words: Thyroid hormone/ breast cancer

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: |
|---|---|---|

| FY-80 MEDCASE Cost: | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective: To determine whether thyroid hormone receptors can be identified in human breast carcinoma.

Technical Approach: Breast tumor is frozen in liquid nitrogen and processed in a receptor binding assay (Lathan et al. J Biol Chem 251: 7388, 1971).

Progress during FY-80: The data from our preliminary study was published in an abstract. Completion of the study is dependent upon some parallel work being done in a tumor bearing strain of mice.

Number of subjects to be studied before completion of study: None planned

Serious/unexpected side effects in subjects participating in project: None

Conclusions: Thyroid hormone receptors exists in human breast cancer. Their significance is unknown.

Publications or Abstracts, FY-80: Clinical Research 28: 421A, 1980.

Work Unit No: 1305-78

Funds Utilized, FY-80:

Funding Requirements, FY-81:

Personnel: $500.00 (McAnally, Kuffler, Bruton, Martin)

Equipment: None

Supplies: $400.00

Travel: $500.00

Other: Reprints $300.00

| Date: | Protocol No: 1307-78 | Status: Interim X<br>Final |
|---|---|---|

Title of Project:
The Effect of Fasting upon TSH Response to TRH

| Starting Date: 79 | Estimated Completion Date: 80 |
|---|---|

Principal Investigator: Kenneth D. Burman, LTC, MC

| Associate Investigators:<br>L. Wartofsky, COL<br>RC Smallridge, LTC | Facility: WRAMC<br>Dept/Svc Dept of Med/Endocrine |
|---|---|

Key Words: TRH/fast

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: |
|---|---|---|

| FY-80 MEDCASE Cost: | Periodic Review Results:<br>(to be filled in by DCI) |
|---|---|

*Study Objective:
To determine if TSH responsiveness is decreased in fasting.

*Technical Approach:
Infuse TRH in fed and fasting patients and measure TSH

*Progress during FY-80:
15 patients studied and each had decreased TSH response.

Number of subjects to be studied before completion of study: 0

Serious/unexpected side effects in subjects participating in project:
None

Conclusions: Fasting decrease TSH responsiveness

Publications or Abstracts, FY-80:

BURMAN, KD et al Metabolism 29:46, 1980

Work unit no.: 1307-78

Funds utilized, FY-80:

Funding requirements, FY-81:

Personnel: Burman

Equipment:

Supplies: $2,500

Travel:

Other:

| Date: 22 Oct 80 | Protocol No: 1300-79 | Status: Interim xFinal |
|---|---|---|

Title of Project: Measurement of Iodothyronines by HPLC

| Starting Date: 18 Aug 80 | Estimated Completion Date: 15 Aug 83 |
|---|---|

Principal Investigator: Kenneth D. Burman, LTC, MC

| Associate Investigators: Rudolph Bongiovanni, CPT, MC | Facility: WRAMC |
|---|---|
| | Dept/Svc Kyle Metabolic Unit |

Key Words: HPLC

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: |
|---|---|---|
| FY-80 MEDCASE Cost: | Periodic Review Results: (to be filled in by DCI) | |

Study Objective: To measure iodothyronines by HPLC

Technical Approach: Use of HCLP

Progress during FY-80: We can accurately measure $T_4$ and $T_3$

Number of subjects to be studied before completion of study:

Serious/unexpected side effects in subjects participating in project:

Conclusions:

Publications or Abstracts, FY-80: none

Work unit no.: 1300-79

Funds utilized, FY-80: $2,888.80

Funding requirements, FY-81:

| | |
|---|---|
| Personnel: | Bongiovanni |
| Equipment: | |
| Supplies: | $4,000 |
| Travel: | 500 |
| Other: | 500 |

| Date: 23 Oct 80 | Protocol No: 1301-79 | Status: Interim |
|---|---|---|

Title of Project: Effect of various metabolic conditions and $T_3$ receptors on circulatory cells.

| Starting Date: 1 Jan 79 | Estimated Completion Date: 1 Jan 82 |
|---|---|

Principal Investigator: Kenneth D. Burman, LTC, MC

| Associate Investigators:<br>Yin-Ying Djuh, GS-11<br>Leonard Wartofsky, COL, MC | Facility: WRAMC<br>Dept/Svc Kyle Metabolic Unit |
|---|---|

Key Words: $T_3$/ receptors

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: |
|---|---|---|

| FY-80 MEDCASE Cost: | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective: To quantitate $T_3$ receptors and ocetylase activity in white cells.

Technical Approach: $^{125}I - T_3$ binding to white cells.

Progress during FY-80: Have determined that $T_3$ and $T_4$ receptors increas in fasting.

Number of subjects to be studied before completion of study: about 12

Serious/unexpected side effects in subjects participating in project:

Conclusions:

Publications or Abstracts, FY-80: none

Work unit no.: 1301-79

Funds utilized, FY-80:

Funding requirements, FY-81:

| | |
|---|---|
| Personnel: | Wartofsky, Burman, Djuh, GS-11 |
| Equipment: | |
| Supplies: | $4,500 |
| Travel: | 500 |
| Other: | |

| Date: 15 October 1980 | Protocol No: 1302-79 | Status: Interim X<br>Final |
|---|---|---|

Title of Project: Prevention of Gonadal Damage in Men Treated with Combination Chemotherapy for Hodgkin's Disease and Histiocytic Lymphomas.

| Starting Date: 7 Nov 1978 | Estimated Completion Date: 30 Sept 83 |
|---|---|

Principal Investigator: Robert A. Vigersky, M.D. MAJ MC

| Associate Investigators: | Facility: WRAMC |
|---|---|
| Ramona Chapman, M.D. MAJ MC<br>Jeffrey Berenberg, M.D. LTC MC | Dept/Svc Kyle Metabolic Unit |

Key Words: Azospermia; Hodgkin's disease; chemotherapy.

| Accumulative MEDCASE Cost: 0 | Accumulative Contract Cost: $4000 | Accumulative Supply Cost: 0 |
|---|---|---|

| FY-80 MEDCASE Cost: 0 | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective: Azospermia is an inevitable outcome in men treated with chemotherapy for Hodgkin's disease and other malignancies. Decreased libido, potency and diminished ability of the Leydig cell to secrete testosterone are also side effects of the therapy. The aim of this study is to protect these men from the ravages of the chemotherapy by the pre-treatment suppression of their pituitary-gonadal axis with high dose testosterone.

Technical Approach: Seminiferous tubular and Leydig cell function are assessed before and after treatment with chemotherapy. Before beginning the therapy, the patients are randomized into a control or treatment arm of the protocol. The latter receive testosterone enanthate 200 mg i.m. weekly beginning 1-2 week before chemotherapy is begun and continuing throughout the duration of their therapy. Follow-up evaluation is performed at 6 month intervals.

Progress during FY-80: 6 men have been entered into the protocol; Leydig cell and seminiferous tubule function have been assessed in these plus an additional 4 men who refused participation.

Number of subjects to be studied before completion of study: 30

Serious/unexpected side effects in subjects participating in project: None

Conclusions: Men with Hodgkin's disease have, in some cases, pretreatment abnormalities of seminiferous tubular and Leydig cell function.

Publications or Abstracts, FY-80: None

| DATE: 30 September 1980 | PROTOCOL NO: 1302-79 | STATUS: Interim / Final |
|---|---|---|

TITLE OF PROJECT: WRAMC # 7810

Prevention of Gonadal Damage in Men Treated with Combination Chemotherapy/Radiotherapy for Hodgkin's Disease and Non-Hodgkin's Lymphoma

| STARTING DATE: Nov 1979 | ESTIMATED COMPLETION DATE: 1983 |
|---|---|
| PRINCIPAL INVESTIGATOR: R. Chapman | |
| ASSOCIATE INVESTIGATORS: R. Vlersky, J. Berenberg | FACILITY: Walter Reed Army Medical Center<br>SERVICE: Hematology-Oncology Department of Medicine |

KEY WORDS:

| ACCUMULATIVE MEDCASE COST: | ACCUMULATIVE CONTRACT COST: | ACCUMULATIVE SUPPLY COST: |
|---|---|---|
| FY-80 MEDCASE COST: | PERIODIC REVIEW RESULTS: | |

STUDY OBJECTIVE:

To ascertain if testosterone administered during chemotherapy will protect germ cells from total extinction in men with lymphoma

TECHNICAL APPROACH: Men are tested for fertility status and then randomized to receive either no hormone therapy or testosterone enanthate weekly until one month after the end of chemotherapy. Post-therapy, men are re-evaluated for fertility status up to 2 years later.

PROGRESS DURING FY-80: 15 men have been evaluated with Hodgkin's Disease and four of these will not be followed after therapy because they declined further follow up (two because of vasectomy (). Four patients have been placed on the non-Hodgkin's lymphoma arm of the study.

NUMBER OF SUBJECTS TO BE STUDIED BEFORE COMPLETION OF STUDY:

SERIOUS/UNEXPECTED SIDE EFFECTS IN SUBJECTS PARTICIPATING IN PROJECT:

CONCLUSIONS: It is too early to reach conclusions. See attached paper of abstract submitted to ASCO for 1981.

PUBLICATIONS/ABSTRACTS; FY-80: Abstract submitted for publication.

Work Unit No.: 1302-79

Funds Utilized, FY-80: $4000

Funding Requirements, FY-81: 10,800

Personnel: None

Equipment: None

Supplies: $1000

Travel: $500

Other: (2572) $9000.; (2400) $300

| Date: | Protocol No: 1304-79 | Status: Interim Xxxx |
|---|---|---|

Title of Project: Thyroid hormones in cerebrospinal fluid

| Starting Date: 24 April 1979 | Estimated Completion Date: September 1981 |
|---|---|

Principal Investigator: Prentice Thompson, LTC, MC

| Associate Investigators:<br>Kenneth D. Burman, LTC, MC<br>Leonard Wartofsky, COL, MC<br>Michael W. Potter, MAJ, MC<br>Frances D. Wright, GS-11 | Facility: WRAMC<br><br>Dept/Svc Kyle Metabolic Unit |
|---|---|

Key Words:

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: |
|---|---|---|
| FY-80 MEDCASE Cost: | Periodic Review Results: (to be filled in by DCI) | |

Study Objective: To determine what role the CSF plays in the transport of thyroid hormones into the central nervous system (CNS), and what role thyroid hormones in the CNS might play in various disease states.

Technical Approach: CSF of patients undergoing lumbar puncture for various disease states (such as herniated disc disease, pituitary tumor, or meningitis) will be studied. One to two ml of CSF beyond that required for routine CSF analysis will be obtained for measurement of T4, T3, rT3 and other metabolites.

Progress during FY-80: Preliminary results obtained and manuscript submitted for publication 26 Sept 80.

Number of subjects to be studied before completion of study:

Serious/unexpected side effects in subjects participating in project:

Conclusions:

Publications or Abstracts, FY-80: Submitted for publication 26 Sept 1980

Work Unit No: 1304-79

Funds Utilized, FY-80:

Funding Requirements, FY-81:

Personnel: $500.00

Equipment: None

Supplies: $2,500.00

Travel: $500.00

Other: Contracts $4,000.00

| Date: | Protocol No: 1305-79 | Status: ~~Revision~~ Final |
|---|---|---|

Title of Project: Thyroid function in liver disease

| Starting Date: | Estimated Completion Date: Terminated |
|---|---|

Principal Investigator: Prentice Thompson, LTC, MC

| Associate Investigators:<br>Kenneth D. Burman, LTC, MC<br>Lawrence F. Johnson, COL, MC<br>Robert C. Smallridge, LTC, MC<br>Leonard Wartofsky, COL, MC | Facility: WRAMC<br>Dept/Svc Kyle Metabolic Unit |
|---|---|

Key Words:

| Accumulative MEDCASE Cost: None | Accumulative Contract Cost: None | Accumulative Supply Cost: None |
|---|---|---|

| FY-80 MEDCASE Cost: None | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective: To determine whether alterations in binding proteins for serum hormones are responsible for the abnormalities in thyroid hormone metabolism observed in patients with various liver diseases.

Technical Approach: Ten patients each will be studied with (a) acute hepatitis (acute and during convalescence); (b) chronic active hepatitis (before and after steroid therapy); and (c) primary biliary cirrhosis. Measurements will be obtained in a baseline state and at intervals during follow-up for measurement of T4, T2, T3, rT3, [illegible], TBI, CBG, TeBG, and FTI. Remaining serum will be stored frozen at -40° pending evaluation of the latter results for consideration of potential [illegible] of cortisol, estrogen, and testosterone as well. TRH stimulation tests will be performed with measurement of TSH and prolactin responses.

Progress during FY-80: Due to the unavailability of the type of patients required, we have terminated this project - parts of which will be incorporated into protocol #

Number of subjects to be studied before completion of study: None

Serious/unexpected side effects in subjects participating in project: None

Conclusions:

Publications or Abstracts, FY-80: none

Work Unit No: 1305-79

Funds Utilized, FY-80: None

Funding Requirements, FY-81: None, Project terminated

Personnel:

Equipment:

Supplies:

Travel:

Other:

| Date: 10 Dec 80 | Protocol No: 1307-79 | Status: Interim x<br>Final |
|---|---|---|

Title of Project: Effect of High Dose Dexamethasone on Subhuman Primates

| Starting Date: | Estimated Completion Date: Dec 1981 |
|---|---|

Principal Investigator: Ira Nehlman, LTC MC

| Associate Investigators:<br>R. Smallridge, H. Williams, P. Perone, M. Schaaf, V. Armbrustmacher | Facility: WRAMC, WRAIR and USUHS |
|---|---|
| | Dept/Svc Medicine/Endocrine |

Key Words:

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: |
|---|---|---|
| FY-80 MEDCASE Cost: | Periodic Review Results:<br>(to be filled in by DCI) | |

Study Objective: Study effects of dexamethasone on thyroid hormone metabolism, pancreatic pathophysiology, hematologic changes, and muscle pathology in subhuman primates (rhesus monkeys)

Technical Approach: 6 control and 6 treated animals observed over 180 days and then sacrificed after observing multiple blood studies and tissue.

Progress during FY-80: Muscles (Type I and II) fibers compared for confirmation of what appears to be a difference in atrophy greater in dex treated. The changes are greatest appearing in animals most Cushingoid.

Number of subjects to be studied before completion of study: tissue collected but mult.

Serious/unexpected side effects in subjects participating in project: specimens to be evaluated of muscle and pancreas.

Conclusions: thyroid studies - basal and TRH responsive TSH not changed from controls definite Type II atrophy $2^{o}$ to dexamethasone - studies pending pancreatic changes observed present studies pending

Publications or Abstracts, FY-80: abstracts

Protocol 1307-79

I. Muscle studies are ongoing - particularly the time consuming aspects of evaluating ratio type II/I atrophy which has been definitely observed. Studies by self and Griffiths and Arbuthnotmacher.

II. Hematologic changes significant and currently eval. by computer analysis - i.e. factor 8 antigen.

III. Pancreatic changes noted, awaiting slides and collaboration with Dr. Powers now at Letterman.

| Date: 10 Sep 80 | Protocol No: 1308-79 | Status: Interim X / Final |
|---|---|---|

Title of Project: Stress-induced amenorrhea in military cadets

| Starting Date: 1979 | Estimated Completion Date: 1983 |
|---|---|

Principal Investigator: Allan R Glass MD MAJ MC

| Associate Investigators: | Facility: WRAMC / West Point |
|---|---|
| Leigh Wheeler MD LTC MC<br>Thomas Klein MD LTC MC | Dept/Svc Kyle Metabolic Unit/ Ob Gyn |

Key Words:
stress, amenorrhea

| Accumulative MEDCASE Cost: 0 | Accumulative Contract Cost: 0 | Accumulative Supply Cost: 0 |
|---|---|---|

| FY-80 MEDCASE Cost: 0 | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective:

To determine the etiology of amenorrhea in female military cadets

Technical Approach:
Measurements of pituitary and gonadal hormones in amenorrheic military cadets and comparison with non-amenorrheic control group.

Progress during FY-80: Work was not begun on this protocol due to inability to obtain permission of hospital commander at West Point to begin study.

Number of subjects to be studied before completion of study: 30

Serious/unexpected side effects in subjects participating in project:

Conclusions:

Deferred

Publications or Abstracts, FY-80:

Work unit no.: 1308-79

Funds utilized, FY-80:

Funding requirements, FY-81:

Personnel:

Equipment:

Supplies: $1,000

Travel:

Other: $3,000

| Date: 15 Oct 1980 | Protocol No: 1309-79 | Status: Interim x<br>Final |
|---|---|---|

Title of Project: The Anti-Estrogenic Effects of $\Delta^1$-Testolactone(Teslac)

| Starting Date: 24 April 79 | Estimated Completion Date: 30 Sept 81 |
|---|---|

Principal Investigator: Robert A. Vigersky, M.D. MAJ MC

| Associate Investigators: | Facility: WRAMC |
|---|---|
| | Dept/Svc Kyle Metabolic Unit |

Key Words: Teslac: Receptors, estrogen

| Accumulative MEDCASE Cost: 0 | Accumulative Contract Cost: 0 | Accumulative Supply Cost: $331.75 |
|---|---|---|

| FY-80 MEDCASE Cost: 0 | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective: To determine whether the improvement in sperm counts in men being treated with Teslac is related to the ability of the drug to act as an anti-estrogen.

Technical Approach: Treatment of castrate immature rats with estrogen alone or estrogen plus Teslac and measurement of the weight of the uterus as an end point. In vitro assessment of the ability of Teslac to interact with the cytosolic estrogen receptor.

Progress during FY-80: Repeated measurement of Teslac's interaction with the estrogen receptor indicates that it has no anti-estrogen activity. Preliminary results suggest that it has no anti-estrogenic activity in vivo, either.

Number of subjects to be studied before completion of study: N/A

Serious/unexpected side effects in subjects participating in project: N/a

Conclusions: Teslac appears to have no anti-estrogen receptor activity in vitro. Further experiments for longer duration in vivo will be performed to confirm this result.

Publications or Abstracts, FY-80: None

Work Unit No.: 1309-79

Funds Utilized, FY-80: $331.75

Funding Requirements, FY-81: $1200

Personnel: None

Equipment: None

Supplies: $1200

Travel: None

Other: None

| Date: 15 October 80 | Protocol No: 1310-79 | Status: Interim X / Final |
|---|---|---|

Title of Project: Pilot Investigation for the Treatment of Hirsutism with Oral Cimetidine.

| Starting Date: 22 May 1979 | Estimated Completion Date: 30 Sept 1982 |
|---|---|

Principal Investigator: Robert A. Vigersky, M.D.

| Associate Investigators: | Facility: WRAMC |
|---|---|
| | Dept/Svc Kyle Metabolic Unit |

Key Words: Cimetidine; hirsutism; androgen receptors.

| Accumulative MEDCASE Cost: $1000 | Accumulative Contract Cost: $7500 | Accumulative Supply Cost: $13,207.00 |
|---|---|---|

| FY-80 MEDCASE Cost: $1000 | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective: To treat women with idiopathic hirsutism with a non-toxic meidication that acts by blocking the ability of androgen (testosterone and dihydrotestosterone) with the androgen receptor in the hair follicle.

Technical Approach: Measurement of the adrenal contribution of androgen by an ACTH stimulation test; the ovarian contribution by frequent sampling over 8 hours for pituitary and gonadal hormones; and the pituitary contribution by measurement of the response of prolactin to TRH. These studies done before and after 3-6 months on oral cimetidine treatment. Measurement of the rate of hair growth is accomplished by shaving a measured area on the face, chest or thigh and weighing the hair that has accumulated over the previous 1-2 weeks. This is performed before and while on the cimetidine.

Progress during FY-80:

10 patients have been entered in to the study. The results of the first five indicate that there is a 50% or more decrease in the rate of hair growth and a marked subjective improvement without any significant changes in serum steroid levels.

Number of subjects to be studied before completion of study: 20

Serious/unexpected side effects in subjects participating in project: None

Conclusions: Cimetidine appears to be a safe and effective treatment for idiopathic hirsutism and its action is most likely mediated by it anti-androgenic properties.

Publications or Abstracts, FY-80: Smith, C., Mehlman, I., and Vigersky, R. "Treatment of Hirsutism with Cimetidine," presented 62nd ann. meeting Endo. Soc., June, 1980.

Work Unit No.: 1310-79

Funds Utilized, FY-80: $21,707

Funding Requirements, FY-81: $7000

Personnel: None

Equipment: None

Supplies: $1200

Travel: $500

Other: (2572) $5000 ; (2400) $300

| Date: | Protocol No: 1311-79 | Status: Interim |
|---|---|---|

Title of Project: Assessment of thyroid function and the intrathyroidal biosynthesis of thyroid hormone during the acute and recovery phases of subacute thyroiditis

| Starting Date: November 1979 | Estimated Completion Date: 2 years |
|---|---|

Principal Investigator: Robert C. Smallridge, LTC, MC

| Associate Investigators: | Facility: WRAMC |
|---|---|
| Leonard Wartofsky, COL, MC<br>Kenneth D. Burman, LTC, MC<br>Richard C. Dimond, LTC, MC<br>Nancy E. Whorton, GS-11 | Dept/Svc Kyle Metabolic Unit |

Key Words: Subacute thyroiditis/biosynthetic defect

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: |
|---|---|---|
| FY-80 MEDCASE Cost: | Periodic Review Results: (to be filled in by DCI) | |

Study Objective: To determine (a) the frequency with which an intrathyroidal biosynthetic defect exists during the course of subacute thyroiditis, (b) where in the resolution of the disease it is impaired, and (c) whether patients with this defect may have a difficult ultimate outcome.

Technical Approach: Blood tests obtained monthly until disease resolves (generally 6-8 months). Fluorescent thyroid scans monthly. At end of study, a 3 hour RAIU with perchlorate discharge, and a TRH test.

Progress during FY-80: Seven (7) patients have enrolled in protocol, and 6 have been followed for at least 6 months.

Number of subjects to be studied before completion of study: 8-10 more

Serious/unexpected side effects in subjects participating in project: None

Conclusions: Deferred

Publications or Abstracts, FY-80: None

Work Unit No: 1311-79

Funds Utilized, FY-80:

Funding Requirements, FY-81:

Personnel: $500.00 (McAnally, Kuffler, Martin, Bruton)

Equipment: None

Supplies: $2,500.00

Travel: $500.00

Other: Reprints $300.00
Contracts 750.00

| Date: 1 October 1980 | Protocol No: 1312-79 | Status: Interim XXX<br>Final |
|---|---|---|

Title of Project: The Effect of Long-Term High Fiber Diets in the Outpatient Management of Insulin Dependent Diabetes Mellitus.

| Starting Date: 26 Sept 1979 | Estimated Completion Date: Uncertain |
|---|---|

Principal Investigator: Timothy M. Boehm, LTC MC

| Associate Investigators: | Facility: WRAMC |
|---|---|
| | Dept/Svc Diabetes Service |

Key Words: Fiber, Insulin Dependent Diabetes Mellitus.

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: |
|---|---|---|

| FY-80 MEDCASE Cost: | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective: To assess the efficacy of high fiber diets in the outpatient treatment of insulin dependent diabetes; to measure various hormonal parameters before and during high fiber diet therapy.

Technical Approach: If high fiber diets are successful on a long-term outpatient basis in the amelioration of postprandial hyperglycemia, these deserve routine use in the treatment of insulin dependent diabetes.

Progress during FY-80: Protocol has not been initiated due to departure of a coinvestigator.

Number of subjects to be studied before completion of study: Uncertain

Serious/unexpected side effects in subjects participating in project: None

Conclusions: None

Publications or Abstracts, FY-80: None

| Date: | Protocol No: 1313-79 | Status: Interim |
|---|---|---|

Title of Project: A radioimmunoassay for human TSH

| Starting Date: November 1979 | Estimated Completion Date: One year |
|---|---|

Principal Investigator: Robert C. Smallridge, LTC, MC

| Associate Investigators:<br>Richard C. Dimond, LTC, MC<br>Nancy E. Whorton, GS-11 | Facility: WRAMC<br>Dept/Svc Kyle Metabolic Unit |
|---|---|

Key Words: TSH/RIA

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: |
|---|---|---|

| FY-80 MEDCASE Cost: | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective:

Technical Approach: venipuncture

Progress during FY-80: Sera have been obtained from 5 volunteers

Number of subjects to be studied before completion of study: five

Serious/unexpected side effects in subjects participating in project: None

Conclusions: None expected

Publications or Abstracts, FY-80: None

Work Unit No: 1313-79

Funds Utilized, FY-80:

Funding Requirements, FY-81:

Personnel: $500.00 (Linda McAnally GS-05, Jesse Martin GS-05, Joseph Bruton GS-14)

Equipment: None

Supplies: $1,000.00

Travel: $500.00

Other: Contractual Svc $500.00

| Date: | Protocol No: 1314-79 | Status: Interim X<br>Final |
|---|---|---|

Title of Project:
Examination of the Effect of Ipodate (Oragrafin) on Thyroid Function

| Starting Date: 8-80 | Estimated Completion Date: 8-82 |
|---|---|

Principal Investigator: Kenneth D. Burman, LTC, MC

| Associate Investigators: | Facility: WRAMC |
|---|---|
| | Dept/Svc: Dept of Med/Endcorine |

Key Words: Ipodate/thyroid function

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: |
|---|---|---|

| FY-80 MEDCASE Cost: | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective: To measure the effect of Ipodate on thyroid hormone levels.

Technical Approach:

TRH tests with or without ipodate and/or T3 in fed and fasting patients.

Progress during FY-80:

Just started

Number of subjects to be studied before completion of study: 25

Serious/unexpected side effects in subjects participating in project:
None

Conclusions: None yet

Publications or Abstracts, FY-80: none

Work unit no.: 1314-79

Funds utilized, FY-80:

Funding requirements, FY-81:

Personnel: Djuh

Equipment:

Supplies: $4,000

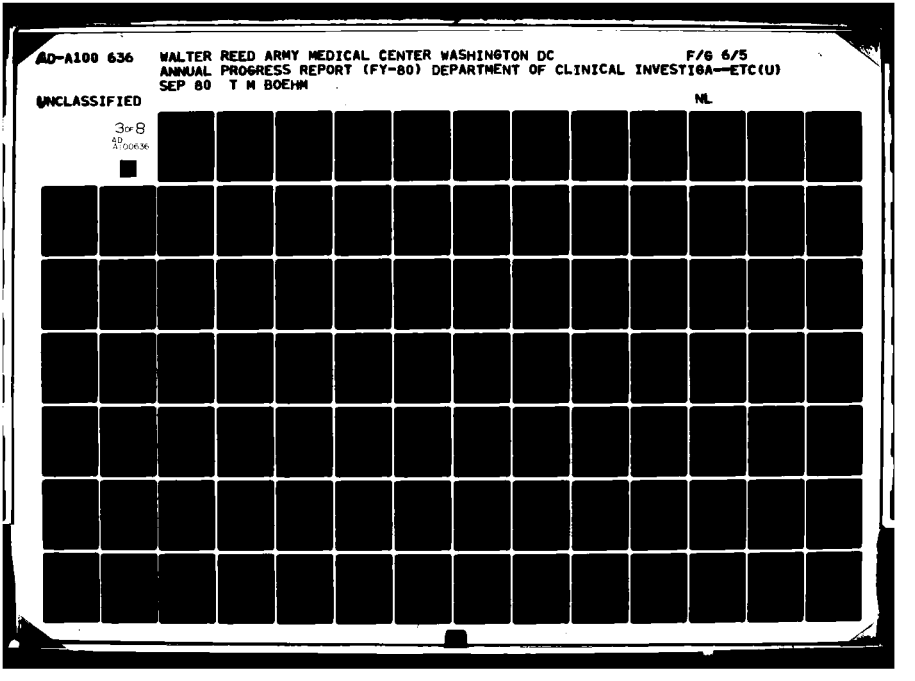
Travel:

Other:

AD-A100 636 WALTER REED ARMY MEDICAL CENTER WASHINGTON DC F/G 6/5
ANNUAL PROGRESS REPORT (FY-80) DEPARTMENT OF CLINICAL INVESTIGA--ETC(U)
SEP 80 T M BOEHM

UNCLASSIFIED NL

3 of 8
AD
A100636



| Date: 15 October 19[illegible] | Protocol No: 1315-80 | Status: Interim x<br>Final |
|---|---|---|

Title of Project: Sex-Steroid Receptor in the Mouse Thymus

| Starting Date: 23 Oct 79 | Estimated Completion Date: 30 Sept 82 |
|---|---|

Principal Investigator: Robert A. Vigersky, M.D. MAJ MC

| Associate Investigators:<br>Elizabeth Raveche, Ph.D. (National Institutes of Health) | Facility: WRAMC |
|---|---|
| | Dept/Svc Kyle Metabolic Unit |

Key Words: Thymus; receptors, estr[illegible]; receptors; androgen

| Accumulative MEDCASE Cost: $2850 | Accumulative Contract Cost: 0 | Accumulative Supply Cost: $10,131.25 |
|---|---|---|
| FY-80 MEDCASE Cost: 0 | Periodic Review Results:<br>(to be filled in by DCI) | |

Study Objective: To determine whether or not there are receptors for sex-steroids in the thymus and to characterize them physico-chemically if they are present. The basis for the marked sex difference in a variety of immunologic disease, e.g. Systemic Lupus Erythematosis, may be due to the difference immunologic response of the thymus based on sex steroids. These differences are most likely mediated through receptor mechanisms.

Technical Approach: Measurement, in thymic cytosol, of the affinity, binding capacity, sex steroid specificity, size, charge, sedimentation coefficient, column elution profile on agarose 0.5 M, and kinetics of association and dissociation of the receptors for androgen and estrogen. Determination of the differences between these parameters in various ages and the differences between the two sexes. Investigation of the relationship of these receptor characteristics to the more "classic" receptors in prostate and uterus of the mouse, rat and human.

Progress during FY-80: The androgen receptor has been detected in the mouse thymus and partially characterized. It appears similar to that in prostate, does not change with age, and is present in both male and female animals to a similar degree. The male NZB mouse cannot translocate the cytosol receptor to the nucleus as do normals.

Number of subjects to be studied before completion of study: N/A

Serious/unexpected side effects in subjects participating in project: N/A

Conclusions: Androgen receptors are present in the mouse thymus. Preliminary studies indicate the presence of estrogen receptors as well. The immune androgen resistance manifested by NZB mice may be explained by the failure to translocate the cytosol receptor to the nucleus.

Publications or Abstracts, FY-80: Raveche, E., Vigersky, [illegible]., Tjio, J.H. and Steinberg, A "Murine Thymic Androgen Receptors." presented Amer. Rheumat. Assoc., May 1980

Work Unit No.: 1315-80

Funds Utilized, FY-80: $10,131 + $2850 = $12,981

Funding Requirements, FY-81: $8800

Personnel: Mary K. Rice, GS-11

Equipment: None

Supplies: $7500

Travel: $500

Other: ( 2572) $500; (2400) $300

| Date: | Protocol No: 1316-80 | Status: Interim X<br>Final |
|---|---|---|

Title of Project:
T3 receptors in human white cells and liver

| Starting Date: 2-12-80 | Estimated Completion Date: 8-83 |
|---|---|

Principal Investigator: Kenneth Burman, LTC, MC

| Associate Investigators: | Facility: WRAMC |
|---|---|
| | Dept/Svc Dept of Med/Endocrine |

Key Words: T3 receptors/Liver/white cells

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: |
|---|---|---|

| FY-80 MEDCASE Cost: | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective:

To determine if T3 receptors exist in human liver and whether they correlate with receptors in white cells.

Technical Approach:

Solubilize human liver T3 receptors

Progress during FY-80:

No definite studies performed yet because we are having technical problem with the small amount of liver tissue obtained.

Number of subjects to be studied before completion of study: 20

Serious/unexpected side effects in subjects participating in project:
none

Conclusions: none yet

Publications or Abstracts, FY-80: none yet

Work unit no.: 1316-80

Funds utilized, FY-80:

Funding requirements, FY-81:

Personnel: Djuh and Burman

Equipment:

Supplies: $5,000

Travel:

Other:

| Date: 15 Oct 80 | Protocol No: 1317-80 | Status: Interim X<br>Final |
|---|---|---|

Title of Project: Investigation of the Etiology of Idiopathic Hirsutism. Determination of Possible Partial Enzyme Defects in Adrenal Metabolism

| Starting Date: 27 Nov 1979 | Estimated Completion Date: 30 Sept 82 |
|---|---|

Principal Investigator: Robert A. Vigersky, M.D. MAJ MC

| Associate Investigators: | Facility: WRAMC |
|---|---|
| | Dept/Svc Kyle Metabolic Unit |

Key Words: Hirsutism; adrenal; androgens.

| Accumulative MEDCASE Cost: 0 | Accumulative Contract Cost: $5800 | Accumulative Supply Cost: 0 |
|---|---|---|

| FY-80 MEDCASE Cost: 0 | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective: To determine whether women, usually classified as having idiopathic hirsutism, have a subtle defect in adrenal steroidogenesis. This would permit the rational treatment of these patients with dexamethasone suppression of the pituitary-adrenal axis.

Technical Approach: Infusion of ACTH over 24 hours with pre-and post-ACTH measurement of adrenal steroids in the urine and plasma.

Progress during FY-80: The first five patients so analyzed have not been found to have a subtle defect in adrenal steroidogenesis.

Number of subjects to be studied before completion of study: 10

Serious/unexpected side effects in subjects participating in project: none

Conclusions: Though the sampling is small, there appear to be few of the patients usually classified as idiopathic hirsutism who actually have a mild form of congenial adrenal hyperplasia.

Publications or Abstracts, FY-80: Smith, C., Mehlman, I., and Vigersky, R., "Treatment of Hirsutism with Cimetidine," presented 62nd ann. meeting Endo. Soc., June 1980.

Work Unit No.: 1317-79

Funds Utilized, FY-80: $5800

Funding Requirements, FY-81: $7800

Personnel: None

Equipment: None

Supplies: $2000

Travel: $500

Other: (2572) $5000 ; (2400) $300

| Date: 23 Oct 80 | Protocol No: 1318-80 | Status: Interim |
|---|---|---|

Title of Project: Development of Fluorescent Immunoassay Procedures.

| Starting Date: April 1981 | Estimated Completion Date: April 1983 |
|---|---|

Principal Investigator: Joseph Bruton, Ph. D.

| Associate Investigators: | Facility: WRAMC |
|---|---|
| H. Linton Wray, LTC, MC<br>Kenneth D. Burman, LTC, MC<br>Robert A. Vigersky, MAJ, MC | Dept/Svc Kyle Metabolic Unit |

Key Words: Immunoassay; Radioimmunoassay vs Fluorescence Immunoassay

| Accumulative MEDCASE Cost: $15,000.00 | Accumulative Contract Cost: $1,000.00 | Accumulative Supply Cost: $5,000.00 |
|---|---|---|

| FY-80 MEDCASE Cost: None | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective: To develope immunoassay procedures using a fluorescent molecule as a substitute for radioactive labeled molecules.

Technical Approach: In order to measure a FIA molecule a suitable instrument capable of detecting the fluorescein-tagged antigen and antibodies immobilized on polyacrylamide beads are required. Such an instrument has been developed and purchase is required to initiate this study. In addition, techniques for producing fluorescein-tagged antigen are now available.

Progress during FY-80:

Number of subjects to be studied before completion of study: Normal subjects (N=25) for each procedure

Serious/unexpected side effects in subjects participating in project: None

Conclusions: We anticipate developing FIA assays for thyronines, cortisol, testosterone, dihydrotestosterone, cAMP, vitamin D, estradiol and prednisone.

Publications or Abstracts, FY-80: None

Work unit no.: 1318-80

Funds utilized, FY-80: None

Funding requirements, FY-81:

Personnel: H. Linton Wray, LTC MC Kenneth D. Burman, LTC Robert A. Vigersky, MAJ MC Susan Barnes GS-09 Phyllis Kessler, GS-06 Vincent Butler, GS-09

Equipment: Bio-Rad Fluoromatic System. A microprocessor based photo-counting fluorometer, consisting of a measurement and a data processing module and an automatic sampling module. (Cost, $15,000)

Supplies: $5,000

Travel: 500

Other: (contracts for service): $1,000 for RIA assays.

| Date: | Protocol No: 1319-80 | Status: Interim / Final |
|---|---|---|

Title of Project:

Does thyroid Hormone Administration Decerase the Size of Cystic Masses in the Thyroid Gland.

| Starting Date: 3-80 | Estimated Completion Date: 8-83 |
|---|---|

Principal Investigator: Kenneth D. Burman, LTC, MC

| Associate Investigators: | Facility: WRAMC |
|---|---|
| | Dept/Svc Dept of Med/Endocrine |

Key Words: thyroid gland cysts

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: |
|---|---|---|

| FY-80 MEDCASE Cost: | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective:

To determine if thyroid hormone suppression alter cyst size.

Technical Approach:

All patients with thyroid gland cysts are studied and are divided into either a no treatment group or a group to be treated with thyroid hormone.

Progress during FY-80:

4 patients entered into protocol

Number of subjects to be studied before completion of study: 30

Serious/unexpected side effects in subjects participating in project: None

Conclusions: None yet

Publications or Abstracts, FY-80: None yet

Work unit no.: 1319-80

Funds utilized, FY-80:

Funding requirements, FY-81:

Personnel: Burman

Equipment:

Supplies: $1,000

Travel:

Other:

| Date: 23 Oct 80 | Protocol No: 1320-80 | Status: Interim |
|---|---|---|

Title of Project: Cyclic AMP response to Glucagon

| Starting Date: 1 Jan 81 | Estimated Completion Date: 1 Jan 84 |
|---|---|

Principal Investigator: Kenneth D. Burman, LTC, MC

| Associate Investigators: H. Linton Wray, LTC, MC | Facility: WRAMC |
|---|---|
| | Dept/Svc Kyle Metabolic Unit |

Key Words: cyclic AMP/Glucagon

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: |
|---|---|---|

| FY-80 MEDCASE Cost: | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective: To determine if fasting alters the cyclic AMP response to glucagon.

Technical Approach: Glucagon infusion and measurement of cyclic AMP by RIA.

Progress during FY-80:

Number of subjects to be studied before completion of study:

Serious/unexpected side effects in subjects participating in project:

Conclusions:

Publications or Abstracts, FY-80: none yet

Work unit no.: 1320-80

Funds utilized, FY-80:

Funding requirements, FY-81:

| | |
|---|---|
| Personnel: | |
| Equipment: | $3,000 |
| Supplies: | 400 |
| Travel: | |
| Other: | |

| Date: | Protocol No: 1321-80 | Status: Interim X<br>Final |
|---|---|---|

Title of Project:
TSH receptors in physiologic States

| Starting Date: 5-80 | Estimated Completion Date: 8-80 |
|---|---|

Principal Investigator: Kenneth D. Burman, LTC, MC

| Associate Investigators: | Facility: WRAMC |
|---|---|
| | Dept/Svc Dept of Med/Endocrine |

Key Words: TSH receptors

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: |
|---|---|---|

| FY-80 MEDCASE Cost: | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective:
To determine if TSh receptors exist in various tissues and to see if they are homeostatically regulated.

Technical Approach:
Develop TSH receptor assay in various tissue

Progress during FY-80:
None yet

Number of subjects to be studied before completion of study: 25

Serious/unexpected side effects in subjects participating in project:
None

Conclusions:
None

Publications or Abstracts, FY-80: None yet

Work unit no.: 1321-80

Funds utilized, FY-80:

Funding requirements, FY-81:

| | |
|---|---|
| Personnel: | Lukes, Burman |
| Equipment: | |
| Supplies: | $5,000 |
| Travel: | 500 |
| Other: | |

| Date: 22 Oct 80 | Protocol No: 1322-80 | Status: Interim / xFinal |
|---|---|---|

Title of Project: The relationship between calcitonin, nitroprusside and $T_3$

| Starting Date: 1 Aug 80 | Estimated Completion Date: 1 Aug 83 |
|---|---|

Principal Investigator: Kenneth D. Burman, LTC, MC

| Associate Investigators: Phyllis Kesler, GS-07 | Facility: WRAMC |
|---|---|
| | Dept/Svc Kyle Metabolic Unit |

Key Words: Calcitonin, nitroprusside, $T_3$

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: |
|---|---|---|

| FY-80 MEDCASE Cost: | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective: To see if calcitonin inhibits $T_4$ to $T_3$ conversion

Technical Approach: In vitro liver homogenates

Progress during FY-80: None

Number of subjects to be studied before completion of study: None

Serious/unexpected side effects in subjects participating in project: None

Conclusions: None

Publications or Abstracts, FY-80:

Work unit no.: 1322--80

Funds utilized, FY-80:

Funding requirements, FY-81:

| | |
|---|---|
| Personnel: | Burman, Lukes |
| Equipment: | |
| Supplies: | $2,000 |
| Travel: | |
| Other: | |

| Date: 22 Oct 80 | Protocol No: 1323-80 | Status: Interim / Final |
|---|---|---|

Title of Project: TSH receptors in human tissue

| Starting Date: Aug 1980 | Estimated Completion Date: Aug 1983 |
|---|---|

Principal Investigator: Kenneth D. Burman, LTC, MC

| Associate Investigators: Yvonne Lukes, GS-11 | Facility: WRAMC |
|---|---|
| | Dept/Svc Kyle Metabolic Unit |

Key Words: TSH

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: |
|---|---|---|

| FY-80 MEDCASE Cost: | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective: To determine TSH receptors in thyroid tissue

Technical Approach: Binding of $^{125}$I TSH.

Progress during FY-80: 3 glands studied

Number of subjects to be studied before completion of study: 3

Serious/unexpected side effects in subjects participating in project: 0

Conclusions: None yet

Publications or Abstracts, FY-80:

Work unit no.: 1323-80

Funds utilized, FY-80:

Funding requirements, FY-81:

Personnel: Lukes, Burman

Equipment:

Supplies: $4,000

Travel:

Other:

# DISPOSITION FORM

For use of this form, see AR 340-15, the proponent agency is TAGCEN.

| REFERENCE OR OFFICE SYMBOL | SUBJECT |
|---|---|
| HSWP-MGI | Clinical Investigation Protocol #1410 |

TO : Chief, Clinical Investigation Service

FROM : Fred H. Goldner
Assistant Chief,
Gastroenterology Svc

DATE : 22 Sept 80

CMT 1

Due to problems in patient acquisition, work on protocol #1410 is not proceeding at a satisfactory pace. It is, therefore, recommended that protocol #1410 be terminated.

Fred H. Goldner, LTC, MC
Assistant Chief
Gastroenterology Service

DA FORM 1 FEB 47 2496 REPLACES DD FORM 96, WHICH IS OBSOLETE.

| Date: 4 September 1980 | Protocol No: 1415 | Status: Interim X / Final |
|---|---|---|

Title of Project: Esophageal Clearing: Quantitated by Radioisotope Scan.

| Starting Date: 13 April 1977 | Estimated Completion Date: 3 years |
|---|---|

Principal Investigator: COL Lawrence F. Johnson, M.D.

| Associate Investigators: | Facility: |
|---|---|
| Roy K.H. Wong, M.D.<br>Donald O. Castell, M.D.<br>Andre Dubois, M.D.<br>Douglas Van Nostrand, M.D. | Walter Reed Army Medical Center<br>Dept/Svc: Gastroenterology Service |

Key Words: Esophageal Clearing

| Accumulative MEDCASE Cost: N/A | Accumulative Contract Cost: N/A | Accumulative Supply Cost: N/A |
|---|---|---|

| FY-80 MEDCASE Cost: | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective: To quantitate the peristaltic ability of the esophagus to clear a measured bolus of fluid into the stomach.

Technical Approach: Diluted .1 normal HCl will be taged with technetium, and an esophageal clearing profile will be quantitated after each swallow using manometric equipment.

Progress during FY-80: Five patients have been studied in FY-80. These patients have been evaluated with a new monitoring probe designed by one of the authors (LFJ) that incorporated a metalic pH sensor at the distal tip and two transitorized pressure monitors within a catheter system that is tapered down for patient comfort in the

Number of subjects to be studied before completion of study: 15

Serious/unexpected side effects in subjects participating in project:

NONE

Conclusions: Data obtained from this protocol represents an advancement in the understanding of gastroesophageal reflux disease and supports our earlier published observations. Publications or abstracts, FY-80; none.

Publications or Abstracts, FY-80:

Continued.

Progress during FY-80:

oropharynx. This system obviates using a profusing system. To date our observation shows that bethanechol improves esophageal acid clearance as well as makes a more competent esophageal gastric junction to prevent reflux.

Two changes have been made in the plan section of this protocol. A commercially available transistorized esophageal catheter with pH and pressure functions is now used. This probe is tapered so that there is greater patient comfort in the oropharynx during the conduct of the protocol. This probe obviated the use of the banded catheter assembly referred to in the original protocol. Secondly, the alpaline bolus referred to in the plan section of the protocol has been omitted because it compromised accurate measurement of the acid bolus. Data obtained from this protocol represents an advancement in the understanding of gastroesophageal reflux disease and therefore this protocol needs to be renewed and completed.

| Date: 4 September 1980 | Protocol No: 1416 | Status: Interim x<br>Final |
|---|---|---|

Title of Project: Esophageal Emptying in Achalasia:
Quantitated by Radioisotope Method

| Starting Date: 28 March 1977 | Estimated Completion Date: 3 years |
|---|---|

Principal Investigator: Col Lawrence F. Johnson, M.D.

| Associate Investigators:<br>Roy K.H. Wong, M.D.<br>Douglas Van Nostrand, M.D. | Facility: WRAMC<br>Dept/Svc: Gastroenterology Sv |
|---|---|

Key Words: Colon Esophageal Emptying

| Accumulative MEDCASE Cost: N/A | Accumulative Contract Cost: N/A | Accumulative Supply Cost: N/A |
|---|---|---|

| FY-80 MEDCASE Cost: N/A | Periodic Review Results:<br>(to be filled in by DCI) |
|---|---|

Study Objective: To quantitate esophageal emptying in achalasia before and after pneanumatic dilation.

Technical Approach: To measure esophageal emptying of a solid meal in patients with achalasia. Technetium was tagged to coneflakes and milk and from this an esophageal emptying profile was established.

Progress during FY-80: The technique proved satisfactory and distinguished asymptomatic controlled volunteers from asymptomatic patients with achalasia. This data was published and sited as an outstanding article; 1) Gross, R.; Johnson, L.F.; Kaminsky, (see second page)

Number of subjects to be studied before completion of study: --

Serious/unexpected side effects in subjects participating in project:
NONE

Conclusions:
See enclosed reprint.

Publications or Abstracts, FY-80:

Continued: Progress during FY-80:

R.J.; Esophageal Emptying in Achalasia: Quantitated by Radioisotope Technique. Digestive Diseases and Sciences; Vol 24, P. 945, Dec. 1979.

2) Year Book of Nuclear Medicine, March 1981

There have been no modification in the plan section of the original protocol.

The undersigned investigator at a later date may modify protocol #1416 and use the esophageal emptying technique to determine which numatic dilation technique offers the best result in terms of esophageal emptying for achalasia. This will be done in collaboration with other investigators at the Medical College of Virginia, as well as possibly the National Naval Medical Center. If this endeaver is undertakened, the protocol will be modified and resubmitted through the appropriate committees.

| Date: 1 October 1980 | Protocol No: 1417 | Status: (Interim) Final |
|---|---|---|

Title of Project:

PLASMA LIGANDIN IN LIVER DISEASE

| Starting Date: 1977 | Estimated Completion Date: 1983 |
|---|---|

Principal Investigator: LTC Robert W. Sjogren, Jr., M.D.

| Associate Investigators: | Facility: |
|---|---|
| COL Lawrence F. Johnson, M.D. | WRAMC |
| | Dept/Svc Medicine/Gastroenterology |

Key Words:

| Accumulative MEDCASE Cost: None | Accumulative Contract Cost: None | Accumulative Supply Cost: None |
|---|---|---|

| FY-80 MEDCASE Cost: None | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective: This study proposes to assess plasma ligandin levels as a potentially more sensitive indicator of hepatic information than currently available serum tests

Technical Approach: Patients having liver biopsies at Walter Reed Army Medical Center have blood drawn for clinical assessment. An aliquot is removed and frozen for plasma ligandin content. Plasma ligandin content is determined by a sensitive and quantitative radioimmunoassay technique at Albert Einstein College of Medicine in New York. Correlations between pathologic diagnosis, enzyme values and ligandin levels will be made by standard statistical methods.

Progress during FY-80: Results of analysis of 200 serum samples at Albert Einstein College of Medicine in New York have been indeterminate owing to small numbers of patients in each diagnostic category. Over the past one year, an

(see continuation sheet)

Number of subjects to be studied before completion of study: Est 500

Serious/unexpected side effects in subjects participating in project:
None

Conclusions:
Not Available

Publications or Abstracts, FY-80: None

Work Unit Number: 1417

Funds Utilized, FY-80: None

Funding Requirements, FY-81:

Personnel: None

Equipment: None

Supplies:

(1) Freezer Vials
Nunc vial, polypropylene with screw cap, 2.0 ml capacity
Landsel Cat #9015-7081
Three cases of 500 at $80/case. Cost $240
Landsel Cyrogenics
5303 46th Ave.
Hyattsville, MD 20781

(2) Bags for Freezer Vials
Lab Tec Multi-Purpose Bag System, Series S
Fisher Cat #1-812-50A
One case of four packs of 250 bags each. Cost $101
Fisher Scientific Co
7722 Fenton St
Silver Spring, MD

Travel: None

Other: None

Progress during FY-80: additional 66 serum samples have been obtained. It is anticipated that continuation of the protocol allowing greater numbers of patients in each diagnostic category will yield results

Continued: Progress during FY-80:

split fram apparatus that now affords televising the manometry record as well as simultaneous photoscopic study all on the same TV screen. In onon-protocol clinically indicated use of this equipment we found the motility record did not project well. For this reason we are in the process of integrating a scilliscope.screen onto our existing motility equipment. This modification should afford the desired quality. Because the quality of the TV image of manometric events was not what we desired. We have not entered any patients to date into this protocol. This last technical challenge should be completed shortly, and the protocol initiated.

ADDENDUM: Cricopharyngeal Bar: A Video Manometric Study

An scilloscope will be attached to our existing manometric equipment to better illustrate the tracing so that the TV camera can better clarify the manometric record. Otherwise, there have been no changes in the existing protocol.

| Date: 4 September 1980 | Protocol No: 1419 | Status: Interim: X<br>Final |
|---|---|---|

Title of Project: Cricopharyngeal Bar: A Video Manometric Study

| Starting Date: 23 August 1977 | Estimated Completion Date: 3 years |
|---|---|

Principal Investigator: COL Lawrence F. Johnson, M.D.

| Associate Investigators:<br>Walter J. Kikendall, M.D.<br>David J. Curtis, M.D. | Facility: WRAMC<br>Dept/Svc: Gastroenterology Service |
|---|---|

Key Words: Cricopharyngeal Bar

| Accumulative MEDCASE Cost: N/A | Accumulative Contract Cost: N/A | Accumulative Supply Cost: N/A |
|---|---|---|

| FY-80 MEDCASE Cost: | Periodic Review Results:<br>(to be filled in by DCI) |
|---|---|

Study Objective: To study the functional significance of a cricopharyngeal bar shown on barium swallow.

Technical Approach: This is a synchronized manometric video tape fluoroscopic study of swallowing disorders of the hypopharynx, cricopharyngeal and upper esophagus.

Progress during FY-80: The slow motion vediotape machine procured by the Department of Radiology and its interface with Walter Reed Army Medical Center's TV Department has functioned well. This equipment has been complimented by WRAMC-TV, acquiring a

(See second page)

Number of subjects to be studied before completion of study:

Serious/unexpected side effects in subjects participating in project:

Conclusions:

Publications or Abstracts, FY-80:

Work Unit: 1420

Title: Adenyl Cyclase and Guanyl Cyclase Activity in the Cat Esophagus.

Investigators:

| | |
|---|---|
| Principal Investigator: | LTC Roy K.H. Wong, M.D. |
| Co-Investigators: | COL Lawrence F. Johnson, M.D.<br>CAPT Donald O. Castell, M.D., USN<br>Cpt. Ben H. Boedeker, DVM., WRAIR |

Objective: To correlate adenyl cyclase and guanyl cyclase activity with lower esophageal sphincter contraction and relaxation.

Technical Approach: Same as initial protocol.

Progress and Results:

1. Over the past year we have received 3 opposums and have been able to study the anatomical location of the lower esophageal sphincter (LES).

2. We have found that the opposum esophagi is an excellent model for extracting the LES without inflicting physical trauma to the LES prior to its removal.

3. The above requirements are essential to obtaining acceptable biochemical results when studying enzymes such as adenyl cyclase.

4. Also, we have recently obtained professional and technical support from Thomas Hichey, PhD in biochemistry in performing these assays.

5. Recently, we have acquired a room in building T-2 which will serve as a laboratory for these studies.

6. Here with the above facts we feel that at the present time continued support is essential and justified.

Funds Utilized FY 80: Approximately $3,000.

Funding Requested FY 81: $3,500

Type of Report: Interim.

| Date: 24 September 1980 | Protocol No: 1422 | Status: Interim XXXXXX |
|---|---|---|

Title of Project: The Sequential Staging of the Liver in Hodgkin's Disease with Laparoscopy and Laparotomy

| Starting Date: | Estimated Completion Date: |
|---|---|

Principal Investigator: LTC DAVID A. PEURA

| Associate Investigators:<br>CPT MORAKINYO OYEWOLE<br>COL LAWRENCE F. JOHNSON<br>COL RICHARD M. HIRATA<br>MAJ MARTIN WELTZ | Facility:<br>Dept/Svc |
|---|---|

Key Words:

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: |
|---|---|---|

| FY-80 MEDCASE Cost: | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective: To evaluate the role of laparoscopy in clinical Stage III or IV Hodgkin's disease patients.

Technical Approach: See Plan Section of original protocol.

Progress during FY-80:

Number of subjects to be studied before completion of study:

Serious/unexpected side effects in subjects participating in project:

Conclusions:

Publications or Abstracts, FY-80:

WORK UNIT NO.: 1422

TITLE: The Sequential Staging of the Liver in Hodgkin's Disease with Laparoscopy and Laparotomy

INVESTIGATORS:


Principal Investigator: LTC David A Peura, M.D.
Assistant Chief, Gastroenterology Service

Co-Investigators: CPT Morakinyo A. Oyewole, M.D.
Fellow, Gastroenterology Service

COL Lawrence F. Johnson, M.D.
Chief, Gastroenterology Service

COL Richard M. Hirata, M.D.
Chief, General Surgery Service

MAJ [illegible], M.D.
Fellow, Hematology-Oncology Service


OBJECTIVE: To evaluate the role of laparoscopy in clinical Stage III or IV Hodgkin's disease patients.

TECHNICAL APPROACH: See Plan Section of orginal protocol.

PROGRESS AND RESULTS: No patients have been assessed under this protocol since the last report. Most patients with Stage III and IV Hodgkin's disease are undergoing laparotomy following their laparoscopic exam. So, their data cannot be included for study purposes. It is felt that continuation of the protocol is to be encouraged since an occasional patient will undergo laparotomy following his laparoscopic procedure.

CONCLUSIONS: No further conclusions can be reached at this time. Further evaluation of the data available seems to indicate that laparoscopy is of benefit in patients with Stage III and Stage IV Hodgkin's disease as a staging tool.

FUNDS UTILIZED FY 80: None

FUNDS REQUESTED FY 81: None

PUBLICATIONS: None

TYPE OF REPORT: Interim

| Date: 10 OCT 1980 | Protocol No: 1423 | Status: Interim / Final |
|---|---|---|

Title of Project: A Study of Trifluoroisoprophyl Cyanoacrylate Polymer (MBR 4197) in the Control of Bleeding Peptic Ulcers of the Stomach and Duodenum

| Starting Date: | Estimated Completion Date: |
|---|---|

Principal Investigator: LTC DAVID A. PEURA, M.D.

| Associate Investigators:<br>LTC EDWARD L. BURKHALTER, M.D.<br>COL LAWRENCE F. JOHNSON, M.D. | Facility:<br>Dept/Svc |
|---|---|

Key Words:

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: |
|---|---|---|

| FY-80 MEDCASE Cost: | Periodic Review Results: (to be filled in by DCI) |
|---|---|

*Study Objective: To determine if the polymer is effective in preventing further bleeding from gastric and duodenal ulcers.

*Technical Approach: See original protocol.

*Progress during FY-80: See reverse side.

Number of subjects to be studied before completion of study:

Serious/unexpected side effects in subjects participating in project:

Conclusions:

Publications or Abstracts, FY-80:

*Progress during FY-80:

A total of 52 patients were studied under the national multi-center protocol. This study failed to show efficacy of MBR-4197 in stopping bleeding from gastric and duodenal ulcers or preventing rebleeding. Use of investigational drug as well as maintenance of drug inventory and the return of unused investigational supplies was monitored by 3M Corporation, in compliance with FDA regulations. There appeared to be no evidence of adverse affects related to the use of MBR-4197. All unused supplies were returned to 3M Corporation. This is a final termination report of the above protocol.

WORK UNIT NO.: 1423

TITLE OF PROJECT: A Study of Trifluoroisopropyl Cyanoacrylate Polymer (MBR 4197) in the Control of Bleeding Peptic Ulcers of the Stomach and Duodenum.

INVESTIGATORS:


Principal Investigator: LTC David A. Peura, M.D.
Assistant Chief, Gastroenterology Service

Co-Investigators: LTC Edward L. Burkhalter, M.D.
Staff, General Medicine Clinic

COL Lawrence F. Johnson, M.D.
Chief, Gastroenterology Service


OBJECTIVES: To determine if the polymer is effective in preventing further bleeding from gastric and duodenal ulcers.

TECHNICAL APPROACH: See original protocol.

PROGRESS: This was a multi-center protocol and a total of 52 patients were assessed in the various centers. Analysis of data seem to indicate that MBR-4197 was no more effective than conventional therapy in stopping bleeding or preventing rebleeding episodes from gastric and duodenal ulcers. Because of the seeming lack of efficacy the study was terminated.

CONCLUSIONS: It was concluded from the compiled data of 52 patients that MBR-4197 was no more effective than placebo in controlling bleeding from gastric and duodenal ulcers or preventing rebleeding.

FUNDS UTILIZED FY 80: None

FUNDS REQUESTED FY 81: None

PUBLICATIONS: A manuscript is currently in preparation for submission to a national journal. In addition, the data from the study was presented by the principal investigator at the William Beaumont Gastroenterology Symposium in El Paso, Texas, in March of 1980.

TYPE OF REPORT: Final

WORK UNIT: 1424

TITLE: A Double Blind Study of Long Term Maintenance Cimetidine Therapy on Gastro-Esophageal Reflux Disease

INVESTIGATORS:

Principle: Roy K.H. Wong, M.D.

Co-investigator: Lawrence F. Johnson, M.D.

STARTING DATE: 1 February 1978

ESTIMATED DATE OF COMPLETION: Study has been terminated by SKF

PROGRESS AND RESULTS: Our participation in the protocol was very sucessful. We entered a total of 15 patients into the study and were ranked #2 in the USA when comparing ourselves with 8 other medical centers. The results of the study are negative and there is debate as to whether the data will be published.

DATE: 15 DECEMBER 1980

PROTOCOL NO.: 1425

STATUS: Interim

TITLE OF PROJECT: "Pulmonary Aspiration from Gastroesophageal Reflux Defined by Pulmonary Scintiscan and Overnight Intraesophageal pH Monitoring"

STARTING DATE: 15 FEBRUARY 1978

ESTIMATED COMPLETION DATE: Indeterminate

PRINCIPAL INVESTIGATOR: MAJ Steven S Shay, M.D.

ASSOCIATE INVESTIGATORS: COL Lawrence [illegible]ohnson, M.D.
LTC Mark R. Stein, M.D.
MAJ [illegible]ski, M.D.

FACILITY: Walter Reed Army Medical Center

DEPT/SVC: Gastroenterology Service, Nuclear Medicine Service, Allergy/Immunology Service

KEY WORDS: Pulmonary Aspiration
Gastroesophageal Reflux

ACCUMULATIVE MEDCASE COST: None

ACCUMULATIVE CONTRACT COST: None

ACCUMULATIVE SUPPLY COST: None

FY-80 MEDICASE COST: None

STUDY OBJECTIVE: To document the occurrence of pulmonary aspiration from nocturnal gastresophageal reflux.

TECHNICAL APPROACH: Patients with symptoms of nocturnal aspiration from gastroesophageal reflux are admitted on day 1 and a manometry/pH probe is placed in the esophagus to determine LES pressure and the presence of acid pH in the stomach (pH < 4). Later in the day (1600) the patients are started on prolonged intraesophageal pH monitoring according to the technique of Johnson et al[1]; and this is continued overnight while they sleep. Reflux is defined as % time pH was < 4 for the duration of the night (minutes). Abnormal nocturnal reflux was defined as a value that exceeded 1.2% since this degree of acid exposure exceeded mean and 2SD for a previsouly defined asymptomatic control population[1]. Prior to bedtime the patients are given 5mci of radioactive technetium (TC 99) sufur colloid. On the morning of day 2, the patients were questioned by two investigators (LFJ, SSS) regarding reflux and pulmonary aspiration symptoms during the previous night. They then had a [illegible] and abdominal scintiscan for location of the technetium.

PROGRESS DURING FY-80: The study population consisted of 13 patients; seven with abnormal gastroesophageal reflux on the overnight pH record, and six with a normal pH record. Lower esophageal sphincter (LES) pressure confirmed the difference in LES competence between the two groups because those with abnormal reflux on the pH record had significantly less LES pressure (3mm Hg) than those with a normal record (10mm Hg, $p < .05$). Despite both the pH record and LES pressure showing a significant difference in reflux between the two groups, two experienced clinicians (LFJ, SSS) after interviewing the patients diagnosed reflux and pulmonary aspiration in 70% (5/7) of the abnormal reflux group; and a comparable 85% (5/6) in those with a normal overnight pH record. All 13 patients had normal pulmonary scintiscan without any evidence of aspiration of gastric contents. Despite the known delay in gastric emptying during sleep, only two patients had technetium present in the stomach the following morning.

CONCLUSIONS: We conclude the incidence of pulmonary aspiration due to reflux remains uknown. The presence of pulmonary aspiration from gastresophageal reflux is not accurately reflected by history. While the technetium scintiscan can document pulmonary aspiration from reflux[2], it is an insensitive test that is probably limited by the short duration the isotope remains in the stomach; and secondly, the infrequency with which patients actually aspirate from gastroesophageal reflux.

PUBLICATIONS OR ABSTRACTS, FY-80:

1. Johnson LF, DeMeester TR: Twenty-four hour pH monitoring of the distal esophagus, a quantitative measure of gastroesophageal reflux. Am J Gastro 62: 325-332, 1974.

2. Chernow B, Johnson LF, Janowitz WR, and Castell DO. Pulmonary aspiration as a consequence of gastroesophageal reflux - A diagnostic approach. Dig Dis & Sci 24:839-844, 1979.

3. This data was presented at the Annual Fitzsimons Respiratory Disease Conference held in October 1979. MAJ Steven S. Shay, M.D. (presenter).

TYPE OF REPORT: Interim
COMMENT: The undersigned senior investigator (LFJ) will modify this protocol (CIS# 1425); and resubmit a modified plan to further pursue our investigation of pulmonary aspiration from gastroesophageal reflux.

| Date: 12/1/80 | Protocol No: 1426 | Status: Interim X<br>Final |
|---|---|---|

Title of Project:

The Effect of Indomethecin on Experimentally Induced Acid Stricture on the Rabbit Esophagus

Starting Date: 23 May 78 | Estimated Completion Date: June 1983

Principal Investigator: Roy K.H. Wong, M.D.

| Associate Investigators: | Facility: WRAMC<br>WRAIR |
|---|---|
| L.F. Johnson, M.D. | Dept/Svc Gastroenterology |

Key Words:
Indomethacin, esophageal stricture, acid, endoscopy, barium swallow

| Accumulative MEDCASE Cost: 9,000.00 | Accumulative Contract Cost: | Accumulative Supply Cost: 3,000.00 |
|---|---|---|

| FY-80 MEDCASE Cost: | Periodic Review Results: (to be filled in by DCI) |
|---|---|

*Study Objective:
This study examines the effect of indomethacin on stricture formation in the esophagus of rabbits. Present data suggests that indomethacin prevents experimental esophagitis but we are focusing on the question of whether stricture formation can be prevented.

*Technical Approach:
Within the last year we have developed a model of strictu of stricture formation in the rabbit. This model is similar to the previous protocol except that we are able to keep the animals alive after severe esophagitis is induced. We are able to do this because of post HCl infusion gastric gavages. We have also be able to document the degree of stricture formation by means of endoscoop and barium swallow.

*Progress during FY-80:
Similar to that noted above.

Number of subjects to be studied before completion of study:

Serious/unexpected side effects in subjects participating in project:

Conclusions:
FY 80 has allowed us to investigate another animal model which is more suited for this study. Previous attempts at completing this study failed because of the high mortality rate.

Publications or Abstracts, FY-80:

Work Unit No.: 1426

Funds Utilized, FY-60:

Funding Requirements, FY-61:

Personnel: (name and grade)

Equipment: (describe in detail including cost)

Supplies: (consumable, animal purchase)

Travel: (mission oriented, training and presentation)

Other: (equipment rentals, contracts for service, animal care and reprints)

Personnel: Corrine Maydonavitch-GS9

Equipment: Hewlett-Packard 8 channel recorder, Arndorfer infusio pump, Olympus pediatric endoscope and light source, X-ray machine Harvard infusion pump, histologic fixing material and cassettes.

Cost: Light source and endoscopes-9,000.00 (Borrowed)

Travel: 1,200.00

Other: Light source-borrowed from dental research. Endoscope-borrowed from pulmonary medicine.

WORK UNIT: 1427

TITLE: Nitroglycerine, Terbutaline, and Aminophylline in the Treatment of Achalasia

INVESTIGATORS: Roy K.H. Wong, M.D. Lawrence F. Johnson, M.D., Donald O. Castell, M.D.

STARTING DATE: 22 August 1979

ESTIMATED DATE OF COMPLETION: August 1981

OBJECTIVE: To determine whether NTG, Aminophylline or Terbutaline change lower esophageal sphincter pressures and if these agents increase esophageal emptying.

KEY WORDS: Achalasia, Nitroglycerine, Aminophylline, Terbutaline, Esophageal Emptying, Lower Esophageal Sphincter

TECHNICAL APPROACH: No changes from previous protocol

PROGRESS AND RESULTS: Attached is a copy of an abstract submitted in Gastroenterology May 1980. Since the writing of the abstract 4 more patients have entered the study without significant differences in the results. We would like to study another 6 patients to make a total of 15 patients.

PROTOCOL NO.: #1428

STATUS: Interim

TITLE OF PROJECT: Maximal Rate of Urea Synthesis in Rats as a Determinant of Functional Hepatic Mass

STARTING DATE: 25 September 1979

PRINCIPAL INVESTIGATOR: COL Lawrence F. Johnson, M.D.

ASSOCIATE INVESTIGATOR: MAJ Michael A. Dunn, M.D.

STUDY OBJECTIVE: To establish an accurate, reproducible whole animal model of maximal urea synthesis. To study the relationship of the maximal rate of urea synthesis to graded reduction in hepatic mass.

TECHNICAL APPROACH: See original protocol.

PROGRESS DURING FY-80: Urea synthesis was quantitated in rats, and reproducibility of this assay was established. Urea synthesis was found to reflect functional hepatic mass in normal rats and in rats with graded hepatectomy. $CCl_4$-induced cirrhosis and portacaval shunts. The potential importance of variation on the composition substrate load was illustrated by marked increases in urea synthesis produced by arginine loading.

CONCLUSIONS: Data from this protocol suggests that urea synthesis may be an important new quantitavie liver function test. Optimal measurement conditions and methods are the subjects of further study.

PUBLICATIONS FY-80:

1. Brewer TG, Dunn MA, Berry WR and Harmon JW: Urea synthesis reflects hepatic mass in rats. Gastroenterology 79 (1980); Abstract, in press.

WORK UNIT NO.: 1429

TITLE: Colchicine Therapy of Alcoholic Liver Disease: A Multi-Center Randomized Controlled Study

INVESTIGATOR:

Principal Investigator: LTC David A. Peura, M.D.
Assistant Chief, Gastroenterology Service
(assuming role in the absence of MAJ Michael A. Dunn)

Co-Investigators:

STARTING DATE:

ESTIMATED DATE OF COMPLETION: 5 years

OBJECTIVE: To see if colchicine can prevent progression to cirrhosis and alcoholic liver disease, or affect already established alcoholic cirrhosis.

TECHNICAL APPROACH: Please refer to original protocol.

PROGRESS AND RESULTS: The protocol was just approved and the investigational drug was just supplied by Eli Lilly Corporation. There have been no patients assessed in the protocol to date.

CONCLUSIONS: Because the protocol has not yet been started, no conclusions can be drawn.

FUNDS UTILIZED FY 80: None

FUNDS REQUIRED FY 80: None

ADDENDUM: The protocol has not officially begun. Therefore, no drug has been dispensed. Drug has recently been received in the form of coded vials containing placebo and colchicine. The supplies were supplied by Eli Lilly Company. These drugs will be maintained and dispensed in the Outpatient Pharmacy, and when the protocol begins the patients will be observed for any possible adverse reactions related to the medication.

| Date: 10 OCT 80 | Protocol No: 1429 | Status: Interim Final |
|---|---|---|

Title of Project: Colchicine Therapy of Alcoholic Liver Disease: A Multi-Center Randomized Controlled Study

| Starting Date: | Estimated Completion Date: 5 Years |
|---|---|

Principal Investigator: LTC DAVID A. PEURA, M.D.

| Associate Investigators: | Facility: |
|---|---|
| | Dept/Svc |

Key Words:

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: |
|---|---|---|
| FY-80 MEDCASE Cost: | Periodic Review Results: (to be filled in by DCI) | |

Study Objective: To see if colchicine can prevent progression to cirrhosis and alcoholic liver disease, or affect already established alcoholic cirrhosis.

Technical Approach: Refer to original protocol.

Progress during FY-80: The protocol was just approved and the investigational drug was just supplied by Eli Lilly & Company. There have been no patients assessed in the protocol to date.

Number of subjects to be studied before completion of study:

Serious/unexpected side effects in subjects participating in project:

Conclusions: Because the protocol has not yet been started, no conclusions can be drawn.

Publications or Abstracts, FY-80:

| Date: 9 August 1980 | Protocol No: 1439 | Status: Interim / Final |
|---|---|---|

Title of Project: Investigation of the potential of various pills to induce local esophagitis

| Starting Date: June 1980 | Estimated Completion Date: Pilot project completed |
|---|---|

Principal Investigator: James Walter Kikendall, MAJ, MC

| Associate Investigators:<br>Ben Boedeker, CPT, VC<br>Lawrence F. Johnson, COL, MC | Facility: WRAIR<br>Dept/Svc: MED/GI - WRAMC<br>VET. MED. - WRAIR |
|---|---|

Key Words: Esophagitis

| Accumulative MEDCASE Cost: NA | Accumulative Cost: NA | Cumulative Supply Cost: NA |
|---|---|---|

| FY-80 MEDCASE Cost: None | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective:
To determine whether the opossum is a suitable model for investigation of the potential of pills to induce local esophagitis.

Technical Approach: As outlined in approved protocol.

Progress during FY-80: Using ascorbic acid and calcium lactate tablets, it was demonstrated that ascorbic acid produced much more esophageal injury than calcium lactate in the tested animals. We have now received approval for another more extensive protocol to enlarge upon this work.

Number of subjects to be studied before completion of study:

Serious/unexpected side effects in subjects participating in project:

Conclusions: The experimental procedures are valid for study of this problem.

Work Unit No.: 1516

Title of Project: CALGB #7291, Role of Post Operative Radiotherapy, and Combinations of Dactinomycin, Vincristine, Cyclophosphamide and Adriamycin in Childhood Rhabdomyosarcoma.

Principal Investigator: C, Hematology-Oncology Service

Associate Investigator:

After numerous requests for an annual progress report on this project, as of 20 Feb 81, there has not been a response. This progress report request was for the period 30 September 1979 to 1 October 1980. We can no longer delay compilation of the reports submitted by those investigators who complied with the regulations, so a supplementary annual progress report will be compiled when this investigator submits his report.

24

| DATE: 30 September 1980 | PROTOCOL NO: CALGB 7411 | STATUS: Interim X<br>Final |
|---|---|---|

TITLE OF PROJECT:

Combination in Childhood Acute Lymphocytic Leukemia

| STARTING DATE: 14 April 1974 | ESTIMATED COMPLETION DATE: Closed 12 Nov 76 |
|---|---|
| PRINCIPAL INVESTIGATOR: Dr. Johannes Blom | |
| ASSOCIATE INVESTIGATORS:<br>Dr. Frederick Ruyman | FACILITY: Walter Reed Army Medical Center<br>SERVICE: Hematology-Oncology Department of Medicine |

KEY WORDS: Cranial Radiation, Lymphocytic Leukemia

| ACCUMULATIVE MEDCASE COST: None | ACCUMULATIVE CONTRACT COST: None | ACCUMULATIVE SUPPLY COST: None |
|---|---|---|
| FY-80 MEDCASE COST: None | PERIODIC REVIEW RESULTS: | |

STUDY OBJECTIVE:

1. To assess the role of early cranial radiation.
2. Determine role of more vigorous induction for high risk patients.
3. Compare three reinforced maintenance regimens.

TECHNICAL APPROACH: Standard risk patient were randomized to Reg I - Vincristine, Prednisone, Methotrexate intrathecally & Lasparaginase Reg II - same plus cranial radiation. High risk patients were randomized to Reg II. Reg III - this arm is identical to Reg II but includes Dauremycin.

PROGRESS DURING FY-80: Note protocol closed in 1976. Six patients remain on study. Follow-up is pending on two. Four remain in complete remission.

NUMBER OF SUBJECTS TO BE STUDIED BEFORE COMPLETION OF STUDY: None

SERIOUS/UNEXPECTED SIDE EFFECTS IN SUBJECTS PARTICIPATING IN PROJECT: None

CONCLUSIONS: See 1978-79 Annual Report

Dr. Ruyman has stated, he will provide subsequent follow-up for annual report.

PUBLICATIONS/ABSTRACTS, FY-80:

Work Unit No.: 1528

Title of Project: CALGB #7391, Clinical Trial of Radiotherapy and Chemotherapy in Managing Non-Metastatic Ewing's Sarcoma.

Principal Investigator: C, Hematology-Oncology Svc

Associate Investigator:

After numerous requests for an annual progress report on this project, as of 20 Feb 81, there has not been a response. This progress report request was for the period 30 September 1979 to 1 October 1980. We can no longer delay compilation of the reports submitted by those investigators who complied with the regulations, so a supplementary annual progress report will be compiled when this investigator submits his report.

WORK UNIT NO. 1532

DATE: 30 September 1980 | PROTOCOL No.: CALGB 7451 | STATUS: Interim X / Final

TITLE OF PROJECT: Combination Radiotherapy and Chemotherapy of Stage III Hodgkin's Disease (Phase III)

STARTING DATE: 6/20/74 CALGB | ESTIMATED COMPLETION DATE:

PRINCIPAL INVESTIGATOR: Jeffrey L. Berenberg, MD, LTC, MC

ASSOCIATE INVESTIGATORS:

FACILITY: Walter Reed Army Medical Center

SERVICE: Hematology-Oncology Department of Medicine

KEY WORDS: Combination Chemotherapy Hodgkin's Disease

| ACCUMULATIVE MEDCASE COST: | ACCUMULATIVE CONTRACT COST: | ACCUMULATIVE SUPPLY COST: |
|---|---|---|
| None | None | None |

FY-80 MEDCASE COST: None

PERIODIC REVIEW RESULTS:

STUDY OBJECTIVE: Primary: To determine if combination induction chemotherapy followed by single agent maintenance therapy produces different frequencies of [illegible] irradiation (RTB) Total nodal RT follows chemotherapy and s/ Chemotherapy followed by total nodal RT.

TECHNICAL APPROACH: Chemotherapy: Vincristine 1.4 mg/M$^2$/week IV x2
Procarbazine 100 mg/M$^2$ day 1-14, DC
BCNU 80 mg/M$^2$ iv day 1
Prednisone 40 mg/M$^2$ po day 1-14
RT: Total nodal irradiation ten out of 15 achieved a C.R.

PROGRESS DURING FY-80: Three of these patients relapsed. Overall - 4 are lost to followup. WRAMC is no longer entering patients on this study. No new patients during 1980.

NUMBER OF SUBJECTS TO BE STUDIED BEFORE COMPLETION OF STUDY: CALGB 80

SERIOUS/UNEXPECTED SIDE EFFECTS IN SUBJECTS PARTICIPATING IN PROJECT: None at WRAMC, See below

CONCLUSIONS:
Chemotherapy followed by radiotherapy had increase bone marrow toxicity and this arm was dropped as CALGB.

PUBLICATIONS/ABSTRACTS, FY-80: Stuzman, L., Nisce, L. and Friedman, M. Increased Toxicity of Total Nodal Irradiation Following Combination Chemotherapy, ASCO, Vol. 20, March 1979, page 391, #C411.

WORK UNIT : 1534

DATE: 30 September 1980 | PROTOCOL NO: CALGB 7521 | STATUS: Interim X / Final

TITLE OF PROJECT: Comparative Study of the Value of Immunotherapy with MER as Adjuvant to Induction and Two Maintenance Chemotherapy Programs in Acute Myelocytic Leukemia

STARTING DATE: 7 May 1975 | ESTIMATED COMPLETION DATE: 10 June 1977

PRINCIPAL INVESTIGATOR: Dr. Johannes Blom

ASSOCIATE INVESTIGATORS: Dr. Jeffrey L. Berenber, LTC, MC

FACILITY: Walter Reed Army Medical Center

SERVICE: Hematology-Oncology Department of Medicine

KEY WORDS: MER, Immunotherapy, Myleocytic Leukemia

| ACCUMULATIVE MEDCASE COST: | ACCUMULATIVE CONTRACT COST: | ACCUMULATIVE SUPPLY COST: |
|---|---|---|
| None | None | None |

FY-80 MEDCASE COST: None

PERIODIC REVIEW RESULTS:

STUDY OBJECTIVE: 1. To determine whether MER immunotherapy increases remission rate or duration. 2. To compare monthly maintenance with ARa-C and 6-thioquanine (GTG) with alternating cycles of ARA-C and GTG with vincristine VCR1, dexamethasone and ARA-C.

TECHNICAL APPROACH: 1. Standard induction with ARA-C 100mg/$M^2$/day by continuous infusion for 10 days plus Daunomycin 45 mg/$M^2$/day IV push on days 1,2,3. 3. Three maintenance arms, two including MER 1 of these with cycling VCR and dexamethasone.

PROGRESS DURING FY-80: Five patients remain alive. Four are still being followed on the protocol. One was transplanted and is still in CR. These patients will be followed for long term toxicity and survival.

NUMBER OF SUBJECTS TO BE STUDIED BEFORE COMPLETION OF STUDY: None

SERIOUS/UNEXPECTED SIDE EFFECTS IN SUBJECTS PARTICIPATING IN PROJECT: None observed in past year.

CONCLUSIONS: See 1978-79 annual report.

PUBLICATIONS/ABSTRACTS, FY-80: Cuttner, J. et al, A Controlled Trial of Chemo-immunotherpy in Acute Myelocyte Leukemia. Proceedings of NCI Immunotherapy Conference, April 1980.

WORK UNIT NO. 1535

DATE: 30 September 1980 | PROTOCOL NO: CALGB 7581 | STATUS: Active X / Final

TITLE OF PROJECT: Long Term Surgical Adjuvant Systemic Chemotherapy with or without Adjuvant Immunotherapy in Mammary Carcinoma.

STARTING DATE: 1975 | ESTIMATED COMPLETION DATE: 1981

PRINCIPAL INVESTIGATOR: LTC Jeffrey L. Bereaberg, M.D. MC

ASSOCIATE INVESTIGATORS:

FACILITY: Walter Reed Army Medical Center

SERVICE: Radiology-Oncology
Department of Medicine

KEY WORDS: Mammary Carcinoma

| ACCUMULATIVE MEDCASE COST: | ACCUMULATIVE CONTRACT COST: | ACCUMULATIVE SUPPLY COST: |
|---|---|---|
| | | |

FY-80 MEDCASE COST:

PERIODIC REVIEW RESULTS:

STUDY OBJECTIVE: It is the specific aim of this study to ascertain if therapy with 3 active agents plus nonspecific immunostimulation is superior to the 3 active agents alone, or given in combination with vincristine and prednisone. The criteria for assessment will be the disease free interval of breast cancer patients with 4 or more positive axillary nodes discovered at radical mastectomy. A corollary comparison to the historical situation in a patient group similarly staged and operated when followed by observation alone or by 3 active agent therapy in Milan will be utilized for an additional comparison.

TECHNICAL APPROACH: This study will compare the length of the disease free period and survival in female patients having operable breast carcinoma with 4 or more metastatic axillary nodes treated with a 5 drug combination, with a 3 drug combination, or with the 3 drug combination plus nonspecific immunotherapy with MER; the therapeutic choice being determined by random allocation. Following radical mastectomy (with, but preferably without, postoperative radiotherapy) and stratification, patients will be randomly assigned to receive induction treatment, followed by random chemotherapy. Patients should be proved to be free from metastatic disease by films and scans wherever possible. Chemotherapy

(CONTINUED ON REVERSE SIDE)

PROGRESS DURING FY-80:

A total of 41 patients have been entered on study at WRAMC, of them; 4 have developed progressive disease, 2 have expired, and 35 remain stable with no evidence of disease.

NUMBER OF SUBJECTS TO BE STUDIED BEFORE COMPLETION OF STUDY: 800

SERIOUS/UNEXPECTED SIDE EFFECTS IN SUBJECTS PARTICIPATING IN PROJECT:

CONCLUSIONS: As of April 1980 accrual is approaching 800 patients. Although the regimens have not yet been decoded, one regimen has a statistically significant better disease-free interval. This study is closed as of April 1980.

PUBLICATIONS/ABSTRACTS, FY-80:

will begin 2 to 4 weeks after mastectomy. If postoperative radiotherapy is used chemotherapy must be delayed until 4 to 8 weeks after completion of radiotherapy is despite discouragement. Chemotherapy will be continued until either evidence of treatment failure has occurred or until 2 years have elapsed, whichever is earlier. Postoperative complications which force delay of chemotherapy beyond 4 weeks from mastectomy in the absence of radiotherapy, or beyond 16 weeks from mastectomy if radiotherapy is given, will render the patient ineligible for study.

WORK UNIT NO. 1537

| DATE: 30 September 1980 | PROTOCOL NO: CALGB 7551 | STATUS: Interim X / Final |
|---|---|---|

TITLE OF PROJECT: Combination Chemotherapy and Radiotherapy for Stage IV and III B Hodgkin's Disease

| STARTING DATE: 8/5/75 activated | ESTIMATED COMPLETION DATE: Closed |
|---|---|
| PRINCIPAL INVESTIGATOR: Jeffrey L. Berenberg, M.D., LTC, MC | |
| ASSOCIATE INVESTIGATORS: | FACILITY: Walter Reed Army Medical Center |
| | SERVICE: Hematology-Oncology Department of Medicine |

KEY WORDS: Combination Chemotherapy, Hodgkin's Stage IV

| ACCUMULATIVE MEDCASE COST: None | ACCUMULATIVE CONTRACT COST: None | ACCUMULATIVE SUPPLY COST: None |
|---|---|---|
| FY-80 MEDCASE COST: None | PERIODIC REVIEW RESULTS: | |

STUDY OBJECTIVE: 1. Compare remission frequency and duration of twelve versus six monthly cycles of CVPP. 2. To determine if radiotherapy augments efficacy six monthly cycles of CVPP. 3. To determine if radiotherapy given between cy 3 and 4 is preferable to that after 6 cycles.

TECHNICAL APPROACH: Chemotherapy CCNU 75 mg/$M^2$ p.o. day 1, Vinblastine 4 mg/$M^2$ IV day 1 and 8, Prorabalie 100 mg/$M^2$ p.o. day 1-14, Prednisone 41 mg/$M^2$ pedal-14, Radiotherapy 2500 rads in 4 weeks to gross disease.

PROGRESS DURING FY-80: WRAMC entered seven patients, six achieved a CR 3 patients remain in complete remission. No follow-up data available on the one at this time. One of the two CR's have relapsed. CALGB entered 256 patients.

NUMBER OF SUBJECTS TO BE STUDIED BEFORE COMPLETION OF STUDY: Closed at WRAMC

SERIOUS/UNEXPECTED SIDE EFFECTS IN SUBJECTS PARTICIPATING IN PROJECT: None

CONCLUSIONS: None of the treatment regimens appears superior to date.

PUBLICATIONS/ABSTRACTS, FY-80: 1. Gotlieb, AJ et al, Nitrosoureas in the Therapy of Lymphomas (manuscript in preparation) 2. Raila, S et al, Toxicity and Preliminary Results of Combined Radiotherapy and Chemotherapy in Hodgkin's Disease. ASTR, Oct 1979

WORK UNIT NO. 1538

| DATE: 30 September 1980 | PROTOCOL NO: CALGB 7552 | STATUS: Interim X Final |
|---|---|---|

TITLE OF PROJECT: Combination Chemotherapy and Immunotherapy for Previously Treated Stage III B & IV Hodgkin's Disease

| STARTING DATE: 7/28/75 | ESTIMATED COMPLETION DATE: |
|---|---|
| PRINCIPAL INVESTIGATOR: LTC Jeffrey L. Berenberg, M.D., MC | |
| ASSOCIATE INVESTIGATORS: | FACILITY: Walter Reed Army Medical Center |
| | SERVICE: Hematology-Oncology Department of Medicine |

KEY WORDS: Hodgkin's Disease

| ACCUMULATIVE MEDCASE COST: None | ACCUMULATIVE CONTRACT COST: None | ACCUMULATIVE SUPPLY COST: |
|---|---|---|
| FY-80 MEDCASE COST: None | PERIODIC REVIEW RESULTS: | |

STUDY OBJECTIVE:
1. Comparison of two different four drug regimens
2. To explore alternating regimens
3. Examine contribution of MER

TECHNICAL APPROACH: Reference appended schema. Note addendum #5 discontinued mainsengne chloigmbucil addendum #6 discontinued MER (methanal extractable residue BCG)

PROGRESS DURING FY-80: WRAMC entered six patients. 3 patients remain in complete remission. No new patients are being added. CALGB entered 21 patients in 1980.

NUMBER OF SUBJECTS TO BE STUDIED BEFORE COMPLETION OF STUDY: 80 CALGB

SERIOUS/UNEXPECTED SIDE EFFECTS IN SUBJECTS PARTICIPATING IN PROJECT:

CONCLUSIONS: At WRAMC, one patient developed acute myelogenous leukemia, one patient developed chronic renal failure 2° to Steptozotocin.

1. MER is of no value in remission - duration or maintenance.
2. Patients with prior chemotherapy have a worse remission duration.

PUBLICATIONS/ABSTRACTS, FY-80: Cancer Clinical Trials - pending publication
Coleman, M. et al, Combination Chemotherapy in Advanced Recurrent Hodgkin's Disease ASCO, Vol 20, March 1979, page 428 #C 568

WORK UNIT NO. 1539

DATE: 30 September 1980 | PROTOCOL NO: CALGB 7541 | STATUS: Interim X / Final

TITLE OF PROJECT: CALGB Protocol 7541: Combination Chemotherapy and Immunotherapy in Previosly Untreated Stage III and IV Neuroblastoma. A Phase III Study.

STARTING DATE: | ESTIMATED COMPLETION DATE:

PRINCIPAL INVESTIGATOR: LTC Jeffrey L. Jeremberg, MC

ASSOCIATE INVESTIGATORS:

FACILITY: Walter Reed Army Medical Center

SERVICE: Hematology-Oncology Department of Medicine

KEY WORDS:

| ACCUMULATIVE MEDCASE COST: | ACCUMULATIVE CONTRACT COST: | ACCUMULATIVE SUPPLY COST: |
|---|---|---|
| FY-80 MEDCASE COST: | PERIODIC REVIEW RESULTS: | |

STUDY OBJECTIVE: To evaluate the role of triple drug (Vincristine, Cyclophophamide, and Adriamycin) combination chemotherapy in previously untreated Stage III and IV neuroblastoma. To evaluate the immunological responsiveness of patients with disseminated neuroblastoma, both prior to and during therapy. To evaluate the role of an [illegible] (MER) thought capable of stimulating immunological [illegible] in terms of the patient's immunological reactivity (to skin tests) and in terms of possible contribution to prolongation of median survival.

TECHNICAL APPROACH: Vincristine, Cyclophosphamide, Adriamycin, versus Vincristin, Cyclophosphamide, Adriamycin, and MER.

PROGRESS DURING FY-80: Five patients have been entered at WRAMC. One patient was ineligible because of prior treatment. Two patients have expired on day 89 and day 700. Follow-up is pending on the other two.

NUMBER OF SUBJECTS TO BE STUDIED BEFORE COMPLETION OF STUDY: Closed to pt. entry

SERIOUS/UNEXPECTED SIDE EFFECTS IN SUBJECTS PARTICIPATING IN PROJECT: None

CONCLUSIONS: Both regimens were effective but no conclusions made as of April 80 meeting of CALGB.

PUBLICATIONS/ABSTRACTS, FY-80:

None

WORK UNIT NO. 1541

| DATE: 30 September 1980 | PROTOCOL NO: CALGB 7542 | STATUS: Interim / Final X |
|---|---|---|

TITLE OF PROJECT:
Treatment of Non-Hodgkin's Lymphoma in Children

| STARTING DATE: | ESTIMATED COMPLETION DATE: |
|---|---|
| PRINCIPAL INVESTIGATOR: Dr. Johannes Blom | |
| ASSOCIATE INVESTIGATORS: Dr. Frederick Ryman | FACILITY: Walter Reed Army Medical Center |
| | SERVICE: Hematology-Oncology Department of Medicine |

KEY WORDS:

| ACCUMULATIVE MEDCASE COST: | ACCUMULATIVE CONTRACT COST: | ACCUMULATIVE SUPPLY COST: |
|---|---|---|
| FY-80 MEDCASE COST: | PERIODIC REVIEW RESULTS: | |

STUDY OBJECTIVE: 1. To develop a combined radiotherapy/chemotherapy regimen of intent
2. To test contribution of [illegible] methotrexate in consolidation.

TECHNICAL APPROACH:

See detailed outline in 1978-79 report.

PROGRESS DURING FY-80: Study close with discontinuing of pediatric segment of CALGB. One WRAMC patient alive in remission will be followed for survival and toxicity.

NUMBER OF SUBJECTS TO BE STUDIED BEFORE COMPLETION OF STUDY: None

SERIOUS/UNEXPECTED SIDE EFFECTS IN SUBJECTS PARTICIPATING IN PROJECT:
None

CONCLUSIONS: Study unable to be completed because of closeout of Pediatric CALGB.

PUBLICATIONS/ABSTRACTS, FY-80:

None

Work Unit No.: 1542

Title of Project: CALGB #7584, Adjuvant Chemotherapy in Osteogenic Sarcoma. Adriamycin Versus Sequential Adriamycin-Cyclophosphamide.

Principal Investigator: Chief, Hematology-Oncology Service

Associate Investigator:

After numerous requests for an annual progress report on this project, as of 20 Feb 81, there has not been a response. This progress report request was for the period 30 September 1979 to 1 October 1980. We can no longer delay compilation of the reports submitted by those investigators who complied with the regulations, so a supplementary annual progress report will be compiled when this investigator submits his report.

WORK UNIT NO. 1543

DATE: 30 September 1980 | PROTOCOL NO: CALGB 7651 | STATUS: Interim X / Final

TITLE OF PROJECT: Combination Chemotherapy for Stages III and IV Lymphocytic Lymphoma In Adults with or without Radiotherapy

STARTING DATE: 1/20/76 | ESTIMATED COMPLETION DATE: Closed 10/6/79

PRINCIPAL INVESTIGATOR: Jeffrey L. Berenberg, M.D., LTC MC

ASSOCIATE INVESTIGATORS:

FACILITY: Walter Reed Army Medical Center

SERVICE: Hematology-Oncology Department of Medicine

KEY WORDS: Lymphocytic Lymphoma

| ACCUMULATIVE MEDCASE COST: | ACCUMULATIVE CONTRACT COST: | ACCUMULATIVE SUPPLY COST: |
|---|---|---|
| None | None | |

| FY-80 MEDCASE COST: | PERIODIC REVIEW RESULTS: |
|---|---|
| None | |

STUDY OBJECTIVE: 1. To confirm improvement in remission induction of lymphocytic lymphoma by adding Streptenigrin to Vincristine and Prednisone.
2. To examine the role of radiotherapy to bulky disease sites in improving remission rate and duration.

TECHNICAL APPROACH: Chemotherapy to all patients. Streptenigrin 1 mg/M$^2$/week po x 6 weeks Vincristine 1 mg/M$^2$ IV x 6 weeks. Prednisone 40 mg/M$^2$ po x 6 week. Maintenance RT 3000-4000 rads to bulky sites followed by (CVP) Cytoxan, Vincristine, and Prednisone or only CVR.

PROGRESS DURING FY-80: 15 patients entered at WRAMC. Seven achieved a C.R. 3 patients have had progression of disease. 1 new patient failed to attain C.R., 4 patients are in complete remission still. CALGB entered 251 patients.

NUMBER OF SUBJECTS TO BE STUDIED BEFORE COMPLETION OF STUDY: None

SERIOUS/UNEXPECTED SIDE EFFECTS IN SUBJECTS PARTICIPATING IN PROJECT: Radiation hepatitis. One patient developed radiation hepatitis? Enhanced by Vincristine.

CONCLUSIONS: 1. RT produced increased toxicity to bone marrow and liver without improving the number or duration of remission.

PUBLICATIONS/ABSTRACTS, FY-80:

See report on CALGB 7652.

WORK UNIT NO. 1544

| DATE: 30 September 1980 | PROTOCOL NO: CALGB 7652 | STATUS: Interim / Final X |
|---|---|---|

TITLE OF PROJECT:
Combination Therapy of Stage III and IV Histiocytic Lymphoma

| STARTING DATE: | ESTIMATED COMPLETION DATE: Closed |
|---|---|
| PRINCIPAL INVESTIGATOR: Dr. Jeffrey L. Berenberg, LTC, MC | |
| ASSOCIATE INVESTIGATORS: | FACILITY: Walter Reed Army Medical Center |
| | SERVICE: Hematology-Oncology Department of Medicine |

KEY WORDS: Histiocytic Lymphoma

| ACCUMULATIVE MEDCASE COST: None | ACCUMULATIVE CONTRACT COST: | ACCUMULATIVE SUPPLY COST: |
|---|---|---|
| FY-80 MEDCASE COST: None | PERIODIC REVIEW RESULTS: | |

STUDY OBJECTIVE: 1. To determine if Streptonigrin increases the response potentiation of Vincristine and Prednisone.
2. Explore consolidation radiation therapy
3. Evaluate consolidation with Adriamycin.

TECHNICAL APPROACH: 1. Induction with Vincristine 1 mg/$M^2$, Streptonigrin 11 m/$M^2$ and Prednisone 40 mg/$M^2$ po day 1-47
2. Consolidation varies with Cytoxan, Vincristine and Prednisone vs Adriamycin, Vincristine and Prednisone vs radiation.

PROGRESS DURING FY-80: Three patients entered, two failed therapy, 1 patient remains in complete remission. CALGB entered no new patients.

NUMBER OF SUBJECTS TO BE STUDIED BEFORE COMPLETION OF STUDY: None

SERIOUS/UNEXPECTED SIDE EFFECTS IN SUBJECTS PARTICIPATING IN PROJECT:
None at WRAMC, Vincristine potential Hepatic Toxicity of Radiotherapy in CALGB experience

CONCLUSIONS: This therapeutic regimen is inferior to current treatment methods. The remaining patients will be followed for survival and long term toxicity. Any toxicity will be reported.

PUBLICATIONS/ABSTRACTS, FY-80: Glickman, A., Vincristine Enhanced Hepatic Radiation Toxicity ASCC May 1979, Vol 20, page 318, #C114.

WORK UNIT NO. 1546

DATE: 30 September 1980 | PROTOCOL NO: CALGB 7611 | STATUS: Interim X / Final

TITLE OF PROJECT: Treatment of Acute Lymphocytic Leukemia in Patients Under Twenty

STARTING DATE: | ESTIMATED COMPLETION DATE: Closed 16 July 1979

PRINCIPAL INVESTIGATOR: Johannes Blom, M.D.

ASSOCIATE INVESTIGATORS: Frederick K.B. Ruyman, M.D., LTC MC

FACILITY: Walter Reed Army Medical Center

SERVICE: Hematology-Oncology Department of Medicine

KEY WORDS: Acute Lymphocytic Leukemia

| ACCUMULATIVE MEDCASE COST: | ACCUMULATIVE CONTRACT COST: | ACCUMULATIVE SUPPLY COST: |
|---|---|---|
| None | None | |

FY-80 MEDCASE COST: None

PERIODIC REVIEW RESULTS:

STUDY OBJECTIVE: 1. To test whether high dose Methotrexate can substitute for cranial irradiation in decreasing the incidence of CNS leukemia.
2. To test whether consolidation with high dose Methotrexate can increase the duration of remission.

TECHNICAL APPROACH: Induction with Vincristine, Prednisone an[illegible] Asparaginase 50% of Patients will receive high dose Methotrexate 500 mg/M² x3 du[illegible] consolidation.

PROGRESS DURING FY-80: WRAMC entered 7 patients. Three remain in complete remission, out of 6 who achieved complete remission. CALGB entered 634 patients 75% of low risk patients remain in complete remission at three years. 60% of high risk patients are in remission of three years.

NUMBER OF SUBJECTS TO BE STUDIED BEFORE COMPLETION OF STUDY: None

SERIOUS/UNEXPECTED SIDE EFFECTS IN SUBJECTS PARTICIPATING IN PROJECT: Severe Mucositis secondary to high dose Methotrexate

CONCLUSIONS:

See 1978-79 report, unchanged.

PUBLICATIONS/ABSTRACTS, FY-80: Abstract will be presented at spring ASCO meetings.

WORK UNIT NO. 1547

DATE: 30 September 1980 | PROTOCOL NO: CALGB 7682 | STATUS: Interim X / Final

TITLE OF PROJECT: Combination Chemotherapy or Chemo-Immunotherapy for Metastatic Recurrent or Inoperable Cancer of the Breast. 3 Treatment Regimens: Cyclophosphamide, Adriamycin, 5-Fluorouracil vs. Cyclophosphamide, Adriamycin, 5-Flouruoracil, Vincristine, Prednisone vs. Cyclophosphamide, Methotrexate, (CONT ON

STARTING DATE: 1976 | ESTIMATED COMPLETION DATE:

PRINCIPAL INVESTIGATOR: LTC Jeffrey L. Berenberg, MC

ASSOCIATE INVESTIGATORS:

FACILITY: Walter Reed Army Medical Center

SERVICE: Hematology-Oncology, Department of Medicine

KEY WORDS:

| ACCUMULATIVE MEDCASE COST: | ACCUMULATIVE CONTRACT COST: | ACCUMULATIVE SUPPLY COST: |
|---|---|---|
| FY-80 MEDCASE COST: | PERIODIC REVIEW RESULTS: | |

STUDY OBJECTIVE: To compare the remission induction frequency and duration of the CMF and the CMF combination individually with the five-drug combination, CAFVP, which appears to be the most combination program in CALGB study [illegible], to test whether the addition of MER to each of the three combinations increases the remission induction frequency or prolongs the remission duration, or both.

TECHNICAL APPROACH: Prior to randomization for treatment, patients will be stratified according to dominance of metastatic area, visceral osseous soft tissue which develop either less than one year from diagnosis or equal to or greater than one year from diagnosis.

PROGRESS DURING FY-80: Of 12 patients entered on study at WRAMC only one remains free of disease. Three patients have expired and the remaining eight patients have all developed progressive disease.

NUMBER OF SUBJECTS TO BE STUDIED BEFORE CONCLUSION OF STUDY: Closed

SERIOUS/UNEXPECTED SIDE EFFECTS IN SUBJECTS PARTICIPATING IN PROJECT:

CONCLUSIONS: This study has been closed following the accrual of 429 patients. The CMF regimen is inferior to the adriamycin containing regimens except in patients who receive MER. All response frequencies are low probably because of the large number of patients with visceral disease.

PUBLICATIONS/ABSTRACTS, FY-80:

CONTINUATION OF TITLE

5-Fluorouracil, all 3 Regimens with or without MER. A Phase III Study.

Work Unit No.: 1548

Title of Project: CALGB #7681, Investigation of the Effects of Adriamycin with and without Added MER in Soft Tissue Sarcomas.

Principal Investigator: C, Hematology-Oncology Service

Associate Investigator:

After numerous requests for an annual progress report on this project, as of 20 Feb 81, there has not been a response. This progress report request was for the period 30 September 1979 to 1 October 1980. We can no longer delay compilation of the reports submitted by those investigators who complied with the regulations, so a supplementary annual progress report will be compiled when this investigator submits his report.

WORK UNIT NO. 1551

DATE: 30 September 1980 | PROTOCOL NO: CALGB 7612 | STATUS: Interim X / Final

TITLE OF PROJECT:

Therapy of Acute Lymphocytic Leukemia in Adults

STARTING DATE: 8/1/76 | ESTIMATED COMPLETION DATE: 9/29/80 Closed

PRINCIPAL INVESTIGATOR: LTC Jeffrey L. Berenberg, M.D. MC

ASSOCIATE INVESTIGATORS:

FACILITY: Walter Reed Army Medical Center

SERVICE: Hematology-Oncology Department of Medicine

KEY WORDS: Acute Lymphocytic Lymphoma

| ACCUMULATIVE MEDCASE COST: | ACCUMULATIVE CONTRACT COST: | ACCUMULATIVE SUPPLY COST: |
|---|---|---|
| None | None | |

| FY-80 MEDCASE COST: | PERIODIC REVIEW RESULTS: |
|---|---|
| None | |

STUDY OBJECTIVE: 1. To determine whether adding Daunomycin to Vincristine and Prednisone followed by Asparaginase will improve frequency and duration of response. 2. To determine if MER will increase remission duration.

TECHNICAL APPROACH: Regimen I Vincristine 2 mg IV/week x3
Prednisone 40 mg/$M^2$ po x21 day
L. Asparaginase 500 iu/ig IV daily x10d beginning
on page 2.
II As above Daunomycin 45 mg/$M^2$ IV daily x3 orally (day 1-3)

PROGRESS DURING FY-80: WRAMC entered 15 patients, 12 attained a complete remission (80%), eight of these have subsequently relapsed, of this group four remain alive and in complete remission. One of the partial remission patients remains alive. CALGB entered 164 patients 78% of these receiving Daunomycin achieved complete remission, 48% of those did not. MER may have had an adverse effect on duration of complete remission.

NUMBER OF SUBJECTS TO BE STUDIED BEFORE COMPLETION OF STUDY: NONE

SERIOUS/UNEXPECTED SIDE EFFECTS IN SUBJECTS PARTICIPATING IN PROJECT:
None

CONCLUSIONS: Daunomycin increases the complete remission rate in adults with acute lymphocytic leukemia. MER immunotherapy does not improve and may impair remission duration.

PUBLICATIONS/ABSTRACTS, FY-80: Abstract presented at American Society of Hematology meetings December, 1979.

WORK UNIT NO. 1552

DATE: 30 September 1980 | PROTOCOL NO: CALGB 7632 | STATUS: Interim X / Final

TITLE OF PROJECT:
Chemotherapy in Indolent Chronic Lymphocytic Leukemia (CLL)

STARTING DATE: 30 Nov 1976 | ESTIMATED COMPLETION DATE: 1982

PRINCIPAL INVESTIGATOR: Dr. Jeffrey Berenberg

ASSOCIATE INVESTIGATORS:

FACILITY: Walter Reed Army Medical Center

SERVICE: Hematology-Oncology
Department of Medicine

KEY WORDS:

| ACCUMULATIVE MEDCASE COST: | ACCUMULATIVE CONTRACT COST: | ACCUMULATIVE SUPPLY COST: |
|---|---|---|
| None | None | None |

FY-80 MEDCASE COST:

PERIODIC REVIEW RESULTS:

STUDY OBJECTIVE: To determine if chemotherapy with chlorambucil in indolent CLL will prolong survival

TECHNICAL APPROACH: After an initial 12 week observation period patients are randomized to Regimen I: No treatment, or Regimen II: Intermittent chlorambucil 0.5 mg/kg po q 28 days.

PROGRESS DURING FY-80: WRAMC three patients were entered, 1 was later found to be ineligible. One patient progressed on the follow-up arm. CALGB not updated at last call-up.

NUMBER OF SUBJECTS TO BE STUDIED BEFORE COMPLETION OF STUDY: $< 50$

SERIOUS/UNEXPECTED SIDE EFFECTS IN SUBJECTS PARTICIPATING IN PROJECT:
None

CONCLUSIONS:
Too early

PUBLICATIONS/ABSTRACTS, FY-80:

None

WORK UNIT NO. 1554

DATE: 22 September 1980 | PROTOCOL NO: CALGB 7691 | STATUS: Interim / Final X

TITLE OF PROJECT:

Comparison of Involved Field Radiotherapy with Adjuvant MOPP Chemotherapy and Extended Field Radiotherapy in the Treatment of Stage I and II Hodgkins Disease in Children

STARTING DATE: October 1976 | ESTIMATED COMPLETION DATE: Closed September 1980

PRINCIPAL INVESTIGATOR: Dr. Johannes Blom

ASSOCIATE INVESTIGATORS: Dr. Frederick Ruymann

FACILITY: Walter Reed Army Medical Center

SERVICE: Hematology-Oncology Department of Medicine

KEY WORDS: Hodgkins Disease, Children

| ACCUMULATIVE MEDCASE COST: None | ACCUMULATIVE CONTRACT COST: None | ACCUMULATIVE SUPPLY COST: |
|---|---|---|

FY-80 MEDCASE COST:

PERIODIC REVIEW RESULTS:

STUDY OBJECTIVE:

To compare the effectiveness of involved field radiotherapy versus IF RT plus MOPP versus extended field radiotherapy in children with stage I and II Hodgkins Disease.

To examine the relative interference of growth and incidence of infections in the three different treatment arms.

TECHNICAL APPROACH:

All patients were laparotomy staged and the randomized to either EF or IF RT, lower limit of radiation being 3500 Rads. Half of IF patients receive standard MOPP for six cycles.

PROGRESS DURING FY-80:

URAMC did not enter any patients on this study. Since the Pediatric section of CALGB was dissolved, this study has been closed.

NUMBER OF SUBJECTS TO BE STUDIED BEFORE COMPLETION OF STUDY: None

SERIOUS/UNEXPECTED SIDE EFFECTS IN SUBJECTS PARTICIPATING IN PROJECT:

None

CONCLUSIONS:

This study is closed.

PUBLICATIONS/ABSTRACTS, FY-80:

None

WORK UNIT NO. 1555

DATE: 30 September 1980 | PROTOCOL NO: CALGB 0702 | STATUS: Interim ___ Final X

TITLE OF PROJECT: Evaluation of Galactitol 1, 2:5, 6-Dianhydro in the Treatment of Advanced Carcinoma of the Lung and Melanoma.

STARTING DATE: | ESTIMATED COMPLETION DATE:

PRINCIPAL INVESTIGATOR: LTC Jeffrey L. Sorenberg, MC

ASSOCIATE INVESTIGATORS:

FACILITY: Walter Reed Army Medical Center

SERVICE: Hematology-Oncology Department of Medicine

KEY WORDS:

| ACCUMULATIVE MEDCASE COST: | ACCUMULATIVE CONTRACT COST: | ACCUMULATIVE SUPPLY COST: |
|---|---|---|
| | | |

FY-80 MEDCASE COST:

PERIODIC REVIEW RESULTS:

STUDY OBJECTIVE: To determine the antitumor effect of galactitol in small cell, large cell, squamous and adenocarcinoma of the lung and melanoma.

TECHNICAL APPROACH: Galactitol Dosage: 60 mg/m$^2$ as a slow intravenous push q 7 days.

PROGRESS DURING FY-80: Closed to patient entry 1 June 1979 - all patients have expired. One patient responded temporarily.

NUMBER OF SUBJECTS TO BE STUDIED BEFORE COMPLETION OF STUDY: Closed to patient entry.

SERIOUS/UNEXPECTED SIDE EFFECTS IN SUBJECTS PARTICIPATING IN PROJECT: None

CONCLUSIONS: Study closed - CALGB for poor response rate, June 1979.

PUBLICATIONS/ABSTRACTS, FY-80:

None

WORK UNIT NO. 1556

DATE: 30 September 1980 | PROTOCOL NO: CALGB 7721 | STATUS: Interim / Final

TITLE OF PROJECT: Comparative Study of Adriamycin vs Daunomycin at Two Dose Levels for Induction and a 4-week vs 8-week Cycle For Maintenance Chemotherapy in Acute Myelocytic Leukemia

STARTING DATE: 10 June 77 | ESTIMATED COMPLETION DATE: 19 Nov 1979

PRINCIPAL INVESTIGATOR: Dr. Jeffrey L. Berenberg

ASSOCIATE INVESTIGATORS:

FACILITY: Walter Reed Army Medical Center

SERVICE: Hematology-Oncology Department of Medicine

KEY WORDS: Acute Myelogenous Leukemia

| ACCUMULATIVE MEDCASE COST: | ACCUMULATIVE CONTRACT COST: | ACCUMULATIVE SUPPLY COST: |
|---|---|---|
| None | None | None |

FY-80 MEDCASE COST: None

PERIODIC REVIEW RESULTS:

STUDY OBJECTIVE: To test whether remission duration and survival of is the same or different with Daunomycin CONRL 45 mg/$M^2$ vs 30 $m^2$
To test whether Adriamycin CADRI 30 mg/$M^2$ can be substituted for DNR.

TECHNICAL APPROACH: 1) DNR 45 mg/$M^2$ IV days 1-3 plus ARA-C 100 mg/$M^2$ IV day 1-10
2) DNR 30 mg/$M^2$ IV days 1-3 plus ARA-C 100 mg/$M^2$ IV day 1-10.
3) ADR 30 mg/$M^2$ IV day 1-3 plus ARa-C 100 mg/$M^2$ IV day 1-10.

PROGRESS DURING FY-80: WRAMC entered 26 patients. 10 obtained a complete remission, 3 partial remission and 13 no response. Only three of the responders remain alive. CALGB entered 709 patients overall remission rate 55%. Twenty-five percent of those who achieved remission are alive in three years. High dose Daunomycin DNR appears more toxic in patients over 60.

NUMBER OF SUBJECTS TO BE STUDIED BEFORE COMPLETION OF STUDY: None

SERIOUS/UNEXPECTED SIDE EFFECTS IN SUBJECTS PARTICIPATING IN PROJECT:
See 1978-79 report. Bleeding and infection.

CONCLUSIONS: Elderly patients may benefit from low doses of DNR during induction.

PUBLICATIONS/ABSTRACTS, FY-80:

Reported at ASCO meeting, May 1980.

WORK UNIT NO. 1558

| DATE: 30 September 1980 | PROTOCOL NO: CALGB 7761 | STATUS: Interim X / Final |
|---|---|---|

TITLE OF PROJECT: A Study to Determine the Effectiveness of Single vs Multiple Alkylating Agents with or without Adriamycin in the Primary Treatment of Multiple Myeloma.

| STARTING DATE: | ESTIMATED COMPLETION DATE: |
|---|---|
| PRINCIPAL INVESTIGATOR: Jeffrey L. Berenberg, LTC, MC | |
| ASSOCIATE INVESTIGATORS: | FACILITY: Walter Reed Army Medical Center |
| | SERVICE: Hematology-Oncology Department of Medicine |

KEY WORDS:

| ACCUMULATIVE MEDCASE COST: | ACCUMULATIVE CONTRACT COST: | ACCUMULATIVE SUPPLY COST: |
|---|---|---|
| FY-80 MEDCASE COST: | PERIODIC REVIEW RESULTS: | |

STUDY OBJECTIVE: To test the hypothesis that three alkylating agents given sequentially produce: Higher frequency of good response and longer duration of disease control than the same alkylating agents given in combination; that addition of adriamycin to a combination of three alkylating agents increases the frequency of good response and prolongs the duration of disease control; the frequency of good response and the duration of disease control are the same after treatment with intravenous L-PAM as after treatment with triple alkylating agents.

TECHNICAL APPROACH: Combination alkylating agents plus prednisone: L-PAM, Cyclophosphamide, and BCNU versus Dequential alkylating agents plus prednisone: L-PAM, Cyclophosphamide, and BCNU versus Combination alkylating agents plus adriamycin plus prednisone: L-PAM, Cyclosphosphamide, and BCNU versus I.V. L-PAM plus prednisone: L-PAM.

PROGRESS DURING FY-80: Eight patients are on this protocol. Seven patients have had partial remissions, the other patient is not evaluable. Two patients with initial responses have relapsed at days 348 and 436 of therapy and have since expired. Six patients remain on study.

NUMBER OF SUBJECTS TO BE STUDIED BEFORE COMPLETION OF STUDY: 440

SERIOUS/UNEXPECTED SIDE EFFECTS IN SUBJECTS PARTICIPATING IN PROJECT:
None

CONCLUSIONS: Regimens seen effective but still too early to evaluate.

PUBLICATIONS/ABSTRACTS, FY-80:
None

WORK UNIT NO. 1559

DATE: 30 September 1980 | PROTOCOL NO: CALGB 7781 | STATUS: Interim X / Final

TITLE OF PROJECT: Small Cell Carcinoma of the Lung: Localized Disease Addendum 5

STARTING DATE: 9/1/77 CALGB | ESTIMATED COMPLETION DATE: 1980

PRINCIPAL INVESTIGATOR: Dr. Jeffrey L. Berenberg

ASSOCIATE INVESTIGATORS:

FACILITY: Walter Reed Army Medical Center

SERVICE: Hematology-Oncology Department of Medicine

KEY WORDS: Small Cell Carcinoma

| ACCUMULATIVE MEDCASE COST: | ACCUMULATIVE CONTRACT COST: | ACCUMULATIVE SUPPLY COST: |
|---|---|---|
| None | None | None |

FY-80 MEDCASE COST: None

PERIODIC REVIEW RESULTS:

STUDY OBJECTIVE:

1. To determine whether CCV/AV plus radiotherapy (RT) gives a greater remission rate and duration than MACC plus RT.

2. To determine if MER immunostimulation increases response and duration of response.

TECHNICAL APPROACH: Regimen 1: Methotrexate 30 mg/M$^2$ IV plus Adriamycin 35 mg/M$^2$ vs CCNU 30 mg/M$^2$ plus Cyclophosphamide 400 mg/M$^2$ IV. Regimen 2: Cyclophosphamide 700 mg/M$^2$ IV plus CCNU 70 mg/M$^2$ po plus Vincristine 1.0 mg/M$^2$ with Adriamycin 50 mg/M$^2$ IV day 21 with Vincristine 1.0 mg/M$^2$ IV. Both regimens include 4500 rads to primary lung tumor plus 3000 rad whole brain.

PROGRESS DURING FY-80: WRAMC had entered 21 patients to date. Eight remain alive. Seven remain in remission. One has relapsed.
CALGB has entered 255 patients. About 50% have achieved a complete remission. 22% remain disease free at 24 months. The two treatment arms appear comparable. MER is of no value.

NUMBER OF SUBJECTS TO BE STUDIED BEFORE COMPLETION OF STUDY: Pending closure

SERIOUS/UNEXPECTED SIDE EFFECTS IN SUBJECTS PARTICIPATING IN PROJECT:
One patient died with wasting syndrome. No autopsy. One patient developed severe pulmonary fibrosis.

CONCLUSIONS:
1. Complete remissions can be attained about 50% in small cell lung carcinoma at 50% level. 2. MER does not appear to be of value.

PUBLICATIONS/ABSTRACTS, FY-80: Eaton, W. et al, Preliminary Results of Combined Radiotherapy and Chemotherapy in the Treatment of Small Cell Carcinoma of the Lung (submitted to the American Radium Society for presentation)

WORK UNIT NO. 1560

DATE: 30 September 1980 | PROTOCOL NO: CALGB 7782 | STATUS: Interim X / Final

TITLE OF PROJECT:
Small Cell Carcinoma of Lung in Extensive Disease.

STARTING DATE: | ESTIMATED COMPLETION DATE: 1980

PRINCIPAL INVESTIGATOR: Dr. Jeffrey L. Berenberg

ASSOCIATE INVESTIGATORS: | FACILITY: Walter Reed Army Medical Center

SERVICE: Hematology-Oncology Department of Medicine

KEY WORDS: Small Cell Carcinoma

| ACCUMULATIVE MEDCASE COST: | ACCUMULATIVE CONTRACT COST: | ACCUMULATIVE SUPPLY COST: |
|---|---|---|
| None | None | None |

FY-80 MEDCASE COST: None

PERTOPIC REVIEW RESULTS:

STUDY OBJECTIVE: 1. To examine whether alternating chemotherapy increases response rate or duration. 2. To determine whether radiotherapy to primary tumor increases response rate over MACC chemotherapy alone.

TECHNICAL APPROACH: Regimen 1, Methotrexate 30 mg/M$^2$, Adriamycin 40 mg/M$^2$ (Adria) CCNU 30 mg/M$^2$ po, Cytoxan (C + X) 400 mg/M$^2$ IV (termed MACC) + RT 3000 rads to primary tumor and draining nodes. Regimen 2. MACC. Regimen 3. Alternating CCNU 70 mg/M$^2$ po + Cytoxan 700 mg/M$^2$ + Vincristine 2 mg IV (VCR) with Cytoxan 700 mg/M$^2$ IV + VCR 2 mg IV with Adria 75 mg/M$^2$ IV + VCR 2 mg IV.

PROGRESS DURING FY-80: WRAMC entered two patients. Overall 10 patients entered only one patient remains alive in remission. The others have died, one in remission with pulmonary toxicity.

NUMBER OF SUBJECTS TO BE STUDIED BEFORE COMPLETION OF STUDY: 50

SERIOUS/UNEXPECTED SIDE EFFECTS IN SUBJECTS PARTICIPATING IN PROJECT:
One patient died of pulmonary toxicity.

CONCLUSIONS: 1. About 15% of patients achieved a complete remission (CR) 2. Only 5% overall are alive at 24 months. 3. No difference apparent yet between treatment arms. 4. Those who do attain a CR have an equal survival to those with limited disease who achieved CR ie 25% at 24 m.

PUBLICATIONS/ABSTRACTS, FY-80:

No publications to date.

WORK UNIT NO. 1562

| DATE: 30 September 1980 | PROTOCOL NO: CALGB 7802 | STATUS: Interim / Final X |
|---|---|---|

TITLE OF PROJECT: Treatment of Advanced Non Small Cell Bronchogenic Carcinoma with Cytoxan, CCNU, Hexamethylmelamine, and Methotrexate

| STARTING DATE: | ESTIMATED COMPLETION DATE: 1 June 79 |
|---|---|
| PRINCIPAL INVESTIGATOR: Dr. Jeffrey L. Berenberg | |
| ASSOCIATE INVESTIGATORS: | FACILITY: Walter Reed Army Medical Center |
| | SERVICE: Hematology-Oncology Department of Medicine |

KEY WORDS: Bronchogenic Carcinoma

| ACCUMULATIVE MEDCASE COST: None | ACCUMULATIVE CONTRACT COST: None | ACCUMULATIVE SUPPLY COST: None |
|---|---|---|
| FY-80 MEDCASE COST: None | PERIODIC REVIEW RESULTS: | |

STUDY OBJECTIVE:

1. To assess response frequencies and duration major histologic subtypes of non-small cell lung carcinoma.

TECHNICAL APPROACH: Treatment with Cytoxan, CCNU, Methotrexate and Hexamethylmelamine.

PROGRESS DURING FY-80: No patients entered. No patients remain alive at WRAMC.

NUMBER OF SUBJECTS TO BE STUDIED BEFORE COMPLETION OF STUDY:

SERIOUS/UNEXPECTED SIDE EFFECTS IN SUBJECTS PARTICIPATING IN PROJECT:

CONCLUSIONS: Low response rate, overall. Performance status 0-1 22% 2-4 = 3%. The performance status appears to predict survival. This may be unrelated to chemotherapy.

PUBLICATIONS/ABSTRACTS, FY-80: Manuscript being prepared. WRAMC will include as a primary author.

WORK UNIT NO. 1563

DATE: 30 September 1980 | PROTOCOL NO: CALGB 7951 | STATUS: Interim X / Final

TITLE OF PROJECT:
The Comparative Effectiveness of Combination Chemotherapy Alone and with Radiation Therapy by Involved Field or Extended Field, in Poor Risk Patients with Stage I or II Hodgkins Disease

STARTING DATE: 1977 | ESTIMATED COMPLETION DATE: 1985

PRINCIPAL INVESTIGATOR: Dr. Jeffrey I. Berenberg, LTC, MC

ASSOCIATE INVESTIGATORS:

FACILITY: Walter Reed Army Medical Center

SERVICE: Hematology-Oncology Department of Medicine

KEY WORDS: Hodgkins Disease

| ACCUMULATIVE MEDCASE COST: | ACCUMULATIVE CONTRACT COST: | ACCUMULATIVE SUPPLY COST: |
|---|---|---|
| None | None | |

| FY-80 MEDCASE COST: | PERIODIC REVIEW RESULTS: |
|---|---|
| None | |

STUDY OBJECTIVE:
To determine if combination chemotherapy alone is as effective and less toxic than chemotherapy plus Involved Field Radiation.

TECHNICAL APPROACH:
Regimen I : Involved Field RT followed by six cycles of CCNU, Vinblastine, Procarbazine, and Prednisone.

Regimen II: Chemotherapy alone.

Addendum II (2/12/79) deleted the arm with extended field RT.

PROGRESS DURING FY-80:
WRAMC has not entered any patients on this study.

CALGB has entered 42 patients. It is too early to examine results.

NUMBER OF SUBJECTS TO BE STUDIED BEFORE COMPLETION OF STUDY: 140

SERIOUS/UNEXPECTED SIDE EFFECTS IN SUBJECTS PARTICIPATING IN PROJECT:
None

CONCLUSIONS:
Too early for analysis.

PUBLICATIONS/ABSTRACTS, FY-80:

None

WORK UNIT NO. 1564

| | | |
|---|---|---|
| DATE: 30 September 1980 | PROTOCOL NO: CALGB 7772 | STATUS: Interim X / Final |
| TITLE OF PROJECT: Phase II Study of Chlorozotocin (NSC 178248) | | |

| | |
|---|---|
| STARTING DATE: July 1978 | ESTIMATED COMPLETION DATE: |
| PRINCIPAL INVESTIGATOR: Jeffrey L. Berenberg, LTC, MC | |
| ASSOCIATE INVESTIGATORS: | FACILITY: Walter Reed Army Medical Center |
| | SERVICE: Hematology-Oncology Department of Medicine |

KEY WORDS:

| | | |
|---|---|---|
| ACCUMULATIVE MEDCASE COST: | ACCUMULATIVE CONTRACT COST: | ACCUMULATIVE SUPPLY COST: |
| FY-80 MEDCASE COST: | PERIODIC REVIEW RESULTS: | |

STUDY OBJECTIVE: Field information concerning the efficacy and safety of this agent. See evidence of activity in tumors of interest to the Group. Activity will be judged by: Percentage of patients achieving an objective response, complete or partial, Duration of response while patient is maintained on continuous chlorozotocin therapy, Quality of response and its relationship to ultimate patient survival. Provide expertise in the design of a phase III protocol, should this phase II study be promising. Enter up to 200 patients with advanced neoplastic disease in the categories of gastrointestinal, pancreatic, lung tumors, melanoma and lymphoma.

CLINICAL APPROACH: Dose and Administration of Chlorozotocin. Chlorozotocin 120 mg/m$^2$ q 6 weeks. The drug will be administered in a bolus over a period of 30 seconds via the tubing of a running intravenous infusion. The failure to achieve a response following the administration of three doses of the drug, will be cause for removal from study.

PROGRESS DURING FY-80: Fifteen patients have been entered on study (6 since June 79). Two patients remain alive with one lost to follow up.

NUMBER OF SUBJECTS TO BE STUDIED BEFORE COMPLETION OF STUDY:

SERIOUS/UNEXPECTED SIDE EFFECTS IN SUBJECTS PARTICIPATING IN PROJECT: One patient had moderate thrombocytopenia (pl to 50,000)

CONCLUSIONS: Response rate seems low but many patients were heavily pre-treated with other chemotherapy. Still too early for evaluation.

PUBLICATIONS/ABSTRACTS, FY-80:

None

WORK UNIT NO. 1565

DATE: 5 September 1980 | PROTOCOL NO: CALGB 7894 | STATUS: Interim / Final

TITLE OF PROJECT:

Cyclophosphamide, Adriamycin, Vincristine, Prednisone in Combination with Low-Dose 5-Day I.V. Bleomycin in the Treatment of Poor Histology Lymphomas and Nodular Poorly Differentiated Lymphocytic Lymphomas

START: DATE: 1978 | EST. COMPLETION DATE: Closed 4 Sept. 79

PRINCIPAL INVESTIGATOR: Dr. Johannes Blom

ASSOCIATE INVESTIGATORS: | FACILITY: Walter Reed Army Medical Center; SERVICE: Hematology-Oncology Department of Medicine

KEY WORDS: Bleomycin, Lyphomas

| ACCUMULATIVE MEDCASE COST: None | ACCUMULATIVE OBLIGATIONS COST: None | ACCUMULATIVE SUPPLY COST: |
|---|---|---|

FY-80 MEDCASE COST: None | PERIODIC REVIEW RESULTS:

STUDY OBJECTIVE:

To determine if aggressive combination chemotherapy will improve the response rate and duration in patients with lyphomas.

TECHNICAL APPROACH:

Cyclophosphamide 750 $mg/m^2$ I.V. bolus, Adriamycin 50 $mg/m^2$ I.V. bolus
Vincristine 1.4 $mg/m^2$ I.V. bolus. All are given on day 1.
Bleomycin 2 u/day continuous infusion I.V. days 1-5.
Prednisone 100 mg/day orally days 1-5.

PROGRESS DURING FY-80:

There were no new patients entered.
One patient with nodular mixed lymphoma relapsed.

CALGB has entered 74 patients. 67% of the diffuse histiocytic patients achieved a complete response. only 20% of these have relapsed.

NUMBER OF SUBJECTS TO BE STUDIED BEFORE COMPLETION OF STUDY: None

SERIOUS/UNEXPECTED SIDE EFFECTS IN SUBJECTS PARTICIPATING IN PROJECT:
None

CONCLUSIONS:

This regimen has substantial activity in aggressive lyphomas.
It was incorporated into a group wide Phase III study.

PUBLICATIONS/ABSTRACTS, FY 80:

Ginsberg, S.J., Gottlieb, A.J., Bloomfield, C.D., Blom, J., Crooke, S.T.: Combination Chemotherapy with Continuous Infusion, Low Dose Bleomycin in Lymphoma. ASCO, vol. 20, March 1979, page 322.

WORK UNIT NO. 1566

DATE: 30 September 1980 | PROTOCOL NO: CALGB 7811 | STATUS: Interim / Final X

TITLE OF PROJECT:
Remission Induction of Recurrent Childhood ALL

STARTING DATE: 1978 | ESTIMATED COMPLETION DATE: Closed

PRINCIPAL INVESTIGATOR: LTC Jeffrey L. Berenberg, MC

ASSOCIATE INVESTIGATORS:

FACILITY: Walter Reed Army Medical Center

SERVICE: Hematology-Oncology Department of Medicine

KEY WORDS:

ACCUMULATIVE MEDCASE COST: None

ACCUMULATIVE CONTRACT COST: None

ACCUMULATIVE SUPPLY COST: None

FY-80 MEDCASE COST: None

PERIODIC REVIEW RESULTS:

STUDY OBJECTIVE: Effective therapy for relapsed childhood ALL.

TECHNICAL APPROACH; Comparison of T. MOPP and T-COAP (See 1979 report)

PROGRESS DURING FY-80: Protocol closed because of lack of funding of CALGB Pediatric group.

NUMBER OF SUBJECTS TO BE STUDIED BEFORE COMPLETION OF STUDY: None

SERIOUS/UNEXPECTED SIDE EFFECTS IN SUBJECTS PARTICIPATING IN PROJECT: Anaphylaxis not experienced.

CONCLUSIONS:
None

PUBLICATIONS/ABSTRACTS, FY-80: None

The reviewer of this report did not approved this annual progress report. When the reviewer's comments are complied with, the revised report will be inserted here.

WORK UNIT NO. 1567

DATE: 22 September 1980 | PROTOCOL NO: CALGB 8283 | Interim / Final X

TITLE OF PROJECT:

Cis-Platinum Diammine Dichloride in Advanced Malignant Lymphomas.

| | |
|---|---|
| STARTING DATE: | ESTIMATED COMPLETION DATE: 9 Nov. 1979 |
| PRINCIPAL INVESTIGATOR: Dr. Johanne& Blum | |
| ASSOCIATE INVESTIGATORS: | FACILITY: Walter Reed Army Medical Center |
| | SERVICE: Hematology-Oncology Department of Medicine |

KEY WORDS:

| | | |
|---|---|---|
| ACCUMULATIVE MEDCASE COST: None | ACCUMULATIVE CONTRACT COST: None | ACCUMULATIVE SUPPLY COST: |
| FY-80 MEDCASE COST: None | PERIODIC REVIEW RESULTS: | |

STUDY OBJECTIVE:

To determine the efficacy of cis-platinum in malignant lymphomas.

TECHNICAL APPROACH:

Cisplatinum 70/$m^2$ I.V. once q 21 days.
This is given with mannitol diuresis.

PROGRESS DURING FY-80:

WRAMC did not enter any patients on this study.
CALGB entered 29 patients and demonstrated modest activity.

NUMBER OF SUBJECTS TO BE STUDIED BEFORE COMPLETION OF STUDY: None

SERIOUS/UNEXPECTED SIDE EFFECTS IN SUBJECTS PARTICIPATING IN PROJECT:
None

CONCLUSIONS:

Cis-platinum may have some effectiveness in the treatment of malignant lymphomas.

PUBLICATIONS/ABSTRACTS, FY-80:

Cavalli, F., et al.: Phase II Trial of Cis-dichlorodiammineplatinum in Advanced Malignant Lymphoma and Small Cell Lung Cancer: Preliminary Results. Cancer Treatment Reports 63: 1599-1603, No. 9-10, September-October 1979.

Work Unit No.: 1568

Title of Project: CALGB #7892, Multimodal Therapy for the Management of Primary, Nonmetastatic Ewing's Sarcoma of Pelvic and Sacral Bones.

Principal Investigator: C, Hematology-Oncology Service

Associate Investigator:

After numerous requests for an annual progress report on this project, as of 22 Feb 81, there has not been a response. This progress report request was for the period 30 September 1979 to 1 October 1980. We can no longer delay compilation of the reports submitted by those investigators who complied with the regulations, so a supplementary annual progress report will be compiled when this investigator submits his report.

Work Unit No.: 1569

Title of Project: CALGB #7893, Multimodal Therapy for the Management of Primary, Nonmetastatic Ewing's Sarcoma of Bone; Pelvic and Sacral Sites Excluded.

Principal Investigator: Chief, Hematology-Oncology Service

Associate Investigator:

After numerous requests for an annual progress report on this project, as of 22 Feb 81, there has not been a response. This progress report request was for the period 30 September 1979 to 1 October 1980. We can no longer delay compilation of the reports submitted by those investigators who complied with the regulations, so a supplementary annual progress report will be compiled when this investigator submits his report.

WORK UNIT NO. 1570

| | | |
|---|---|---|
| DATE: 30 September 1980 | PROTOCOL NO: CALGB 7851 | STATUS: Interim X / Final |
| TITLE OF PROJECT: Treatment of Advanced Diffuse Histiocytic Lymphoma | | |

| | |
|---|---|
| STARTING DATE: 4/30/79 CALGB | ESTIMATED COMPLETION DATE: 1982 |
| PRINCIPAL INVESTIGATOR: Jeffrey L. Berenberg, M.D., LTC MC | |
| ASSOCIATE INVESTIGATORS: | FACILITY: Walter Reed Army Medical Center |
| | SERVICE: Hematology-Oncology Department of Medicine |

KEY WORDS: Histiocytic Lymphoma

| | | |
|---|---|---|
| ACCUMULATIVE MEDCASE COST: None | ACCUMULATIVE CONTRACT COST: None | ACCUMULATIVE SUPPLY COST: |
| FY-80 MEDCASE COST: None | PERIODIC REVIEW RESULTS: | |

STUDY OBJECTIVE: 1. Test whether the addition of continuous bleomycin infusions increase the response rate and duration of cyclophosphamide, vincristine, adriamycin and prednisone. (CHOP) 2. Test contribution of high dose methotrexate to abso[illegible] system in particular whether it is prophylactic against [illegible] and nervous system relapses.

CLINICAL APPROACH: 1. Treatment categories expanded to other poor histology lymphomas. 2. CHOP therapy with and without continous bleomycin infusion x 3 courses with randomization followed by standard or high dose methotrexate. (See attached sheet)

PROGRESS DURING FY-80: 111 patients remain in complete remission. CALGB have entered 56 patients.

NUMBER OF SUBJECTS TO BE STUDIED BEFORE COMPLETION OF STUDY: 320

SERIOUS/UNEXPECTED SIDE EFFECTS IN SUBJECTS PARTICIPATING IN PROJECT: None

CONCLUSIONS: Too early for conclusions.

PUBLICATIONS/ABSTRACTS, FY-80: None

Work Unit No.: 1571

Title of Project: CALGB #7891, Intergroup Rhabdomyosarcoma Study II.

Principal Investigator: Chief, Hematology-Oncology Service

Associate Investigator:

After numerous requests for an annual progress report on this project, as of 22 Feb 81, there has not been a response. This progress report request was for the period 30 September 1979 to 1 October 1980. We can no longer delay compilation of the reports submitted by those investigators who complied with the regulations, so a supplementary annual progress report will be compiled when this investigator submits his report.

WORK UNIT NO. 1572

DATE: 30 September 1980 | PROTOCOL NO: CALGB 7971 | STATUS: Interim X / Final

TITLE OF PROJECT: Phase II Study of M-AMSA (NSC 249992) in Treatment for Melanoma, Ovarian Carcinoma, Breast Carcinoma, Hypernephroma, and Hepatoma.

| | |
|---|---|
| STARTING DATE: May 1979 | ESTIMATED COMPLETION DATE: 1983 |
| PRINCIPAL INVESTIGATOR: LTC Jeffrey L. Berenberg, MC | |
| ASSOCIATE INVESTIGATORS: | FACILITY: Walter Reed Army Medical Center |
| | SERVICE: Hematology-Oncology Department of Medicine |

KEY WORDS: M-AMSA, Melanoma, Ovarian Carcinoma, Breast Carcinoma, Hypernephroma, Hepatoma

| | | |
|---|---|---|
| ACCUMULATIVE MEDCASE COST: | ACCUMULATIVE CONTRACT COST: | ACCUMULATIVE SUPPLY COST: |
| FY-80 MEDCASE COST: | PERIODIC REVIEW RESULTS: | |

STUDY OBJECTIVE: This Phase II study of M-AMSA (NSC 249992) is designed to: Determine the complete or partial response frequencies of the various selected tumors (Sec. 4.2) to treatment with M-AMSA, Determine the duration of response in those objective responding to continued M-AMSA administration, Collect additional clinical and laboratory data regarding toxicity.

TECHNICAL APPROACH: The first treatment dose will be 120 mg/M$^2$. Patients previously heavily treated with chemotherapy (especially nitrosourea) or radiotherapy or with hepatic dysfunction may start at 60 mg/M$^2$. Every three weeks the dose will be increased by 20 mg/M$^2$ over the previous dose until 160 mg/M$^2$ is reached, or until myelosuppression is encountered. Myelosuppression will require dose modification. Other severe toxicities such as extreme nausea and vomiting, mucositis, and hepatic toxicity may also be indications for dose modification.

PROGRESS DURING FY-80: Six patients are entered on this study. There have been no responses. Three patients have subsequently expired and three remain on study.

NUMBER OF SUBJECTS TO BE STUDIED BEFORE COMPLETION OF STUDY: 162

SERIOUS/UNEXPECTED SIDE EFFECTS IN SUBJECTS PARTICIPATING IN PROJECT:

none

CONCLUSIONS:

none

Reviewer of this report did not approve it. We are waiting for investigator's comments.

PUBLICATIONS/ABSTRACTS, FY-80:

none

WORK UNIT NO. 1573

DATE: 30 September 1980 | PROTOCOL NO: CALGB 7911 | STATUS: Interim / Final X

TITLE OF PROJECT:
Treatment of Primary Untreated Acute Lymphocytic Leukemia.

STARTING DATE: 25 [illegible] 79 | ESTIMATED COMPLETION DATE: Close 4/12/80

PRINCIPAL INVESTIGATOR: Dr. Jeffrey L. Berenberg

ASSOCIATE INVESTIGATORS:

FACILITY: Walter Reed Army Medical Center

SERVICE: Hematology-Oncology Department of Medicine

KEY WORDS: Acute Lymphocytic Leukemia

| ACCUMULATIVE MEDCASE COST: | ACCUMULATIVE CONTRACT COST: | ACCUMULATIVE SUPPLY COST: |
|---|---|---|
| None | None | None |

FY-80 MEDCASE COST: None

PERIODIC REVIEW RESULTS:

STUDY OBJECTIVE: 1. To improve response rate and duration in acute lymphocytic leukemia by testing high dose vs low dose prednisone in induction.

TECHNICAL APPROACH: Three arm protocol comparing prednisone 40 mg/$M^2$ with 120 mg/$M^2$ and vs prednisone 40 mg/$M^2$ plus dexamethasone 12 mg/$M^2$. All patients receive vincristine 2 mg/$M^2$ IV q week x 4.

PROGRESS DURING FY-80: One patient entered, achieved complete remission. Protocol closed because of lack of funding of Pediatric group - CALGB.

NUMBER OF SUBJECTS TO BE STUDIED BEFORE COMPLETION OF STUDY: N/A

SERIOUS/UNEXPECTED SIDE EFFECTS IN SUBJECTS PARTICIPATING IN PROJECT:

CONCLUSIONS: The only patient treated will be followed for long term toxicity and survival. No subsequent reports will be submitted.

PUBLICATIONS/ABSTRACTS, FY-80: None

Reviewer did not approve this report.
Investigator must answer his comments.

Work Unit No.: 1574

Title of Project: CALGB #7981, Comparison of FAM Versus MA in Locally Advanced or Metastatic Gastric Cancer.

Principal Investigator: C, Hematology-Oncology Service

Associate Investigator:

After numerous requests for an annual progress report on this project, as of 22 Feb 81, there has not been a response. This progress report request was for the period 30 September 1979 to 1 October 1980. We can no longer delay compilation of the reports submitted by those investigators who complied with the regulations, so a supplementary annual progress report will be compiled when this investigator submits his report.

WORK UNIT NO. 1575

DATE: 30 September 1980 | PROTOCOL NO: CALGB 7972 | STATUS: Interim X / Final

TITLE OF PROJECT: A Phase II Trial of AMSA for Refractory Hodgkin's Disease, Diffuse Histiocytic Lymphoma and Diffuse Poorly Differentiated Lymphocytic Lymphoma.

STARTING DATE: | ESTIMATED COMPLETION DATE:

PRINCIPAL INVESTIGATOR: LTC Jeffrey L. Berenberg, MC

ASSOCIATE INVESTIGATORS:

FACILITY: Walter Reed Army Medical Center

SERVICE: Hematology-Oncology
Department of Medicine

KEY WORDS:

| ACCUMULATIVE MEDCASE COST: | ACCUMULATIVE CONTRACT COST: | ACCUMULATIVE SUPPLY COST: |
|---|---|---|
| FY-80 MEDCASE COST: | PERIODIC REVIEW RESULTS: | |

STUDY OBJECTIVE: This Phase II study of M-AMSA is designed to: Determine the complete or partial response frequency of refractory Hodgkin's disease, diffuse histocytic lymphoma and poorly differentiated lymphocytic lymphoma to treatment with M-AMSA. Determine the duration of response in those Hodgkin's and lymphoma types noted above to continued M-AMSA administration. Provide additional clinical and laboratory data regarding toxicity.

TECHNICAL APPROACH: The first treatment dose will be 120 mg/M$^2$, although patients previously heavily treated with chemotherapy, <u>especially nitrosoureas or radiotherapy</u> or <u>with hepatic dysfunction</u>, may start at 60 mg/M$^2$. Every 3 weeks the dose will be increased by 20 mg/M$^2$ over the previous dose until 160 mg/M$^2$ is reached, or until myelosuppression is encountered. Myelosuppression will require dose modification. Other severe toxicity such as extreme nausea and vomiting, mucositis, and hepatic toxicity may be grounds for dose modification.

PROGRESS DURING FY-80: Two patients entered on study. One had progressive disease but remains alive with decline after responding to another protocol. The other is not evaluable. She refused further therapy after 2 weeks and died with progressive effusions and pneumonia.

NUMBER OF SUBJECTS TO BE STUDIED BEFORE COMPLETION OF STUDY: 100

UNEXPECTED SIDE EFFECTS IN SUBJECTS PARTICIPATING IN PROJECT:
None

None

, FY-80:

None

WORK UNIT NO. 1576

DATE: 30 September 1980 | PROTOCOL NO: CALGB 7982 | STATUS: Interim X / Final

TITLE OF PROJECT: Chemotherapy of Advanced Pancreatic Cancer. A Comparative Phase II Study.

STARTING DATE: December 1979 | ESTIMATED COMPLETION DATE:

PRINCIPAL INVESTIGATOR: LTC Jeffrey L. Berenberg, MC

ASSOCIATE INVESTIGATORS:

FACILITY: Walter Reed Army Medical Center

SERVICE: Hematology-Oncology Department of Medicine

KEY WORDS:

| ACCUMULATIVE MEDCASE COST: | ACCUMULATIVE CONTRACT COST: | ACCUMULATIVE SUPPLY COST: |
|---|---|---|

FY-80 MEDCASE COST:

PERIODIC REVIEW RESULTS:

STUDY OBJECTIVE: To establish the activity of two combination chemotherapeutic regimens (SMF vs. FAM) against advanced pancreatic carcinoma with respect to response frequencies, remission, and survival duration. Moreover, the relationship of response and its quality to patient survival will be determined. To study psychologic distress in patients with diagnosed unresectable pancreatic cancer with particular reference to depression in terms of the frequency, severity and nature of symptoms, as compared to a group of patients with locally advanced gastric cancer (CALGB protocol 7981).

TECHNICAL APPROACH: 5-Fluorouracil, Streptozotocin and Mitomycin-C versus 5-Fluoroucil, Adriamycin, and Mitomycin-C.

PROGRESS DURING FY-80: One patient entered. No response of measurable disease. Patient expired on day 117 with progressive debilitation with infection.

NUMBER OF SUBJECTS TO BE STUDIED BEFORE COMPLETION OF STUDY: 100

SERIOUS/UNEXPECTED SIDE EFFECTS IN SUBJECTS PARTICIPATING IN PROJECT:
None

CONCLUSIONS:
Too early for evaluation.

PUBLICATIONS/ABSTRACTS, FY-80:
None

WORK UNIT NO. 1577

DATE: 30 September 1980 | PROTOCOL NO: CALGB 7921 | STATUS: Interim X / Final

TITLE OF PROJECT:
Comparative Study of Three Remission Induction Regimens and Two Maintenance Regimens in Acute Myelogenous Leukemia

STARTING DATE: 20 Jan 80 | ESTIMATED COMPLETION DATE: 1982

PRINCIPAL INVESTIGATOR: Dr. Jeffrey L. Berenberg

ASSOCIATE INVESTIGATORS:

FACILITY: Walter Reed Army Medical Center

SERVICE: Hematology-Oncology Department of Medicine

KEY WORDS: Acute Myelogenous Leukemia

| ACCUMULATIVE MEDCASE COST: | ACCUMULATIVE CONTRACT COST: | ACCUMULATIVE SUPPLY COST: |
|---|---|---|
| None | None | None |

FY-80 MEDCASE COST: None

PERIODIC REVIEW RESULTS:

STUDY OBJECTIVE: 1. To determine if increasing intensity of induction therapy will increase remission rate. 2. To determine if clotrimoxazole will decrease infection rate during remission induction.

TECHNICAL APPROACH: Randomized: Regimen A with CO-Trimoxazole po bid during induction. Regimen B without CO-Trimoxazole. Randomize between Regimen 1) Daunomycin (DNR) 45 mg/$M^2$ IV days 1,2,3 + ARA-C 100 mg/$M^2$ IV by continous infusion day 1-7. Regimen 2) DNR 45 mg/$M^2$ IV days 1, 2, 3 + ARA-C 100 mg/$M^2$ IV by continuous infusion 6-Thoguainine 100 mg/$M^2$ po days 1-7. Regimen 3) DNR 45 mg/$M^2$ IV + ARA-C 100mg/$M^2$ IV by continuous infusion days 1-10.

PROGRESS DURING FY-80: Two WRAMC patients entered, both achieved a complete remission. CALGB - accrual not reported.

NUMBER OF SUBJECTS TO BE STUDIED BEFORE COMPLETION OF STUDY: 550

SERIOUS/UNEXPECTED SIDE EFFECTS IN SUBJECTS PARTICIPATING IN PROJECT:
None

CONCLUSIONS: Too early to evaluate.

This report has not been approved by the reviewer. We are waiting for the investigator to answer his comments.

PUBLICATIONS/ABSTRACTS, FY-80:

None

WORK UNIT NO. 1578

DATE: 30 September 1980 | PROTOCOL NO: CALGB 8081 | STATUS: Interim X

TITLE OF PROJECT: A Randomized Study Comparing the Combination of Hormonal Therapy and Chemotherapy with Chemotherapy alone for the Treatment of Advanced Breast Cancer in Postmenopausal Women. Final

STARTING DATE: July 1980 | ESTIMATED COMPLETION DATE: 1982

PRINCIPAL INVESTIGATOR: LTC Jeffrey L. Berenberg, M.D. MC

ASSOCIATE INVESTIGATORS:

FACILITY: Walter Reed Army Medical Center

SERVICE: Hematology-Oncology
Department of Medicine

KEY WORDS: Advanced Breast Cancer

| ACCUMULATIVE MEDCASE COST: | ACCUMULATIVE CONTRACT COST: | ACCUMULATIVE SUPPLY COST: |
|---|---|---|
| | | |

FY-80 MEDCASE COST:

PERIODIC DEVICE RESULTS:

STUDY OBJECTIVE: To determine the effectiveness of combination chemotherapy versus combination chemotherapy plus hormonal therapy in improving response to treatment and survival in patients with advanced breast cancer.

TECHNICAL APPROACH: Patients entered on study are randomized to receive either combination chemotherapy with cytoxan, adriamycin, 5-fluorouracil and tamoxifen in a 28 day cycle or combination chemotherapy with the same drugs and dosages without tamoxifen.

PROGRESS DURING FY-80: Of three patients entered on study in 1980, one has stable disease and two have had partial responses.

NUMBER OF SUBJECTS TO BE STUDIED BEFORE COMPLETION OF STUDY: 300

SERIOUS/UNEXPECTED SIDE EFFECTS IN SUBJECTS PARTICIPATING IN PROJECT:

CONCLUSIONS: Too early.

PUBLICATIONS/ABSTRACTS, FY-80:

None

WORK UNIT NO. 1579

DATE: 30 September 1980 PROTOCOL NO: CALGB 7283 STATUS: Interim X

TITLE OF PROJECT: Surgical Adjuvant Systemic Chemotherapy [illegible] with 5-FU, Adriamycin, and Mitomycin-C VS Observation only in Gastric Adenocarcinoma.

STARTING DATE: 1979 | ESTIMATED COMPLETION DATE: 1982

PRINCIPAL INVESTIGATOR: LTC Jeffrey L. Berenberg, M.D. MC

ASSOCIATE INVESTIGATORS:

FACILITY: Walter Reed Army Medical Center

SERVICE: Hematology-Oncology, Department of Medicine

KEY WORDS: Gastric Adenocarcinoma

| ACCUMULATIVE MEDCASE COST: | ACCUMULATIVE CONTRACT COST: | ACCUMULATIVE SUPPLY COST: |
|---|---|---|
| | | |

FY-80 MEDCASE COST:

PERIODIC REVIEW RESULTS:

STUDY OBJECTIVE: The specific aim of this study is to ascertain if 6 two monthly cycles of fluorouracil, adriamycin and mitomycin-C following potentially curative surgery for adenocarcinoma of the stomach produces a [illegible] disease free survival in comparison to standard surgical resection alone.

TECHNICAL APPROACH: Regimen I: Observation only. Regimen II: Adjuvant Chemotherapy, 5-Fluorouracil 600 mg/M$^2$ i.v. days 1, 8, 29 and 36 of each cycle, Mitomycin-C 10 mg/M$^2$ i.v. day 1 of each cycle, Adriamycin 30 mg/M$^2$ i.v. days 1 and 29 of each cycle.

PROGRESS DURING FY-80: Too early for accual of patients.

NUMBER OF SUBJECTS TO BE STUDIED BEFORE COMPLETION OF STUDY: 176

SERIOUS/UNEXPECTED SIDE EFFECTS IN SUBJECTS PARTICIPATING IN PROJECT:

CONCLUSIONS: None

This report has not been approved. Investigator did not answer reviewer's comments.

PUBLICATIONS/ABSTRACTS, FY-80:

WORK UNIT NO. 1603

DATE: 30 September 1980 | PROTOCOL NO: 7206 | STATUS: Interim ___ Final X

TITLE OF PROJECT: WRAMC Protocol 7206 - The Use of Methyl-CCNU (1-(2-chloroethyl)-3-(4-methylcyclohexyl)-1-nitrosourea-) (NSC 95441) in the Treatment of Brain Tumors

STARTING DATE: | ESTIMATED COMPLETION DATE: September 1978

PRINCIPAL INVESTIGATOR: Jeffrey J. Berenberg, M.D., LTC, MC

ASSOCIATE INVESTIGATORS:

FACILITY: Walter Reed Army Medical Center

SERVICE: Hematology-Oncology Department of Medicine

KEY WORDS:

| ACCUMULATIVE MEDCASE COST: | ACCUMULATIVE CONTRACT COST: | ACCUMULATIVE SUPPLY COST: |
|---|---|---|
| FY-80 MEDCASE COST: | PERIODIC REVIEW RESULTS: | |

STUDY OBJECTIVE: To evaluate the effectiveness of MeCCNU in the treatment of CNS tumors as measured by tumor shrinkage with possible neurological improvement and duration of survival.

TECHNICAL APPROACH: Each patient will receive: Me-CCNU 150 mg/$m^2$ po in a single dose every 6 weeks. The drug is given in one single dose on an empty stomach.

PROGRESS DURING FY-80: Closed to patient entry Sept 78. This study demonstrated a median survival of 47 weeks which was not sifnificantly different form and and tumor matched historical controls from the 5 years prior to the onset of this study. All patients entered on study have expired or been lost to follow-up.

NUMBER OF SUBJECTS TO BE STUDIED BEFORE COMPLETION OF STUDY: Closed

SERIOUS/UNEXPECTED SIDE EFFECTS IN SUBJECTS PARTICIPATING IN PROJECT:

None

CONCLUSIONS: This study's results were similar to those from other institutions. Approximately 3 months was added to median survival with Methyl-CCNU but no statistical significance.

PUBLICATIONS/ABSTRACTS, FY-80:

None

Work Unit No.: 1604

Title of Project: WRAMC #7205, Phase II, Combination Chemotherapy with Dimethyl Triazeno Imidazole Carboxamide and Adriamycin in Soft Tissue and Bone Sarcoma.

Principal Investigator: Chief, Hematology-Oncology Service

Associate Investigator:

After numerous requests for an annual progress report on this project, as of 22 Feb 81, there has not been a response. This progress report request was for the period 30 September 1979 to 1 October 1980. We can no longer delay compilation of the reports submitted by those investigators who complied with the regulations, so a supplementary annual progress report will be compiled when this investigator submits his report.

WORK UNIT NO. 1610

DATE: 30 September 1980 | PROTOCOL NO: WRAMC /307 | STATUS: Interim / Final X

TITLE OF PROJECT: Phase I-II Evaluation of Dibromodulcitol in Previously Treated Patients with Metastatic Carcinoma of the Breast.

STARTING DATE: 1973 | ESTIMATED COMPLETION DATE: Jan 1979

PRINCIPAL INVESTIGATOR: LTC Jeffrey L. Berenberg, M.D. MC

ASSOCIATE INVESTIGATORS:

FACILITY: Walter Reed Army Medical Center

SERVICE: Hematology-Oncology Department of Medicine

KEY WORDS: Metastatic Breast Cancer

| ACCUMULATIVE MEDCASE COST: | ACCUMULATIVE CONTRACT COST: | ACCUMULATIVE SUPPLY COST: |
|---|---|---|
| | | |

FY-80 MEDCASE COST:

PERIODIC REVIEW RESULTS:

STUDY OBJECTIVE: Evaluation of dibromodulcitol in patients who have been treated with and are resistant to standard modes of therapy.

TECHNICAL APPROACH: Dibromodulcitol p.o. days 1-10 each 21 day cycle.

PROGRESS DURING FY-80: This study was closed to patient entry in December 1978.

NUMBER OF SUBJECTS TO BE STUDIED BEFORE COMPLETION OF STUDY: 29

SERIOUS/UNEXPECTED SIDE EFFECTS IN SUBJECTS PARTICIPATING IN PROJECT:
Low blood count.

CONCLUSIONS: Despite responses observed in 4 patients, of 14 evaluable patients, all have developed progressive disease or expired. In the present study DBD has little effectiveness in metastatic breast cancer.

PUBLICATIONS/ABSTRACTS, FY-80:

None

Work Unit No.: 1626

Title of Project: WRAMC #7405, Treatment of Advanced Renal Cell Carcinoma with with a Combination 1-(Chlorethyl)-3-Cyclohexy-1-Nitrosourea (CCNU) and Bleomycin.

Principal Investigator: Chief, Hematology-Oncology Service

Associate Investigator:

After numerous requests for an annual progress report on this project, as of 22 Feb 81, there has not been a response. This progress report request was for the period 30 September 1979 to 1 October 1980. We can no longer delay compilation of the reports submitted by those investigators who complied with the regulations, so a supplementary annual progress report will be compiled when this investigator submits his report.

WORK UNIT NO. 1627

| | | |
|---|---|---|
| TE: 30 September 1980 | PROTOCOL NO: WRAMC 7404 | STATUS: Interim X / Final |

TLE OF PROJECT: Immunological Evaluation and
apotherapy of [illegible] with Carcinoma of the Lung

| | |
|---|---|
| RTING DATE: | ESTIMATED COMPLETION DATE: Closed |
| NCIPAL INVESTIGATOR: Dr. Jeffrey L. Berenberg | |
| SOCIATE INVESTIGATORS: | FACILITY: Walter Reed Army Medical Center |
| | SERVICE: Hematology-Oncology Department of Medicine |

Y WORDS: Immunotherapy, Lung Carcinoma

| | | |
|---|---|---|
| CUMULATIVE MEDCASE OST: None | ACCUMULATIVE CONTRACT COST: None | ACCUMULATIVE SUPPLY COST: None |

-80 MEDCASE COST: None

PERIODIC REVIEW RESULTS:

TUDY OBJECTIVE: 1. To determine therapeutic efficacy of BCG given by scarification o patients with lung carcinoma. 2. To determine if allogenic tumor cells benefit. . Correlation of *in vivo* and *in vitro* cellular immunity with clinical status.

CHNICAL APPROACH: 1. Stage I (A) patients were randomized between BCG, tumor cells nd BCG or follow-up alone. 2. Stage II - debulked surgically received radiotherapy 5000 ads plus randomization vs above. They also received Cytoxan 500 mg/M$^2$ Methotrexate 0 mg/M$^2$ iv + Vincristine 2.0 mg IV on day 1 - 8 q28d.

ROGRESS DURING FY-80: The single stage B patient left on study relapsed and died f progressive disease. The stage A patients remain free of disease.

BER OF SUBJECTS TO BE STUDIED BEFORE COMPLETION OF STUDY: None

IOUS/UNEXPECTED SIDE EFFECTS IN SUBJECTS PARTICIPATING IN PROJECT: None in 1980

NCLUSIONS: Immunotherapy may be of value to lung carcinoma patients with limited disease.

LICATIONS/ABSTRACTS, FY-80: See FY-79 report.

This report has not been approved. Waiting for investigator's comments in answer to reviewer.

WORK UNIT NO. 1628

DATE: 30 September 1980 | PROTOCOL NO: WRAMC 7406 | STATUS: Letter X

TITLE OF PROJECT: Chemoimmunotherapy of Carcinoma of the Large Bowel.

STARTING DATE: 1976 | [illegible] DATE: May 1978

PRINCIPAL INVESTIGATOR: LTC Jeffrey Berenberg, MC

ASSOCIATE INVESTIGATORS: MAJ Salvatore J. Scialla, MC

FACILITY: Walter Reed Army Medical Center

SERVICE: Radiology-Oncology, Department of Medicine

KEY WORDS: Carcinoma, Large Bowel

| ACCUMULATIVE MEDCASE COST: | ACCUMULATIVE CONTRACT COST: | ACCUMULATIVE SUPPLY COST: |
|---|---|---|
| | | |

FY-80 MEDCASE COST:

PERTINENT INTERIM RESULTS:

STUDY OBJECTIVE: To investigate the therapeutic efficacy of BCG by dermal scarification in patients with carcinoma of the colon or rectum when combined with 5-FU and combination 5-FU/MeCCNU.

TECHNICAL APPROACH: All patients are classified according to Duke's C classification: Type II (Stage $B_1$) - Extension into but not through muscularis. (Stage $B_2$) - Extension to or through serosa; negative nodes. III (Stage $C_1$) - Limited to serosa; positive nodes. IV - Locally metastatic disease beyond lymphatics, the bulk of which can be removed, but with some tumor remaining. Cannot tolerate surgery. Tumor of such size or fixed so that surgery would not be undertaken. V (Stage D) - Distant metastases.

PROGRESS DURING FY-80: No further accrual of patients.

NUMBER OF SUBJECTS TO BE STUDIED BEFORE CONCLUSION OF STUDY: Closed.

SERIOUS/UNEXPECTED SIDE EFFECTS IN SUBJECTS PARTICIPATING IN PROJECT:

CONCLUSIONS:

Will be analyzed for publication in 1983. 5 year survival information.

PUBLICATIONS/ABSTRACTS, FY-80:

WORK UNIT NO. 1629

DATE: 30 September 1980 | PROTOCOL NO: WRAMC 7407 | STATUS: Interim / Final X

TITLE OF PROJECT:

Chemoimmunotherapy of Malignant Melanoma

STARTING DATE: Nov. 1974 | ESTIMATED COMPLETION DATE: Closed May 1978

PRINCIPAL INVESTIGATOR: Dr. Johannes Blom

ASSOCIATE INVESTIGATORS:

FACILITY: Walter Reed Army Medical Center

SERVICE: Hematology-Oncology Department of Medicine

KEY WORDS: Melanoma

| ACCUMULATIVE MEDCASE COST: | ACCUMULATIVE CONTRACT COST: | ACCUMULATIVE SUPPLY COST: |
|---|---|---|
| None | None | |

FY-80 MEDCASE COST: None

PERIODIC REVIEW RESULTS:

STUDY OBJECTIVE:

To determine if nonspecific immunotherapy with BCG would prolonge disease free survival in melanoma both Stage I and advanced Stages II-IV.

TECHNICAL APPROACH:

BCG was given by dermal scarification to Stage I patients. More advanced patients received BCG and ICDT 700 mg/m$^2$ every 21 days.

PROGRESS DURING FY-80:

This study was closed in 1978. Detailed analysis was performed last year. Since then one additional patient with Stage II disease has relapsed. Because of the small number of patients entered and the lack of a concurrent control group, this study is not suitable for publication.

NUMBER OF SUBJECTS TO BE STUDIED BEFORE COMPLETION OF STUDY: None

SERIOUS/UNEXPECTED SIDE EFFECTS IN SUBJECTS PARTICIPATING IN PROJECT:

None

CONCLUSIONS:

Recommend that the follow up be for long term toxicity and that this be the final report.

PUBLICATIONS/ABSTRACTS, FY-80:

None

WORK UNIT NO. 1630

DATE: [illegible] 1982 PROTOCOL NO: WRAIR 7405 [illegible] X

TITLE OF PROTOCOL: Comparative Trial of Tamoxifen and Fluoxymesterone plus Tamoxifen in Metastatic Breast Cancer

| | |
|---|---|
| STARTING DATE: 1974 | ESTIMATED COMPLETION DATE: 1982 |
| PRINCIPAL INVESTIGATOR: LTC Jeffrey L. Berenberg, MC | |
| ASSOCIATE INVESTIGATORS: | FACILITY: Walter Reed Army Medical Center |
| | SERVICE: Hem-Oncology Department of Medicine |

KEY WORDS: Metastatic Breast Cancer

| | | |
|---|---|---|
| ACCUMULATIVE MEDCASE COST: | ACCUMULATIVE CONTRACT COST: | ACCUMULATIVE SUPPLY COST: |
| FY-80 MEDCASE COST: | PERIODIC REALIZED RESULTS: | |

STUDY OBJECTIVE: Response rates and durations will be compared to assess the relative therapeutic benefit of the two regimens and also the quality of survival. Prognostic importance of a variety of pretherapy characteristic factors will be evaluated.

TECHNICAL APPROACH: Regimen A - Tamoxifen 2 mg/$m^2$ p.o. tid. Regimen B - Fluoxymesterone 7 mg/$m^2$ p.o. bid, Tamoxifen 2 mg/$m^2$ p.o. bid. The dose of tamoxifen will gradually be increased. Addendum #1 changed the tamoxifen dose to bid.

PROGRESS DURING FY-80: A total of 40 patients have been entered on study. No new patients entered in 1980. Six patients remain stable. Of the remainder, three are not evaluable and twenty-nine developed progressive disease.

NUMBER OF SUBJECTS TO BE STUDIED BEFORE COMPLETION OF STUDY:

SERIOUS/UNEXPECTED SIDE EFFECTS IN SUBJECTS PARTICIPATING IN PROJECT:

CONCLUSIONS: Await analysis of disease control intervals.

PUBLICATIONS/ABSTRACTS, FY-80:

| Date: 1 December 1980 | Protocol No: 1643 | Status: Interim / Final X |
|---|---|---|

Title of Project:

The Use of Auto Factor IX Concentrate, Human, Dried in the Treatment of Patients with Bleeding Due to Factor VIII Inhibitors and the Treatment of Factor VIII Inhibitors

| Starting Date: November 1975 | Estimated Completion Date: The study should be closed at this time. |
|---|---|

Principal Investigator: Daniel B. Kimball, Jr., COL, MC

| Associate Investigators: | Facility: WRAMC |
|---|---|
| | Dept/Svc Department of Medicine |

Key Words:

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: |
|---|---|---|
| FY-80 MEDCASE Cost: | Periodic Review Results: (to be filled in by DCJ) | |

Study Objective:

To study the usefulness, efficacy and safety of Auto Factor IX Concentrate in the treatment of inhibitors to Factor VIII.

Technical Approach:

Progress during FY-80:

Since the activation of this study, only one patient has presented with bleeding and an inhibitor to Factor VIII. She was ineligible for the study because of concomitant liver disease.

Number of subjects to be studied before completion of study:

Serious/unexpected side effects in subjects participating in project:

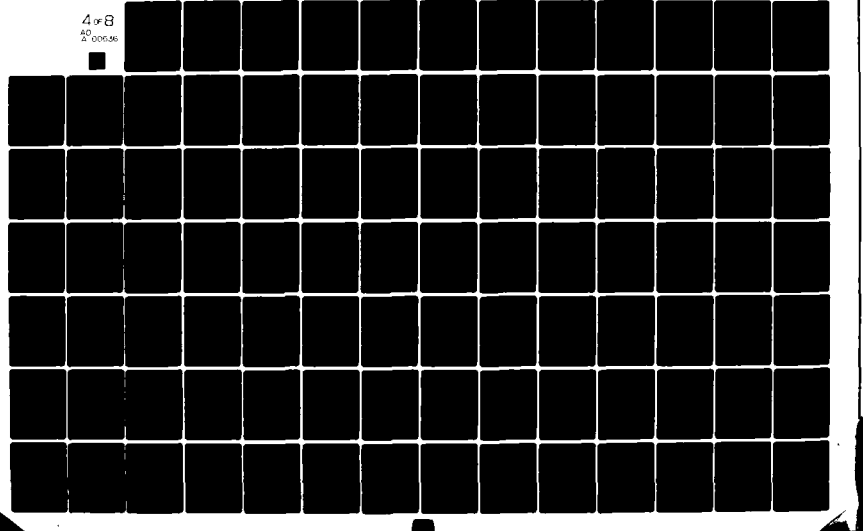
Conclusions:

In the five years that this study has been activated, only one patient has presented and she was ineligible for placement on the study and, therefore, I feel this study should be concluded.

Publications or Abstracts, FY-80: None.

AD-A100 636 WALTER REED ARMY MEDICAL CENTER WASHINGTON DC F/G 6/5
ANNUAL PROGRESS REPORT (FY-80) DEPARTMENT OF CLINICAL INVESTIGA--ETC(U)
SEP 80 T M BOEHM

UNCLASSIFIED NL



Work Unit No.: 1644

Title of Project: WRAMC #7501, Evaluation of Adriamycin and Cis-Platinum Combination Chemotherapy in Treatment of Malignant Disease.

Principal Investigator: Chief, Hematology-Oncology Service

Associate Investigator:

After numerous requests for an annual progress report on this project, as of 22 Feb 81, there has not been a response. This progress report request was for the period 30 September 1979 to 1 October 1980. We can no longer delay compilation of the reports submitted by those investigators who complied with the regulations, so a supplementary annual progress report will be compiled when this investigator submits his report.

Work Unit No.: 1649

Title of Project: WRAMC #7602, Chemoimmunotherapy of Prostatic Carcinoma.

Principal Investigator: Chief, Hematology-Oncology Service

Associate Investigator:

After numerous requests for an annual progress report on this project, as of 22 Feb 81, there has not been a response. This progress report request was for the period 30 September 1979 to 1 October 1980. We can no longer delay compilation of the reports submitted by those investigators who complied with the regulations, so a supplementary annual progress report will be compiled when this investigator submits his report.

WORK UNIT NO. 1651

DATE: 30 September 1980 PROTOCOL NO: WRAMC 7604 [illegible]

TITLE OF PROJECT: Combination Chemotherapy for the Treatment of Advanced Gastric Carcinoma with either 1-Tetra-Hydro-2-Furanyl-5-Fluorouracil (Ftorafur), Adriamycin and Mitomycin-C vs. 5-Fluorouracil, Adriamycin and Mitomycin-C.

| | |
|---|---|
| STARTING DATE: 1976 | [illegible] DATE: 1978 |
| PRINCIPAL INVESTIGATOR: LTC Jeffrey Berenberg, MC | |
| ASSOCIATE INVESTIGATORS: | FACILITY: [illegible] Army Medical Center<br>SERVICE: [illegible]<br>Department of Medicine |

KEY WORDS: Advanced Gastric Carcinoma

| | | |
|---|---|---|
| ACCUMULATIVE MEDCASE COST: | ACCUMULATIVE [illegible] COST: | ACCUMULATIVE SUPPLY COST: |
| FY-80 MEDCASE COST: | PERIODIC REVIEW RESULTS: | |

STUDY OBJECTIVE: To study the efficacy of and compare the results of treatment with Ftorafur, adriamycin, and mitomycin-C with 5-fluorouracil, adriamycin, and mitomycin-C.

TECHNICAL APPROACH: Ftorafur 1500 mg/$m^2$ I.V. days 1-5 during week 1 and 5 of each 8-week cycle. Adriamycin 30 mg/$m^2$ I.V. days 1 and 29. Mitomycin-C 10 mg/$m^2$ I.V. day 1 of each 8-week cycle. 5-Fluorouracil 600 mg/$m^2$ I.V. days 1 and 8 and days 29 and 36 of each 8-week cycle. Adriamycin 30 mg/$m^2$ I.V. days 1 and 29 of each 8-week cycle. Mitomycin-C 10 mg/$m^2$ I.V. day 1 of each 8-week cycle. Ftorafur was discontinued on 1 July 1977.

PROGRESS DURING FY-80: No further entries.

NUMBER OF SUBJECTS TO BE STUDIED BEFORE COMPLETION OF STUDY: Closed to patient entry.

SERIOUS/UNEXPECTED SIDE EFFECTS IN SUBJECTS PARTICIPATING IN PROJECT:

CONCLUSIONS: Short responses in those evaluable patients however all evaluable patients had progressive disease by 18 months with 4 shortly thereafter - Awaiting group wide study with new Phase II agents.

PUBLICATIONS/ABSTRACTS, FY-80:

WORK UNIT NO. 1654

| DATE: 30 September 1980 | PROTOCOL NO: WRAMC 7404 | STATUS: Interim / Final X |
|---|---|---|

TITLE OF PROJECT:

Treatment of Unresectable Bronchogenic Carcinoma

| STARTING DATE: | ESTIMATED COMPLETION DATE: Closed June 1977 |
|---|---|
| PRINCIPAL INVESTIGATOR: Dr. Johannes Blom | |
| ASSOCIATE INVESTIGATORS: Dr. Char | FACILITY: Walter Reed Army Medical Center |
| | SERVICE: Hematology-Oncology Department of Medicine |

KEY WORDS: Lung Cancer

| ACCUMULATIVE MEDCASE COST: None | ACCUMULATIVE CONTRACT COST: None | ACCUMULATIVE SUPPLY COST: reprints |
|---|---|---|
| FY-80 MEDCASE COST: None | PERIODIC REVIEW RESULTS: | |

STUDY OBJECTIVE: To determine whether combination chemotherapy with radiotherapy would prolong survival in unresectable bronchogenic cancer.

TECHNICAL APPROACH: Chemotherapy with CCNU, Cytoxan, Adriamycin, Hexamethylmelamine, Procarbazine and Methetrexate befor radiotherapy/RT or after in those who failed RT.

PROGRESS DURING FY-80: Thirty-seven patients entered, three entered a complete remission. One patient remains alive and is being followed. She is stable without disease.

NUMBER OF SUBJECTS TO BE STUDIED BEFORE COMPLETION OF STUDY: None

SERIOUS/UNEXPECTED SIDE EFFECTS IN SUBJECTS PARTICIPATING IN PROJECT: See 1978-79 Report

CONCLUSIONS:

See 1978-79 Report. Since only one patient remains alive this study should be closed. The remaining patient will be followed for long term toxicity.

PUBLICATIONS/ABSTRACTS, FY-80:

WORK UNIT NO. 1655

| DATE: 30 September 1980 | PROTOCOL NO: WRAMC 7607 | STATUS: Interim / Final X |
|---|---|---|

TITLE OF PROJECT: Chemoimmunotherapy of Carcinoma of the Lung Using High-Dose Methotrexate and Citrovorum Factor with or without BCG.

| STARTING DATE: 27 July 1976 | ESTIMATED COMPLETION DATE: 2 Jan 1979 |
|---|---|
| PRINCIPAL INVESTIGATOR: Dr. Johannes Blom | |
| ASSOCIATE INVESTIGATORS: LTC Charles Miller | FACILITY: Walter Reed Army Medical Center |
| | SERVICE: Hematology-Oncology Department of Medicine |

KEY WORDS: Chemoimmunotherapy, Lung Cancer

| ACCUMULATIVE MEDCASE COST: None | ACCUMULATIVE CONTRACT COST: None | ACCUMULATIVE SUPPLY COST: |
|---|---|---|
| FY-80 MEDCASE COST: None | PERIODIC REVIEW RESULTS: | |

STUDY OBJECTIVE:

1. Evaluate response obtained with high dose methotrexate and radiation therapy in patient with residual lung carcinoma.

2. Evaluate role of immunotherapy with BCG.

TECHNICAL APPROACH: 1. Escalating doses of methotrexate 17 mg/kg 300 mg/g followed by radiation therapy 1500 rads with recycling to chemotherapy.

2. Half the patients will receive BCG.

PROGRESS DURING FY-80: One patient remains NED after chemotherapy and radiation. She has lived 4 yrs. She will be followed for long term toxicity and survival.

NUMBER OF SUBJECTS TO BE STUDIED BEFORE COMPLETION OF STUDY: None

SERIOUS/UNEXPECTED SIDE EFFECTS IN SUBJECTS PARTICIPATING IN PROJECT: None

CONCLUSIONS:

Same as 79-80

PUBLICATIONS/ABSTRACTS, FY-80:

None

WORK UNIT NO. 1657

DATE: 30 September 1980 | PROTOCOL NO: WRAMC 7701 | STATUS: Interim / Final X

TITLE OF PROJECT: Velban, Bleomycin, and Cis-Platinum in the Treatment of Head and Neck Malignancies

| | |
|---|---|
| STARTING DATE: 8 March 1977 | ESTIMATED COMPLETION DATE: 30 Sept 1980 |
| PRINCIPAL INVESTIGATOR: LTC Jeffrey L. Berenberg, MC | |
| ASSOCIATE INVESTIGATORS: MAJ Martin D. Weltz, MC; MAJ David J. Perry, MC | FACILITY: Walter Reed Army Medical Center |
| | SERVICE: Hematology-Oncology, Department of Medicine |
| KEY WORDS: Head and Neck Malignancies | |

| | | |
|---|---|---|
| ACCUMULATIVE MEDCASE COST: | ACCUMULATIVE CONTRACT COST: | ACCUMULATIVE SUPPLY COST: |
| FY-80 MEDCASE COST: | PERIODIC REVIEW RESULTS: | |

STUDY OBJECTIVE: To evaluate the efficacy of the combination of Velban, Bleomycin, and Cis-Platinum in SCC of the head and neck recurring after radiation, surgery or previous chemotherapy. To evaluate the efficacy of this regimen as preoperative or pre-radiation treatment in preventing recurrence.

TECHNICAL APPROACH: Pre-operative/pre-radiation induction: Velban 4.0 mg/$m^2$ I.V. day 1, Bleomycin 15 mg I.M. qd days 1-7, Cis-platinum 60 mg/$m^2$ I.V. day 8, plus mannitol and fluids. Maintenance: Methotrexate 20 mg/$m^2$ p.o. twice weekly to begin on day 15 from onset of final induction course. Cis-platinum 60 mg/$m^2$ will be given every 29 days x3 courses then every 57 days x3 courses. Patients with recurrent disease after previous definitive treatment will be treated with the induction regimen every three weeks as long as there is continued tumor regression until the maximum dose of bleomycin (250 mg/$m^2$) has been reached.

PROGRESS DURING FY-80: 119 patients have been entered on study; 109 with head and neck cancer, 7 with uterine cervical CA, 2 with esophageal CA and 1 with SCC anus. 2 records were not available for review. One hundred seven patients with Stage III and IV squamous cell carcinomas of the head and neck received combination chemotherapy consisting of Velban 4 mg/$m^2$ IV day 1, Bleomycin 15 mg in days 1-7 and cis-platinum 60 mg/$M^2$ IV with Mannitol diuresis day 8. Patients received from one to four cycles at three week intervals. Of 64 previously untreated patients, 14 (22.0%) achieved complete response, 30 (44.0%) were partial responders and 22 (34%) were less than partial responders.
(CONTINUED ON REVERSE SIDE)

NUMBER OF SUBJECTS TO BE STUDIED BEFORE COMPLETION OF STUDY: 120

SERIOUS/UNEXPECTED SIDE EFFECTS IN SUBJECTS PARTICIPATING IN PROJECT:
Two creatinine 3.0; two with Bleomycin - related pulmonary infiltrates.

CONCLUSIONS: The combination regimen is effective in producing complete and partial responders who have superior survival to those who do not respond. Subsequent surgery and radiotherapy can be given without major morbidity. This regimen is planned for a randomized, prospective adjuvant trial.

PUBLICATIONS/ABSTRACTS, FY-80:
Brown AN Jr, Blom J, Garcia-Guerrero G, Richardson ME, Henderson RL: Combination chemotherapy with vinblastine, bleomycin, and cis-diamminedichloroplatinum (II) in squamous cell carcinoma of the head and neck. Cancer 45:2830-2835, 1980.

PROGRESS DURING FY 80 (CONT)

The response rate for all patients was 66%. 24 month actuarial survival for the complete responders was 83.2%, for the partial responder 39.3% and for nonresponders 0%. Of 42 previously treated or recurrent patients, 6 (14%) were complete responders, 13 (30%) were partial responders and 25 (56.5%) were nonresponders. The response rate was 44%. 24 month actuarial survival was 80% for complete responders, 12.8% for partial responders and 4% for nonresponders. Toxicity was mild with dermatitis, mild renal insufficiency and nausea and vomiting most commonly seen. Two patients developed renal insufficiency with creatinines of 3.0; two developed pulmonary infiltrates without symptoms; there were no drug related deaths. 24 month actuarial survival for the 64 previously untreated patients was 41.7%; 24 month actuarial survival for a retrospectively matched site and stage group was 34.5%. (Logrank test, $p > 0.10$). This combination has activity in advanced head and neck cancer; no improvement in survival over historical controls was demonstrated.

Work Unit No.: 1658

Title of Project: WRAMC #7702, Adjuvant Chemotherapy of Prostatic Carcinoma with Adriamycin and Cis-Diamminedichloroplatinum II.

Principal Investigator: Chief, Hematology-Oncology Service

Associate Investigator:

After numerous requests for an annual progress report on this project, as of 22 Feb 81, there has not been a response. This progress report request was for the period 30 September 1979 to 1 October 1980. We can no longer delay compilation of the reports submitted by those investigators who complied with the regulations, so a supplementary annual progress report will be compiled when this investigator submits his report.

| Date: 1 December 1980 | Protocol No: 1661 | Status: Interim X<br>Final |
|---|---|---|

Title of Project: Polycythemia Vera Study Group (PVSG) Protocols

| Starting Date: FY 78 | Estimated Completion Date: Protocols 1 & 10 are closed to patient accrual, but patients randomized continue to be followed and protocol 5 continues to be open for patient accrual with no near term completion date projected by the national group. |
|---|---|
| Principal Investigator: Daniel B. Kimball, Jr., COL, MC | |
| Associate Investigators:<br>Staff and Fellows of the Hematology-Oncology Service | Facility: WRAMC<br>Dept/Svc Department of Medicine |

Key Words:

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: |
|---|---|---|
| FY-80 MEDCASE Cost: | Periodic Review Results: (to be filled in by DCI) | |

Study Objective: To study the therapeutic medalities and natural history of several of the myeloproliferative diseases.

Technical Approach:

Progress during FY-80: In FY 1980 WRAMC followed patients registered on polycythemia vera study group Protocols 1, 5 and 10:
Protocol 01: Protocol 01 has been closed for several years to accrual. Mrs. E. J., a WRAMC patient living in Fayetteville, North Carolina, continues to be followed on this (over)

Number of subjects to be studied before completion of study:

Serious/unexpected side effects in subjects participating in project:

Conclusions: As noted previously, Protocols 1 & 10 are closed for further patient accrual. The patients currently randomized will continue to be followed and Protocol 5 remains open for accrual.

Publications or Abstracts, FY-80: None.

Alkeran with no complications and good control of his platelet count. As noted above, the study has been closed. Patients who would be eligible for this study would now be appropriately randomized for Protocol 12. The advantage of Alkeran in this study was marginal compared to P32 and it was felt that inpart that it might be because of the lower dose used.

Progress during FY80: (Continued)
protocol having been last evaluated this past spring at the Walter Reed Army Medical Center and receiving a dose of P32 for control of her elevated platelet count. Follow-up continues in the national office on 431 randomized patients with the median followup being 5.3 years on phlebotomy, 5.4 years on Chlorambucil and 6.1 years on P32 as of the 15 February 1980. The median survival time is 7.8 years on Chlorambucil, 9.7 years on P32 and the median has not been reached on phlebotomy therapy. The differences in survival are not statistically significant. The excess incidence of leukemia in patients treated with Chlorambucil which was identified previously continued with 16 documented cases from those patients treated with Chlorambucil as compared with 1 case on patients treated with phlebotomy and 9 on patients treated with P32. Also the increased incidence of cancer in patients treated with Chlorambucil continues although it is not statistically significant. There is as previously noted an excess incidence of thrombotic complications for patients treated on the phlebotomy arm as compared to those treated on the Chlorambucil or P32 arm. However, once the patients have been followed on any form of therapy for more than 3 years, the incidence of thrombotic complications appears comparable in all 3 groups.
Protocol 05: The three patients from Walter Reed continue to be followed on Protocol 5 and are all being followed without complications. Because of the previously noted incidence of leukemia, this study was designed to test the role of phlebotomy plus anti-aggregating agents as compared to P32 in the treatment of polycythemia rubra vera. Nationally 138 patients have been entered on the study with a median followup time of 42-56 weeks. Two deaths have been reported on the study, one due to suicide and a second due to a Budd-Chiari Syndrome at 86 weeks on the study. A total of 16 hemorrhagic or thrombotic complications have been observed ranging from moderate to severe with both arms of the protocol having had recorded complications and at this point there appears to be no difference in incidence of the complications. As noted previously, the study continues to be open for patient accrual. It would certainly appear that if the arm of phlebotomy plus antiaggregating agents can be shown to be equivalent to the P32 arm that this may be the future treatment of choice for this disease.
Protocol 10: Two patients from WRAMC have been randomized to this study which is designed to compare the therapeutic efficacy of P32 versus an oral akalating agent, phenylalanine mustard (Alkeran) for the control of primary thrombocytosis. Mrs. R.B. continues to be followed on the study although her therapy has had to be discontinued because of major cytopenia and a hypoplastic marrow. She has become significantly symptomatic because of the panocytopenia with anemia and has required transfusion. Whether this may evolve into a leukemic picture is unknown at the present time. The other patient who is randomized for the study at Walter Reed is receiving daily oral

(See above)

WORK UNIT NO. 1664

DATE: 30 September 1980 | PROTOCOL NO: WRAIR 1705 | STATUS: Interim / Final X

TITLE OF PROJECT: Metastatic Colorectal Carcinoma.

| | |
|---|---|
| STARTING DATE: July 1977 | ESTIMATED COMPLETION DATE: July 1979 |
| PRINCIPAL INVESTIGATOR: LTC Jeffrey Berenberg, MC | |
| ASSOCIATE INVESTIGATORS:<br>MAJ Martin Weltz, MC<br>MAJ Salvatore Scialla, MC | FACILITY: Walter Reed Army Medical Center<br>SERVICE: Hematology-Oncology<br>Department of Medicine |

KEY WORDS: Metastatic Colorectal Carcinoma

| | | |
|---|---|---|
| ACCUMULATIVE MEDCASE COST: | ACCUMULATIVE CONTRACT COST: | ACCUMULATIVE SUPPLY COST: |
| FY-80 MEDCASE COST: | PERIODIC REVIEW RESULTS: | |

STUDY OBJECTIVE: To investigate the therapeutic efficacy of mitomycin-C alone versus mitomycin-C plus ICRF-159 in patients with advanced colorectal neoplasms. To evaluate the hypercoagulable state which exists in metastatic colon patients.

TECHNICAL APPROACH: Regimen I - Mitomycin-C 7 mg/m$^2$ I.V. every 6 weeks. If there is progression after one dose, or stabilization after two doses, switch over to Regimen II. Regimen II - Mitomycin-C 7 mg/m$^2$ I.V. every 6 weeks ICRF-159 500 mg/m$^2$ p.o. day 1,2,3 every 3 weeks in divided doses every 8 hours. If there is objective progression after one course, the patient is to be taken off protocol. Addendum 1 changed the randomization. All patients will be entered on the ICRF-159 plus mitomycin-C regimen only.

PROGRESS DURING FY-80: No further entries.

NUMBER OF SUBJECTS TO BE STUDIED BEFORE COMPLETION OF STUDY: Closed

SERIOUS/UNEXPECTED SIDE EFFECTS IN SUBJECTS PARTICIPATING IN PROJECT:

CONCLUSIONS: Closed because of lack of therapeutic efficacy in the 12 patients that were evaluable on study.

PUBLICATIONS/ABSTRACTS, FY-80:

WORK UNIT NO. 1665

DATE: 30 September 1980 | PROTOCOL NO: WRAMC 7706 | STATUS: Active X

TITLE OF PROJECT: Treatment of Refractory Gastrointestinal Tumors with Chlorambucil and Methotrexate

| | |
|---|---|
| STARTING DATE: 1977 | ESTIMATED COMPLETION DATE: June 1981 |
| PRINCIPAL INVESTIGATOR: MAJ Martin D. Weltz, MC | |
| ASSOCIATE INVESTIGATORS: | FACILITY: Walter Reed Army Medical Center |
| | SERVICE: Hematology-Oncology Department of Medicine |

KEY WORDS: Refractory GI Tumors; chlorambucil; methotrexate

| | | |
|---|---|---|
| ACCUMULATIVE MEDCASE COST: | ACCUMULATIVE CONTRACT COST: | ACCUMULATIVE SUPPLY COST: |
| FY-80 MEDCASE COST: | PERIODIC REVIEW RESULTS: | |

STUDY OBJECTIVE: To test the therapeutic efficacy of chlorambucil and methotrexate in patients with advanced gastrointestinal tumors.

TECHNICAL APPROACH: Chlorambucil 6.0 mg/m$^2$ days 1-14
Methotrexate 10 mg/m$^2$ days 1,4,8,12 (p.o.)

This course is repeated every 28 days. For patients who have had prior chemotherapy or radiotherapy, 75% of the dosage is given for the first cycle.

PROGRESS DURING FY-80: Bethesda Naval Hospital has not entered any further patients. WRAMC entered two patients.

NUMBER OF SUBJECTS TO BE STUDIED BEFORE COMPLETION OF STUDY:

SERIOUS/UNEXPECTED SIDE EFFECTS IN SUBJECTS PARTICIPATING IN PROJECT:

CONCLUSIONS: No efficacy seen as far as response and survival; will enter a total of six more patients; if 16 patients are without response, will close study.

PUBLICATIONS/ABSTRACTS, FY-80:

Work Unit No.: 1666

Title of Project: WRAMC #7801, Immunological Evaluation and Phase I Immunotherapy Trial of Patients with Various Carcinomas.

Principal Investigator: Chief, Hematology-Oncology Service

Associate Investigator:

After numerous requests for an annual progress report on this project, as of 22 Feb 81, there has not been a response. This progress report request was for the period 30 September 1979 to 1 October 1980. We can no longer delay compilation of the reports submitted by those investigators who complied with the regulations, so a supplementary annual progress report will be compiled when this investigator submits his report.

WORK UNIT NO. 1667

DATE: 30 September 1980 | PROTOCOL NO: WRAMC 7803 | STATUS: Interim X / Final

TITLE OF PROJECT: Metastatic Breast Carcinoma

| | |
|---|---|
| STARTING DATE: | ESTIMATED COMPLETION DATE: |
| PRINCIPAL INVESTIGATOR: LTC Jeffrey L. Berenberg, M.D. MC | |
| ASSOCIATE INVESTIGATORS: MAJ Martin D. Weltz, M.D. MC | FACILITY: Walter Reed Army Medical Center |
| | SERVICE: Hematology-Oncology Department of Medicine |

KEY WORDS: Metastatic Breast Carcinoma

| | | |
|---|---|---|
| ACCUMULATIVE MEDCASE COST: | ACCUMULATIVE CONTRACT COST: | ACCUMULATIVE SUPPLY COST: |
| FY-80 MEDCASE COST: | PERIODIC REVIEW RESULTS: | |

STUDY OBJECTIVE: To evaluate response rates, mean duration of response and survival in two patient populations with advanced breast carcinoma. In the first group, patients who have failed CMF chemotherapy or single or combination therapy not to include adriamycin will be randomized to treatment with BCNU and mitomycin-C vs adriamycin alone, in an attempt to determine if BCNU and mitomycin-C provide an equivalent or improved response rate when compared to adriamycin. In the second group, patients who have progressed on CAF regimens and who have had prior exposure to methotrexate will be randomized to treatment regimen consisting of BCNU, methotrexate and vincristine, with and without cytoxan, in an attempt to test the synergism of BCNU and cytoxan.

TECHNICAL APPROACH:
Regimen I - BCNU 100 mg/$m^2$ I.V. infusion day 1, Cytoxan 400 mg/$m^2$ I.V. push day 1, Vincristine 1.4 mg/$m^2$ I.V. push day 1, Methotrexate 30 mg/$m^2$ I.V. push day 21. This cycle will be repeated every 28 days. Regimen II - BCNU 100 mg/$m^2$ I.V. in 30 cc of 5% D5W over 30 minutes on day 1, Vincristine 1.4 mg/$m^2$ I.V. push day 1, Methotrexate 30 mg/$m^2$ I.V. push day 21. This cycle will be repeated every 28 days.

PROGRESS DURING FY-80: Of twelve patients entered on study, three are lost to follow-up, four patients have progressed on treatment, three patients have expired and three patients have stable disease.

NUMBER OF SUBJECTS TO BE STUDIED BEFORE COMPLETION OF STUDY: 60

SERIOUS/UNEXPECTED SIDE EFFECTS IN SUBJECTS PARTICIPATING IN PROJECT:

CONCLUSIONS:
Continue to accumulate patients as present findings are inconclusive.

PUBLICATIONS/ABSTRACTS, FY-80: None

WORK UNIT NO. 1668

| DATE: 30 September 1980 | PROTOCOL NO: WRAMC 7807 | STATUS: Interim X / Final |
|---|---|---|
| TITLE OF PROJECT: Effect of N-Acetyl-Cysteine on Adriamycin-Induced Acute Cardiac Damage | | |

| STARTING DATE: November 1978 | ESTIMATED COMPLETION DATE: June 1981 |
|---|---|
| PRINCIPAL INVESTIGATOR: MAJ Martin D. Weltz, MC | |
| ASSOCIATE INVESTIGATORS: | FACILITY: Walter Reed Army Medical Center |
| | SERVICE: Hematology-Oncology Department of Medicine |

KEY WORDS: Adriamycin-Induced Acute Cardiac Damage

| ACCUMULATIVE MEDCASE COST: | ACCUMULATIVE CONTRACT COST: | ACCUMULATIVE SUPPLY COST: |
|---|---|---|
| FY-80 MEDCASE COST: | PERIODIC REVIEW RESULTS: | |

STUDY OBJECTIVE: To test the effect of N-acetyl-cysteine on adriamycin's acute cardiac toxicity. The study will provide information on the development of acute and chronic cardiomyopathy and the possible protective effect of N-acetyl-cysteine. ECG-gated cineangiography will be obtained at regular intervals in patients receiving adriamycin with or without N-acetyl-cysteine and the rate of progression of the cardiomyopahty will be determined in "protected" versus "non-protected" patients.

TECHNICAL APPROACH: Randomization: Regimen A - Oral placebo followed in 1 hour by adriamycin 60 mg/$m^2$ I.V. every 4 weeks. Regimen B - Oral N-acetyl-cysteine 5.6 mg/$m^2$ followed in 1 hour by adriamycin 60 mg/$m^2$ I.V. every 4 weeks.

PROGRESS DURING FY-80: This is a joint study with the National Cancer Institute. Approval was recently granted for the use of N-acetyl-cysteine. Thus far, the NCI has entered 9 patients, four on adriamycin plus N-acetyl-cysteine and five on adriamycin alone. Two patients on the adriamycin alone have developed congestive heart failure; no patients on adriamycin plus N-acetyl-cysteine have developed CHF. No patients have been entered at WRAMC because of eligibility requirements, however, several patients were considered.

NUMBER OF SUBJECTS TO BE STUDIED BEFORE COMPLETION OF STUDY:

SERIOUS/UNEXPECTED SIDE EFFECTS IN SUBJECTS PARTICIPATING IN PROJECT:
None

CONCLUSIONS: In 2 years; no patients accrued at this institution, will close study for our participation in next 9 months if no accrual.

PUBLICATIONS/ABSTRACTS, FY-80:

None

WORK UNIT NO. 1669

| DATE: 30 September 1980 | PROTOCOL NO: WRAMC 7805 | STATUS: Interim |
|---|---|---|
| TITLE OF PROJECT: Chemotherapy of Carcinoma of the Urinary Bladder. | | Final X |

| STARTING DATE: | ESTIMATED COMPLETION DATE: |
|---|---|
| PRINCIPAL INVESTIGATOR: Jeffrey L. Berenber, LTC, MC | |
| ASSOCIATE INVESTIGATORS: | FACILITY: Walter Reed Army Medical Center |
| | SERVICE: Hematology-Oncology Department of Medicine |

KEY WORDS:

| ACCUMULATIVE MEDCASE COST: | ACCUMULATIVE CONTRACT COST: | ACCUMULATIVE SUPPLY COST: |
|---|---|---|
| FY-80 MEDCASE COST: | PERIODIC REVIEW RESULTS: | |

STUDY OBJECTIVE: To examine the efficacy of cis-diamminechloroplatinum (DDP) as a post-operative adjuvant therapy for patients with stages C and $D_1$ transitional cell carcinoma of the urinary bladder who have had all gross disease removed at the time of surger. To study the usefulness of combination chemotherapy with cis-diamminedichloroplatinum (DDP), mitomycin-C (MTC) and methotrexate (MTX) in patients with metastatic (stage $D_2$) transitional cell carcinoma of the urinary bladder. To use this protocol as a pilot study for eventual expansion into a large clinical trial under the auspices of a cooperative group (CALGB) if initial results are promising.

TECHNICAL APPROACH: Adjuvant Chemotherapy - Cis-diamminedichloroplatinum 60 mg/$m^2$ I.V. infusion, every 28 days. Advanced or Recurrent Disease - Mitomycin-C 10 mg/$m^2$ I.V. day 1. Cis-diamminedichloroplatinum 60 mg/$m^2$ days 1 and 21. Methotrexate 20 mg/$m^2$ p.o. days 8 and 15.

PROGRESS DURING FY-80: Two patients entered. no patients entered during FY80. Study has been closed to patient entry for poor accrural. One patient remains free of disease at day 770. The other patient progressed after 3 months and has been lost to follow-up.

NUMBER OF SUBJECTS TO BE STUDIED BEFORE COMPLETION OF STUDY:

SERIOUS/UNEXPECTED SIDE EFFECTS IN SUBJECTS PARTICIPATING IN PROJECT:
None

CONCLUSIONS:
None

PUBLICATIONS/ABSTRACTS, FY-80:
None

WORK UNIT NO. 1670

DATE: 30 September 1980 | PROTOCOL NO: WRAMC 7902 | STATUS: Interim / Final X

TITLE OF PROJECT: Clinical Trial of Specific Immunotherapy as an Adjuvant to Surgery

STARTING DATE: Not started | ESTIMATED COMPLETION DATE: Not formally activated

PRINCIPAL INVESTIGATOR: Dr. Johannes Blom

ASSOCIATE INVESTIGATORS: | FACILITY: Walter Reed Army Medical Center | SERVICE: Hematology-Oncology Department of Medicine

KEY WORDS: Immunotherapy, Lung Cancer

| ACCUMULATIVE MEDCASE COST: None | ACCUMULATIVE CONTRACT COST: None | ACCUMULATIVE SUPPLY COST: None |
|---|---|---|

FY-80 MEDCASE COST: None | PERIODIC REVIEW RESULTS:

STUDY OBJECTIVE:

To determine if specific immunotherapy would improve post-operative survival in operable lung carcinoma.

TECHNICAL APPROACH:

Administration of a tumor associated antigen with adjuvant controls, surgery alone, adjuvant alone.

PROGRESS DURING FY-80:

Unable to cross file on IND, therefore protocol not activated.

NUMBER OF SUBJECTS TO BE STUDIED BEFORE COMPLETION OF STUDY: N/A

SERIOUS/UNEXPECTED SIDE EFFECTS IN SUBJECTS PARTICIPATING IN PROJECT: N/A

CONCLUSIONS:

Close out study

PUBLICATIONS/ABSTRACTS, FY-80:

None

WORK UNIT NO. 1671

DATE: 30 September 1980 | PROJECT NO: WRAMC 7901 | STATUS: Interim X / Final

TITLE OF PROJECT: Protocol for Adjuvant Antiplatelet Therapy for Dukes $B_2$ or C Cancer of the Colon

| | |
|---|---|
| STARTING DATE: 1979 | ESTIMATED COMPLETION DATE: June 1984 |
| PRINCIPAL INVESTIGATOR: LTC Jeffrey L. Berenberg, M.D. MC | |
| ASSOCIATE INVESTIGATORS: | FACILITY: Walter Reed Army Medical Center |
| | SERVICE: Hematology-Oncology Department of Medicine |

KEY WORDS: Cancer, Colon

| | | |
|---|---|---|
| ACCUMULATIVE MEDCASE COST: | ACCUMULATIVE CONTRACT COST: | ACCUMULATIVE SUPPLY COST: |
| FY-80 MEDCASE COST: | PERIODIC REVIEW RESULTS: | |

STUDY OBJECTIVE: The aim of this study is to seek evidence for an increase in the disease-free period (or survival) in patients with Duke's "$B_2$" or "C" colorectal cancer who are treated for a prolonged period with a platelet inhibitory agent-aspirin.

TECHNICAL APPROACH: A coagulation screen, Factor VIII complex, salicylate level and platelet function tests (aggregation and membrane analysis) will be done prior to treatment and one month post treatment. The patients will then be followed according to the protocol with subsequent coagulation studies at 4-month intervals or whenever bleeding or thrombosis appears.

PROGRESS DURING FY-80: 5 Patients were entered on protocol. One death 2° myocardial infarction post-op surgery for recurrence.

NUMBER OF SUBJECTS TO BE STUDIED BEFORE COMPLETION OF STUDY: 60

SERIOUS/UNEXPECTED SIDE EFFECTS IN SUBJECTS PARTICIPATING IN PROJECT:

CONCLUSIONS: Need 30 patients in each of 2 Arms. Information is being combined with Hershey Medical School same protocol. Too early to evaluate.

PUBLICATIONS/ABSTRACTS, FY-80:

WORK UNIT NO. 1672

DATE: 30 September 1980 | PROTOCOL NO.: | STATUS: Interim X

TITLE OF PROJECT: Tumor Tissue for Extract Preparation | Final

STARTING DATE: 1978 | ESTIMATED COMPLETION DATE: 1981

PRINCIPAL INVESTIGATOR: LTC Jeffrey L. Berenberg, MC

ASSOCIATE INVESTIGATORS:

FACILITY: Walter Reed Army Medical Center

SERVICE: Hematology-Oncology
Department of Medicine

KEY WORDS: Tumor tissue; extract preparation; colon cancer; antigen

| ACCUMULATIVE MEDCASE COST: | ACCUMULATIVE CONTRACT COST: | ACCUMULATIVE SUPPLY COST: |
|---|---|---|
| | | |

FY-80 MEDCASE COST:

PERIODIC REVIEW RESULTS:

STUDY OBJECTIVE: Evaluation of immunotherapy in carcinoma of the colon using an antigen prepared from human colon tumor tissue.

TECHNICAL APPROACH: Obtain tumor tissue remaining after the Department of Pathology has obtained the necessary samples for diagnostic purposes. Tissue should not be deposited in formalin, should be kept sterile, and rinsed with normal saline. Tumor tissue should be trimmed of fat and other tissue as much as possible.

PROGRESS DURING FY-80: No tissue obtained to date.

NUMBER OF SUBJECTS TO BE STUDIED BEFORE COMPLETION OF STUDY:

SERIOUS/UNEXPECTED SIDE EFFECTS IN SUBJECTS PARTICIPATING IN PROJECT:

CONCLUSIONS: No data for evaluation. Study will be closed if no tissue is obtained within next 6 months.

This report is not approved.
Investigator has not answered reivewer's comments.

PUBLICATIONS/ABSTRACTS, FY-80:

WORK UNIT NO. 1673

DATE: 30 September 1980 | PROTOCOL NO: TC-179 | STATUS: Interim X / Final ___

TITLE OF PROJECT: Testicular Cancer Intergroup Study.

| | |
|---|---|
| STARTING DATE: 1979 | ESTIMATED COMPLETION DATE: 1983 |
| PRINCIPAL INVESTIGATOR: LTC Jeffrey L. Berenberg, M.D. MC | |
| ASSOCIATE INVESTIGATORS: | FACILITY: Walter Reed Army Medical Center |
| | SERVICE: Hematology-Oncology Department of Medicine |

KEY WORDS: Testicular Cancer

| ACCUMULATIVE MEDCASE COST: | ACCUMULATIVE CONTRACT COST: | ACCUMULATIVE SUPPLY COST: |
|---|---|---|
| | | |

| FY-80 MEDCASE COST: | PERIODIC REVIEW RESULTS: |
|---|---|
| | |

STUDY OBJECTIVE:

To compare disease free and overall survival for surgery alone versus surgery plus early adjuvant chemotherapy in patients with resectable stage II disease.

TECHNICAL APPROACH: Stage II patients with resectable abdominal disease and negative serum tumor markers will be randomized to treatment arms with no adjuvant chemotherapy versus adjuvant chemotherapy with Vinblastine, Actinomycin-D, Cyclophosphamide, Bleomycin, and Cis-platinum.

PROGRESS DURING FY-80: 10 Patients entered on study. Two patients randomized to no adjuvant therapy have developed progressive disease. Both patients had bulky abdominal disease at surgery.

NUMBER OF SUBJECTS TO BE STUDIED BEFORE COMPLETION OF STUDY:

SERIOUS/UNEXPECTED SIDE EFFECTS IN SUBJECTS PARTICIPATING IN PROJECT:

CONCLUSIONS:

Too early.

PUBLICATIONS/ABSTRACTS, FY-80:

WORK UNIT NO. 1674

| DATE: 30 September 1980 | PROTOCOL NO: WRAMC 780/A | STATUS: Interim X / Final |
|---|---|---|

TITLE OF PROJECT: Effect of Indocyanine Green Clearance on Plasma Levels of Adriamycin

| STARTING DATE: 1978 | ESTIMATED COMPLETION DATE: June 1981 |
|---|---|
| PRINCIPAL INVESTIGATOR: MAJ Martin D. Weltz, M.D. MC | |
| ASSOCIATE INVESTIGATORS: | FACILITY: Walter Reed Army Medical Center |
| | SERVICE: Hematology-Oncology Department of Medicine |

KEY WORDS: Adriamycin

| ACCUMULATIVE MEDCASE COST: | ACCUMULATIVE CONTRACT COST: | ACCUMULATIVE SUPPLY COST: |
|---|---|---|
| FY-80 MEDCASE COST: | PERIODIC REVIEW RESULTS: | |

STUDY OBJECTIVE: To correlate indocyanine green (ICG) clearances in each patient with plasma levels of adriamycin.

TECHNICAL APPROACH: Indocyanine green clearance is to be obtained prior to the first administration of adriamycin. If there is a change in adriamycin dosage and/or a 50% increase or decrease in LFT's it is to be repeated once again prior to a dose of adriamycin. A total of 50 indocyanine analyses should allow for all permutations of liver dysfunction, dosages of adriamycin, and clinical toxicity. It is expected that the study will be completed 12 months from the time of entry of the first patient.

PROGRESS DURING FY-80: Patients only with liver disease who received adria are being studied - Accrual is slow 2° highly selected patients are needed.

NUMBER OF SUBJECTS TO BE STUDIED BEFORE COMPLETION OF STUDY: 26

SERIOUS/UNEXPECTED SIDE EFFECTS IN SUBJECTS PARTICIPATING IN PROJECT:

CONCLUSIONS: Require 6 more patients on adria alone to evaluate peak adria level with disease of liver - and toxicity.

PUBLICATIONS/ABSTRACTS, FY-80:

WORK UNIT NO. 1675

DATE: 30 September 1980 | PROTOCOL NO: WRAMC 1903 | STATUS: Interim / Final

TITLE OF PROJECT: Hepatic Artery Adriamycin Infusion- A Clinical and Pharmacokinetic Study

STARTING DATE: 1979 | ESTIMATED COMPLETION DATE: June 1982

PRINCIPAL INVESTIGATOR: MAJ Martin D. Weltz, M.C. MC

ASSOCIATE INVESTIGATORS:

FACILITY: Walter Reed Army Medical Center

SERVICE: Hematology-Oncology Department of Medicine

KEY WORDS: Hepatic Artery Adriamycin Infusion

| ACCUMULATIVE MEDCASE COST: | ACCUMULATIVE CONTRACT COST: | ACCUMULATIVE SUPPLY COST: |
|---|---|---|

FY-80 MEDCASE COST:

PERIODIC REVIEW RESULTS:

STUDY OBJECTIVE: To evaluate the efficacy of hepatic artery infusion of adriamycin in patients with metastatic liver disease. To evaluate the pharmacokinetics of adriamycin and its metabolites in patients with impaired liver function. To correlate the dose response with clinical toxicity. To evaluate radionuclide scan, angiogram, and liver-spleen scan as parameters of liver dysfunction in a comparative fashion.

TECHNICAL APPROACH: Special diagnostics will place hepatic artery catheter via axillary artery and hepatic vein catheter via femoral vein. Complete angiogram will be obtained at that time. Immediately thereafter the patient is sent to Nuclear Medicine for $^{99m}$Tc-sulfur colloid infusion (rate: 1 ml/minute dose, 4 millicuries) into the hepatic artery to evaluate initial catheter placement and hepatic blood flow distribution. This information will help assess subsequent patterns of hepatic distribution of adriamycin. The patient, upon arriving on the ward, will next have assessment of hepatic function by indocyanine green clearance.

PROGRESS DURING FY-80: Two patients entered to date.

NUMBER OF SUBJECTS TO BE STUDIED BEFORE COMPLETION OF STUDY:

SERIOUS/UNEXPECTED SIDE EFFECTS IN SUBJECTS PARTICIPATING IN PROJECT:

CONCLUSIONS: Too early; need 12 evaluable patients to determine therapeutic efficiency.

PUBLICATIONS/ABSTRACTS, FY-80:

WORK UNIT NO. 1677

DATE: 30 September 1980 | PROTOCOL NO: WRAMC 7905 | STATUS: Interim X / Final

TITLE OF PROJECT: Therapy of Acute Leukemia with low Dose Adriamycin Infusion

START[illegible]G DATE: 25 September 1979 | ESTIMATED COMPLETION DATE: 1982

PRINCIPAL INVESTIGATOR: H. Grant Taylor, M.D.

ASSOCIATE INVESTIGATORS: Martin Weltz, N.D.

FACILITY: Walter Reed Army Medical Center

SERVICE: Hematology-Oncology Department of Medicine

KEY WORDS:

| ACCUMULATIVE MEDCASE COST: | ACCUMULATIVE CONTRACT COST: | ACCUMULATIVE SUPPLY COST: |
|---|---|---|
| N/A | N/A | N/A |

FY-80 MEDCASE COST: N/A

PERIODIC REVIEW RESULTS:

STUDY OBJECTIVE:

1. To determine if kinetic alteration of the administration of Adriamycin would chance it's efficacy in advanced leukemia patients previously failing Anthracycline therapy.
2. Also to determine toxicity.

TECHNICAL APPROACH:

TRN dose infusions of Adriamycin 10 mg/$M^2$/day x 10d with possible escalation if tolerated. With measurement of Adriakinetics and cell cycle kinetics of leukemic cells by FACS.

PROGRESS DURING FY-80:

Four patients were entered on study although blast counts were lowered in all patients, no patient achieved a complete remission. All patients developed mucotoxicity by day 10 of study. Drug levels and kinetics being determined.

NUMBER OF SUBJECTS TO BE STUDIED BEFORE COMPLETION OF STUDY: 3-6

SERIOUS/UNEXPECTED SIDE EFFECTS IN SUBJECTS PARTICIPATING IN PROJECT:
Severe mucositis

CONCLUSIONS: Too early. Plan to accumulate a total of 10 patients. Depending upon toxicity and remission success.

PUBLICATIONS/ABSTRACTS, FY-80:

WORK UNIT NO: 1678

| DATE: 30 September 1980 | PROTOCOL NO: WRAMC 7914 | STATUS: Interim X / Final |
|---|---|---|

TITLE OF PROJECT: Metastatic Colo Rectal Carcinoma

| STARTING DATE: 25 September 1979 | ESTIMATED COMPLETION DATE: January 1981 |
|---|---|
| PRINCIPAL INVESTIGATOR: MAJ Martin D. Weltz, MC | |
| ASSOCIATE INVESTIGATORS: | FACILITY: Walter Reed Army Medical Center |
| | SERVICE: Hematology-Oncology Department of Medicine |

KEY WORDS: Metastatic Colo-Rectal Carcinoma

| ACCUMULATIVE MEDCASE COST: | ACCUMULATIVE CONTRACT COST: | ACCUMULATIVE SUPPLY COST: |
|---|---|---|
| FY-80 MEDCASE COST: | PERIODIC REVIEW RESULTS: | |

STUDY OBJECTIVE: To investigate the therapeutic efficacy of MOF-streptozotocin in advanced measurable colo-rectal carcinoma.

TECHNICAL APPROACH: 5-Fluorouracil 300 mg/$m^2$ I.V. daily for 5 consecutive days beginning on day 1. Repeat every 35 days. Methyl CCNU 30 mg/$m^2$ p.o. daily for 5 consecutive days beginning on day 2. Repeat every 72 days. Vincristine 1 mg I.V. push day 1. Repeat every 35 days. Streptozotocin 500 mg/$m^2$ I.V. weekly beginning on day 1. Two complete courses should be given to fully evaluate efficacy of regimen. If there is progression of measurable disease after 2 courses (see 11.4) or anytime thereafter the patient is removed from protocol and followed for survival information.

PROGRESS DURING FY-80: Excellent accrual; most patients followed at WRAMC with complete records.

NUMBER OF SUBJECTS TO BE STUDIED BEFORE COMPLETION OF STUDY: 36

SERIOUS/UNEXPECTED SIDE EFFECTS IN SUBJECTS PARTICIPATING IN PROJECT:

CONCLUSIONS: Will need additional 10 patients because of NE & LFU patients to be able to evaulate 20 fully treated patients.

PUBLICATIONS/ABSTRACTS, FY-80:

WORK UNIT NO. 1679

DATE: 30 September 1980 | PROTOCOL NO: WRAMC 7907 | STATUS: Interim / Final

TITLE OF PROJECT: Use of Methyl CCNU in the Treatment of melanoma, Colon and Gastric CA.

STARTING DATE: October 1979 | ESTIMATED COMPLETION DATE:

PRINCIPAL INVESTIGATOR: LTC Jeffery L. Berenberg, MC

ASSOCIATE INVESTIGATORS:

FACILITY: Walter Reed Army Medical Center

SERVICE: Hematology-Oncology Department of Medicine

KEY WORDS:

| ACCUMULATIVE MEDCASE COST: | ACCUMULATIVE CONTRACT COST: | ACCUMULATIVE SUPPLY COST: |
|---|---|---|
| FY-80 MEDCASE COST: | PERIODIC REVIEW RESULTS: | |

STUDY OBJECTIVE: The nitrosoureas (BCNU, CCNU, Methyl CCNU) are a group of rationally synthesized anticancer agents. Their mechanism of action is unknown, although they possess some biologic properties of alkylating agents. They have high lipid solubility and are known to cross the blood-brain barrier. They are highly active cytotoxic agents in a number of animal tumor systems. Clinical studies with Methyl CCNU have been ongoing since 1971. Methyl CCNU has shown activity as a single agent in the treatment of melanoma. Minimal activity in colon and gastric cancer has been seen with Methyl CCNU as a single agent, but in combination with 5-FU some trials reported the efficacy is increased.

TECHNICAL APPROACH:
Methyl CCNU (Semustine): 200-225 mg/$m^2$ PO every 6-8 weeks.

PROGRESS DURING FY-80: Two patients entered - one died on day 25 due to sepsis from a perforated colonic cancer. The other is alive with disease but still to early to evaluate for response. This is a cooperative effort with the NCI to gather response with toxicity data for Class "C" drugs.

NUMBER OF SUBJECTS TO BE STUDIED BEFORE COMPLETION OF STUDY:

SERIOUS/UNEXPECTED SIDE EFFECTS IN SUBJECTS PARTICIPATING IN PROJECT:
None

CONCLUSIONS:
None

PUBLICATIONS/ABSTRACTS, FY-80:

None

Work Unit #1680

DATE: 30 September 1980 | PROTOCOL NO: WRAMC 7908 | STATUS: Interim X / Final

TITLE OF PROJECT: Use of Streptozotocin in the Treatment of Metastatic Islet Cell Carcinoma of the Pancreas and Metastatic Carcinoid

STARTING DATE: Oct 79 | ESTIMATED COMPLETION DATE:

PRINCIPAL INVESTIGATOR: LTC Jeffery L. Berenberg, MC

ASSOCIATE INVESTIGATORS:

FACILITY: Walter Reed Army Medical Center

SERVICE: Hematology-Oncology Department of Medicine

KEY WORDS:

| ACCUMULATIVE MEDCASE COST: | ACCUMULATIVE CONTRACT COST: | ACCUMULATIVE SUPPLY COST: |
|---|---|---|
| FY-80 MEDCASE COST: | PERIODIC REVIEW RESULTS: | |

STUDY OBJECTIVE: Streptozotocin has shown a great degree of effectiveness in metastatic islet cell carcinoma of the pancreas and metastatic carcinoid. Clinical responses have been reported in patients with malignant islet cell tumors. Streptozotocin yields an overall response rate of approximately 70%. Even if an objective response does not occur, amelioration of symptoms from hormonal producing tumors (insulinoma and carcinoid) may occur. Adequate clinical trials with this drug have not yet been performed in other tumor types.

TECHNICAL APPROACH: Strptozotocin is available for intravenous administration only. Both a five-day intensive course regimen and a weekly regimen have been widely employed using this drug, with current favor given to a schedule of 500 mg/$m^2$ IV bolus daily x 5 every 4-6 weeks. The weekly schedule has usually been 1 gm/$m^2$/week x 4 weeks.

PROGRESS DURING FY-80: These patients entered on study - all patients had clinical diagnosis of carcinoid tumors. There were no responses and all patients have expired. At post mortem, one patient was found to have metastatic melanoma instead of carcinoid. This is part of a cooperative effort with NCI to study response with toxicity of class "C" drugs.

This report has not been approved.
Investigator has not answered reviewer's comments.

NUMBER OF SUBJECTS TO BE STUDIED BEFORE COMPLETION OF STUDY:

SERIOUS/UNEXPECTED SIDE EFFECTS IN SUBJECTS PARTICIPATING IN PROJECT:
None.

CONCLUSIONS:

None.

PUBLICATIONS/ABSTRACTS, FY-80:

None.

WORK UNIT NO. 1681

DATE: 30 September 1980 | PROTOCOL NO: WRAMC 7909 | STATUS: Interim X / Final

TITLE OF PROJECT: Use of Daunomycin in the Treatment of ALL, ANL., and Other Leukemias in Adults and Children.

STARTING DATE: October 1979 | ESTIMATED COMPLETION DATE:

PRINCIPAL INVESTIGATOR: LTC Jeffery L. Berenberg, MC

ASSOCIATE INVESTIGATORS:

FACILITY: Walter Reed Army Medical Center

SERVICE: Hematology-Oncology Department of Medicine

KEY WORDS:

| ACCUMULATIVE MEDCASE COST: | ACCUMULATIVE CONTRACT COST: | ACCUMULATIVE SUPPLY COST: |
|---|---|---|
| | | |

FY-80 MEDCASE COST:

PERIODIC REVIEW RESULTS:

STUDY OBJECTIVE: Daunomycin is known by several other names. For information purposes they include daunorubicine, rubidomycin, rubomycin C, Cerubidine® and NSC 82151.

TECHNICAL APPROACH: The currently recommended dosage of daunomycin when it is used as a single agent is 60 mg/m$^2$/day IV for three days. The course is usually repeated at intervals of three to six weeks, depending on the status of bone marrow and peripheral counts.

PROGRESS DURING FY-80: Two patients entered one achieved a CR at day 53 but relapsed on day 111 and subsequently died. The other patient died on day 31 of therapy. This is a cooperative effort with the NCI to gather response with toxicity data on Class "C" drugs.

NUMBER OF SUBJECTS TO BE STUDIED BEFORE COMPLETION OF STUDY:

SERIOUS/UNEXPECTED SIDE EFFECTS IN SUBJECTS PARTICIPATING IN PROJECT:
None

CONCLUSIONS:

Too early for conclusions.

PUBLICATIONS/ABSTRACTS, FY-80:
None

WORK UNIT NO. 1682

DATE: 30 September 1980 | PROTOCOL NO: WRAMC 7910 | STATUS: Interim X / Final

TITLE OF PROJECT: Use of 5-Azacytidine in the Treatment of Acute Granulocytic Leukemia in Adults and Children.

STARTING DATE: October 1979 | ESTIMATED COMPLETION DATE:

PRINCIPAL INVESTIGATOR: LTC Jeffery L. Berenberg, MC

ASSOCIATE INVESTIGATORS:

FACILITY: Walter Reed Army Medical Center

SERVICE: Hematology-Oncology Department of Medicine

KEY WORDS:

| ACCUMULATIVE MEDCASE COST: | ACCUMULATIVE CONTRACT COST: | ACCUMULATIVE SUPPLY COST: |
|---|---|---|
| FY-80 MEDCASE COST: | PERIODIC REVIEW RESULTS: | |

STUDY OBJECTIVE: At this point in time, 5-azacytidine has demonstrated clinical effectiveness for the induction of remission in acute granulocytic leukemia of adults and children previously refractory to other active antileukemic drugs. Response rates in solid tumors and other types of leukemia have not been great enough to warrant the use of 5-azacytidine.

TECHNICAL APPROACH: 150-200 $mg/m^2$/day intravenously for five days as a rapid injection. This drug course can be repeated every 14-21 days, depending upon recovery from myelosuppression and the bone marrow findings.

PROGRESS DURING FY-80: Two patients entered on 30 June 80. There have been no responses, however both patients had failed standard therapy for leukemia. This is a cooperative effort with NCI to gather response with toxicity data on Class "C" drugs.

NUMBER OF SUBJECTS TO BE STUDIED BEFORE COMPLETION OF STUDY: -

SERIOUS/UNEXPECTED SIDE EFFECTS IN SUBJECTS PARTICIPATING IN PROJECT:

None.

CONCLUSIONS:

Too early.

PUBLICATIONS/ABSTRACTS, FY-80:

None

WORK UNIT NO. 1683

| DATE: 30 September 1980 | PROTOCOL NO: WRAMC 7911 | STATUS: Interim X / Final |
|---|---|---|

TITLE OF PROJECT: Use of L-Asparaginase in the Treatment of Acute Lymphoblastic Leukemia in Adults and Children

| STARTING DATE: October 1979 | ESTIMATED COMPLETION DATE: |
|---|---|
| PRINCIPAL INVESTIGATOR: LTC Jeffery L. Berenberg, MC | |
| ASSOCIATE INVESTIGATORS: | FACILITY: Walter Reed Army Medical Center |
| | SERVICE: Hematology-Oncology Department of Medicine |

KEY WORDS:

| ACCUMULATIVE MEDCASE COST: | ACCUMULATIVE CONTRACT COST: | ACCUMULATIVE SUPPLY COST: |
|---|---|---|
| FY-80 MEDCASE COST: | PERIODIC REVIEW RESULTS: | |

STUDY OBJECTIVE: Erwina Cartovora asparaginase is an antigenically noncross-reactive asparaginase. It has activity comparable to that of the E. Coli preparation in both animal tumor systems and in human ALL. Compared with E. Coli asparaginase its toxicity is qualitatively and quantitatively the same. Therefore, this drug represents an alternative to E. Coli asparaginase in those situations where repeat coursed of asparaginase therapy are required or where allergic reactions force the discontinuance of the E. Coli preparation.

TECHNICAL APPROACH: Intravenously 1,000 IU/Kg 30,000 IU/$m^2$ per day x 10-20 days. Intramuscularly 6,000 IU/$m^2$ t.i.w. x 3 weeks (9 doses).

PROGRESS DURING FY-80: No patients entered.

This report has not been approved.
Investigator has not answered reviewer's comments.

NUMBER OF SUBJECTS TO BE STUDIED BEFORE COMPLETION OF STUDY:

SERIOUS/UNEXPECTED SIDE EFFECTS IN SUBJECTS PARTICIPATING IN PROJECT: None

CONCLUSIONS: None

PUBLICATIONS/ABSTRACTS, FY-80:

WORK UNIT NO. 1684

| DATE: 30 September 1980 | PROTOCOL NO: WRAMC 7912 | STATUS: Interim X / Final |
|---|---|---|

TITLE OF PROJECT: Use of Hexamethylmelamine in the Treatment of Ovarian Cancer.

| STARTING DATE: October 1979 | ESTIMATED COMPLETION DATE: |
|---|---|
| PRINCIPAL INVESTIGATOR: LTC Jeffery L. Berenberg, MC | |
| ASSOCIATE INVESTIGATORS: | FACILITY: Walter Reed Army Medical Center |
| | SERVICE: Hematology-Oncology Department of Medicine |

KEY WORDS:

| ACCUMULATIVE MEDCASE COST: | ACCUMULATIVE CONTRACT COST: | ACCUMULATIVE SUPPLY COST: |
|---|---|---|
| FY-80 MEDCASE COST: | PERIODIC REVIEW RESULTS: | |

STUDY OBJECTIVE: Cancer of the ovary is the tumor in which HMM has been shown to have definite antitumor activity. Its uses may be indicated in patients who have become refractory to therapy with alkylating agents, or in patients where therapy with alkylating agents is contraindicated (e.g. compromised bone marrow function due to prior radiotherapy).

TECHNICAL APPROACH: The currently recommended dosage of hexamethylmelamine when used as a single agent is 8 mg/kg/day (300 mg/$m^2$) X 90 or indefinitely if tolerated. The total dose is usually divided into four equal parts and given after meals and at bedtime. An intermittent regimen; i.e., 21 days (8 mg/kg/day) on and 21 days off drug, may be better tolerated and required if gastrointestinal or neurotoxicity becomes prohibitive. A reduction of the dose to 6 mg/kg/day may also be necessary. Therapy should be stopped in the presence of severe leukopenia (less than 2,000/$mm^3$) or severe thrombocytopenia (less than 75,000/$mm^3$), until marrow function has recovered.

PROGRESS DURING FY-80: No patients entered as of 1 July 80 - This is a cooperative effort with the NCI to gather response with toxicity data from Class "C" drugs.

NUMBER OF SUBJECTS TO BE STUDIED BEFORE COMPLETION OF STUDY:

SERIOUS/UNEXPECTED SIDE EFFECTS IN SUBJECTS PARTICIPATING IN PROJECT:
None

CONCLUSIONS:
Too early

PUBLICATIONS/ABSTRACTS, FY-80:

None

WORK UNIT NO. 1685

| DATE: 30 September 1980 | PROTOCOL NO: WRAMC 7913 | STATUS: Interim X / Final |
|---|---|---|

TITLE OF PROJECT: Use of VP-16 in the Treatment of Small Cell Carcinoma of the Lung.

| STARTING DATE: October 1979 | ESTIMATED COMPLETION DATE: |
|---|---|
| PRINCIPAL INVESTIGATOR: LTC Jeffery L. Berenberg, MC | |
| ASSOCIATE INVESTIGATORS: | FACILITY: Walter Reed Army Medical Center |
| | SERVICE: Hematology-Oncology Department of Medicine |

KEY WORDS:

| ACCUMULATIVE MEDCASE COST: | ACCUMULATIVE CONTRACT COST: | ACCUMULATIVE SUPPLY COST: |
|---|---|---|
| FY-80 MEDCASE COST: | PERIODIC REVIEW RESULTS: | |

STUDY OBJECTIVE: VP 16-213 has producedpartial responses in previously treated patients with a frequency ranging from 0-58% in the treatment of small cell carcinoma of the lung. Although the current recommendation is that its use should be limited to patients refractory to "standard therapy" for this disease, experimental data suggest that the response rates produced in previously untreated patients may be considerably higher.

TECHNICAL APPROACH: VP 16-213 should be administered intravenously overa a 30-minute period. Two dose schedules have been used successfully: 60 mg/m$^2$/day x 5 every 2-3 weeks or 125 mg/m$^2$/day 1,3,5, every 4-5 weeks. The exact interval between subsequent courses is modified, depending upon the time required for recovery from toxic manifestations.

PROGRESS DURING FY-80: Two patients with Testicular tumors have been treated with VP-16 - one pediatric patient with recurrent Sarcoma. Both patients with Testicular tumors are alive ivthout evidence of disease. The patient with recurrent Sarcoma is not evaluable at this time (entered June 80) - This study is part of a cooperative effort with the NCI to gather response with Toxicity data on Class C drugs.

NUMBER OF SUBJECTS TO BE STUDIED BEFORE COMPLETION OF STUDY:

SERIOUS/UNEXPECTED SIDE EFFECTS IN SUBJECTS PARTICIPATING IN PROJECT:
None

CONCLUSIONS:

None

PUBLICATIONS/ABSTRACTS, FY-80:

None

WORK UNIT NO. 1686

DATE: 30 September 1980 | PROTOCOL NO: WRAMC 7915 | STATUS: Interim / Final

TITLE OF PROJECT: Prevention of Gonadal Damage in Women Treated with Combination Chemotherapy for Hodgkin's Disease or NHC

STARTING DATE: | ESTIMATED COMPLETION DATE:

PRINCIPAL INVESTIGATOR: Ramona Chapman, M.D.

ASSOCIATE INVESTIGATORS:
T. Klein
R. Vigersky
J. Berenberg

FACILITY: Walter Reed Army Medical Center

SERVICE: Hematology-Oncology Department of Medicine

KEY WORDS:

| ACCUMULATIVE MEDCASE COST: | ACCUMULATIVE CONTRACT COST: | ACCUMULATIVE SUPPLY COST: |
|---|---|---|
| | | |

FY-80 MEDCASE COST: | PERIODIC REVIEW RESULTS:

STUDY OBJECTIVE: To protect women from ovarian failure 2° chemotherapy for Hodgkin's disease or non-H.D. lymphoma

TECHNICAL APPROACH: Randomize to received combined oral contraceptives or serve as a control with no hormonal agents during chemotherapy.

PROGRESS DURING FY-80: Three women chose to take oral contraceptives without randomization. None are off therapy.

NUMBER OF SUBJECTS TO BE STUDIED BEFORE COMPLETION OF STUDY: 20

SERIOUS/UNEXPECTED SIDE EFFECTS IN SUBJECTS PARTICIPATING IN PROJECT:

CONCLUSIONS: No patients are complaining of hot flushes. Too early to assess ovarian function.

PUBLICATIONS/ABSTRACTS, FY-80:

None

WORK UNIT NO. 1687

DATE: 30 September 1980 | PROTOCOL NO: WRAMC 8002 | STATUS: Interim X / Final

TITLE OF PROJECT: Phase II Evaluation of Methyl Glyoxal Bix-Guanyl Hydrazone (Methyl-GAG) in Advanced Esophageal Carcinoma, Head and Neck, and Cervix

STARTING DATE: | ESTIMATED COMPLETION DATE:

PRINCIPAL INVESTIGATOR: MAJ Martin D. Weltz, MC

ASSOCIATE INVESTIGATORS:

FACILITY: Walter Reed Army Medical Center

SERVICE: Hematology-Oncology
Department of Medicine

KEY WORDS:

| ACCUMULATIVE MEDCASE COST: | ACCUMULATIVE CONTRACT COST: | ACCUMULATIVE SUPPLY COST: |
|---|---|---|
| FY-80 MEDCASE COST: | PERIODIC REVIEW RESULTS: | |

STUDY OBJECTIVE: To define the response rate, and remission duration utilizing a weekly schedule of methyl-GAG in patients with advanced esophageal carcinoma, Head and neck cancer, or cervix.

TECHNICAL APPROACH: Methyl-G 500 mg/$M^2$, to be given as an intravenous infusion in D5W or normal saline over no less than 30 minutes, into a freely running IV.

PROGRESS DURING FY-80: Six patients entered from April to August 1980 all patients had squamous cell tumors. There was one partial remission and 5 with "stabilization fo disease" for variable periods of time - Two patients have expired and 4 remain on study with decrease.

NUMBER OF SUBJECTS TO BE STUDIED BEFORE COMPLETION OF STUDY:

SERIOUS/UNEXPECTED SIDE EFFECTS IN SUBJECTS PARTICIPATING IN PROJECT:
Expected Neuropathy

CONCLUSIONS: Too early

PUBLICATIONS/ABSTRACTS, FY-80:
None

WORK UNIT NO. 1688

DATE: 30 September 1980 | PROTOCOL NO: WRAMC 8001 | STATUS: Interim X / Final

TITLE OF PROJECT: Feasibility Study of the Multidisciplinary Approach to Inoperable Lung Cancer Patients

STARTING DATE: April 1980 | ESTIMATED COMPLETION DATE: April 1981

PRINCIPAL INVESTIGATOR: WRAMC Oncology Multidisciplinary Team

ASSOCIATE INVESTIGATORS:

FACILITY: Walter Reed Army Medical Center

SERVICE: Hematology-Oncology
Department of Medicine

KEY WORDS: Lung cancer; psychosocial aspects of illness; multidisciplinary approach

| ACCUMULATIVE MEDCASE COST: | ACCUMULATIVE CONTRACT COST: | ACCUMULATIVE SUPPLY COST: |
|---|---|---|
| | | |

FY-80 MEDCASE COST:

PERIODIC REVIEW RESULTS:

STUDY OBJECTIVE: To conduct a descriptive study to determine the feasibility and utilization of a multidisciplinary oncology approach to the treatment and management of inoperable lung cancer patients at WRAMC.

TECHNICAL APPROACH: A resource providing patients and their families an opportunity to work with skilled incividuals in order to deal with some of the psychosocial aspects of illness, and to maintain their general well being.

PROGRESS DURING FY-80: Eight patients were entered on study.

NUMBER OF SUBJECTS TO BE STUDIED BEFORE COMPLETION OF STUDY: 12

SERIOUS/UNEXPECTED SIDE EFFECTS IN SUBJECTS PARTICIPATING IN PROJECT:

CONCLUSIONS: Team approach is beneficial to patients for pain control and discharge planning (social work and community health nurse).

PUBLICATIONS/ABSTRACTS, FY-80:

| Date: 9 December 1980 | Protocol No: 1700 | Status: Interim XX<br>Final |
|---|---|---|

Title of Project:

Sleep Apnea in Hypothyroid Patients

| Starting Date: 15 June 80 | Estimated Completion Date: 31 May 82 |
|---|---|

Principal Investigator: Krishnan R. Rajagopal

| Associate Investigators:<br>Sarkis S. Derderian<br>Claude J. Tellis<br>Kenneth D. Burman<br>Rahman Jahbari<br>Keith K. Hunt, Jr. | Facility: WRAMC Pulmonary Clinic<br>Dept/Svc Medicine/Pulmonary |
|---|---|

Key Words:
Apnea, Hypothyroid

| Accumulative MEDCASE Cost: N/A | Accumulative Contract Cost: N/A | Accumulative Supply Cost: N/A |
|---|---|---|

| FY-80 MEDCASE Cost: | Periodic Review Results:<br>(to be filled in by DCI) |
|---|---|

Study Objective: To demonstrate and better define periods of apnea during sleep in patients with hypothyroidism.

Technical Approach: Using standard polysonochographic techniques patients with hypothyroidism (decreased T4 and/or increased TSH) will be monitored and the records analyzed for the relative frequency and type of apnea during sleep.

Progress during FY-80: Five hypothyroid subjects studied have shown several episodes of obstructive sle p apnea.

Number of subjects to be studied before completion of study: 10

Serious/unexpected side effects in subjects participating in project:
N/A

Conclusions: Work in satisfactory progress - will be completed after monitoring 10 more subjects.

Publications or Abstracts, FY-80: Abstract submitted for the American Thoracic Society Meeting in May 1981.

Work Unit No.: 1700

Funds Utilized, FY-80:

Funding Requirements, FY-81:

| | | Total |
|---|---|---|
| Personnel: | N/A | |
| Equipment: | (Maintenance) $500. | $500.00 |
| Supplies: | (consumable) EEG paper @$13.63 per box with 1 patient per box, for 10 patients $140. | $140.00 |
| | H.P. Paper @ $53.00 per box with one patient per box $530.00 | $530.00 |
| Travel: | For presentation at Annual Meeting $700.00 | $700.00 |
| Other: | Preperation , publication costs and reprints $500.00 | $500.00 |
| | Miscellaneous $200.00 | $200.00 |
| | Total | $2.570.00 |

Annual Report and Request for Continuation (Protocol in force since 1978)

Work Unit No.: 1903

Title of Project: Detection of T. pallidum in the CSF in patients with neurosyphilis.

Investigators:

Principal Investigator: S.M. Harrison, CPT MC

Associate Investigators: Charles N. Oster, MAJ MC
W. J. Herald
E. C. Tramont, LTC MC

Starting Date: (Approved Nov 1976) Patients not entered until microbiologist became available Sept78.

Estimated Date of Completion: Sept 1981.

Objective:

1. To determine the frequency with which Treponema pallidum can be isolated from the CSF of patients who have received an inadequate course of treatment for primary or secondary syphilis (see Reference 1).

2. To attempt isolation in patients with late latent syphilis or apparent asymptomatic neurosyphilis.

3. To explore and improve procedures for Treponemal antigen detection as an indication of neurosyphilis, and an indication for therapy.

Technical Approach: T. pallidum isolation (as modified by DF Dec 1979). Patients from the Military District of Washington who have latent syphilis will have a lumbar puncture for determining therapy. If cerebrospinal fluid exam is positive for VDRL, FTA-absorbed, FTA-unabsorbed or if there is abnormal protein, glucose, or cell count suggestive of possible neurosyphilis, then the CSF will be passed into two experimental rabbits and one control rabbit. (Negative RPR and FTA virgin male rabbits will be used). The two experimental rabbits will be carried for 40 days, sacrificed and testicular homogenates passed in second rabbits. At the end of 80 days, the rabbits will be sacrificed, testes homogenized, and examined for Treponemes by darkfield and direct fluorescent antibody. RPR, VDRL and FTA will be determined on all test rabbits.

T. pallidum antigen detection. The Nichols' strain of T. pallidum passed in rabbits will be used for simulating infected CSF. After extraction, pooled CSF will be infected with T. pallidum, and antigen will be determined by gas chromatography, limulus lysate, or solid phase radioimmunoassay.

Progress and Results: Although 19 more patients have been examined this year, no rabbit syphilomas nor serologic changes have been identified. Preliminary studies on antigen determination have begun.

Conclusions: There is insufficient data for conclusion at this point.

Funding Requirements FY-79: $10,000.00

Funding Requirements FY-80: $12,000.00

Funding Requirements FY-81: $11,000.00

Within Funding Requirements:

Personnel: W. J. Herald, GS-9
S. M. Harrison
C. N. Oster
E. C. Tramont

Equipment: Already available through the Infectious Disease Labs, CIS.

Consumables:

| | |
|---|---|
| Animals and care | $ 9,000.00 |
| Chemicals, reagents & glassware | 1,500.00 |
| Travel | 500.00 |

Publications:

Tramont, EC, Chapter 180, Treponema pallidum (syphilis) in PRINCIPLES & PRACTICE OF INFECTIOUS DISEASE, 1979. Editors Mandell, Bennett and Douglas, McGraw Hill, New York.

Type of Report: Interim.

References:

Tramont, EC. Persistence of Treponema pallidum in Cerebrospinal Fluid Following Recommended Penicillin G Therapy. JAMA 236:22-6-2207, 1976.

# DISPOSITION FORM

For use of this form, see AR 340-15, the proponent agency is TAGCEN.

| REFERENCE OR OFFICE SYMBOL | SUBJECT |
|---|---|
| HSWP-MI | Continuation of Protocol #1905 |

TO C, Clinical Investigation Svc FROM C, Infectious Dis Svc DATE 18 Sept 80 CMT 1

1. Request continuation of Protocol #1905 entitled "Local Immune Response to Neisseria gonorrhoeae".

2. The objectives of the original protocol were as follows:

"The objective of this research is to study the kinetics of local immunity as it pertains to bacterial infections, in particular, N. gonorrhoeae, such that a well-tolerated local immunogen capable of inducing protection in man might be developed in the future.

Briefly, our hypothesis holds: 1) that the initial event of many infections is implantation on mucosal cells of the offending agent to which a local immunological response develops. Gonococcal infection is primarily a local disease and, therefore, well suited for studying local immunity; 2) that there are associated with gonococcal organisms, antigenic determinants which when isolated, purified and concentrated will upon local administration induce significant protection to infection.

The specific objectives were to

(1) Development of New Techniques to Determine Inhibition of Epithelial Cell Attachment (IEA) of Gonococci

(2) To determine which antigenic determinants against which the human local immune response is directed the following antigens will be isolated, characterized and purified: acetone or formalin killed whole organisms, native outer cell wall complex, lipopolysaccharide (endotoxin), and pili. These antigens in turn will be used to block inhibition of epithelial cell attachment.

(3) An attempt will be made to better understand the kinetics of local and parenteral antibody formation by determining concurrently the ability of serum and local antibodies obtained concurrently to inhibit epithelial cell adhesion of the homologous infecting organisms.

(4) An attempt to shed some light on the mechanisms of recurrent gonococcal infections will be undertaken by examining the ability of antibody raised in rabbits to inhibit epithelial cell attachment of recidivistic strains isolated from the same patient at different times.

3. The majority of these objectives have been met, and can be summarized as follows:

(1) Attempts to develop new techniques to measure IEA have been unsuccessful so far (Annual Report 1976).

(2) The SPRIA has been modified for measuring local antibody (Annual Report 1978).

(3) The principal antigen mediating attachment of gonococci to epithelial cells are pili (Annual Report 1978, 79, 80) but other antigens are also involved (Annual Report 1979).

18 Sep 80

JECT: Continuation of Protocol #1905

Tramont EC, Ciak J, Boslego JW, McChesney DG, Brinton CC and Zollinger W. Antigenic Specificity of Antibodies in Vaginal Secretions During Infection with Neisseria gonorrhoeae. J Infect Dis 142:23-31, 1980.

Tramont EC. Role of Adhesion of N. gonorrhoeae in Disease, Ciba Foundation Symposium, London, UK, 1980.

Boslego JW, McChesney DG, Sadoff J, Ciak J, Tramont EC. Human Genital Antibody Response to a Gonococcal Pilus Vaccine (Abstract). ICCAC, New Orleans, 1980.

. Projected costs: FY-81

Equipment: new gamma counter $20,000. Old equipment is in need of constant repair secondary to heavy use.

Consumable supplies: $15,000.

(4) Recurrent gonococcal infections may be due to antigenic heterogenicity of gonococcal pili (Annual Report 1978).

(5) Parenteral immunization with a gonococcal pilus vaccine induces local antibody capable of inhibiting attachment (Annual Report 1980).

4. Future directions

(1) The kinetics of this local response will be studied by examining the serum and local responses concurrently.

(2) The response to local vaccination with a gonococcal pilus vaccine will be studied.

(3) The response to parenteral followed by local immunization and vice versa will also be studied.

(4) Other attachment antigens besides pili involved in attachment will be determined and studied.

5. Bibliography (1978-1980)

Tramont EC, Ciak J. Antigonococcal antibodies in Genital Secretions. 1978 in Immunobiology of Neisseria gonorrhoeae, pp 274-276.

Tramont EC. Human Immune Response to Neisseria gonorrhoeae - Prospectives for Vaccine Development. Presented at 32nd Annual Meeting, Soc. Med. Consultants to the Armed Forces. Nov. 1977. (Abstract)

Tramont EC, Ciak J, Gilbreath M, Brinton C (Abstract) Blockage of Local Antigonococcal Antibody by Gonococcal Antigens. ICCAC, Atlanta, Georgia, 1978.

Tramont EC, Hodges W, Ciak J. Importance of Antigenic Differences in Gonococcal Reinfection. (Abstract) Clin Res. 1978.

Tramont EC, Hodges W, Ciak J, Gilbreath M. Importance of Differences in Attachment Antigens in Gonococcal Reinfections. J Clin Lab Med 93:730-735, 1978.

Tramont EC, Ciak J, McChesney D, Boslego JW, Brinton CC. Cross Reactivity of Gonococcal Pili as Determined by Inhibition of Epithelial Cell Attachment. (Abstract) presented ICCAC, Boston, Mass. 1979.

Tramont EC, Boslego JW, Sadoff J, Zollinger W, Lolik A, Bryan J, Brinton CC. Safety and Immunogenicity Study of Gonococcal Pilus Vaccine. (Abstract) presented ICCAC, Boston, Mass. 1979.

| Date: 20 September 1980 | Protocol No: 1985 | Status: Interim |
|---|---|---|

Title of Project: Local Immune Response to Neisseria gonorrhoeae in Humans

| Starting Date: 27 Sep 77 | Estimated Completion Date: 1983 |
|---|---|

Principal Investigator: Edmund C. Tramont

| Associate Investigators:<br>John Boslego, MAJ MC<br>Jennie Ciak, GS 12 | Facility: Walter Reed Army Medical Center<br>Dept/Svc Infectious Disease |
|---|---|

Key Words: Neisseria gonorrhoeae, local immunity

| Accumulative MEDCASE Cost: $20,000.00 | Accumulative Contract Cost: $1,000.00 | Accumulative Supply Cost: $15,000.00 |
|---|---|---|

| FY-80 MEDCASE Cost: $36,000.00 | Periodic Review Results:<br>(to be filled in by DCI) |
|---|---|

Study Objective:

To study the local immune response to mucosal infection or immunization with a gonococcal vaccine.

Technical Approach:

The immune response is to be studied using an inhibition of attachment and solid phase radioimmunoassay (see previous annual reports).

Progress during FY-80:

See attached sheets.

Number of subjects to be studied before completion of study:

Serious/unexpected side effects in subjects participating in project:

Conclusions:

See attached sheets

Publications or Abstracts, FY-80: See attached sheets

Progress during FY-80

1) A parenterally administered gonococcal pilus vaccine was shown to induce local antibody.

A prototype gonococcal vaccine manufactured at the University of Pittsburgh and in collaboration with WRAIR, was tested for safety and immunogenicity in volunteers at WRAMC and at Fort Bragg, North Carolina. Vaginal washings and seminal fluid were obtained and tested for local antibody by the standard inhibition of attachment assay developed by us and the standard Solid Phase radioimmunoassay developed by Dr. Wendell Zollinger at WRAIR.

Eleven female volunteers were given two intramuscular injections of 100, 200, 500, or 1000 ug of a gonococcal pilus vaccine (PGH 3-2, Lot 001) one month apart. Antipilus antibodies (IgG, IgA) were measured in vaginal secretions by solid phase radioimmunoassay (SPRIA) and expressed as micrograms (ugs) of specific antipilus antibody/ugs of total IgG in the vaginal secretion. Measurements were made for 8 weeks after the initial vaccination. All 11 volunteers had antibody rises; 10/11 within 2 weeks after the initial vaccination. The geometric mean of the maximal fold rises were: IgG 4.6, IgA 7.6. The antibody rises appeared to be dose dependent, although individual variation was seen.

Four male volunteers were given 2 mg subcutaneous booster injections of PGH 3-2 vaccine one year after initial vaccination. Antipilus antibodies were measured in seminal fluid by SPRIA and standardized for total IgG as above. Measurements were made for 6 weeks after vaccination. All volunteers demonstrated an antibody response within 2 weeks. The geometric mean of the maximal fold rises were: IgG 9.4, IgM 2.7, IgA 4.4. The secretory antibody responses appeared to parallel that seen in the serum (Fig 1, Fig 2, Fig 3).

The local genital antibodies were also capable of functional activity, namely in vitro inhibition of attachment of the gonococcus to epithelial cells (Table 1).

2) A prototype gonococcal pilus vaccine PGH 3-2 was previously shown to be safe and immunogenic. The probable functional aspects of a gonococcal vaccine were demonstrated by the ability of these antibodies to block attachment of the gonococci to human buccal epithelial cells. The antigenic determinant responsible for blocking attachment was shown to be pili (Table 3). The antibodies also blocked attachment of heterologous strains (Table 4).

3) The cross reactivity of antibodies from patients with naturally occurring N. gonorrhoeae infections to homologous and heterologous GC pili were studied in the SPRIA. All patients studied showed antibody rises to the homologous strain. Three of the six strains demonstrated significant levels of antibody against several of the heterologous strains.

Five of six normal controls demonstrated low levels of antibody against all pili tested. One of the normal controls had high levels of antibody against 6 of the 7 pili strains.

4) An IgA protease was isolated from liquid GC media in which N. gonorrhoeae was grown. This protease was capable of splitting serum IgA isolated from a IgA myeloma patient into two fragments. The activity of this enzyme on local secretory antibody from patients infected is being studied or from volunteers who received the PGH 3-2 gonococcal pilus vaccine.



360

TABLE 1

INHIBITION OF ATTACHMENT OF PGH 3-2 GONOCOCCI WITH GENITAL SECRETIONS FROM VOLUNTEERS IMMUNIZED PARENTERALLY WITH PGH 3-2 GONOCOCCUS PILUS VACCINE

| | WEEKS | | | | |
|---|---|---|---|---|---|
| Vol(1) | preimm | 2 | 4 | 6 | 8 |
| 2 | < 1:1 | < 1:1 | < 1:1 | < 1:1 | |
| 4 | < 1:1 | 1:4 | | < 1:1 | < 1:1 |
| 25 | 1:4 | 1:8 | 1:16 | 1:16 | 1:32 |
| 28 | 1:2 | 1:8 | 1:8 | 1:4 | 1:2 |

(1) Volunteers 2 and 4 were men given a booster injection one year after the initial vaccination. Volunteers 25 and 28 were women given a booster vaccination at the 4th week.

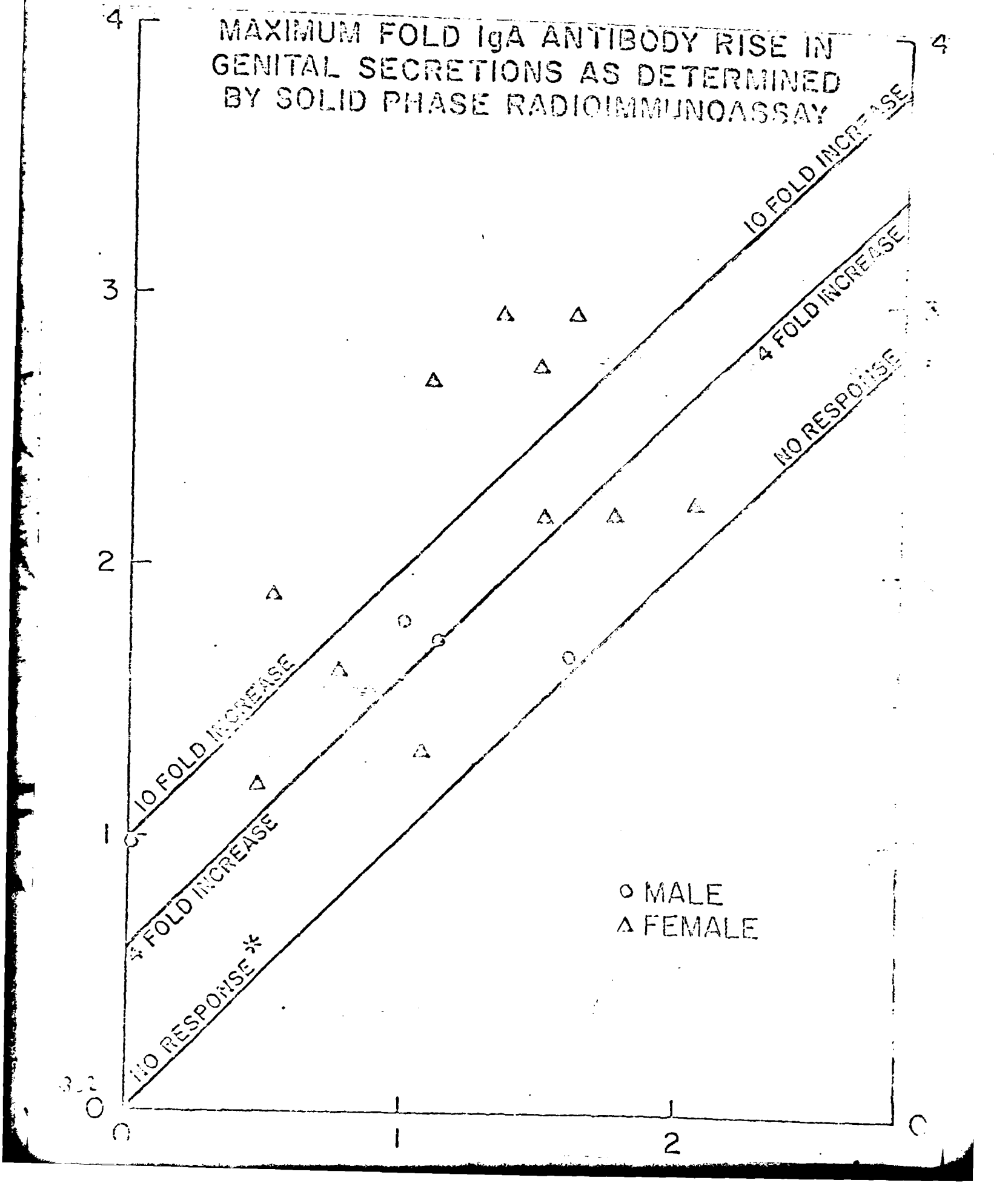
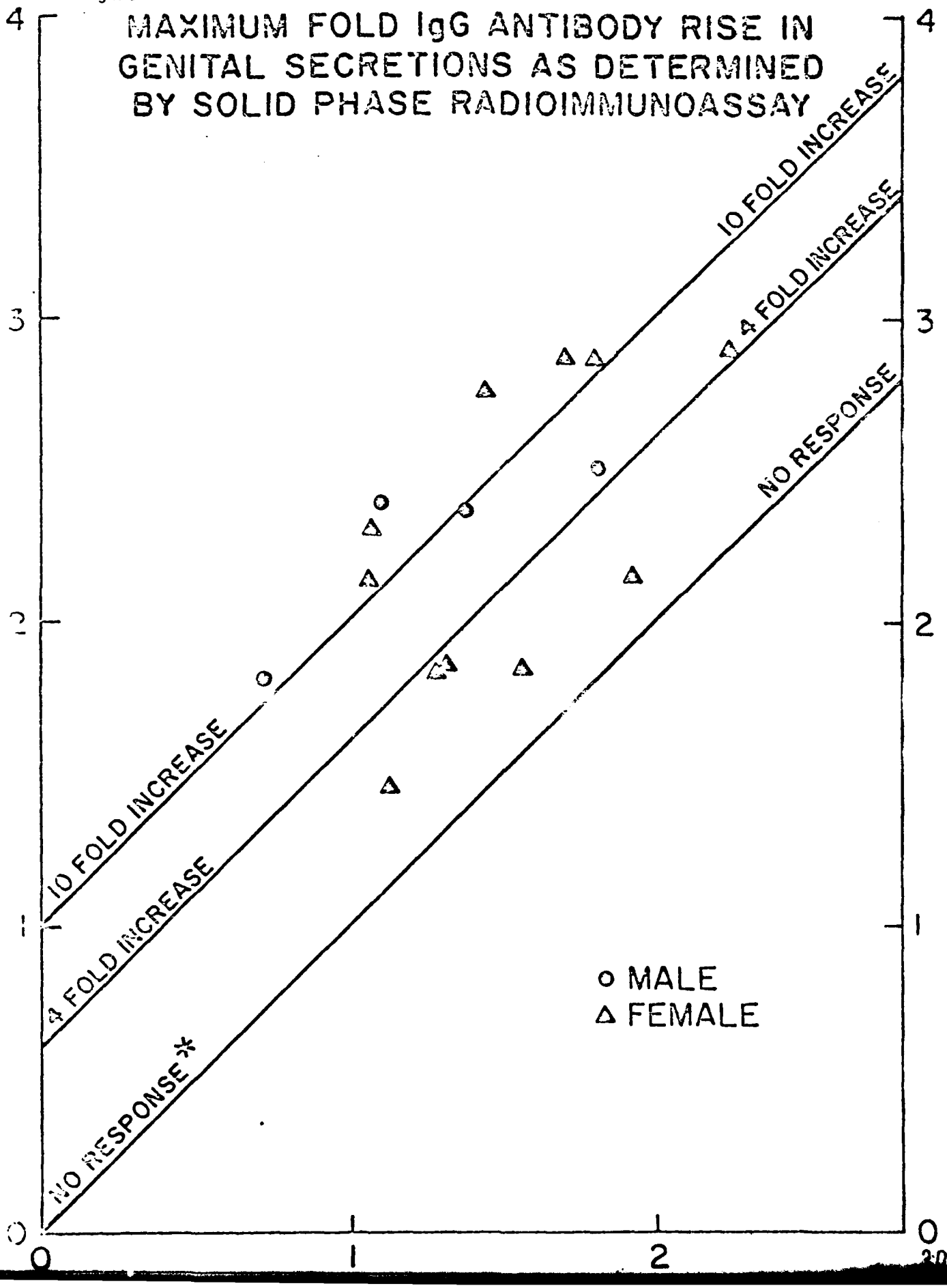

MAXIMUM FOLD IgA ANTIBODY RISE IN GENITAL SECRETIONS AS DETERMINED BY SOLID PHASE RADIOIMMUNOASSAY
10 FOLD INCREASE
4 FOLD INCREASE
NO RESPONSE
10 FOLD INCREASE
4 FOLD INCREASE
NO RESPONSE *
o MALE
Δ FEMALE
0
1
2
3
4

Figure 2


MAXIMUM FOLD IgG ANTIBODY RISE IN GENITAL SECRETIONS AS DETERMINED BY SOLID PHASE RADIOIMMUNOASSAY
10 FOLD INCREASE
4 FOLD INCREASE
NO RESPONSE
10 FOLD INCREASE
4 FOLD INCREASE
NO RESPONSE *
o MALE
Δ FEMALE
0
1
2
3
4

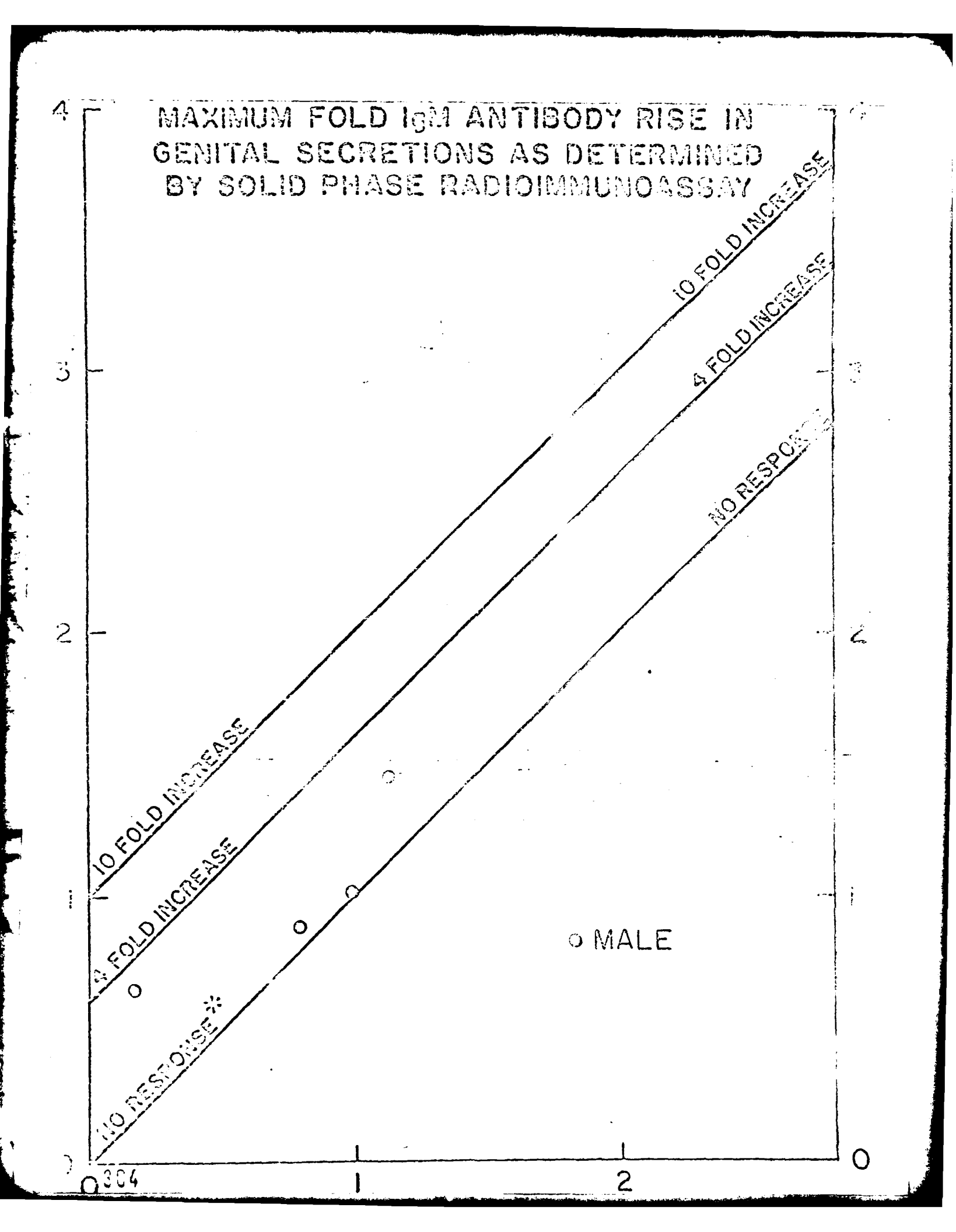

MAXIMUM FOLD IgM ANTIBODY RISE IN GENITAL SECRETIONS AS DETERMINED BY SOLID PHASE RADIOIMMUNOASSAY
10 FOLD INCREASE
4 FOLD INCREASE
NO RESPONSE
10 FOLD INCREASE
4 FOLD INCREASE
NO RESPONSE*
MALE
0
1
2
3
4
0
1
2
3
4

Table 2

Post vaccination sera absorbed with PGH 3-2 LPS and PGH 3-2 pili

| Serum | IEA | SPRIA | |
|---|---|---|---|
| | | LPS/µg/ml | pili/µg/ml |
| pre-immunization | < 1:1 | 0.51 | 4.56 |
| post-imm. unabsorbed | 1:16 | 0.75 | 17.41 |
| post-imm. absorbed LPS | 1:32 | 0.59 | 16.93 |
| post-imm. absorbed pili | < 1:1 | 0.41 | 4.90 |

Serum from volunteer #4 (1 mg dose) was absorbed with Pgh 3-2 LPS, then with vaccine pili. Absorption with LPS did not effect the IEA titer, while absorption with pili reduced the titer to pre-immunization levels.

Table 3

Inhibition of attachment of heterologous strains

| Serum (wk) | Pgh 3-2(2) | Phi 3(2) | Phi 5(2) | Phi 8(2) | Phi 19(2) | 135(3) | 222(3) | 769(3) | 339(4) |
|---|---|---|---|---|---|---|---|---|---|
| Vol 1 (pre) | 1:1 | 1:1 | 1:1 | | | 1:1 | | 1:1 | |
| Vol 1 (7wk) | 1:8 | 1:2 | 1:4 | | | 1:4 | | 1:2 | |
| Vol 9 (pre) | 1:2 | | | 1:2 | 1:1 | | 1:1 | | 1:2 |
| Vol 9 (7wk) | 1:16 | | | 1:8 | 1:8 | | 1:2 | | 1:4 |
| Vol 4 (pre) | 1:1 | < 1:1 | | < 1:1 | | | | 1:1 | 1:1 |
| Vol 4 (4wk) | 1:8 | 1:1 | | 1:4 | | | | 1:2 | 1:4 |

(1) vaccine strain

(2) Philippine strain

(3) U.S. strain

(4) Korean strain

Conclusions

(1) A parenterally administered pilus vaccine was shown to induce local antibody.

(2) This local antibody was capable of functional activity, namely inhibition of attachment.

(3) This antibody appears to be cross-reactive against other strains.

Publications and Abstracts, FY-80

Tramont, EC, Ciak J, Boslego JW, McChesney DG, Brinton CC and Zollinger W. Antigenic Specificity of Antibodies in Vaginal Secretions During Infection with Neisseria gonorrhoeae. J Infect Dis 142:23-31.

Tramont EC. Role of Adhesion of N. gonorrhoeae in Disease, Ciba Foundation Symposium, London, UK, 1980.

Boslego, JW, McChesney DG, Sadoff J, Ciak J, Tramont EC. Human Genital Antibody Response to a Gonococcal Pilus Vaccine. ICCAC, New Orleans, 1980.

# DISPOSITION FORM

For use of this form, see AR 340-15, the proponent agency is TAGCEN.

| REFERENCE OR OFFICE SYMBOL | SUBJECT |
|---|---|
| HSWP-MI | Justification of fund |

TOC, Dept of Clin Investigation FROM Principal Investigator DATE 5 Jan 1981 CMT 1
Protocol #1965

1. A new gamma counter is needed for the following reasons:

   a) The principle antibody test employed by us is the solid phase radioimmunoassay (SPRIA). This test is sensitive enough to quantitate local antibodies, a major technical problem in conducting these studies.

   b) The SPRIA will also be adapted for measuring antigens, similar to tests now employed in the Virus Department, WRAIR, for measuring hepatitis A & B antigens.

   c) The present gamma counter which we have at our disposal is outmoded, outdated and has been down a total of four months in the past twelve resulting in interruption in study and lost man hours. Also it does not have the computer capabilities which we need for storing and correlating our data. This requires many man hours to calculate the data by hand.

   d) Finally, it is only partially automated and has a limited sample capacity; productivity is greatly enhanced when samples can be run automatically overnight.

2. Supplies

| | |
|---|---|
| isotopes | $ 2,000.00 |
| purified GC pili | 4,000.00 |
| monoclonal antibodies | 4,500.00 |
| animals | 1,500.00 |
| (rabbits housed at WRAIR) | |
| expendible misc. supplies | 3,500.00 |
| i.e. collection cups | |
| vaginal tampons | |
| Kellogg's GC culture media | |
| liquid nitrogen | |
| silk labels | |
| Calgiswabs | |
| minitek CTA's | |
| flexible microtiter plates | |
| pipette tips | |
| teletype paper for gamma counter | |
| teletype ribbons | |
| Wheaton vials | |
| etc. | |
| | $15,000.00 |

Hilda Cargelli
for EDMUND C. TRAMONT, M.D.
LTC , MC
Chief, Infectious Disease Service

DA FORM 2496 REPLACES DD FORM 96, WHICH IS OBSOLETE. GPO-1975-665-422/1063

| Date: 7 October 1980 | Protocol No: 1906 | Status: Final |
|---|---|---|

Title of Project: The Limulus Lysate Assay for the Determination of Gram Negative Meningitis Septic Arthritis and Contamination of Intravenous Fluids.

| Starting Date: | Estimated Completion Date: 10/80 |
|---|---|

Principal Investigator: Charles Oster, MAJ MC

| Associate Investigators: | Facility: WRAMC |
|---|---|
| Arthur Dobek, Ph.D.<br>Edmund C. Tramont, LTC MC | Dept/Svc Med/Infectious Disease |

Key Words:

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: |
|---|---|---|

| FY-80 MEDCASE Cost: | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective: To select a reliable and sensitive test to determine the presence of bacterial endotoxin in fluids, especially cerebrospinal fluid, from clinical cases chosen by the Infectious Disease Service.

Technical Approach: The last 14 patients' cerebrospinal fluids analyzed in 1979 were done by the improved procedure described in last years annual report. This procedure was used for all specimens analyzed in the current year. As in the previous year all specimens were provided by the Infectious Disease Service, WRAMC.

Progress during FY-80: The following data in Table 1 represent the analyses for the current fiscal year. (See Continuation Sheet)

Number of subjects to be studied before completion of study: 0

Serious/unexpected side effects in subjects participating in project: N/A

Conclusions: (See attached page)

Publications or Abstracts, FY-80: None

| Patient Designation | Endotoxin (ng/ml) | Time interval with multiple specimens |
|---|---|---|
| A | .052 | |
| B | .074 | |
| C | .055 | Day 1 |
| | .084 | Day 3 |
| D | .023 | |
| E | .400 | |
| F | 0* | |
| G | .265 | |
| H | 0 | |
| I | 0 | |
| J | 0 | |
| K | .060** | |
| L | 0 | |
| M | 038 | |
| N | 0 | |
| O | 0 | |
| P | 0 | Day 1 |
| | 0 | Day 7 |
| Q | .048 | Day 1 |
| | .195 | |
| | .038 | Day 7 |
| R | .088 | |
| S | 0 | |
| T | .070 | |
| U | .094 | |
| V | 0 | |
| | .034*** | |
| W | .220 | Day 1 |
| | .200 | Day 6 |

* OD reading below standard baseline of graph and, therefore, considered as 0 ng/ml of endotoxin.
** dialysate
*** pleural fluid

Conclusions: The limulus lysate assay is a sensitive test for the detection of endotoxin in body fluids. No further research is needed. This assay should now be done in the Department of Pathology Clinical Laboratory in direct support of patient care.

Date: 8 Oct 1980 | Protocol No: 1908 | Status: ( Interim ) Final

Title of Project: Evaluation of sodium stibogluconate (Pentostam) in the treatment of cutaneous leishmaniasis

Starting Date: 4 Apr 78 | Estimated Completion Date: 1983

Principal Investigator: Charles N. Oster, M.D., MAJ MC

Associate Investigators:
Edmund C. Tramont, MD, LTC(P)MC
Craig J. Canfield, MD, COL MC
Larry D. Hendricks, Ph.D., MAJ MSC
Charles Pamplin, MD, MAJ MC
Jeffrey D. Chulay, MD, LTC MC

Facility: WRAMC

Dept/Svc: Medicine/Infectious Disease

Key Words:
Leishmaniasis; pentavalent antimony

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: |
|---|---|---|
| 0 | 0 | $4,000.00 |

FY-80 MEDCASE Cost: | Periodic Review Results: (to be filled in by DCI)

Study Objective: (a) To evaluate the efficacy of different regimens of sodium stibogluconate (Pentostam) for the treatment of cutaneous leishmaniasis.
(b) To observe for long term sequelae of leishmaniasis and its treatment in military personnel.

Technical Approach: Unchanged

Progress during FY-80: 10 patients with leishmaniasis were seen during the period 1 Oct 79 to 30 Sep 80. Three had been previously treated at WRAMC and were re-admitted for treatment of recurrent disease; one was treated with a fourth course of sodium stibogluconate with apparent resolution; the second was treated with

Number of subjects to be studied before completion of study: 60

Serious/unexpected side effects in subjects participating in project: None

Conclusions: See following sheet

Publications or Abstracts, FY-80: Chulay JD, Tramont EC, Hendricks, LD, Takafuji E. Clinical manifestations of cutaneous leishmaniasis. Manuscript in preparation.

Progress during FY-80:(Continued)Amphotericin-B, one gram total dose, but still had positive post-treatment cultures; the third had continued disease involving skin graft sites on an old burn wound. He had had three courses of sodium stibogluconate and overthree grams of amphotericin-B previously; therefore he was treated with local heat therapy with improvement.

Two patients were treated previously elsewhere, one in Panama, and the other in Colombia. The first was retreated at WRAMC using the standard regimen of sodium stibogluconate. The second, a civilian Peace Corps volunteer was referred to the National Institutes of Health for treatment.

The remaining six patients were enrolled in the experimental limb of the protocol. Two were treated in Group A (600 mg I.V.once a day for 10 doses), three in Group B (600 mg I.V. loading dose followed by a continuous I.V. infusion of 600 mg per day for 9 days), and one in Group C (600 mg I.V. loading dose followed by 200 mg I.V. every eight hours for 27 doses). All healed after their treatment; however, since the follow-up period has been short, it is premature to consider these patients cured.

Sodium stibogluconate has been well tolerated by all patients. We have not had to curtail its administration due to an adverse reaction. Side effects, including headache (1 patient), chest pain (1 patient), and paresthesias (1 patient), were minor and transient.

Conclusions: It is clear that sodium stibogluconate is effective for the treatment of cutaneous leishmaniasis. However, 25-30% of the patients treated at WRAMC have not been cured with the initial ten day course, and there is no apparent difference, at this time, in the failure rate of the experimental treatment groups. Our data suggests that higher dose or longer treatment regimens using sodium stibogluconate will be required.

Work Unit No.: 1908

Funds Utilized, FY-80: $2,000.00

Funding Requirements, FY-81: $2,000.00

Personnel: None

Equipment: None

Supplies: $1,500.00

Travel: $500.00

| Date: 9 October 1980 | Protocol No: 1909 | Status: (Interim) XXXXX |
|---|---|---|

Title of Project: Immunological evaluation of patients with cutaneous leishmaniasis

| Starting Date: 21 Feb 1978 | Estimated Completion Date: 30 Sep 1981 |
|---|---|

Principal Investigator: Charles N. Oster, M.D., MAJ MC

| Associate Investigators:<br>Franklin A. Neva, M.D., NIH<br>Eskild A. Petersen, M.D., NIH<br>Edmund C. Tramont, M.D. LTC(P) MC<br>Jeffrey D. Chulay, M.D., LTC MC | Facility: WRAMC<br>Dept/Svc Medicine/Infectious Disease |
|---|---|

Key Words: Leishmaniasis/immunology/lymphocyte

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: $5,000.00 |
|---|---|---|

| FY-80 MEDCASE Cost: | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective: To study the antigen-specific and nonspecific humoral and cellular immune responses in patients with cutaneous leishmaniasis.

Technical Approach: No change in this fiscal year.

Progress during FY-80: In vitro cellular immune responses of eight patients were studied in FY80. One patient was studied twice. 7/8 patients responded to leishmanial antigens in vitro, with lymphocyte transformation responses 4-56 (Cont'd)

Number of subjects to be studied before completion of study: 20

Serious/unexpected side effects in subjects participating in project: None

Conclusions: Most patients with cutaneous leishmaniasis develop antigen specific cell mediated immunity, as documented by in vitro lymphocyte responses. This responsiveness may prove useful as an adjunctive diagnostic test. The poor

Publications or Abstracts, FY-80: None (Cont'd)

Progress during FY-80: (Cont'd) times control levels. The eighth patient had levels only 1.3-2.0 times control; this patient has continued active disease despite three courses of sodium stibogluconate and over 3 grams of amphotericin B. The other patient who is unresponsive to therapy (two courses of sodium stibogluconate and one gram of amphotericin B) has the next lowest in vitro lymphocyte responses, ranging 1-4.6 times control. The other patients who responded to therapy had responses 9-56 times control. These data are provocative and suggest that immunodeficiency may be contributing to these two patients prolonged, unresponsive disease.

Passage of the peripheral blood mononuclear cells (PBM) over nylon wool columns abolished the antigen-induced transformation of lymphocytes of all patients, suggesting a role for macrophages in antigen-processing or presentation. Culture of the PBM's in the presence of indomethacin had no effect on the transformation responses of five of eight of these patients. One patient's response decreased, and two patient's responses increased with indomethacin. One of these latter patients was a poor responder initially. With indomethacin his responses were 30 times control levels, suggesting the possibility of a prostaglandin-mediated suppression.

Conclusions: (Cont'd) responsiveness of lymphocytes from two patients with recalcitrant disease suggests that an immunodeficiency may prevent resolution of leishmaniasis. These interesting preliminary findings will be pursued.

Funds Utilized, FY-80: $3,000.00

Funding Requirements, FY-81: $5,000.00

Equipment: Multiple-channel automated sample harvester $1,500.00

Supplies: $3,000.00

Travel: $500.00

| Date: 4 October 1980 | Protocol No: 1911 | Status: Interim X / Final |
|---|---|---|

Title of Project:

In Vitro Inhibitory Activity of a Series of 2-Acetylpyridine thiosemicarbazones

| Starting Date: 27 Feb 79 | Estimated Completion Date: Oct 81 |
|---|---|

Principal Investigator: Arthur Dobek, Ph.D.

| Associate Investigators: | Facility: Walter Reed Army Medical Center |
|---|---|
| Edmund Tramont, M.D., LTC MC<br>Daniel Klayman, Ph.D. | Dept/Svc Department of Clinical Investigation |

Key Words:

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: |
|---|---|---|

| FY-80 MEDCASE Cost: | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective: To determine the in vitro inhibitory activity of a series of 2-Acetylpyridine thiosemicarbazones and related compounds toward a collection of clinically significant bacterial organisms.

Technical Approach: The minimum inhibitory concentration of 65 compounds which included 50 of 2-acetylpyridine thiosemicarbazones [26$N^4$ monosubstituted, 6$N^4$,$N^4$-disubstituted (noncyclic), and 18$N^4$,$N^4$-disubstituted (azacyclic)], 9 derivatives of other 2-acylpyridine thiosemicarbazones and 6 miscellaneous compounds related to 2-acylpyridine thiosemicarbazones were determined for the following clinical isolates using the standard macro-broth dilution procedure: 5 Staphylococcus aureus, 5 group D enterococcus, 5 Pseudomonas spp,

(Continued on attached page)

Progress during FY-80:

MICs of 0.002 to 0.062 ug/ml were obtained with 23% of the compounds for N. gonorrhoeae and 0.016 to 0.062 ug/ml with 17% of the compounds for

(Continued on attached page)

Number of subjects to be studied before completion of study:

Serious/unexpected side effects in subjects participating in project:

Conclusions: Thirty additional compounds of various chemical structure have become available for testing. The major emphasis will be on finding potential inhibitors for the enteric and Pseudomonas bacilli.

Publications or Abstracts, FY-80: (See attached page)

Technical Approach - (Continuation): 5 Klebsiella - Enterobacter spp., 4 Shigella spp., 1 Escherichia coli (invasive), 5 Proteus mirabilis and 5 Neisseria meningitidis. The standard agar dilution method was used with 30 N. gonorrhoeae isolates.

Progress during FY-80 (Continuation): N. meningitidis. S. aureus was inhibited in the MIC range of 0.125 to 0.5 ug/ml by 18% of the compounds, whereas 26% inhibited group D interococcus with an MIC of 0.025 to 2.0 ug/ml. Poor antibacterial activity was shown toward gram-negative bacilli. These data have been published (1).

Publications or Abstracts, FY-80:

1. Dobek, Arthur, D. Klayman, E. Dickson Jr., J. Scovill, and E. Tramont: Inhibition of Clinically Significant Bacterial Organisms In Vitro by 2-acetylpyridine thiosemicarbazone, Antimicrobial Agents and Chemotherapy, 18(1): 27-36, (1980).

| Date: 9 October 1980 | Protocol No: 1912 | Status: Interim (Final) |
|---|---|---|

Title of Project: Determination of vancomycin levels in clinical samples using high pressure liquid chromatography (HPLC)

| Starting Date: 27 March 1979 | Estimated Completion Date: 30 Sep 80 |
|---|---|

Principal Investigator: Charles N. Oster, M.D.

| Associate Investigators: Rudolfo Bongiovanni, CPT MSC; Edmund C. Tramont, MD LTC(P)MC | Facility: WRAMC |
|---|---|
| | Dept/Svc Medicine/Infectious Disease |

Key Words: Vancomycin/antibiotic assay

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: $12,000.00 |
|---|---|---|

| FY-80 MEDCASE Cost: | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective: 1. To discover the liquid chromatographic characteristics of vancomycin.

2. To develop a rapid assay for vancomycin in clinical samples uing HPLC.

Technical Approach: There have been no changes in the technical approach in the fiscal year

Progress during FY-80. The technical aspects of sample preparation and chromatography were described in the FY-79 report.

Further studies were designed to develop an internal standard and to determine if commonly used clinical pharmaceuticals would interfere with this assay. (Cont'd)

Number of subjects to be studied before completion of study: 0

Serious/unexpected side effects in subjects participating in project: N/A

Conclusions: The first objective, defining vancomycin's HPLC characteristics, has been achieved. However, limited availability of HPLC time prevented further assessment of this assay method for vancomycin in clinical samples. This technique

Publications or Abstracts, FY-80: McClain JBL, Bongiovanni R. (continued)
Quantitation of vancomycin by high pressure liquid chromatography. Manuscript in preparation.

Progress during FY-80: (Continued). Unfortunately, we were unable to secure access to the HPLC equipment, and work on this project was necessarily curtailed.

Conclusions: (Continued) (HPLC) is potentially extremely useful, not only for the rapid assay of vancomycin, but also for other antibiotics. Strong consideration must be given to allocating more access to HPLC equipment for this work.

Funds Utilized, FY-80: #1,000.00

Funding Requirements, FY-81: 0

Personnel: None

Equipment: None

Supplies: None

Travel: None

| Date: 13 October 1980 | Protocol No: 1913 | Status: ( Interim ) Final |
|---|---|---|

Title of Project: Laboratory Investigation of New Antibiotics

| Starting Date: 22 January 1980 | Estimated Completion Date: January 1983 |
|---|---|

Principal Investigator: Charles N. Oster, MAJ MC; Alan S. Cross, LTC MC

| Associate Investigators: Edmund C. Tramont, MD; Arthur S. Dobek, Ph.D.; John F. Keiser, MD; Dennis Kopecko, PhD; Ronald K. Porpatich, M.S. | Facility: WRAMC |
|---|---|
| | Dept/Sve Medicine/Infectious Disease Svc |

Key Words: Antibiotics/Bacterial susceptibility/resistance mechanisms

| Accumulative MEDCASE Cost: 0 | Accumulative Contract Cost: 0 | Accumulative Supply Cost: $6,000.00 |
|---|---|---|

| FY-80 MEDCASE Cost: 0 | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective: 1. To investigate the in vitro antibacterial activities of new antibiotics against bacteria isolated from patients at WRAMC.
2. To investigate the mechanisms of bacterial antibiotic resistance.

Technical Approach: In vitro antibacterial activities of antibiotics are determined using standard agar-dilution techniques.

Progress during FY-80: In vitro antibacterial activities of the investigational drugs piperacillin (P), cefotaxine (H), moxalactam (L), and cefoperazone (E) were determined for two collections of bacterial isolates. One collection was a series of recent consecutive isolates from WRAMC's Clinical Microbiology Laboratory. The (Cont'd)

Number of subjects to be studied before completion of study: None

Serious/unexpected side effects in subjects participating in project: N/A

Conclusions: Only cefoperazone and piperacillin, of the new antibiotics investigated, have sufficient in vitro activity against antibiotic-resistant Pseudomonas to be potentially useful clinically. Cefotaxime and moxalactam have good activity against (Cont'd)

Publications or Abstracts, FY-80: In Vitro Activity of Cefotaxine, Moxalactam, Cefoperazone, and Piperacillin against multiply antibiotic resistant Gram-negative bacteria

Progress during FY-80: (Cont'd): second collection was a group of antibiotic-resistant gram-negative bacteria gathered at WRAMC over the last several years. Sensitivity of these bacteria to carbenicillin (CB), gentamicin (G), tobramycin (N) and amikacin (A) were also determined for comparison with the investigational antibiotics.

Consecutive recent bacterial isolates

| | Number Isolates | Percent Susceptible | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | H | L | I | P | CB | G | N | A |
| Escherichia coli | 124 | 98 | 77 | 99 | 98 | 73 | 97 | 98 | 100 |
| Klebsiella-Enterobacter | 97 | 100 | 91 | 94 | 92 | 44 | 93 | 92 | 99 |
| Proteus species | 93 | 97 | 92 | 100 | 98 | 78 | 85 | 94 | 99 |
| Pseudomonas aeruginosa | 122 | 84 | 84 | 93 | 98 | 52 | 63 | 90 | 93 |

Antibiotic-resistant bacteria

| | Number Isolates | Percent Susceptible | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | H | L | I | P | CB | G | N | A |
| Escherichia coli | 98 | 100 | 99 | 100 | 91 | 53 | 89 | 85 | 99 |
| Klebsiella-Enterobacter | 74 | 95 | 99 | 84 | 26 | 12 | 16 | 12 | 91 |
| Pseudomonas aeruginosa | 102 | 59 | 53 | 94 | 93 | 35 | 17 | 39 | 92 |

Conclusions: (Cont'd):Enterobacteriaceae, but are less active against Pseudomonas.

Publications or Abstracts, FY-80:(Cont'd): C.N. Oster, A.S. Dobek, A.S. Cross, E.C. Tramont. Submitted to ASM Annual Meeting, March 1981.

Funds Utilized, FY-80: $6,000.00

Funding Requirements, FY-81: $7,500.00

| | |
|---|---|
| Media | $1,000.00 |
| Disposable plastic ware | 3,500.00 |
| Other consumables | 2,500.00 |
| Travel, publications | 500.00 |

| Date: 27 October 1980 | Protocol No: 2000 | Status: Interim X<br>Final |
|---|---|---|

Title of Project: The Effects of Gastric Surgery on the Release of Pancreatic Polypeptide

| Starting Date: 1973 | Estimated Completion Date: 1983 |
|---|---|

Principal Investigator: John Harmon

| Associate Investigators: | Facility: Walter Reed Army Medical Center |
|---|---|
| Lawrence Johnson MD<br>Richard Hirata MD<br>Ian Taylor MD | Dept/Svc Surgery |

Key Words:
Pancreatic polypeptide, ulcer, hormone

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: |
|---|---|---|
| | | |

| FY-80 MEDCASE Cost: | Periodic Review Results: (to be filled in by DCI) |
|---|---|
| | |

Study Objective:

To determine the roles of the vagus nerve and the antrum of the stomach in the release of pancreatic polypeptide into the blood from the pancreas

Technical Approach:

To compare meal stimulated serum pancreatic polypeptide values in patients before and after surgery on the stomach

Progress during FY-80:
Serum samples were collected from 15 patients in anticipation of surgery. Thirteen patients have had surgery of whom 8 have had repeat collection of serum samples. The samples were sent to LA for measurement of serum pancreatic polypeptide in Apr 80.

Number of subjects to be studied before completion of study:

Serious/unexpected side effects in subjects participating in project:

Conclusions:
Satisfactory progress has been made in collecting specimens. No unexpected problems have arisen. The protocol has not interfered significantly with patient care.

Publications or Abstracts, FY-80:

FUNDING REQUIREMENTS

CLINICAL INVESTIGATION PROGRAM

| ORK UNIT NO.: 2000 | TITLE: Use of Co-Polymer as a Lattice for the Growth of Neogur | FY- DATE W/U A |
|---|---|---|
| PC: | PRINCIPAL INVESTIGATOR: Col HARMON | |

| MENT OF PENSE | | FY 81 | FY 82 | REMARKS |
|---|---|---|---|---|
| 0 - 1200 | Personnel: | | | We were authorized 50% of a technician but we have not bee able to impliment this as of this date. |
| 1400 | Travel: | | | |
| | Mission | | | |
| | Conference | 600 | 600 | |
| | Patient | | | |
| 2319 | Rental Equip: | | | |
| 2400 | Printing and Reproduction: | | | |
| 2572 | Contractual Svc Lab Contracts: | | | |
| 3500 | Consumable Supplies and Experimental Animals | 4000 | 4000 | Rabbit acquisition & boarding |
| Other: | | | | |
| Total: | | | | |
| Requirement Ranks | | No | No | WORK UNITS: |

| Date: 27 October 1980 | Protocol No: 2003 | Status: Interim X Final |
|---|---|---|

Title of Project: Use of Copolymer as a Lattice for the Growth of Neogut

| Starting Date: March 1980 | Estimated Completion Date: March 1982 |
|---|---|

Principal Investigator: John W. Harmon, LTC MC

| Associate Investigators: William Berry CPT MC<br>Keith Lillemoe CPT MC | Facility: Walter Reed Army Institute of Research |
|---|---|
| | Dept/Svc Division of Surgery |

Key Words: Small intestine, surgery

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: |
|---|---|---|
| FY-80 MEDCASE Cost: | Periodic Review Results: (to be filled in by DCI) | |

Study Objective:

To investigate methods of expanding the surface area of the small bowel mucosa

Technical Approach:

Rabbits are studied. Animal surgery is performed on the ileum

Progress during FY-80:

Dacron and dexon polymer have been studied with similar results (see abstract attached)

Number of subjects to be studied before completion of study: none

Previous/unexpected side effects in subjects participating in project:

None

Conclusions.

Currently autogenous muscle grafts seen to be a superior lattice, as compared with foreign material.

Publications or Abstracts, FY-80:

(Surgical Forum 30:365-6 1979)

FUNDING REQUIREMENTS

CLINICAL INVESTIGATION PROGRAM

| | | |
|---|---|---|
| K UNIT NO.: 2003 | TITLE: The Effects of Gastric Surgery on the Release of Pancreatic Polypeptide | FY: |
| | | DATE: W/U A |
| C: | PRINCIPAL INVESTIGATOR: John W Harmon | |
| | Chas. Harmon | |

| ENT OF NSE | | FY 81 | FY 82 | REMARKS |
|---|---|---|---|---|
| 1200 | Personnel: | None | None | |
| 00 | Travel: | | | |
| | Mission | 800 | 800 | Confer with collaborators in Los Angeles |
| | Conference | 600 | 600 | Present material |
| | Patient | | | |
| 0 | Rental Equip: | | | |
| 0 | Printing and Reproduction: | | | |
| | Contractual Svc | 50 | 50 | Freight transport of specimens |
| | Lab Contracts: | | | |
| | Consumable Supplies and Experimental Animals | | | |
| | | | | |
| | | | | |
| | Increment Ranks | No | No | WORK UNITS: |

Work Unit Number: 2106

Title of Project: Management of the Hemodynamically Significant, Asymptomatic Carotid Bruit

Investigators:

Principal: LTC G. Patrick Clagett

Associates: COL George J. Collins, Jr.
COL Norman M. Rich
LTC James M. Salander
MAJ Michael J. Spebar

Objectives: (1) To determine the most appropriate management of patients with asymptomatic, hemodynamically significant carotid bruits, (2) To determine the natural history of asymptomatic extracranial vascular disease; (3) To determine the role of non-invasive diagnostic techniques in the management of patients with asymptomatic extracranial vascular disease.

Technical Approach: Consenting patients who are asymptomatic for cerebrovascular disease who have hemodynamically significant carotid stenoses (as determined by non-invasive studies) are eligible for randomization into two groups. Patients ineligible for randomization include those who have had carotid endarterectomy on the side in question, those judged too frail to undergo carotid endarterectomy, and those who don't consent. Patients randomized into the surgical group will undergo arteriography and carotid endarterectomy if an operable lesion is found. Patients randomized into the second group will be treated with aspirin, 650 mg twice daily, and followed closely (every 3 months). If patients in the second group develop symptoms, they will then undergo arteriography and carotid endarterectomy.

Progress and Results: Since initiating this project, 22 patients have been identified with hemodynamically asymptomatic carotid bruits. Of these, 14 have consented to join the study and 8 have refused. Of those who have entered, 8 have been randomized into the aspirin group and 6 have been allocated to the surgical treatment group. The mean follow-up period for all patients entered is 10 months. In the aspirin group, there was one death from a cardiac cause. Two patients in the aspirin treatment group developed symptoms. The first patient developed non-focal global symptoms of cerebrovascular insufficiency manifested by dizziness and disequilibrium. This

technically was considered a failure of aspiring therapy and the patient underwent arteriography which demonstrated two critical stenoses, one at the carotid bifurcation and one in the siphon region. Because of the tandem lesions, the latter of which was not amenable to surgical therapy, the patient was considered inoperable. The second aspirin failure patient developed amaurosis fugax and underwent arteriography which demonstrated a tight stenosis of the internal carotid artery which was reconstructed with a carotid endarterectomy. His course and follow-up have been uneventful.

Of the 6 patients allocated to the surgical group, 4 have undergone uneventful prophylactic carotid endarterectomies. One of these patients died in the follow-up period because of complications of another vascular procedure. The remaining three patients have had uneventful follow-up following carotid endarterectomy. One patient developed anaphylaxis and a subsequent myocardial infarction during angiography. At present, he is considered too poor an operative risk and is being followed by medical therapy. The final patient in the surgical group has steadfastly refused arteriography after being allocated to the surgical group. She also is being followed on medical therapy. The 8 patients who refused entrance into the study comprise any interesting group from which valuable information may be obtained. All of these patients declined entrance into the study because they did not want to have a 50% chance of having surgery. All of these patients have been followed on aspirin therapy. One of these patients developed a mild stroke and underwent arteriography and operation which demonstrated an occluded internal carotid artery which could not be reopened. Another patient, although remaining asymptomatic, was seen at another hospital and underwent bilateral carotid endarterectomies there.

Conclusion: As with the annual report last year, the number of patients is too small and the follow-up period too brief to draw firm conclusions. The study will have to be continued for another 2-3 years to reach meaningful conclusions.

Funding Requirements: None.

Publications: None.

Type of Report: Interim.

Work Unit Number: 2109

Title of Project: Etiologic Factors for Recurrent Carotid Stenosis

Investigators:

Principal: LTC G. Patrick Clagett
COL Norman Rich

Associates: LTC George J. Collins, Jr.
LTC James M. Salander
MAJ Michael J. Spebar
MAJ William L. Eddleman
LTC Salverio Cabellon

Objectives: (1) To determine risk factors for the development of recurrent carotid stenosis following successful carotid endarterectomy

Technical Approach: Patients with surgically or angiographically proven carotid restenosis comprise the study group. These patients are age and sex matched with patients who underwent carotid endarterectomy during the same year. The second group of patients comprises the control group. On all patients, the following information is obtained: symptoms and other indications mandating first procedure, angiographic findings, operative details, immediate postoperative morbidity and mortality, histopathologic findings, and presence of atherosclerotic risk factors. In addition to these data, study patients and control patients will have blood drawn for determination of cholesterol and triglyceride levels as well lipid fractionation studies to determine the relative amounts of HDL, LDL and VLDL cholesterol. Furthermore, both groups of patients will undergo threshold dose response platelet aggregometry to ADP epinephrine and collagen.

Progress and Results: To date, 25 patients have been identified with recurrent carotid stenosis following successful carotid endarterectomy. Ten patients with restenosis have been matched with control patients and all have had their studies completed. The data have not been analyzed. We are waiting from complete follow-up on all patients with carotid restenosis, as well the necessity for finding matched controls for these patients. It is anticipated that one more year of surgery will be necessary to meet these requirements and complete the study.

Conclusions: The study is incomplete and no definite conclusions can be drawn. The one striking finding that has surfaced is that greater than 50% of the patients with carotid restenosis have been females. Because this does not parallel the ratio of male to female (4:1) in

our population undergoing carotid endarterectomy, sex difference appears to be an obvious etiologic factor for carotid restenosis.

Funding Requirements: There have been no funding requirements. The clinical laboratory has performed the lipid determinations and Dr. George J. Collins' laboratory has performed the platelet aggregometry.

Publications: None

Type of Report: Interim.

# DISPOSITION FORM

For use of this form, see AR 340-15, the proponent agency is TAGCEN.

| REFERENCE OR OFFICE SYMBOL | SUBJECT |
|---|---|
| HSWP-SPV | Work Unit #2110<br>Protocol: Participation of the Reticuloendothelial System in Shortening Platelet Survival |

| TO | FROM | DATE | CMT 1 |
|---|---|---|---|
| C, Clinical Investigation | Acting C, Per Vas Surg Svc | 15 Jan 1981 | |

1. The protocol, Participation of the Reticuloendothelial System in Shortening Platelet Survival, has been withdrawn from those supported by the Clinical Investigation Service. This protocol is now being carried out in the Division of Surgery at Walter Reed Army Institute of Research with support from OMA funds.

2. This protocol involved no human subjects.

J. Patrick Clagett

G. PATRICK CLAGETT, M.D.
LTC, MC, USA
Acting Chief, Peripheral Vascular
Surgery Service

DA FORM 2496

REPLACES DD FORM 96, WHICH IS OBSOLETE.

☆GPO-1975-665-422/1063

330

| Date: 28 August 1980 | Protocol No: 2336 | Status: Interim<br>Final XX |
|---|---|---|

Title of Project:
CLINICAL QUANTIFICATION OF INTRAOCULAR MALIGNANT MELANOMA VOLUME

| Starting Date: 20 March 1975 | Estimated Completion Date: 22 August 1980 |
|---|---|

Principal Investigator: LTC KENYON K. KRAMER, MC

| Associate Investigators: | Facility: WRAMC |
|---|---|
| None | Dept/Svc Ophthalmology |

Key Words: Ultrasound, Intraocular Tumor, Malignant Melanoma

| Accumulative MEDCASE Cost: Unknown | Accumulative Contract Cost: None | Accumulative Supply Cost: None |
|---|---|---|

| FY-80 MEDCASE Cost: None | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective: Please see attached abstract from ARVO, 1980, Orlando, Florida. The following abstract was presented at the Annual Association in Research and Vision in Ophthalmology meeting, Orlando, Florida, 4 May - 9 May 1980.

Technical Approach:
See above

Progress during FY-80:
See above

Number of subjects to be studied before completion of study: 19

Serious/unexpected side effects in subjects participating in project:
None

Conclusions:

See above

Publications or Abstracts, FY-80: See above

# ULTRASONOGRAPHIC MEASUREMENT OF CHOROIDAL MELANOMA

Kenyon K. Kramer, M.D.
Walter Reed Army Medical Center
Washington, D.C.

The size of choroidal malignant melanomas continues to be important clinically, influencing managment in many cases. Nineteen melanomas have been measured in three dimensions with ultrasound in vivo and the results compared to histopathology dimensions. Both the "Coleman" apparatus and the Bronson Turner were used. The height measurements were the most accurate but one tumor was overestimated by 3.5 mm and one underestimated by 2.5 mm. Tumor base size estimates showed considerably more scatter. Lesions posterior to the equator were generally overestimated. (One tumor by 7 mm by one method.) Tumors located on the equator were generally more accurately measured and the errors better centered about a zero error line (one mass underestimated by 4 mm). These differences in errors depending on the location were statisdtically significant at the .01 level for one diamter of the tumor base. These data suggest that empirically derived correction factors may offer improved accuracy in ultrasound size estimations of choroidal tumors in vivo.

ARVO abstracts
19[illegible], Orlando, Florida

| Date: 15 October 1980 | Protocol No: 2308 | Status: Interim / Final XX |
|---|---|---|

**Title of Project:** Scleral Buckling Experience at WRAMC 1973 - 1976: A Retrospective View

| Starting Date: 1978 | Estimated Completion Date: 1980 |
|---|---|

**Principal Investigator:** Cary L. Burton, MAJ, MC

| **Associate Investigators:** | **Facility:** Walter Reed Army Medical Center |
|---|---|
| Paul V. Whitmore, COL, MC<br>Fleming D. Wertz, LTC, MC | **Dept/Svc** Ophthalmology Service<br>Department of Surgery |

**Key Words:** Scleral buckle, silicone

| Accumulative MEDCASE Cost: 0 | Accumulative Contract Cost: 0 | Accumulative Supply Cost: 0 |
|---|---|---|

| FY-80 MEDCASE Cost: 0 | Periodic Review Results: (to be filled in by DCI) |
|---|---|

**Study Objective:**
To review surgical results of Retina Service, Ophthalmology, concerning scleral buckling operations.

**Technical Approach:**
Chart review

**Progress during FY-80:** Scleral buckling procedures using solid silicone elements results in an outcome with no statistical difference as compared to using expandable silicone elements.

Number of subjects to be studied before completion of study:

Serious/unexpected side effects in subjects participating in project:

**Conclusions:** Expanding silicone buckling elements are not necessary to achieve good results, as claimed by some authors. Furthermore, our results compare favorably with other reported series.

**Publications or Abstracts, FY-80:**
None

| Date: 10 October 1980 | Protocol No: 2309 | Status: Interim XX<br>Final |
|---|---|---|

Title of Project:
A Study of Eye Trauma and Treatment in the Military

| Starting Date: 27 Dec 77 | Estimated Completion Date: June 1980 |
|---|---|

Principal Investigator: Howard P. Cupples, CAPT, MC, USN

| Associate Investigators:<br>Paul V. Whitmore, COL, MC, USA | Facility: National Naval Medical Center & Walter Reed Army Medical Center<br>Dept/Svc Ophthalmology Service, Dept of Surgery |
|---|---|

Key Words: Vitreous surgery, ocular trauma

| Accumulative MEDCASE Cost: 0 | Accumulative Contract Cost: 0 | Accumulative Supply Cost: 0 |
|---|---|---|

| FY-80 MEDCASE Cost: 0 | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective: To determine the role of vitreous surgery in the management of ocular trauma. To compare the results of ocular trauma cases managed by vitreous surgery with the results of ocular trauma cases managed in the past by conventional methods. To develop plans for the efficient management of ocular combat injuries based upon the analysis of data collected during the study.

Technical Approach:
A series of cases of ocular trauma managed by vitreous surgery techniques will be compared with a similar series drawn retrospectively from records of NNMC and WRAMC during the Vietnam era and managed by conventional surgical techniques.

Progress during FY-80: To date, 103 cases of ocular trauma have been managed in the combined series at WRAMC and NNMC. The prospective series is therefore completed and the retrospective study of Vitenam era cases is expected to be completed by June 1980.

Number of subjects to be studied before completion of study: 100

Serious/unexpected side effects in subjects participating in project
No serious unexpected side effects to vitreous surgery have been found in the management of these trauma cases.

Conclusions: Conclusions as to the effectiveness of vitreous surgical techniques will be reviewed at this time, until comparison can be made with the group treated by conventional surgery.

Publications - Abstracts, FY [illegible]

| Date: 14 August 1980 | Protocol No: 2310 | Status: Interim XX<br>Final |
|---|---|---|

Title of Project: INTRAOCULAR LENSES

| Starting Date: 13 April 1978 | Estimated Completion Date: 12 August 1931<br>(Final termination of this protocol will be determined by the FDA) |
|---|---|

Principal Investigator: COL FLOYD L. WERSELAND, JR., MC

| Associate Investigators: | Facility: Walter Reed Army Medical Center |
|---|---|
| None | Dept/Svc Ophthalmology Service |

Key Words: Intraocular Lenses

| Accumulative MEDCASE Cost: None | Accumulative Contract Cost: None | Accumulative Supply Cost: $4500 FY-79 |
|---|---|---|

| FY-80 MEDCASE Cost: None | Periodic Review Results:<br>(to be filled in by DCI) |
|---|---|

Study Objective: To evaluate intraocular lenses with regard to safety in the treatment of aphakia

Technical Approach: Intraocular lenses will be implanted in selected patients either at the time of cataract extraction or in a second operation following cataract extraction. This is part of a nationwide collaborative study to determine the incidenc of adverse effects.

Progress during FY-80: 53 patients have had lens implants or attempted lens implants. One adverse result mentioned in the preceding report has been corrected with a final visual acuity of 20/20. A second adverse result is not directly attributable to the intraocular lens.

Number of subjects to be studied before completion of study: Unknown (FDA will determine)

Serious/unexpected side effects in subjects participating in project:

None

Conclusions: The generally good results indicate sufficient value to continue with this protocol.

Publications or Abstracts, FY-80: None

| Date: 20 June 80 | Work Unit No. 2312 | Status: Final |
|---|---|---|

Title of Project: Corneal Endothelial Cell Loss Following Various Cataract Extraction Techniques.

| Starting Date: May 1979 | Completion Date: 20 June 1980 |
|---|---|

Principal Investigator: R. Jeffrey Bergquist, MAJ, MC

| Service: Ophthalmology | Facility: WRAMC |
|---|---|
| Key Words: Corneal Endothelium | Asso. Investigators: None |

| Accum. MEDCASE | Accum. Contract | Accum. Supply |
|---|---|---|
| Cost: None<br>FY 80: None | Cost: None<br>FY 80: None | Cost: $64.80<br>FY 80: None |

Objectives: To compare the amount of corneal endothelial damage resulting from the "standard cataract" extraction versus the "small incision extraction.

Technical Approach: Corneal endothelial cell counts were measured pre and post op in each group of patients.

Progress during FY 80: 14 patients from the "standard cataract" group were studied of which 4 were eliminated due to post operative complications, trauma or cancellation of surgery. 3 patients from the "small incision" group were studied. Greater numbers were not obtained in this group because of the relative infrequency of nontraumatic cataracts in young persons who are old enough to cooperate for the endothelial cell [illegible] and who ultimately receive a small incision extraction as opposed to one of the other techniques. Because of my transfer to Fort Polk, LA, I am terminating this project.

Conclusions: Since the study is incomplete, no conclusions can be drawn.

Publications: None

Side Effects: There were no side effects or complications with any of the patients.

| Date: 6 October 1980 | Protocol No.: 2516 | Status: Final |
|---|---|---|

Title of Project: The Effect of Amplification on Limited High-Frequency Hearing Loss

| Starting Date: August 1976 | Estimated Completion Date: October 1980 |
|---|---|

Principal Investigator: Rauna K. Surr, M.S.

| Associate Investigator: Daniel M. Schwartz, Ph.D. | Facility: Army Audiology and Speech Center, WRAMC |
|---|---|
| | Dept/Svc: Department of Surgery, Otolaryngology Service |

Key Words: California Consonant Test, consonant recognition, consonant confusions, high frequency hearing loss

| Accumulative MEDCASE Cost:_____ | Accumulative Contract Cost:_____ | Accumulative Supply Cost:_____ |
|---|---|---|

| FY-80 MEDCASE Cost:_____ | Periodic Review Results: |
|---|---|

Study Objective: 1) Assessment of the California Consonant Test (CCT) as a tool in clinical hearing aid evaluation on the population with limited high-frequency hearing loss. 2) Assessment of benefit of amplification for individuals with hearing loss limited to frequencies above 2000 Hz.

Technical Approach: Completed.

Progress during FY-80: The fourth and final paper under this protocol entitled Extended High Frequency Amplification for Hearing Loss Above 2000 Hz was presented in Atlanta, Georgia, last November. The abstract for this paper appeared in ASHA, Sept. 1979, a journal of the American Speech-Language-Hearing Association.

The pilot study immediately preceeding the above paper has been accepted for publication in EAR and HEARING.

The final stage of this project will be preparation of the fourth paper into manuscript form for publication.

Number of subjects to be studied before completion of study: n/a

Serious/unexpected side effects in subjects participating in project: n/a

Conclusions: The research by us as well as by others over the past four years has been very fruitful and has demonstrated the sensitivity of the CCT to the phoneme recognition problems associated with high frequency sensorineural hearing impairment. Superiority of the CCT, however, in conventional comparative hearing aid evaluations over other speech test materials currently in use has not been demonstrated.

Future clinical applications of the CCT will probably be in aural rehabilitation through analysis of phonemic changes achieved with training and amplification.

Publications or Abstracts, FY-80:

Schwartz, D.M. and Surr, R.K. Three Experiments on the California Consonant Test. J. Speech Hear. Dis., February, 1979.

Schwartz, D.M., Surr, R.K. et al. Performance of High Frequency Impaired Listeners with Conventional and Extended High Frequency Amplification. Audiology, 18, 1979.

Schwartz, D.M. and Surr, R.K. High-Pass and Conventional High Frequency Hearing Aids for Listeners with High Frequency Sensorineural Hearing Loss. Auditory and Hearing Prosthetic Research, Larson, V.D., Egolf, D. and Kirlin, L. (Eds.), Grune & Stratton, 1979.

*Note: Copies of the first two publications have been forwarded to DCI; a copy of the third publication is attached.

WORK UNIT NO.: 2516

FUNDS UTILIZED, FY-80: $159.00 to present results at national meeting

$260.00 for reprints

FUNDING REQUIREMENTS, FY-81:

REPRINTS: $100.95

WORK UNIT NUMBER: 2516

TITLE: The Effect of Amplification on Limited High-Frequency Hearing Loss

INVESTIGATORS: Principal: Rauna K. Surr, M.S.
Associate: Daniel M. Schwartz, Ph.D.

OBJECTIVES: 1. Assessment of the California Consonant Test (CCT) as a clinical tool. 2. Assessment of benefit of amplification for individuals with limited high-frequency sensorineural hearing loss.

TECHNICAL APPROACH: Speech audiometry is considered one of the more important measurements in clinical audiology. Because research has shown that pure tone audiometry provides limited information about the speech processing characteristics of the auditory system, clinicians have long been interested in evaluating an individual's ability to hear and understand speech. Ideally, speech testing should reflect the communication handicap created by the hearing loss and should differentiate between normal hearers and those with sensorineural impairment. The most widely used word recognition test is the CID W-22 lists (Hirsch et al., 1952). It has been shown to be relatively insensitive to high-frequency sensorineural hearing impairment, which is very prevalent in the U.S. Armed Forces secondary to noise exposure. Several new speech materials have been developed because of the problems associated with CID W-22. Among them is the Northwestern University Auditory Test Number 6 (NU-6) by Tillman and Carhart (1966) which is now used routinely within the United States Army and Air Force audiology clinics. More recently (1977) Owens and Schubert introduced a consonant discrimination test, the California Consonant Test (CCT), which is purported to be highly sensitive to high-frequency hearing impairment. Over the past four years we have completed several studies to evaluate the CCT as a clinical tool.

PROGRESS AND RESULTS: Initially, performance-intensity functions were obtained for both normal hearers and those with high-frequency sensorineural hearing loss. The results demonstrated almost a linear function for both subject groups, approaching asymptote at 50 dB SL, as compared to the typical sigmoidal function obtained with conventional (CID W-22 and NU-6) word recognition tests. CCT scores were also compared to scores on NU-6 lists in 60 subjects with high frequency noise-induced hearing loss. Consistent with previous findings, relatively high word recognition scores were obtained for the NU-6 materials, whereas the range of scores on the CCT approximated a normal distribution.

The second phase was designed to examine the sensitivity of the CCT in differentiating among hearing aids. We sought to determine if a high-pass hearing aid can provide increased improvement in word recognition and consonant discrimination over that of a conventional high frequency emphasis hearing aid in listeners with hearing loss limited to frequencies above 1000 Hz. Word and consonant discrimination were assessed in quiet and in the presence of 12 talker speech babble for ten subjects under three listening conditions: 1) unaided; 2) wearing a conventional high frequency emphasis hearing aid; and 3) wearing an experimental high-pass instrument. The speech testing materials included: 1) NU-6; 2) CCT; and 3) eight voiceless English consonants. The results indicated that both instruments provided similar benefit in quiet. For the noise condition, however, the experimental high-pass

aid provided a considerable advantage, as suggested by mean data. No notable difference was observed in the mean percent improvement between the NU-6 and the CCT scores. Effect of noise at different signal-to-noise ratios needed further examination.

The third phase examined the effects of multi-talker competing speech and half vs. full-list usage on the variability of the CCT scores in sound field in an effort to establish some guidelines for a significant difference between scores when comparing different hearing aids for individual patients. Phoneme recognition was assessed in a sound field in quiet and under four message-to-competition ratio conditions for normal hearing subjects and in three MCR conditions for listeners with bilateral high-frequency sensorineural hearing loss. Noise interference functions for both subject groups were characterized by a gradual decline in recognition performance as the signal-to-noise ratio decreased. The slope of the function for the two groups was parallel with the mean scores for the hearing-impaired subjects approximately 30% lower than that for the normal hearers. Test-retest reliability across conditions was examined via correlational analysis and by computing test-retest difference scores for individual subjects. Increased test variability with half-lists and with the introduction of a competing message makes the CCT under these two conditions of questionable value in routine hearing aid evaluation procedures.

The final phase of this protocol assessed the usefulness of the CCT in predicting aided benefit for individuals with hearing loss limited to frequencies above 2000 Hz. In addition to assessment of phoneme recognition by the CCT, Social Hearing Handicap Index (SHI) developed by Ewertsen and Birk-Nielsen (1973) and follow-up hearing aid use questionnaires were used. The results indicated that despite the sensitivity of the CCT to the phoneme recognition problems associated with high-frequency sensorineural hearing impairment, no appreciable aided improvement was demonstrated with this measure for this group of subjects. On the other hand, the follow-up assessment was somewhat more encouraging. Usage and subjective reports of improved daily communication suggested that many of these hearing aid fittings for the limited high frequency hearing loss group can be considered successful.

CONCLUSIONS: The research here as well as elsewhere in the past four years has been very fruitful and has demonstrated the sensitivity of the CCT to the phoneme recognition problems associated with high-frequency sensorineural hearing impairment. Superiority of the CCT, however, in conventional comparative hearing aid evaluations over other speech test materials currently in use has not been demonstrated.

Future clinical applications of the CCT will probably be in aural rehabilitation through analysis of phonemic changes achieved with training and amplification.

REFERENCES:

Ewertsen, H. W., and Birk-Nielsen, H., Social Hearing Handicap Index. Audiology, 12, 180-187, 1973.

Hirsch, I. J., Davis, H., Silverman, S. R., Reynolds, E. G., Elbert, E., and Benson, R. W., Development of materials for speech audiometry. J. Speech Hearing Dis., 17, 321-337, 1952.

Owens, E., and Schubert, E. D., Development of the California Consonant Test. J. Speech Hearing Res., 20, 463-474, 1977.

Tillman, T., and Carhart, R., An expanded test for speech discrimination utilizing CNC monosyllabic words (Northwestern University Auditory Test Number 6) SAM-TR-66-55, 1966.

FUNDS UTILIZED: FY-77: Travel to Chicago, Illinois, for paper presentation
FY-78: None
FY-79: None
FY-80: Travel to Atlanta, Georgia, for presentation of paper and purchase of reprints.

FUNDING REQUIREMENTS, FY-81: Purchase of reprints, requested.

PUBLICATIONS:

Schwartz, D. M., and Surr, R. K., Three experiments on the California Consonant Test. J. Speech Hearing Dis., February, 1979.

Schwartz, D. M., Surr, R. K., Montgomery, A. A., Prosek, R. A., and Walden, B. E., Performance of high frequency impaired listeners with conventional and extended high frequency amplification. Audiology, 18, 1979.

Schwartz, D. M., and Surr, R. K., High-pass and conventional high frequency hearing aids for listeners with high frequency sensorineural hearing loss. Auditory and Hearing Prosthetic Research, Larson, V. D., Egolf, D., and Kerlin, L. (Eds.), Grune & Stratton, 1979.

Surr, R. K., and Schwartz, D. M., Effects of multi-talker competing speech on the variability of the California Consonant Test. Manuscript accepted for publication, Ear and Hearing, November, 1980.

TYPE OF REPORT: Final

DATE PREPARED: 24 October 1980

| Date: 7 October 1980 | Protocol No.: 2517 | Status: Interim |
|---|---|---|

Title of Project: Evaluation of a Specialized Technique for Training Audio-visual Integration

| Starting Date: 22 August 1977 | Estimated Completion Date: January 1981 |
|---|---|


Principal Investigator: Allen A. Montgomery, Ph.D.

| Associate Investigators:<br>Brian E. Walden, Ph.D.<br>Daniel M. Schwartz, Ph.D.<br>Robert A. Prosek, Ph.D.<br>Earl Wilkinson, MD, MAJ, MC | Facility: Army Audiology and Speech Center, WRAMC |
|---|---|
| | Dept/Svc: Department of Surgery, Oto-laryngology Service |



Key Words: Aural rehabilitation, rehabilitation, lipreading, auditory-visual integration


| Accumulative MEDCASE Cost:_____ | Accumulative Contract Cost:_____ | Accumulative Supply Cost:_____ |
|---|---|---|

| FY-80 MEDCASE Cost:_____ | Periodic Review Results: |
|---|---|

Study Objective: This study is designed to evaluate the effectiveness of a newly-developed training procedure for improving patients' ability to use the audible and visible aspects of speech simultaneously [audio-visual integration (AVI)].

Technical Approach: Thirty hard-of-hearing patients were divided into control and experimental groups and tested before and after receiving either traditional rehabilitation or the AVI technique. The AVI training was done individually in 10 one-hour sessions by trained rehabilitationists. The before and after testing consisted of a 100-item sentence test presented audiovisually in noise, and the data were analyzed with parametric statistics (t-tests and ANACOVA). In addition, a group of 12 normally-hearing people were tested at a similar interval to assess the learning effects of the test.

Progress during FY-80: All data have been collected and analyzed, and very encouraging results have been obtained. Both groups show significant improvement following training, and the experimental group shows significantly more improvement than the controls. No learning was evidenced by the normals.

Number of subjects to be studied before completion of study: none

Conclusions: The technique appears to be a useful and efficient way to improve new hearing aid users' ability to use the visual (lipreading) component and the auditory component of speech simultaneously.

Publications or Abstracts, FY-80: Manuscript in preparation for submission to J. Speech & Hearing Disorders.

WORK UNIT NO.: 2517

FUNDS UTILIZED, FY-80: None

FUNDING REQUIREMENTS, FY-81:

REPRINTS/PAGE CHARGES: $300.00

| Date: 6 October 1980 | Protocol No.: 2523 | Status: Interim |
|---|---|---|

Title of Project: The Relationship Between Electroacoustic Parameters and Perceived Sound Quality of Hearing Aids

| Starting Date: June 1978 | Estimated Completion Date: November 1980 |
|---|---|

Principal Investigator: Daniel M. Schwartz, Ph.D.

| Associate Investigators:<br>Allen A. Montgomery, Ph.D.<br>Brian E. Walden, Ph.D.<br>Robert A. Prosek, Ph.D.<br>David H. Layland, MD, MAJ, MC | Facility: Army Audiology and Speech Center, WRAMC<br><br>Dept/Svc: Department of Surgery, Oto-laryngology Service |
|---|---|

Key Words: Hearing aid processed speech, multidimensional scaling, hearing aid sound quality, electroacoustic characteristics

| Accumulative MEDCASE Cost: $18,650 | Accumulative Contract Cost: | Accumulative Supply Cost: $256.40 |
|---|---|---|

| FY-80 MEDCASE COST: | Periodic Review Results: |
|---|---|

Study Objective: To determine the relationship between various perceptual dimensions and the physical characteristics of hearing aids in judging the sound quality of hearing aid processed speech.

Technical Approach: A single 20 second tape recorded passage consisting of an interpretive reading from "The Adventures of Tom Sawyer" was hearing aid processed through each of 20 commercially available hearing aids in a paired comparison format. The recording procedure was accomplished using KEMAR equipped with Zwislocki-type ear simulators.

For the playback phase 10 normal hearers, 10 subjects with high frequency hearing loss, and 10 with flat loss were each instructed to furnish two types of responses; ratings of similarity and judgments of preference based on the quality of the hearing aid processed speech. Similarity ratings were made on a 7-point equal appearing interval scale, where 1 represented very similar and 7 dissimilar. Preference judgments consisted of identifying the aid within each pair which had preferable sound quality.

Progress during FY-80: This research has culminated in the presentation of two papers at the 1978 and 1979 annual meetings of the American Speech-Language-Hearing Association. The abstract of each of these papers appearing in ASHA, Sept. 1978, 1979.

The first paper dealing with results obtained on normal hearing subjects was recently published in the J. of the Acoustical Society of America, 68, 2, 458-466 (1980). The second paper reporting results for 20 patients with hearing loss (10 sloping, 10 flat configuration) is in the process of being submitted for publication to the J. Acoust. Soc. Am.

Results of this investigation revealed that one perceptual dimension, low cut-off frequency (LCO) dominated the judgment of hearing aid sound quality for both normal hearing and hearing impaired subjects. That is, listeners strongly preferred hearing aids with relatively low LCO's

Number of subjects to be studied before completion of study: 30

Serious/unexpected side effects in subjects participating in project: n/a

Conclusions: The finding that LCO dominates listener judgments of hearing aid sound quality is in direct contrast to the amplification needs of hearing impaired patients. That is, an extensive body of research literature suggests that amplification of low frequency speech sounds and noise may create an upward spread of masking and thus degrade the intelligibility of speech. Hence, the data of the present study reveals that the electroacoustic characteristic that results in the best sound quality, i.e., low low-cut-off frequency, may not be the one that results in improved speech understanding with a hearing aid.

Publications or Abstracts, FY-80:

Punch, J.L., Montgomery, A.A., Schwartz, D.M., Walden, B.E. et al. Multidimensional scaling of quality judgments of speech signals processed by hearing aids. J. Acoust. Soc. Am., 68, 2, 458-466, 1980.

Schwartz, D.M., Montgomery, A.A., Punch, J.L., Walden, B.E. et al. Electroacoustic correlates of hearing aid quality judgments (submitted for publication - J. Acoust. Soc. Am.).

WORK UNIT NO.: 2523

FUNDS UTILIZED, FY-80: $256.40 - case of 4 rolls of hardcopy paper

FUNDING REQUIREMENTS, FY-81:

REPRINTS/PAGE CHARGES: $500.00

| Date: 7 October 1980 | Protocol No.: 2525 | Status: Interim |
|---|---|---|

Title of Project: Generation and Evaluation of Synthetic Facial Images for Studying and Training Lipreading

| Starting Date: 21 August 1978 | Estimated Completion Date: September 1981 |
|---|---|

Principal Investigator: Allen A. Montgomery, Ph.D.

| Associate Investigators:<br>Brian E. Walden, Ph.D.<br>Robert A. Prosek, Ph.D.<br>Daniel M. Schwartz, Ph.D.<br>Kweon I. Stenbaugh, MD, CPT, MC | Facility: Army Audiology and Speech Center, WRAMC |
|---|---|
| | Dept/Svc: Department of Surgery, Otolaryngology Service |

Key Words: Lipreading, synthetic speech, computer graphics, aural rehabilitation

| Accumulative MEDCASE Cost: $7,595.00 | Accumulative Contract Cost: | Accumulative Supply Cost: $622.60 |
|---|---|---|

| FY-80 MEDCASE Cost: $7,595.00 | Periodic Review Results: |
|---|---|

Study Objective: This study is designed to evaluate the feasibility of simulating on a computer graphics system, the information-bearing elements of the talker's mouth and face during speech, for the purpose of studying lipreading in hard-of-hearing patients.

Technical Approach: The third year of this project has been devoted to refining the algorithm (in the form of a FORTRAN program) that produces sequences of up to five consonants and vowels. The primary approach has been to incorporate a mechanically-based model of coarticulation with linear interpolation between primative images and experimenter - controlled amounts of forward and backward coarticulation.

Progress during FY-80: The basic algorithm has been completed and is in the process of being debugged. One subroutine, designed to blank invisible portions of the upper teeth coincident with upper lip movements, is completed but not yet incorporated into the main program.

Number of Subjects to be studied before completion of study: 30

Serious/unexpected side effects in subjects participating in project: n/a

Conclusions: Progress this year has been substantial, with successful generation of simple coarticulated lip shapes (see abstract referenced below). The final evaluation of the system will take place this fiscal year.

Publications or Abstracts, FY-80: "Coarticulation and lipreading: comparison of synthetic and real stimuli", presented at ASHA Convention, November 1979, Abstract in ASHA, Nov., 1979.

WORK UNIT NO.: 2525

FUNDS UTILIZED, FY-80:

| | |
|---|---|
| $5,000.00 | - Camera, compact video color |
| $2,595.00 | - Video Tape Recorder/Reprod. Editor |
| $ 452.60 | - (20) 1/2", 2400' reel-to-reel videotape on 7" reel |
| $ 170.00 | - Front loading disk cartridge for RK05, DEC disk drive |

FUNDING REQUIREMENTS, FY-81:

TRAVEL: $582.00 (to present results at national meeting)

SUPPLIES: $160.00 for magnetic storage medium for data

REPRINTS/PAGE CHARGES: $500.00

| Date: 3 October 1980 | Protocol No.: 2526 | Status: Interim |
|---|---|---|

Title of Project: Development of a Communication Self-Assessment Inventory of the Hearing Impaired Soldier

| Starting Date: January 1979 | Estimated Completion Date: September 1981 |
|---|---|

Principal Investigator: Brian E. Walden, Ph.D.

| Associate Investigators:<br>Marilyn D. Wang, Ph.D.<br>Sue A. Erdman, M.A.<br>Roy K. Sedge, Ph.D., MAJ, MSC<br>Daniel E. Speilman, M.D., MAJ, MC | Facility: Army Audiology and Speech Center, WRAMC |
|---|---|
| | Dept/Svc: Department of Surgery, Otolaryngology Service |

Key Words: Self-assessment, inventory, hearing impaired, communication

| Accumulative MEDCASE Cost:_____ | Accumulative Contract Cost:_____ | Accumulative Supply Cost:_____ |
|---|---|---|

| FY-80 MEDCASE Cost:_____ | Periodic Review Results: |
|---|---|
| Personnel Cost: $7,243.00 | |

Study Objective: The objective of this project is to develop a communication self-assessment inventory to be used in the inpatient Aural Rehabilitation Program of the Army Audiology and Speech Center, WRAMC. The specific purposes of this inventory are:

a. To assess progress in environmental control, and in emotional, social, familial, and vocational adjustment to the handicap as a result of the Aural Rehabilitation Program (i.e., a quantitative index of improvement provided by pre- and post-program scores).

b. To establish a baseline for planning a patient's environmental control training and adjustment counseling in the Aural Rehabilitation Program.

c. To provide prognostic indicators of short-term success in the Program (pre-program administration).

d. To provide prognostic indicators of long-term success in communication after returning to duty station (post-program administration).

Technical Approach: The original Application for Clinical Research Project proposed that the Government contract for the development of a self-assessment inventory of communication ability. Following the approval of the original protocol by the Department of Clinical Investigation, requests for funding were made to the Medical Research and Development Command and to the Health Services Command. In both cases, funding was not obtained.

In May, 1979, a new communication self-assessment inventory appeared in the literature. The Hearing Performance Inventory (T.C. Giolas, E. Owens, S.H. Lamb and E.D. Schubert, Journal of Speech and Hearing Disorders, 1979) appeared to have potential for use with a military population. Given that funding was not obtained for the original proposal, the project was modified to be an evaluation of the Hearing Performance Inventory (HPI). Among the specific goals of this evaluation were the following:

a. To determine the clinical applicability of the HPI for a military population;

b. To accomplish a detailed statistical analysis of the reliability of the HPI; and

c. To determine the prognostic value of the HPI for the military population.

As a result of the work accomplished during FY-80 (see "Progress during FY-80"), it became apparent that the HPI could not be modified to fulfill each of the purposes of a self-assessment inventory outlined in the original protocol. It appears, therefore, that the original proposal - to develop an inventory tailored to the specific needs of the Army - is the only viable option remaining.

Since the initiation of this project, considerable technology in test design, construction and evaluation has been acquired. As a result, it is probable that a communication self-assessment inventory can be developed in-house that will meet all of the Army's major needs. It will be essential, however, that an experimental psychologist be available part-time for a period of one year to provide technical guidance in test construction, data acquisition and statistical evaluation.

Progress during FY-80: Work during the past year focused on an assessment of the HPI as a potentially suitable self-assessment communication inventory of the hearing impaired soldier. The complete 158-item inventory was administered to a total of 254 patients entering the Army Audiology and Speech Center's Inpatient Aural Rehabilitation Program. Extensive analyses of the scales and subscales of the HPI were accomplished via computer. The major findings of this work were:

a. The Speech Scale items could be drastically reduced in number, with virtually no loss of reliability.

b. The Intensity Scale items could be reduced in number to produce a scale containing equal numbers of items in two subscales: Detecting Common Sounds and Detection and Loudness of Speech.

c. Although the Reaction to Auditory Failure Scale is closely concerned with one of the goals of the project, items of this type are underrepresented in the Inventory as compared to other Scales.

d. The Personal Adjustment Scale, while potentially useful as predictors of adjustment and program evaluation, proved to be too general in nature and not sufficiently applicable to the military population.

e. The Social Scale may be eliminated since it is completely redundant with the Speech and Reaction to Auditory Failure Scales.

f. The Occupational Scale items should be eliminated because the structure of these items mirrors that of the Speech, Reaction to Auditory Failure and Personal Scales.

As a result of item and factor analyses of the original 158-item inventory, an 80-item revision was developed. The basic strategy for item selection/elimination was to select items for the shortened scales so as to maximize coefficient $\alpha$. (In general, this means selecting the items with the

highest item-total correlations.) The revised 80-item inventory was administered to an additional 75 patients as they entered Program and at the conclusion of the two weeks. Additional data obtained include a) testing at the soldier's duty station 2-4 weeks prior to entering program and retesting at beginning of program (25 patients; as estimate of test-retest reliability), and b) testing with complete 158-item inventory at least six months following program (75 patients; as estimate of long-term effect of program).

While the analyses of these data are not yet complete, it is clear that:

a. The 80-item inventory has acceptable test-retest reliability.

b. Those items most applicable to the AA&SC's inpatient program and military population show potential for prognostic applications and program evaluation.

c. A large percentage of the items appear largely irrelevant to the purposes outlined in the original protocol.

d. There is a high degree of redundancy among items.

While the basic approach utilized by the HPI (e.g., Likert-type scale, subscale organization, etc.) appears reasonable and the test has good internal consistency, it is not likely to fulfill our basic requirements. We have been forced to return to the original proposal to develop a communication self-assessment inventory tailored to the military population. A working outline of the inventory has been developed, a pool of possible items is being generated, and a preliminary experimental design has been constructed to assess reliability and validity. Work has been slowed since August because the Experimental Psychologist working on the project has not yet been rehired.

Number of subjects to be studied before completion of study: Approx. 600

Serious/unexpected side effects in subjects participating in project: n/a

Conclusions: n/a

Publications or Abstracts, FY-80: Not applicable at the present time.

WORK UNIT NO.: 2526

FUNDS UTILIZED, FY-80: $7,243 (salary - Experimental Psychologist)

FUNDING REQUIREMENTS, FY-81:

PERSONNEL: $12,000 (Dr. Marilyn Wang, GS-[illegible] Experimental Psychologist, 40% time)

TRAVEL: $312.00 to present HPI analysis to Annual Convention of American-Speech-Language-Hearing Association, Detroit, November 1980

REPRINTS: $200.00

PAGE CHARGES: $500.00

| Date: 30 September 1980 | Protocol No.: 2527 | Status: Interim |
|---|---|---|

Title or Project: Assessing Laryngeal Function via Residue Inverse Filtering

| Starting Date: 1 July 1979 | Estimated Completion Date: 31 December 1980 |
|---|---|

Principal Investigator: Robert A. Prosek, Ph.D.

| Associate Investigators:<br>Allen A. Montgomery, Ph.D.<br>Daniel M. Schwartz, Ph.D.<br>Brian E. Walden, Ph.D.<br>Robert L. Henderson, M.D., COL, MC | Facility: Army Audiology and Speech Center, WRAMC<br>Dept/Svc: Dept of Surgery, Otolaryngology Service |
|---|---|

Key Words: Voice disorders, digital signal processing, linear predictive coding, inverse filtering, voice severity judgments

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: $800.00 |
|---|---|---|

| FY-80 MEDCASE Cost: | Periodic Review Results: |
|---|---|

Study Objective: To establish the relationship between voice severity ratings and acoustic measurements obtained by means of Linear Predictive Coding for patients with voice disorders.

Technical Approach: Patients with various vocal complaints who were seen at the Army Audiology and Speech Center and the Otolaryngology Service, WRAMC, were the subjects for this experiment. Each patient recorded the vowel /a/ at a comfortable pitch and loudness. Each vowel was digitized, inverse filtered to obtain a residue signal, and measured to obtain the following residue features: pitch perturbation quotient, amplitude perturbation quotient, pitch amplitude, coefficient of excess, spectral flatness of the residue signal. These six measures constitute the primary independent measure of the study.

Two-second samples of the vowels were randomized on audio tape and presented to a panel of nine speech-language pathologists who judged the severity of each sample on a seven-point, equal-appearing interval scale. The nine severity judgments were averaged for each sample, and the mean severity judgments constitute the dependent variable of the study.

Two changes have been made in the procedures. First, a two-second sample has been digitized, instead of a 400 msec sample, in order to determine if the residue feature values change significantly across time. Second, the speech-language pathologists have been asked to judge the severity of the voice

disorder, rather than voice quality. Severity judgments are more amenable to an equal-appearing interval scale than quality judgments which are basically nominal. Also, judging severity is a routine clinical procedure familiar to all the judges.

Progress during FY-80: Forty-eight male and forty-two female patients with vocal complaints have been recorded. The mean age of the subjects is 44.3 years with a range of 18 years to 76 years. The following disorders were represented in this sample: laryngitis (16 patients), vocal nodules (14 patients), unilateral vocal fold paralysis (12 patients), vocal polyps (10 patients), vocal papilloma (5 patients), spastic dysphonia (4 patients), contact ulcers (one patient), and undetermined pathology (28 patients). This latter category included those patients whose diagnosis was not complete at the time of the recording, or patients who had no visible pathology of the larynx. Each of the ninety patients recorded the vowel /a/, and the residue features were measured using the Speech and Hearing Data Acquisition System (SHDAS).

The perceptual judgments of severity were obtained from a panel of nine speech-language pathologists. The judges were instructed to rate the severity of each sample on a seven-point, equal-appearing interval scale where "1" represented normal voice. The judgment procedure was repeated on three consecutive days, with the data of the first session to be disregarded in subsequent analyses. The average correlation between the second and third sessions, across the nine judges, was 0.90 (range: 0.86 - 0.93). The interjudge reliability, calculated with the data obtained in the third session, was 0.95. These numbers indicate that the judges were consistent between and within themselves.

The analysis of the data has just begun. One multiple linear regression, using the six residue features as predictors and the mean severity ratings as the criterion, has been completed. The multiple correlation coefficient for this analysis was 0.80, indicating that 64% of the variability in the severity ratings was accounted for by the residue features. Additional analyses to be performed include separate regression analyses for all combinations of the residue features, significance tests to determine which features contribute heavily to the regression, split-half multiple regressions, and a multiple discriminant analysis of the data.

Number of subjects to be studied before completion of study: 90

Serious/unexpected side effects in subjects participating in project: n/a

Conclusions: While firm conclusions cannot be drawn at the present time, the magnitude of the multiple correlation coefficient is certainly encouraging. The residue features appear to provide quantitative information which characterizes, at some level, the functioning of the voice.

Publications or Abstracts, FY-80: Not applicable at the present time.

FUNDS UTILIZED, FY-80: $400.00

FUNDING REQUIREMENTS, FY-81:

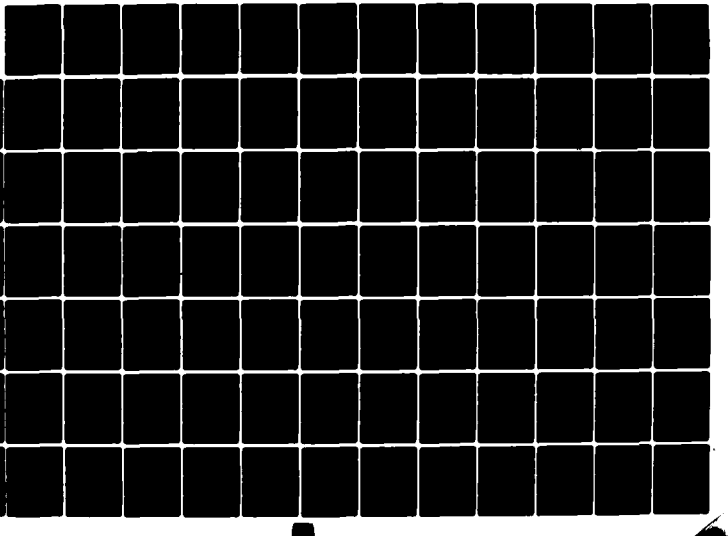
TRAVEL: $600.00 (to present results at a [illegible])

REPRINT [illegible]

AD-A100 636 WALTER REED ARMY MEDICAL CENTER WASHINGTON DC F/G 6/5
ANNUAL PROGRESS REPORT (FY-80) DEPARTMENT OF CLINICAL INVESTIGA--ETC(U)
SEP 80 T M BOEHM

UNCLASSIFIED NL

5 of 8
AD A100636



Work unit number: 2528

Title: The Effects of Chronic Low Doses of Quinine in Tonic Water on the Electronysagmogram (ENG) in Humans.

Principal Investigator: Joan T. Zajtchuk, COL, MC, USA

Associate Investigators: Michael J. Dunne, CAPT, MC, USN, Rebecca A. Merriken, Capt, USAF, BSC, John S. Jewell, MAJ, MSC, USA, Earl V. Wilkinson, MAJ, MC, USAF, Susan G. Chadwick, & Hollis J. Nosler

Starting date: 5 November 1979

Completion date: 31 July 1980

Status: Final

Facility: Otolaryngology Service and Audiology/Speech Center, Walter Reed Army Medical Center; Toxicology Department and Forensic Pathology, Department of Pathology, Armed Forces Institute of Pathology, Washington, D.C. 20012

Service: Otolaryngology

Key words: low dose quinine, tonic water, electronystagmogram

Objective: The object is to quanitate the ENG response in humans after daily ingestions of low doses of quinine in tonic water over a two week period.

Technical approach: Four control subjects, nine test subjects drinking 52.5 mg of quinine in tonic water daily and test subjects drinking 105 mg of quinine in tonic water daily were tested using 5 serial ENG's on days 1,3,7,10 and 14. ENG testing consisted of horizontal and vertical gaze OKN, tracking, positionals, positioning bi-thermal calories and fixation supression with interpretation under double blind conditions.

Conclusions: The pilot project was completed using the above test groups. All controlled subjects had five normal ENG's, and showed no habituation to calori stimulation. The nine subjects drinking 52.5 mg per day of quinine in tonic water over a two week period showed no ENG abnormalities. Three of four subjects in the high dose group (105 mg per day) showed positional abnormalities in at leas one ENG. Random blood quinine levels cannot be used to predict the incidence of symptomatology or ENG abnormalities in persons drinking chronic low doses of quinine in tonic water. Transient positional abnormalities may occur in persons drinking 105 mg of quinine in tonic water daily.

Number of subjects to be studied before completion of study: 15

Serious or unexpected side effects from subjects participating in the project: None

Publications or Abstracts, FY 80: The Effects of Chronic Low Doses of Quinine in Tonic Water on the Electronystagmogram (ENG) in Humans, is being presented as a poster presentation for the American Academy of Otolaryngology at their national meeting in September 1980 in Anaheim, California. Additionally the Armed Forces Institute of Pathology is presenting the data at the Joint Committee on Aviation Pathology in the next fiscal year.

Funds utilized, FY 80: Approximately $400.00 worth allocated out of the clinic investigation services for consumerable supplies. Susan G. Chadwick and Hollis J. Nosler had travel expenses funded for the poster presentation in Anaheim, California for this fiscal year.

Funding requirements, FY 81: None

| Date: 6 October 1980 | Protocol No.: 2529 | Status: Interim |
|---|---|---|

Title of Project: Effect of High Frequency Sensorineural Hearing Loss on the Latency of the Brain Stem Response

| Starting Date: upon purchase of instrumentation | Estimated Completion Date: 2 yrs. after starting date |
|---|---|

Principal Investigator: Daniel M. Schwartz, Ph.D.

| Associate Investigators:<br>Don B. Blakeslee, MD, MAJ, MC<br>Roy K. Sedge, Ph.D., MAJ, MSC<br>Robert L. Henderson, MD, COL, MC | Facility: Army Audiology and Speech Center, WRAMC |
|---|---|
| | Dept/Svc: Department of Surgery, Otolaryngology Service |

Key Words: Auditory Brain Stem Response, Wave V Latency, High Frequency Hearing Loss and Brain Stem Response

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: $25.00 |
|---|---|---|

| FY-80 MEDCASE Cost: | Periodic Review Results: |
|---|---|

Study Objective: To calculate the slope coefficient for predicting the degree of latency delay on the auditory brain stem response created by the presence of varying degrees of high frequency hearing loss.

Technical Approach: Auditory brain stem responses are recorded monaurally with surface disc electrodes attached to the vertex and earlobes. Responses to acoustic clicks at 60 dB SL are recorded for stimulus rates of 11.3, 30.3, 60.3 and 80.3 per second.

Progress during FY-80: No progress has been made on this project since the instrumentation necessary to record and store the brain stem response data was not purchased in FY-80.

Number of subjects to be studied before completion of study: 100

Serious/unexpected side effects in subjects participating in project: n/a

Conclusions: Not applicable at this time.

Publications or Abstracts, FY-80: Not applicable at this time.

WORK UNIT NO.: 2529

FUNDS UTILIZED, FY-80: $25.00 for gold disc electrodes

FUNDING REQUIREMENTS, FY-81:

EQUIPMENT: $35,000 for a versatile microprocessor based auditory brain stem response unit

SUPPLIES: $200.00 for electrodes, recording paper, electrode paste

TRAVEL: $450.00 to visit the Kresge Hearing Research Lab, New Orleans, LA

REPRINTS/PAGE CHARGES: $650.00

| Date: 7 October 1980 | Protocol No.: 2530 | Status: Interim |
|---|---|---|

Title of Project: Test of the Assumptions Underlying the Comparative Hearing Aid Evaluation

| Starting Date: May 1980 | Estimated Completion Date: December 1981 |
|---|---|

Principal Investigator: Brian E. Walden, Ph.D.

| Associate Investigators:<br>Joanne M. Crowley, M.A.<br>Daniel M. Schwartz, Ph.D.<br>Dennis L. Williams, M.A., CPT, MSC<br>Michael H. Mayer, MD, CPT, MC | Facility: Army Audiology and Speech Center, WRAMC<br><br>Dept/Svc: Department of Surgery, Otolaryngology Service |
|---|---|

Key Words: Comparative Hearing Aid Evaluation, hearing aids, validity, reliability

| Accumulative MEDCASE Cost:_____ | Accumulative Contract Cost:_____ | Accumulative Supply Cost:_____ |
|---|---|---|

| FY-80 MEDCASE Cost:_____ | Periodic Review Results: |
|---|---|

Study Objective: The purpose of this research is to test the assumptions which underlie the comparative hearing aid evaluation (CHAE). Among the questions to be answered are: a) Do clinically and statistically significant performance differences exist among hearing aids preselected to be appropriate to the patient's hearing loss? b) Does the same instrument tend to be best for all patients? c) Are available test materials sufficiently reliable for use in hearing aid selection? d) Are the results of a CHAE stable over time? e) Do the results of a CHAE predict patient performance in the real world?

Technical Approach: Hearing-impaired subjects selected from the Aural Rehabilitation Program of the Army Audiology and Speech Center are administered a modified comparative hearing aid evaluation (CHAE) using three behind-the-ear instruments. The binomial model (at .95 confidence) is used to determine if significant differences exist among the aided monosyllabic word recognition in noise scores. In those cases where the inter-aid differences exceeded chance performance, two additional steps were taken. First, the patient was allowed to wear each of the three instruments for an extended period of time during the week following the initial CHAE. At the end of this trial use period, the patient indicated which aid was most acceptable and which was least acceptable. Second, following the trial use period, the CHAE was repeated.

Progress during FY-80:

Experiment #1 - Initially, three electroacoustically similar hearing aids were selected for use. All three were appropriate for use with high frequency noise induced hearing loss. Of the 75 total inter-aid comparisons, only seven difference scores exceeded the .95 confidence level. Since this number of significant differences could occur due to chance alone, there was no basis for concluding that any of the differences among aids represented actual significant performance differences.

Experiment #2 - Data collection has begun on a follow-up experiment, identical to the first in design, but utilizing three instruments that are electroacoustically quite dissimilar. The three aids are all housed in identical cases and a double-blind paradigm is being employed to avoid subject or experimenter bias. To date, six subjects have been run on the follow-up experiment. Of the 18 possible pre-trial inter-aid differences, 12 exceed statistical significance. Ten of these, however, were between Aid C and either Aids A or B. For the post-trial CHAE, seven of the 18 differences were significant. Six of the seven were between Aid C and either Aids A or B. The data (to date) for the trial use judgments reveal that the subjective acceptance ratings were consistent with the word recognition scores for 11 of the 12 significant inter-aid comparisons. That is, when two scores were significantly different, either the aid that scored higher was the most preferred aid, or the aid that scored lower was the least preferred aid. Of the seven significant inter-aid differences on the post-trial use CHAE, four were confirmed by the subjective judgments.

A comparison of the pre-trial and post-trial CHAE word recognition scores revealed that, of the 18 significance pre-trial differences, only five were replicated on the post-trial testing. From a clinical perspective, the aid of choice on the initial CHAE (i.e., the highest score irrespective of statistical significance) would also have been the aid of choice on the post-trial CHAE for only three of the six patients. Further, the aid of choice on the initial CHAE was the aid preferred by the patient in four of the six cases. The aid of choice on the post-trial CHAE was the preferred aid in two of the six cases.

Number of subjects to be studied before completion of study: 50

Serious/unexpected side effects in subjects participating in project: n/a

Conclusions: The following tentative conclusions are supported by the data -

1. For hearing aids preselected to be appropriate to the patient's hearing impairment (i.e., electroacoustically homogeneous), the frequency with which statistically significant inter-aid differences occur does not exceed chance.

2. For electroacoustically dissimilar aids, significant inter-aid differences in word recognition occur frequently. In general, however, relatively few interactions between aids and patients are observed. Specifically, the same aid was generally poorest for all patients.

3. There is not a high degree of agreement between relative word recognition scores and subjective preference ratings.

Publications or Abstracts, FY-80: Not applicable.

WORK UNIT NO.: 2530

FUNDS UTILIZED, FY-80: none

FUNDING REQUIREMENTS, FY-81:

EQUIPMENT: $10,000 for a two-channel diagnostic audiometer

TRAVEL: $607.00 (to present results at a national meeting)

REPRINTS: $200.00

PAGE CHARGES: $500.00

| Date: 30 September 1980 | Protocol No.: 2531 | Status: Interim |
|---|---|---|

Title of Project: Maintenance of Speech Fluency Following an Intensive Stuttering Therapy Program

| Starting Date: 2 September 1980 | Estimated Completion Date: 31 August 1982 |
|---|---|

Principal Investigator: Marcia D. Bond-Liebertz, M.A.

| Associate Investigators: | Facility: Army Audiology and Speech Center, WRAMC |
|---|---|
| Pamela Silverwood, M.A.<br>Patryce F. Thompson, M.A.<br>Brenda W. Lohsen, M.A.<br>Joyce Gurevich-Uvena, M.A.<br>Christine Fair, M.Ed.<br>Gloria Chi, M.A.<br>Robert A. Prosek, Ph.D. | Dept/Svc: Department of Surgery, Otolaryngology Service |

Key Words: Stuttering, follow-up, disfluency, speech

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: $251.60 |
|---|---|---|

| FY-80 MEDCASE Cost: | Periodic Review Results: |
|---|---|

Study Objective: To determine the extent to which fluency improvement is maintained by adult stutterers participating in the Precision Fluency Shaping Program during a nine-month period following release from treatment.

Technical Approach: Thirty stutterers who are participating in the Precision Fluency Shaping Program at Walter Reed will be the subjects for this study. Tape-recorded telephone monologues will be obtained from each subject on five occasions: 1) prior to the initiation of therapy (baseline), 2) immediately after completing the program (four weeks after baseline), 3) three months post-therapy, 4) six months post-therapy, and 5) nine months post-therapy. After giving permission to record the monologue, the subject will be instructed to speak for five minutes about his speech, or his hobbies, or about any topic that interests him (the specific content of the monologue is not important).

Two general measures of fluency, percent syllables stuttered (%SS) and syllables per minute (SPM), will be obtained for each of the 150 monologues. The improvement in each of these measurements relative to the baseline session will be calculated for each subject for each post-therapy recording. Appropriate statistics will be applied to these data to determine if the fluency gains made by the program are retained when the subject finishes treatment.

Progress during FY-80: Data acquisition has just begun. Four subjects have been recorded in the baseline and immediate post-therapy conditions.

Number of subjects to be studied before completion of study: 30

Serious/unexpected side effects in subjects participating in project: n/a

Conclusions: Not applicable at the present time.

Publications or Abstracts, FY-80: n/a

WORK UNIT NO.: 2531

FUNDS UTILIZED, FY-80: $251.60

FUNDING REQUIREMENTS, FY-81:

| | |
|---|---|
| EQUIPMENT: | Stop watches with independent reset capability, as per original protocol (qty, 2; cost, $55.00 each). |
| SUPPLIES: | Cassette tapes as per original protocol (qty, 88; cost, $4.50 each). |
| TRAVEL: | $750.00 (to present results at a national meeting). |

Work Unit No.: 2532

Title of Project: The Effects of Age and Brain Damage on Fluid Intelligence in Aphasic Adults with Lesions in Dominant Hemisphere.

Principal Investigator: Barbara C. Sonies, MA

This protocol has been terminated due to lack of acceptable patients for the project.

# DISPOSITION FORM

For use of this form, see AR 340-15, the proponent agency is TAGCEN.

| REFERENCE OR OFFICE SYMBOL | SUBJECT |
|---|---|
| HSWP-SOT | Progress Reports on Work Units 2610, 2615, 2616, 2618, 2619 |

XX THRU: C, Dept of Surgery FROM C, Transplant Svc DATE 24 Nov 80 CMT 1

TO: C, Dept of Clin Invest

1. Progress reports on the above numbered work units are attached.
   2610 - ALG
   2615 - Immunological Monitoring
   2616 - Graft Vs Host - Terminated
   2618 - Intentional Donor Specific Transfusion
   2619 - Histocompatibility, Antigens and Interstitial Cystitis.

2. The progress report on WU 2615 is expanded, reviewing the past three years performance. Hopefully it will serve as a final report for this work unit, established in 1977, which has provided most of the funding for transplant research. This year, transplant immunology laboratory work supporting the remaining approved protocols (ALG, Transfusion, and Thoracic duct drainage - HSC approval pending) has been charged to the appropriate work unit.

3. Current immunological monitoring work bears little resemblance to the 1977 protocol. Therefore individual protocols covering the seven aspects of present monitoring research are being finalized for presentation and approval at the January, 1981 C.I.S. meeting. Please bear in mind that this research is presently in progress under the expiring WU #2615.

5 Enc

JIMMY A. LIGHT, MD
COL, MC
Chief, Transplant Service

DA FORM 1 FEB 57 2496 REPLACES DD FORM 96, WHICH IS OBSOLETE.

| Date: 11 October 1980 | Protocol No: 2610 | Status: Interim X<br>Final |
|---|---|---|

Title of Project: ALG and Kidney Transplantation

| Starting Date: 1973 | Estimated Completion Date: Open; present addendum expires 1982 |
|---|---|

Principal Investigator: J. A. Light

| Associate Investigators: None | Facility: Walter Reed Army Medical Center |
|---|---|
| | Dept/Svc Surgery/Transplant |

Key Words: Immunosuppression; Rejection; Rejection Reversal; ALG

| Accumulative MEDCASE Cost: None | Accumulative Contract Cost: None | Accumulative Supply Cost: None |
|---|---|---|

| FY-80 MEDCASE Cost: None | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objectives: To better define the role of ALG in kidney transplantation

Technical Approach: Transplant recipients experiencing severe allograft rejection which had failed to respond to standard antirejection therapy received ALG as a therapy instead of removing the kidney. T rosettes were measured during treatment scheduled which varied in length from 6 to 25 days and in dose from 5-30 mg/kg/day.

Progress during FY-80: A. Steroid resistent allograft rejection - ALG is effective
B. Short vs. long treatment schedules - Short course may be as effective
C. Correlation of results with T-rosette suppression - no correlation (See
D. Correlation of results with ALG serum levels and rosettes - pending (attached sheet)

Number of subjects to be studied before completion of study: Approx. 50

Serious/unexpected side effects in subjects participating in project: None

Conclusions: Although original objectives of this protocol were never achieved, useful original work has been accomplished. New objectives identified altering approaches under protocol addendum during this fiscal year.

Publications or Abstracts, FY-80: ALG Reverses Irreversible Rejection. Abstract accepted; presented Jul 80 to Transpl. Society. Ms to be published Mar 81.

Progress (continued)

ALG had been previously thought to be effective only as prophylaxis in the early post transplant period. We showed that ALG effectively reversed rejection episodes resistant to standard antirejection therapy. These kidneys would have been lost to rejection without ALG. Our work defined parameters when ALG should be used for rejection, helped define duration of therapy needed, and showed that monitoring assays (performed under WU 2615) failed to predict a successful outcome.

Work was presented at the VIII International Transplantation Congress in 1980. The manuscript will appear in the Transplant Proceedings, March, 1981. Serum collected from patients receiving ALG is being analyzed for ALG levels and will be compared with T-rosette levels, biopsy or nephrectomy pathology, and antibody eluates of rejected kidneys where appropriate. This will be original work and should result in publication.

New work under this protocol is detailed in the addendum submitted and approved recently. Briefly the thrust of that work is to randomize cadaveric transplant recipients into two treatment groups:

A. Prophylaxis - ALG given for 20 days starting on the first post-operative day.

B. Nonprophylaxis - These patients will receive ALG only if they experience graft rejection and will be treated for only 8 days.

The hypothesis is that ALG given only for rejection will lead to results equivalent to those achieved with ALG prophylaxis. This type of study has not been performed elsewhere to date.

T-rosettes will continue to be measured. They serve two purposes. Failure to produce rosette suppression with ALG may be associated with a poor response to ALG, whereas profound T-rosette suppression may be associated with increased opportunistic infection.

Work Unit No.: #2610

Funds Utilized, FY-80: $5,822.54

Funding Requirements, FY-81: $7,970.92

Personnel: (name and grade) Faith May, GS-7
PFC Donna Morgan

Equipment: (describe in detail including cost)

Supplies: (consumable, animal purchase) ALG - operating funds

Travel: (mission oriented, training and presentation) $750

Other: (equipment rentals, contracts for service, animal care and reprints) - $250
Specimen mailing - $100

FUNDING REQUIREMENT

Clinical Investigation Program

| Work Unit No: 2610 | Title: Organ Transplant Clinical Research Laboratory Antilymphocyte Globulin (ALG) and Kidney Transplantation | FY: |
|---|---|---|
| RPC: A24P | Principal Investigator: J.A. Light, COL, MC | Date Work Unit Approved: |

| Element of Expense: | | FY-81 | FY-82 | Remarks |
|---|---|---|---|---|
| 2100 | Travel- | | | |
| | Mission | 650.00 | 750.00 | |
| | Conference | 375.00 | 425.00 | |
| 2400 | Reprints and reproduction | 250.00 | 290.00 | |
| 2600 | Consumable Supplies | 6695.92 | 7700.31 | |
| 3100 | Non-Expendable Equipment | | | |
| 2372 | Lab Contracts | -00- | | |
| | | 7,970.92 | 9,165.31 | |

THIS REQUIREMENT RANKS NO 3 OF 5 WORK UNITS.

# DISPOSITION FORM

For use of this form, see AR 340-15, the proponent agency is TAGCEN.

| REFERENCE OR OFFICE SYMBOL | SUBJECT |
|---|---|
| HSWP-SOT | Termination of WU 2615, Immunological Monitoring of the Transplant Recipient. |

~~XX~~ THRU: C, Dept Surgery ~~(WU)~~ FROM C, Transplant Svc DATE 29 Sep 80 CMT 1
COL Light/fs/61462

TO: C, Clin Invest Svc

1. The above mentioned work unit is scheduled for termination 30 September 1980, unless an addendum justifying continuation is submitted prior to that date.

2. There has been extensive research in nearly all areas specified in the protocol which have yielded negative results in general, documented in an abstract earlier this year. These results and other unpublished results will be presented in the annual report. An additional abstract on monitoring has been accepted for presentation in November, 1980, and publication in 1981. Older data is being re-examined using newer statistical methods and may be helpful in explaining the lack of predictability of the monitoring assays.

3. Meanwhile related work has been initiated examining new culture techniques and new assays for cell mediated immunity and rejection activity. These tests look very promising. The present protocol is being extensively revised and can be submitted as an addendum in October along with the annual report. It will not be ready by the above mentioned deadline.

4. Research conducted under the support of this work unit supports research under Work Units 2610, 2617, and 2618. Request continuing support for WU 2615 for one month until appropriate addendum is created.

JIMMY A. LIGHT, MD
COL, MC
Chief, Transplant Service

DA FORM 2496 REPLACES DD FORM 96, WHICH IS OBSOLETE.

| Date: 5 Nov 80 | Protocol No: 2616 | Status: Interim / Final |
|---|---|---|

Title of Project: Obviating the Graft Vs Host Response

| Starting Date: 1977 | Estimated Completion Date: 1980 |
|---|---|

Principal Investigator: Annable, C.R. COL, MC

| Associate Investigators: None | Facility: Walter Reed Army Medical Center |
|---|---|
| | Dept/Svc Surgery/Transplant |

Key Words:

| Accumulative MEDCASE Cost: None | Accumulative Contract Cost: None | Accumulative Supply Cost: None |
|---|---|---|

| FY-80 MEDCASE Cost: None | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective: GVH is the major problem with bone marrow transplantation. The objective of this experimental animal protocol was to determine a means of obviating this response to permit BM transplantation across a major histocompatibility barrier.

Technical Approach: Histoincompatible bone marrow donors were given recipient antigen at intervals prior to transplanting their bone marrow. With the appropriate antigen dose and timing, lethally irradiated recipients could be successfully reconstituted with allogeneic bone marrow without any GVH. Although the results were promising, work was suspended when the primary investigator was reassigned. No abstracts, publications nor final report was written.

Progress during FY-80: None

Funding utilized, FY-80: $4,800

Number of subjects to be studied before completion of study: N/A

Serious/unexpected side effects in subjects participating in project: N/A

Conclusions: Recommend termination

Publications or Abstracts, FY-80: None

| Date: 6 November 1980 | Protocol No: 2618 | Status: Interim / Final |
|---|---|---|

Title of Project: Intentional Donor Specific Pretransplant Transfusion

| Starting Date: Approval date | Estimated Completion Date: 1983 |
|---|---|

Principal Investigator: Light, J.A.

| Associate Investigators: Kumar, Oddenino, Biggers | Facility: Walter Reed Army Medical Center |
|---|---|
| | Dept/Svc Surgery/Transplant |

Key Words: Transplant, Transfusion

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: |
|---|---|---|

| FY-80 MEDCASE Cost: | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective: 1. Decrease incidence of rejection and improve long term results of transplantation.
2. Determine which type of blood is most efficient.
3. Determine antibody production to T and B lymphocytes and red cell antigens with the types of transfusion.
4. Measure MLC and CML responses before and after transfusion.

Technical Approach: Recipients receive either fresh or stored donor specific blood transfusion at two week intervals prior to transplantation. Frequent antibody screens and crossmatches are performed. MLC and CMC assays are performed before and after transfusion.

Progress during FY-80: 5 patients have been entered in the study. Preliminary observations suggest that both types of blood are effective. Sensitization rates may be decreased, by using stored blood rather than fresh blood. Th~~will be a significant contribution since presently about 35% of recipients are ser~~
Number of subjects to be studied before completion of study: 20-30 /tized by the trans
Serious/unexpected side effects in subjects participating in project: /fusion process.

Conclusions: None

Publications or Abstracts, FY-80: None

CLINICAL INVESTIGATION PROGRAM

Work Unit No.: 2618

Funds Utilized, FY-80: N/A

Funding Requirements, FY-81: $19,562.00

Personnel: (name and grade)

Equipment: (describe in detail including cost)

Supplies: (consumable, animal purchase) consumable: $18,400.00

Travel: (mission oriented, training and presentation) Patient $ 0.0
Mission: $362.0
Conference: $300.00

Other: (equipment rentals, contracts for service, animal care and reprints) Reprints and reproduction: $500.00

MLC, CML 40 x $150.00
Ab Screen 80 x 80.00
Crossmatch 40 x 150.00

**DISPOSITION FORM**

For use of this form, see AR 340-15, the proponent agency is TAGCEN.

| REFERENCE OR OFFICE SYMBOL | SUBJECT |
|---|---|
| HSWP-SOT | Response to Reviewer Comments on W/U 2618 |

TO C, Dept of Clin. Invest. FROM C, Transplant Svc DATE 29 Dec 80 CMT 1

1. This protocol was approved in July 1980 and details of the work to be performed are in the referenced protocol. The funding request for 1981 represents the costs the experimental studies to be performed. This work was previously done under the funding for W/U 2615 which has now expired.

2. Our present plans are to change our funding requests from one large work unit (as it was for the past several years under W/U 2615) to specific funding for each protocol. The funds requested to support W/U 2618 reflect that administrative change. Further description of the specific funding requirement is attached.

JIMMY A. LIGHT, MD
COL, MC
Chief, Transplant Service

370

| Date: 6 November 1980 | Protocol No: 2619 | Status: (Interim) / Final |
|---|---|---|

Title of Project: Histocompatibility Antigens and Interstitial Cystitis

| Starting Date: 1980 | Estimated Completion Date: 1981 |
|---|---|

Principal Investigator: Fowler/Light

| Associate Investigators: | Facility: Walter Reed Army Medical Center |
|---|---|
| | Dept/Svc Surgery/Transplant |

Key Words: HLA, cystitis

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: |
|---|---|---|

| FY-80 MEDCASE Cost: | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective: To determine whether patients with interstitial cystitis have a particular histocompatibility profile which might be associated with the disease.

Technical Approach: ____ patients were tissue typed for HLA - A, B, C and Dr.

Progress during FY-80: Tissue typing has been completed. Data Analysis presently being completed. Work will be completed in this FY.

Number of subjects to be studied before completion of study: Study completed

Serious/unexpected side effects in subjects participating in project: None

Conclusions: Pending

Publications or Abstracts, FY-80: None

CLINICAL INVESTIGATION PROGRAM

Work Unit No.: 2619

Funds Utilized, FY-80: New Project - No funds used in 80

Funding Requirements, FY-81: $4,198

Personnel: (name and grade)

Equipment: (describe in detail including cost)

Supplies: (consumable, animal purchase) consumable: $3,173 (19 typings x $167.00

Travel: (mission oriented, training and presentation) mission: $475 conference: $200

Other: (equipment rentals, contracts for service, animal care and reprints)
Reprints and reproduction: $350

# DISPOSITION FORM

For use of this form, see AR 340-15, the proponent agency is TAGCEN.

| REFERENCE OR OFFICE SYMBOL | SUBJECT |
|---|---|
| HSWP-SOT | Response to Reviewer of APR W/U #2619 |

TO C, Dept of Clin Invest FROM C, Transplant Svc DATE 29 Dec 1980 CMT 1

1. This protocol was approved 24 June 1980, but funds were apparently not allocated. Nonetheless tissue typing studies were completed on 19 patients, since the primary investigator was leaving WRAMC shortly thereafter. Twelve of these patients' typings were included in the statistical analysis. A manuscript has been drafted and is being revised prior to submission for publication. The abstract is attached.

2. Funding request submitted for FY 31 represents the cost of the work already performed in FY 80 and publication/presentation costs.

JIMMY A. LIGHT, MD
COL, MC
Chief, Transplant Service

DA FORM 2496 REPLACES DD FORM 95, WHICH IS OBSOLETE.

## Abstract

We studied the histocompatibility profiles in 12 Caucasian patients with convincing clinical and cystoscopic evidence of early interstitial cystitis. There were no statistically significant increases in HLA - A, B, C, or DR in these patients when compared with a control population. Susceptibility to early interstitial cystitis does not appear to be associated with HLA.

| Date: 14 October 1980 | Protocol No: 2809 | Status: Interim xx<br>Final |
|---|---|---|

Title of Project: Relationship between Prostatic Cancer and Excretion of Urinary Cholesterol

| Starting Date: | Estimated Completion Date: |
|---|---|

Principal Investigator: Harry Y.C. Wong, Phd

| Associate Investigators: | Facility: |
|---|---|
| David G. McLeod, MD, COL, MC, USA<br>Eustus Nelson, MD, CPT, MC, USAF | Dept/Svc Urology |

Key Words: prostate, CA and non-esterfied cholesterol

| Accumulative MEDCASE Cost: 0 | Accumulative Contract Cost: 0 | Accumulative Supply Cost: 0 |
|---|---|---|

| FY-80 MEDCASE Cost: 0 | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective:

To determine urinary levels of non-estrified cholesterol in patients with carcinoma of the prostate; Attempt to establish a correlation between elevated urinary levels of N.E.C. in various stages of Prostatic CA, and hopefully utilize this method as a means to earlt diagnosis of the disease, and as a prognostic indication.

Technical Approach: 24 Hour urine specimens are obtained on patients with carcinoma of the prostate. No funds needed.

Progress during FY-80: Several samples were obtained and sent to Howard University but we got behind due to other protocols.

Number of subjects to be studied before completion of study: 30

Serious/unexpected side effects in subjects participating in project: N/A

Conclusions: None

Publications or Abstracts, FY-80: None

| Date: 5 December 1980 | Protocol No: 2811 | Status: Interim / Final X |
|---|---|---|

Title of Project: The value of excretory urography, cystography and cystoscopy in the evaluation of adult women with urinary infection.

| Starting Date: ? | Estimated Completion Date: Completed |
|---|---|

Principal Investigator: MAJOR JACKSON E. FOWLER, JR. MD, MC, USA

| Associate Investigators: None | Facility: Walter Reed Army Medical Center Washington, D.C. 20012 |
|---|---|
| | Dept/Svc Urology Service |

Key Words: Urinary Infections

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: |
|---|---|---|

| FY-80 MEDCASE Cost: | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective:

Cost containment of the work-up of urinary tract infections.

Technical Approach.

Progress during FY-80:

Doctor Fowler left the Service in September 1980, so I assume he completed this project before he left.

Number of subjects to be studied before completion of study:

Serious/unexpected side effects in subjects participating in project:

Conclusions:

I had nothing to do with this project. I am sure that Doctor Fowler cleared the project with Doctor Stutzman to begin it.

Publications or Abstracts. FY 80: None

| Date: October 1980 | Protocol No: 2812 | Status: Interim X<br>Final |
|---|---|---|

Title of Project:

Human Chorionic Gonadotropin (HGT) Producing Cells in Seminomatous Germ Cell Tumors of The Testis: A Prospective and Retrospective Correlation with Tumor Histology and Response to Therapy.

Starting Date: 25 Mar 1980 | Estimated Completion Date: 1 Year

Principal Investigator: DAVID G. McLEOD, MD, COL, MC, USA

| Associate Investigators: | Facility: |
|---|---|
| CHARLES DAVIS, COL, MC, USA<br>SUSAN KERN, CPT, MC | WRAMC<br>Dept/Svc Urology, Pathology, AFIP Genito-urinar |

Key Words: Testis Tumor (Seminoma)

| Accumulative MEDCASE Cost: 0 | Accumulative Contract Cost: 0 | Accumulative Supply Cost: 0 |
|---|---|---|

| FY-80 MEDCASE Cost: 0 | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective:

To see if there is any correlation between HGC producing tumors and degree of malignancy in seminomas.

Technical Approach: We are trying to collect, for examination, tissue blocks, as outlined in the protocol. No funds asked and no funds needed.

Progress during FY-80: Little progress has been made as most tissue blocks are in a warehouse at Fort Meade, Maryland, but Doctor Kern is pressing ahead.

Number of ~~subjects~~ tissue blocks to be studied before completion of study: 50-60 On-going

Serious/unexpected side effects in subjects participating in project: None

Conclusions: None at present

Publications or Abstracts, FY-80: None

| Date: October 1980 | Protocol No: 2813 | Status: Interim / Final X |
|---|---|---|

Title of Project: Alpha fetoprotein (AFP) and human chorionic gonadotropin (HCG) producing cells in non-seminomatous germ cell tumors of the testis; a retrospective correlation with serum AFP and HCG levels, tumor histology and response to therapy

Starting Date: 25 Mar 80 | Estimated Completion Date: N/A

Principal Investigator: FOWLER, JACKSON E. JR. MD, MAJOR, MC, USA

| Associate Investigators: | Facility: WRAMC |
|---|---|
| RAY E. STUTZMAN, MD, COL., MC, USA | Dept/Svc UROLOGY, PATHOLOGY & GU BRANCH OF HI |

Key Words: Cystic tumors

| Accumulative MEDCASE Cost: 0 | Accumulative Contract Cost: 0 | Accumulative Supply Cost: 0 |
|---|---|---|

| FY-80 MEDCASE Cost: 0 | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective:

To see if there is any correlation between tumor markers and degree of malignancy.

Technical Approach:

Progress during FY-80:

Number of subjects to be studied before completion of study:

Serious/unexpected side effects in subjects participating in project: None

Conclusions:

Complete

Publications or Abstracts, FY-80: None

| Date: 13 October 1980 | Protocol No: 2815 | Status: Interim XXX<br>Final |
|---|---|---|

Title of Project:

An Epdemilogic Investigation of Testicular Cancer

| Starting Date: 22 May 1980 | Estimated Completion Date: 2 Years |
|---|---|

Principal Investigator: RAY E. STUTZMAN, MC, COL, MC, USA

| Associate Investigators: | Facility: Walter Reed Army Medical Center<br>Washington, D.C. 20012 |
|---|---|
| | Dept/Svc Urology Service |

Key Words: testi tumors

| Accumulative MEDCASE Cost: 0 | Accumulative Contract Cost: 0 | Accumulative Supply Cost: 0 |
|---|---|---|

| FY-80 MEDCASE Cost: 0 | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective:

To determine epidemilogical characteristics of testicular tumor patients

Technical Approach: Case/Control study - Interviewing patients both as inpatients and outpatients. There is no funding needed.

Progress during FY-80: Study is progressing well. Staff has been very supportive and patients are interested in cooperating with researchers. Approximately 20-30 patients studied to date

Number of subjects to be studied before completion of study: Undetermined

Serious/unexpected side effects in subjects participating in project:
None

Conclusions:

Publications or Abstracts, FY-80: None

| Date: Nov 15, 1980 | Protocol No: 2901 | Status: Interim x<br>Final |
|---|---|---|

Title of Project: Neovascularization of the Microvascular Free-flap

| Starting Date: Aug. 1, 1980 | Estimated Completion Date: Jan. 31, 1982 |
|---|---|

Principal Investigator: J.A. Chow, MAJOR, MC

| Associate Investigators:<br>H.D. Peterson, COL, MC<br>Sp 4 M. Callahan | Facility: Walter Reed Army Medical Center and Walter Reed Army Institute of Research<br>Dept/Svc Plastic and Reconstructive Surgery |
|---|---|

Key Words:
Neovascularization Microvascular Free Flap

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: |
|---|---|---|

| FY-80 MEDCASE Cost: | Periodic Review Results:<br>(to be filled in by DCI) |
|---|---|

Study Objective: To study the specific time interval in the postoperative period necessary for adequate Neovascularization of successfully performed Microvascular Free-flaps, so as the flap will continue to survive despite occlusion (ligation) of the feeding vessels of the flap. The study is mission-orientated because the information obtained will indicate when the secondary bone grafts, nerve grafts or tendon grafts maybe safely performed on patients following successfull free-flap coverage for traumatic gun-shot wounds or blast injuries to the lower extremity.

Technical Approach: Microvascular free-flaps based on the inferior epigastric vessels are used for the canine model of this study.

Progress during FY-80: The results were obtained in eight dogs: primary data indicates that the microvascular free-flap may survive following lipetion of the vessels at post-op twelve (12) days.

Number of subjects to be studied before completion of study: 60

Serious/unexpected side effects in subjects participating in project:

Conclusions: Final conclusion may not be drawn until completion of the study on all canine models. The preliminary data is promising.

Addendum to FY-80 Annual Progress Report ( APR ) for Work Unit #2901

Funding Budget Justification for FY-81

This research project was designed to be carried out during the latter portion of FY-80 and the entire portion of FY-81, and may possibly extend to the first 2 months of FY-82.

According to the protocol, neovascularization ( the specific post-operative time intervals required ) on 60 successful microvascular free flaps of dogs will be studied, so as to obtain the necessary statistically significant data.

During FY-80, Satisfactory results were obtained from the work performed on 8 dogs. Therefore, during FY-81, further research work is necessary to be performed on the remaining 52 dogs.

From the allocation on the FY-80 Buget Funding, consumable supplies were acquired for the work on 20 dogs. ( This is the only money or funding spent on this project.) Therefore, during the FY-81, further funding budget is necessary so as to obtain the consumable supplies for the operative investigation of the other 40 dogs. ( This had been previously checked out with Mr. Burton and MAJ Reed, and was considered to be correct. )

The continuation of this research project is highly desirable, because it is directly applicable to clinical situations, and is mission essential in the surgical care of military personnel sustained with gun-shot or shrapnel wounds of the lower extremities as well as in the management of soldiers with open fractures of the tibia and/or fibula ( motor-cycle or jeep accidents ).

It is planned that the findings and conclusions of this clinical research project will be presented in the national meeting of the Plastic Surgery Research Council in the Spring of 1982.

Funds requested: $3,930.

Work Unit No.: 3138

Title of Project: Immunologic Mechanisms of Cutaneous Reactions to Inhalant Allergens

Investigators:

Principal: Richard D. deShazo, M.D.

Associate: H.M. Dvorak, M.D.

Objectives: To define the immunologic mechanisms responsible for untoward cutaneous reactions seen with the injection of inhalant allergens

Technical Approach: Immediate hypersensitivity skin tests, punch skin biopsy, light and fluorescent microscopy, RAST IgE.

Progress and Results: During the last year we have concluded the originally initiated work in collaboration with investigators at FAMC, extending our observations on the etiology of late cutaneous allergic responses to antigen. This protocol has involved the use of $H_1$ and $H_2$ antihistimines and aspirin in an attempt to block the late cutaneous allergic response. In addition, we have observed the effects of these antihistamines on insulin reactions, which we are studying under a separate protocol. The work of last year has been extended by observing the histology of blocked late cutaneous reactions using punch biopsy and 1 micron Giemsa stain sections. These sections, obtained on 3 patients, revealed that reactions which appeared to be blocked clinically by common antihistamine combinations, are indeed blocked histopathologically as well.

To summarize, during this protocol we have been able to establish that late in time dermal reactions to antigens which occur after intradermal injection of ragweed are IgE-mediated. These reactions may be blocked by combinations of $H_1$ and $H_2$ antihistamines. We have further established that histamine itself is unable to induce such late reactions. Therefore, a pharmacologic mediator other than histamine appears to be acting either alone or in conjunction with histamine at histamine receptors to provide the vasopermeability event necessary for subsequent late reactions. Since aspirin has no effects on these responses, the mediator is probably not prostaglandin. These important findings form the basis for further research being carried on by a number of investigators to further

characterize IgE-mediated late in time reactions.

Funding Requirements for FY 81:

The principal investigator for this protocol has left service and therefore the protocol is to be terminated at this time.

Publications:

1. deShazo RD, Levinson HI, Dvorak HM, Davis RW. Late phase skin reaction. J Immunol 122:692, 1979.

2. Smith JA, Mansfield LE, deShazo Rd, Nelson HS. An evaluation of the pharmacologic inhibition of the immediate and late cutaneous reaction to allergen. J Allergy Clin Immunol 65:119, 1980.

Presentations:

Presentations were made on the basis of the work at the American Academy of Allergy in 1979 and in 1980.

Complications: None

Type of Report: Termination

| Date: 20 October 1980 | Protocol No: 3144 | Status: Interim X / Final |
|---|---|---|

Title of Project: Neurophysiologic, Immunologic and Biochemical Aspects of Bronchial Asthma.

| Starting Date: 8 March 1977 | Estimated Completion Date. October 1981 |
|---|---|

Principal Investigator: Laurie J. Smith, M.D.

| Associate Investigators: | Facility: Allergy-Immunology Service |
|---|---|
| Richard Evans III, CGL MC<br>Richard Summers, LTC MC | Dept/Svc |

Key Words:

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: |
|---|---|---|

| FY-80 MEDCASE Cost: | Periodic Review Results: (to be filled in by DCA) |
|---|---|

Study Objective: To characterize a group of atopic asthmatics by their alpha and beta adrenergic as well as cholinergic responses, looking in particular for a cholinergic imbalance.

Technical Approach: All patients will have extensive initial allergy workup including skin testing to inhalant allergens and an antigen bronchial challenge. The following tests will be performed at NIH: 1) Oral aspirin challenge; 2) Eccrine sweat responses to saline mecholyl and propranolol; 3) Pupillometry to measure pupil responses to Carbachol and Phenylephrine; 4) Response of cyclic nucleotides to intravenous injections of very low doses of isuprel. The following tests will be performed at WRAMC Allergy Clinic: 1) Mecholyl bronchial challenge with air and He/02; 2) Histamine bronchial challenge with air and He/02. Note: Certain equipment must be expanded and modified.

Progress during FY-80: We have expanded our study group to include 14 parents of children with cystic fibrosis, 4 patients with intrinsic asthma, 9 patients with allergic rhinitis and 16 nonallergic normal control and 23 allergic asthmatics. These subjects have all undergone studies of alpha adrenergic and cholinergic nervous system and some have undergone studies of beta adrenergic nervous system.

Number of subjects to be studied before completion of study: 30 more asthmatics are to be studied: 2 groups: 1) allergic asthma, 2) exercise asthma

Serious/unexpected side effects in subjects participating in project: None

Conclusions:

See attached sheet.

Publications or Abstracts, FY-80. See attached sheet.

Conclusions:

In summary:

1) Allergic asthmatics show increased sensitivity to alpha adrenergic and cholinergic stimulation and decreased sensitivity to beta adrenergic stimulation.

2) Intrinsic asthmatics show these defects similarly but to a greater degree.

3) Patients with cystic fibrosis and their parents, with and without asthma, also demonstrate these abnormalities.

4) These studies suggest autonomic nervous system abnormalities are not enough alone to result in bronchial asthma.

5) There have been no serious or unexpected side effects or complications in subjects participating in this study.

Publications or Abstracts, FY-80:

1. Abstract: Autonomic nervous system dysfunction in patients with cystic fibrosis. L. Smith, M. Kaliner, P. Davis, J. Shelhamer, V. Hubbard, J. Allergy Clin. Immunol. 65:217, 1980.

2. The cholinergic nervous system and immediate hypersensitivity II. An analysis of pupillary responses. L. Smith, J. Shelhamer, M. Kaliner, accepted for publication, J. Allergy Clin. Immunol.

3. Autonomic nervous system abnormalities in allergy, asthma and cystic fibrosis. Michael Kaliner, James Shelhamer, Pamela Davis, Laurie Smith, J. Cray Venter, accepted for publication, Annals of Internal Medicine.

4. Abnormal adrenergic responsiveness in allergic subjects: analysis of isoproterenol-induced cardiovascular and plasma cystic AMP responses, J. H. Shelhamer, D. D. Metcalf, L. J. Smith, and M. Kaliner, J. Allergy Clin. Immunol. 66:52-61, 1980.

Work Unit No.: 3144

Funds Utilized, FY-60: $800.00

Funding Requirements, FY-61: $1700.00

Personnel: (name and grade) No additional requirements.

Equipment: (describe in detail including cost) No additional requirements

Supplies: (consumable, animal purchase) No additional requirements

Travel: (mission oriented, training and presentation) $1000.00

Other: (equipment rentals, contracts for service, animal care and reprints) $700.00

Work Unit No.: 3146

Title of Project: Immunotherapy Kit Potency Persistence

Investigators:

Principal: Richard J. Summers, M.D. LTC MC

Associates: Richard Evans III, M.D. COL MC
Michael S. Edwards, CPT MSC

Objective: The study is designed to determine the persistence of biological potency of allergy extracts during shipment and use.

Technical Approach: RAST (Radioallergosorbent Test) will be performed to determine potency persistence.

Progress & Results: The extracts have been shipped and returned. Aliquots are being taken at intervals. Final results are awaiting standardization of RAST inhibition.

Conclusions: No conclusions can be made until all results are in.

Funds Utilized, FY-78: $500 of estimated total cost of protocol.

Funds Utilized, FY-79: $500 of estimated total cost of protocol.

Funding Requirements, FY-80:

| | | |
|---|---|---|
| Personnel: | One GS-7 technician, currently employed, 2 weeks/year | |
| Equipment: | No new equipment is required | |
| Supplies: | Consummable - needles, syringes and RAST testing | $4,000.00 |
| Travel: | None | |
| | Total | $4,000.00 |

Publications: None

Type of Report: Interim

Addendum:

Principal Investigator: Richard J. Summers, M.D. LTC MC

Associate Investigator: Richard Evans III, M.D. COL MC

Associate Investigator: Michael S. Edwards, CPT MSC

ADDENDUM

WORK UNIT # 3146

TITLE OF PROJECT: Immunotherapy Kit Potency Persistence.

PRINCIPAL INVESTIGATOR: Richard J. Summers, LTC MC

DATE OF APPROVAL AT WRAMC: 26 April 1977

DATE OF APPROVAL AT CTSS (NOT REQUIRED)

COPY OF ANNUAL PROGRESS REPORT FY-79 IS ATTACHED: YES

ADDENDUM: Continuation of this protocol is desired. It was not possible to complete standardization of RAST inhibition during FY-80 due to lack of standards from Bureau of Biologics at FDA. Hopefully these will become available during FY-81 and the project can be completed over the next 6-9 months. An increase in funding is requested because the price per RAST inhibition is now up to $400.

# DISPOSITION FORM

For use of this form, see AR 340-15, the proponent agency is TAGCEN.

| REFERENCE OR OFFICE SYMBOL | SUBJECT |
|---|---|
| HSWP-QAI | Termination Request for Work Unit #3147 |

TO C, Clin Inv Svc FROM C, Allergy-Immuno Svc DATE 30 July 1980 CMT 1
Dr Evans/mm/6-1853/4

1. This is a termination request for Work Unit #3147 entitled: "Hymenoptera Venom Safety and Efficacy Evaluation as Allergen Immunotherapy in Insect Sting Allergy Patients."

2. Insect venoms for diagnostic and treatment of insect sting allergy were approved for use in the general population in April 1979.

3. We have continued to follow approximately 14 patients in this protocol with specific IgG and IgE antibody titer until the beginning of this calendar year. These patients continue to receive insect venom immunotherapy but this treatment is not considered investigative.

RICHARD EVANS III, M.D.
COL, MC
Chief, Allergy-Clinical Immunology Service

DA FORM 1 FEB 57 2496 REPLACES DD FORM 96, WHICH IS OBSOLETE.

| Date: 14 Oct 80 | Protocol No: 3147 | Status: Interim / Final ✓ |
|---|---|---|

**Title of Project:** Hymenoptera Venom Safety and Efficacy Evaluation as Allergen Immunotherapy in Insect Sting Allergy Patients.

| Starting Date: | Estimated Completion Date: |
|---|---|

**Principal Investigator:** Daniel A. Ramirez, MAJ MC

| **Associate Investigators:** | **Facility:** Walter Reed Army Medical Center |
|---|---|
| Richard Evans III, COL MC | **Dept/Svc** Clinical Investigation |

**Key Words:**

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: |
|---|---|---|

| FY-80 MEDCASE Cost: | Periodic Review Results: (to be filled in by DCI) |
|---|---|

**Study Objective:** To establish the safety and effectiveness by hymenoptera venom preparations in the prevention of anaphylactic reactions following hymenoptera stings.

**Technical Approach:** Patients with history of having systemic reactions following a hymenoptera sting are evaluated by skin testing using a skin test titration technique from $10^{-3}$ ug/ml up to 1 ug/ml. Concordant venom RAST titers are also obtained. Routine chemistries, CBC, with sedimentation rate urinalysis, C3, C4, FANA and venom specific titers of IgE and IgG have been followed every 3 months.

**Progress during FY-80:** Of the 24 selected patients for venom immunotherapy, 19 patients have moved from the area and are no longer in the study. These patients are on clinical allergy treatment with licensed materials. Five patients who had reached the 100 ug of venom per month continue attending to periodical follow up visits as to 14 Oct 80. (contd)

Number of subjects to be studied before completion of study: Completed 30 July 1980

Serious/unexpected side effects in subjects participating in project: No patients have experienced a systemic reaction; no abnormalities of the laboratory parameters have thus far been detected.

**Conclusions:** Hymenoptera venom extracts have so far been shown to be safe for use in immunotherapy. Efficacy in preventing anaphylactic reactions upon subsequent stings has also been demonstrated. The specific IgE titer increased with immunotherapy in approximately half of the patients and the specific IgG antibody increased with immunotherapy in all patients.

**Publications or Abstracts, FY-80:**

See continuation sheet

Progress during FY-80:

The protocol was terminated 30 July 1980. On 18 August 1980 an FDA inspector reviewed this project. No significant deficiencies were found.

Publications or Abstracts, FY-80:

1. Ramirez, D.A. and Evans III, R: The diagnosis of Hymenoptera hypersensitivity, J. Allergy Clinical Immunol. (Abstract).

2. Ramirez, D.A. and Evans III, R: The diagnosis of Hymenoptera hypersensitivity. J. Allergy Clinical Immunol. In press 1980.

Presentations:

1. An abstract for presentation by Dr. Ramirez of part of these data regarding diagnosis has been accepted for the scientific section of the American Academy of Allergy meeting in March 1979.

2. An abstract for presentation by Dr. Evans of part of these data regarding treatment has been accepted for a scientific workshop of the American Academy of Allergy meeting in March 1979.

3. Presented to Penn Allergy Society June 1980.

4. Accepted for presentation AACIA, Las Vegas, Nevada, November 1980.

| Date: DEC 1 1986 | Protocol No: 3149 | Status: Interim / Final X |
|---|---|---|

Title of Project:

Investigation of Immunologic Imbalance in Atopic Dermatitis.

| Starting Date: | Estimated Completion Date: |
|---|---|

Principal Investigator: DONNA LYNN SCHUSTER

| Associate Investigators: | Facility: |
|---|---|
| RICHARD EVANS III. COL MC<br>CONSULTANT: ARNOLD I. LEVINSON<br>UNIVERSITY OF PENN<br>PHILA.. PA | WALTER REED ARMY MEDICAL CENTER |
| | Dept/Svc ALLERGY - IMMUNOLOGY SERVICE |

Key Words:

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: |
|---|---|---|
| FY-80 MEDCASE Cost: | Periodic Review Results: (to be filled in by DCI) | |

Study Objective:

The purpose of this study is to further delineate the immunologic imbalances found in atopic dermatitis and to study the cellular regulation of IgE in this patient population..

Technical Approach:

Peripheral blood mononuclear cells from both normal and atopic dermatitis patients were cultured for 1 hour with a B adrenergic agonist (Isuprel), B adrenergic antagonist propanolol) alpha adrenergic agonist (phenylephrine), alpha antagonist (atropine) or aminophylline. After an hour's incubation with these agents the cells were then washed and lymphocyte subpopulations were determined. The resulting technique used for characterizing these subpopulations consisted of rising OxRBC sensitized with either rabbit IgM or rabbit IgG anti OxRBC to identify Tu (helper cells) or T (suppressor cell) respectively.

In addition, we have developed a sensitive assay for the measurement of extremely low levels of IgE by a modification of the Phadibas IgE PRIST. This direct radiolabelled anti IgE ($DE_2$ specific) antibody obtained from the phadibas IgE RAST for the less specific PRIST anti IgE $I^{125}$. This method proved useful in quantitating in vitro IgE synthesized by human blood mononuclear cells after 7 days in culture with or without pokeweed mitogen stimulation.R

Progress during FY-80:

This decrease could be reversed with prior incubation with atropine before the addition of methacholine. In the atopic dermatitis population studied there was no change in the levels of T cells after incubation with any of the above agents.

Our new sensitive method for the measurement of IgE has been found to be sensitive to 40 ph/ml of IgE and reproducible with different lot numbers of reagents. The coefficient of variation among multiple experiments was 11% at 220 pg/ml of IgE and 21% at 40 gv/ml of IgE.

This new method allowed us to quantify in vitro IgE synthesized by human blood mononuclear cells. Atopic patients were found to synthesize significantly more IgE than normal subjects. The addition of pokeweed mitogen to the cultures did not significantly enhance IgE synthesis by either the atopic or non-atopic cells.

Conclusions:

Atopic dermatitis may be related to a B adrenergic blocade.

In addition, we have found that atopic patients were found to synthesize significantly more IgE than normal subjects. IgE synthesis in either normal or atopic cells was not simulated in the immunologic aberrancies and cellular regulation if IgE in atopic dermatitis will be carried out at a different institution.

| Date: 14 Oct 80 | Protocol No: 2151 | Status: Interim / Final X |
|---|---|---|

Title of Project: Allergic Disease Center
Study of Hymenoptera Venom as an Agent for Diagnosis

| Starting Date: | Estimated Completion Date: |
|---|---|

Principal Investigator: Richard Evans III, COL MC

| Associate Investigators: | Facility: Walter Reed Army Medical Center |
|---|---|
| Michael S. Edwards, CPT MSC | Dept/Svc Clinical Investigation |

Key Words:

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: |
|---|---|---|
| FY-80 MEDCASE Cost: | Periodic Review Results: (to be filled in by DCI) | |

Study Objective: To establish the effectiveness of hymenoptera venoms as testing agents in making the diagnosis of insect sting allergy.

Technical Approach: Patients with a history of allergic reactions to hymenoptera stings were skin tested with the commercially available whole body extracts and with insect venoms using a skin test titration of $10^{-3}$ ug/ml up to 1 ug/ml. Venoms from Honey Bee, Yellow Jacket, Yellow Hornet, White Faced Hornet and Wasp were provided by the NIAID, NIH. Catalog was A(63)1635,-902-585, received November 1978. Venom materials were given FDA approval for human use in April 1979. These materials have therefore not been investigative since that date.

Progress during FY-80: 395 patients have been skin tested with insect venoms. 3 groups with positive skin test reactions have been identified; 1) systemic reactions, 2) large local reactions, 3) either of above with patients previously treated with whole body extracts.

Number of subjects to be studied before completion of study: Completed 30 July 1980

Serious/unexpected side effects in subjects participating in project: None

Conclusions: Direct skin tests with insect venoms clearly separate patients with a history of previous systemic reaction from the control population. Patients with a history of large local reaction to an insect sting have positive direct skin tests to venom with a surprisingly large frequency. Considerable cross reactivity or (contd)

Publications or Abstracts, FY-80: none

multiple sensitivity was found to the insect venoms of the vespids (yellow jacket and hornets). There is also an unexpectedly high incidence of positive skin tests to venoms in the previously whole body extract treated group. It is concluded that skin tests with venoms alone do not identify patients at risk for a subsequent systemic reaction.

| Date: 15-10-80 | Protocol No: 3152 | Status: Interim / Final X |
|---|---|---|

**Title of Project:** Factors affecting theophylline half life

| Starting Date: | Estimated Completion Date: |
|---|---|

**Principal Investigator:** Paul F. Walker, MAJ MC

| Associate Investigators: | Facility: |
|---|---|
| Rodolfo Bongiovanni, CPT MSC<br>Richard Evans, COL MC | Allergy Laboratory<br>Dept. of Clinical Investigation<br>Biochemistry Lab. |
| | Dept/Svc: Department of Clinical Investigation<br>Allergy Clinic |

**Key Words:**
Aminophylline, Solu-medrol, terbutaline, clearance, pharmacokinetics

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: N/A | Accumulative Supply Cost: $7,500 |
|---|---|---|

| FY-80 MEDCASE Cost: $3,750 | Periodic Review Results: (to be filled in by DCI) |
|---|---|

**Study Objective:** Determine variations of biologic half-life of theophylline emparing values obtained following intravenous infusion of theophylline in normal volunteers and asthmatics under various clinical status and treatment program.

**Technical Approach:** Pharmacokinetics studies will be carried out on a normal population. The patient population will be studied under conditions of clinically stable and acute asthma.

**Progress during FY-80:** The normal volunteer population have been completed. Seven patients were studied under conditions of clinically stable and acute asthma.

Number of subjects to be studied before completion of study: None

Serious/unexpected side effects in subjects participating in project: None

**Conclusions:**
In all cases so studied, there is no difference in the rate of clearance and in the T ½ Beta.

**Publications or Abstracts, FY-80:** None

| Date: 10 October 1980 | Protocol No: 3154 | Status: Interim XXXX |
|---|---|---|

Title of Project: Evaluation of Prostaglandin Secreting Suppressor Cells in Cancer Patients. WRAMC #7802.

| Starting Date: 14 Apr 78 | Estimated Completion Date: 1 October 1981 |
|---|---|

Principal Investigator: Cynthia H. Ewel, 1LT, MSC
Anthony J. Deutsch, MAJ, MC

Associate Investigators:
Barbara Bongiovanni, BS
Sonnya Londono, BS

Facility: WRAMC

Dept/Svc: Immunology Experimental Lab
Allergy-Immunology Service

Key Words: Hodgkin's Disease, prostaglandin, antioxidant

| Accumulative MEDCASE Cost: NA | Accumulative Contract Cost: NA | Accumulative Supply Cost: $36,673.72 |
|---|---|---|

| FY-80 MEDCASE Cost: NA | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective:

To confirm the presence of previously reported prostaglandin producing cells capable of suppressing cell mediated immunity in patients with Hodgkin's Disease (HD) and establish their in vivo and in vitro sensitivity to a prostaglandin (PG) synthetase inhibitor (indomethacin) and certain inhibitors of toxic oxygen metabolite production (catalase and a-tocopherol)

Technical Approach:

In vitro lymphocyte cultures were set up with the mitogen PHA with and without indomethacin. Cocultures were also done with indomethacin and catalase or a-tocopherol. Delayed hypersensitivity skin tests were performed to screen for anergy.

Progress during FY-80:

Peripheral blood mononuclear cells from 10 patients with Hodgkin's Disease were stimulated in culture with the mitogen PHA in the presence of the (see attached sheet)

Number of subjects to be studied before completion of study: 18-20

Serious/unexpected side effects in subjects participating in project: None

Conclusions: Abnormal lymphocyte proliferative responses seen in Hodgkin's Disease may result in part from the excessive production of toxic oxygen metabolites as well as prostaglandins by adherent cell populations.

Publications or Abstracts, FY-80: Evidence for the Involvement of Monocyte-Derived Toxic Oxygen Metabolites in the Lymphocyte Dysfunction of Hodgkin's Disease. (Submitted for publication).

(continued from front sheet)

prostaglandin inhibitor indomethacin and the antioxidants catalase or a-tocopherol. Patient lymphocytes showed significant increases in PHA induced proliferation at all PHA doses when cultured with indomethacin. Further augmentation of lymphocyte proliferation was achieved with the addition of catalase or a-tocopherol to indomethacin in the culture system. The increase in proliferation was greatest in patients with more depressed PHA responses; and was abrogated by removal of adherent cells from the culture system.

| Date: 10 Nov 80 | Protocol No: 3155 | Status: Interim XXX<br>Final |
|---|---|---|

Title of Project: Evaluation of Suppressor Immunoregulatory Cells in the Pathogensis of Deficiency Disease.

| Starting Date: 18 March 1978 | Estimated Completion Date: 1 October 1981 |
|---|---|
| Principal Investigator: Cynthia N. Ewel, 1LT MSC<br>Anthony J. Deutsch, MAJ MC | |
| Associate Investigators:<br>Tami Hase, BS | Facility: Experimental Immunology Lab WRAMC<br>Dept/Svc Allergy Immunology Service |

Key Words: chemotaxis, histamine

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: $12,986.24 |
|---|---|---|
| FY-80 MEDCASE Cost: | Periodic Review Results: (to be filled in by DCI) | |

Study Objective:

Technical Approach:

Progress during FY-80:

Number of subjects to be studied before completion of study:

Serious/unexpected side effects in subjects participating in project:

Conclusions:

TITLE OF PROJECT: Project # 3155 Evaluation of Suppressor Immunoregulatory Cells in the Pathogenesis of Deficiency Disease

OBJECT: To detect the etiology of abnormal leukocyte chemotactic responses associated with recurrent infections in patients with atopic dermatitis.

TECHNICAL APPROACH: The chromium-labelled radiochemotactic assay was used in this study.

PROGRESS IN FY 80: During FY 80, fifteen patients with atopic dermatitis and 25 normal controls have been studied. Patients were bled and their white cells fractionated by density gradient methods into monocytes and neutrophils. These cells were placed in the upper chamber of Boyden chambers after being labelled with chromium 51 isotope, and subjected to 3 to 4 hour incubation across a chemotactic gradient. This gradient was produced with partially purified C3A. Chemotaxis was performed in the presence of various concentrations of histamine phosphate from $10^{-6}$ to $10^{-8}$ molar.

There was no evidence of inhibition of either monocyte or polymorphonuclear leukocyte chemotaxis in the normal control subject chemotaxis on exposure to varying concentrations of histamine. Likewise, no inhibition of leukocyte chemotaxis was noted in atopic dermatitis patient assays when chemotaxing cells were exposed to histamine. However, histamine inhibited patient monocyte chemotaxis in a dose-response fashion. This was seen in each of the patients studied, but was not noted in any control.

CONCLUSION: Histamine seems to selectively inhibit monocyte chemotaxis in patients with atopic dermatitis. The specificity of this inhibition (as to which histamine receptor is stimulated) is under further investigation. Histamine release in the skin of patients with atopic dermatitis may form the basis for recurrent dermal infections in these individuals. This may occur by inhibition of the ingress of mononuclear phagocytic cells into infected sites.

PLAN: A) The manuscript for this data is being prepared.

B) We hope to study the specificity of this response by performing chemotactic assays in the presence of various $H_1$ and $H_2$ anatagonists.

| Date: 1 October 1980 | Protocol No: 3158 | Status: Interim |
|---|---|---|

Title of Project: Evaluation of the Immune Pathologic Mechanisms Operative in Dermal Reactions to Insulin.

| Starting Date: 18 June 1979 | Estimated Completion Date: 1982 |
|---|---|

Principal Investigator: Timothy M. Boehm, LTC MC

| Associate Investigators: | Facility: WRAMC |
|---|---|
| Richard deShazo, MD | Dept/Svc Dept of Clinical Investigation and Allergy Service |

Key Words:

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: $7,250.00 | Accumulative Supply Cost: $1,856.20 |
|---|---|---|

| FY-80 MEDCASE Cost: | Periodic Review Results: (to be filled in by DCI) |
|---|---|

*Study Objective: To determine the mechanism underlying dermal reactions to insulin.

Technical Approach: Skin testing with various insulin preparations and skin biopsies of reaction sites with light and immunofluorescent microscopy.

Progress during FY-80: In all fourteen patients were studied and the immunofluorescent microscopy was completed of the biopsies.

Number of subjects to be studied before completion of study: *

Serious/unexpected side effects in subjects participating in project: None

Conclusions: (See attached abstract.) There are at least 3 distinct types of local reactions to insulin: 1) IgE dependent "late phase"; 2) "Arthus" local vasculitic; 3) delayed hypersensitivity.

Publications or Abstracts, FY-80: Persistent Local Reactions to Insulin. Evidence for Three Immunologic Mechanisms. (Abstract) R.D. deShazo, T.M. Boehm, D.D. Kumar, and J.A. Galloway. American Academy of Allergy meeting, 1980.

*Uncertain. Although the present study is complete, an addendum may be submitted as new insulins become available with potentially different types of reactions.

| Date: 13 October 1980 | Protocol No. 3159-R | Annual Report X<br>Final |
|---|---|---|

Title of Project:
In vivo Removal of Circulating Antibodies and Immune Complexes by Immunoadsorption

| Starting Date: | Estimated Completion Date: |
|---|---|

Principal Investigator: Bernard H. Berne, MD, PhD.

| Associate Investigators: | Facility: WRAMC |
|---|---|
| | Dept/Svc Medicine/Rheumatology Service |

Key Words: Immunoadsorption, antibodies, Immune complexes

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost. $1,284.50 |
|---|---|---|
| FY-80 MEDCASE Cost: $650.00 | Periodic Review Results: (to be filled in by DCI) | |

Study Objective:

See attached sheet.

Technical Approach:

See attached sheet.

Progress during FY-80:

See attached sheet.

Number of subjects to be studied before completion of study: No human subjects (animal subjects)

Serious, unexpected side effects in subjects participating in project: None

Conclusions:

See attached sheet.

Publications resulting from this project: none

Objectives:

a. To develop systems containing immunoadsorbents capable of removing proteins from the blood of rabbits by extracorporeal circulation.

b. To remove circulating antibodies and immune complexes (IC) from rabbits and to determine their clearance and reappearance rates during and after their removal.

c. To develop a procedure for removing circulating antibodies and IC that is devoid of adverse clinical and hematological effects and which can serve as a prototype for human use.

Technical Approach:

Phase I -- Initial experiments will test the albumin-anti-albumin system, since this has been extensively investigated already by others. We will immunize rabbits with a subcutaneous and an intramuscular injection of 5 mg of bovine serum albumin (BSA) in complete Freund's adjuvant. Antibodies to BSA should develop within two weeks; their appearance will be ascertained by radioimmunoassay. Following the appearance of antibodies, a dose of BSA will be given intravenously. This should result in the formation of immune complexes between the BSA and the anti-BSA. These will be detected by an assay for IC that we have already developed.

The amount of BSA to be injected intravenously for IC induction will have to be determined empirically, and will probably differ for each animal since each will most likely develop different antibody levels. The radioimmunoassay for anti-BSA antibodies will provide the titer of antibodies in each animal. By adding BSA to the antibody *in vitro*, we will be able to determine the amount of BSA necessary to form soluble complexes detectable by the immune complex assay. Taking into account the blood volume of the rabbit, we will then calculate the amount of BSA to be injected to form soluble immune complexes *in vivo*. We will then inject this amount of BSA into the rabbits and determine whether the *in vivo* formation of complexes requires the same or a different antigen/antibody ratio as compared to the *in vitro* model. If the *in vivo* formation of IC requires a different ratio, this will be used in future trials.

Technical Approach Continuation:

Five adult male rabbits housed at WRAIR will initially be immunized with BSA. The appearance of antibodies will be monitored by bleeding from an ear vein once every three days. After the intravenous injection of antigen, the animals will be bled daily until it is ascertained that the induced immune complexes have been cleared from the circulation. The animals will then be sacrificed and autopsied. Histological examination of the kidneys will be performed with the assistance of the Veterinary Pathology Division of WRAIR. Personnel of this division will perform autopsies on all animals that are sacrificed or die during the experiments.

Gross pathological examinations of all organs and hemotoxylin-eosin staining of rabbit kidneys will be performed, and the pathological findings will be interpreted in light of the experiments performed. Antigen, antibody and IC deposition in the kidneys will be detected by immunofluorescent microscopy for the presence of albumin, IgG, IgM, C3 and C4. Kidney slices will be incubated at low pH to elute complexes which can be detected in radioimmunoassays for albumin, anti-albumin, and IC.

With each group of five animals tested in the study, 2-5 rabbits will be set aside as untreated controls. These will be sacrificed after 4 weeks and autopsied for evidence of renal immune complexes deposited as a result of infectious processes. Complement fixation assays for agents (primarily protozoal) causing such deposits will be performed on sera from all animals in the test and control groups, and only

rabbits that appear free from these agents will be used in the studies.

If none of the original five rabbits develope detectable immune complexes after the intravenous injection of BSA, these animals will be sacrificed and a dose of BSA three times as high will be injected into a second group of five immunized rabbits. Although unlikely, it is possible that we will not succeed in inducing IC formation in either of the first two test groups. If no complexes form after ten animals have been tested, we will inject complexes formed in vitro into five unimmunized rabbits and will study the kinetics of their disappearance in these animals, as well as the pathological sequelae of the injection.

As a part of Phase 1, several radioimmunoassays will be developed. We will design an assay for BSA and for anti-BSA using a double antibody technique. BSA will be labelled with 125-I by the Chloramine T or the Bolton-Hunter method, depending upon reagent availability and labelling efficiency. A commercial rabbit antiserum to BSA will be reacted with this, and a goat antiserum to rabbit immunoglobulin will be used as a second antibody. In the test for BSA as an antigen, the BSA circulating in rabbits and present in serum will act as an unlabelled inhibitor of the precipitation of labelled BSA. In the test for antibodies to BSA, rabbit serum suspected of containing anti-BSA will be substituted for the commercial antiserum to BSA; the amount of labelled BSA precipitated will increase as the titer of anti-BSA antibody rises.

We have already developed an assay for monitoring immune complex levels based on the binding of IC by iodinated C1q and the precipitation of the bound C1q by 25g/L of polyethylene glycol (MW 6000). This assay will be applied to the measurement of IC in tested and control rabbits.

Some IC may not be detectable by the C1q binding assay, although this is one of the more sensitive tests for these. If the assay detects no IC in any rabbits which develop circulating antibodies, we will develop an IC assay based on precipitation with monoclonal rheumatoid factor or bovine conglutinin.

Phase 2 - After we establish a method for monitoring the development and persistence of anti-BSA antibodies and IC, we will begin the second phase of the study. We estimate that this will start four months after the beginning of the project. In this phase, we will establish a method for attaching BSA to immunoabsorbent columns and for monitoring the effluent from these columns.

In the initial studies of this phase, BSA will be attached covalently to Sepharose beads with cyanogen bromide. After the BSA is attached

and the beads are rinsed, serum containing [illegible] BSA will be passed through the column. The anti-BSA will be absorbed by the column, and will be eluted at pH 3.0. These purified antibodies will then be labelled with 125-I. The labelled antibodies will then be used to determine the absorptive capacity of this and other columns. Labelled antibodies will be passed through the column, and the amount eluted before and after treatment of the column with a buffer at pH 3.0. Measurement of the labelled antibodies will be performed with a gamma scintillation counter.

Columns containing bound BSA will be tested for antigen leakage by binding 125-I labelled BSA to the Sepharose. After the adsorbent has been thoroughly rinsed with buffer, it will be poured through a column and normal rabbit serum will be passed through it. The amount of radioactivity escaping from the immunoadsorbent will be monitored and will determine the leakage rate of the adsorbent in the presence of rabbit serum. Similar studies will be performed with columns containing bound human C1q which will be designed to remove IC from serum.

Phase 3 - In this phase, we will study the effects of removing circulating antibodies to BSA and IC from the sera of rabbits as part of an extracorporeal circulation system. These studies should begin six to nine months after the start of the project and are dependent upon the successful completion of the first two phases.

Eight rabbits will be injected with BSA as in Phase 1. All eight will be treated by extracorporeal circulation. Five of these will be connected to an immunoadsorbent column containing BSA linked to Sepharose beads and their blood will be perfused through the column. The remaining three will act as controls and will be connected to a column containing rabbit serum albumin linked to the beads. It is expected that the column containing BSA will remove circulating anti-BSA antibodies, while the column containing rabbit serum albumin will not.

The amount of albumin on the columns will be determined by the studies done previously in Phase 2. Columns will be enlarged if there is little antibody removal in the first perfusion studies.

Since these experiments will be directed primarily toward testing the perfusion apparatus, rather than toward the permanent alteration of the immune response, each rabbit will undergo only a single perfusion. The perfusion will be timed to occur when a high level of anti-BSA antibodies are detectable in the serum. BSA, anti-BSA and IC levels will be monitored immediately before and after the perfusion, and every three days thereafter for a period of two weeks. Rabbits will then be sacrificed and autopsied.

Phase 4 - This phase will begin after the conclusion of the previous studies, probably 9-12 months after the start of the project. Studies in this phase will be similar to those in Phase 3, except that immune complexes will be removed, rather than antibodies.

In eight rabbits, IC will either be induced or injected, as determined by the earlier Phase 1 studies. Blood from five of the eight rabbits will be perfused through a column containing human C1q bound to Sepharose beads, while blood from the remaining three will be perfused through a column containing only Sepharose beads. As in the Phase 3 studies, BSA, anti-BSA and IC levels will be measured before and after the perfusions, and the animals will be sacrificed and autopsied two weeks after the perfusions.

Animal Treatments: All rabbits will be fed and watered ad libidum and will be treated in a humane manner designed to minimize pain and discomfort. Before perfusion studies, rabbits will be premedicated by injections of atropine (2 mg) and heparin (1000 U/kg) intravenously into an ear vein. Thirty minutes later, they will be anaesthetized by a slow intravenous injection of sodium pentobarbital (30 mg/kg), which will be repeated if the animals appear to regain consciousness or show discomfort.

Bleeding of rabbits for routine testing will be performed by incising a peripheral ear vein with a scalpel after a local application of xylene to induce vasodilation. Animals will be sacrificed by an overdose of Somethal injected intravenously.

Immunoadsorption and Perfusion Techniques: We have arranged a collaborative investigation with Dr. Franco Castino of the American Red Cross Blood Research Laboratory in Bethesda, Maryland for our extracorporeal perfusion studies. Dr. Castino has developed a plasmapheresis system which filters plasma proteins through a membrane with 0.6 micron pores. Filtration of plasma through this membrane is said to be less destructive of platelets than is plasmapheresis with a centrifugal cell separator. A small model of the apparatus is available for our use in rabbit experiments.

Dr. Castino is currently isolating Factor VIII from plasma using an immunoadsorbent containing antibodies to the factor that are bound covalently to Sepharose CL beads with cyanogen bromide. Purified Factor VIII is removed from the immunoadsorbent by 1 M NaCl or 0.1 M $CaCl_2$. We shall use these techniques, with appropriate modifications, for binding and eluting BSA from the immunoadsorbent.

We plan to routinely house our rabbits at WRAIR, which will allow us to observe and study them near our laboratory. We will transport the rabbits to the American Red Cross laboratory for each perfusion and will return them to WRAIR after treatment.

The rabbits will be anticoagulated and connected to the Red Cross

laboratory in most instances, although in some cases the rabbits may be premedicated at WRAIR before transportation to save time during the preinduction phase of anesthesia. After the rabbits are fully anaesthetized, a femoral artery and vein will be cannulated and connected to the plasmapheresis system. Assisted by a peristaltic pump, blood will flow through the perfusion system and plasma will pass through the pores in the system's membrane. The separated plasma will then pass through an on-line immunoadsorbent column containing a specific protein bound covalently to Sepharose beads. Antibodies to BSA will be removed by binding BSA to the beads, as outlined above. It is expected that IC will be removed by both the columns containing BSA and those containing $C1_q$, and we will determine which of the two methods is more efficient for this either in the studies described above or in later ones.

After the plasma has passed through the immunoadsorbent, it will then be returned to the rabbit together with the cells, which will have bypassed the loop containing the adsorbent. This bypass will spare the cells any possible trauma or removal which might occur if they were allowed to come into contact with the adsorbent.

After the perfusion is completed, the cannulae will be removed and the wounds will be repaired. Rabbits will be allowed to recover from their anaesthesia and will be returned to WRAIR for studies of their post-operative clinical state. The immunoadsorbent will be recycled by removing bound antibodies and immune complexes with high molarity salt solution and buffers with low pH. The perfusion system will be cleaned, sterilized, and used in later studies.

Several investigators have previously perfused rabbits with extracorporeal immunoadsorption devices. Rabbits were anticoagulated with doses of heparin similar to those that we will use. It did not appear necessary to neutralize the anticoagulant after treatment. In our inital studies, we will not attempt to neutralize the anticoagulant and will rely on meticulous surgery to prevent post-operative bleeding from the wound. If excessive bleeding does occur, we will neutralize the heparin with protamine, but it seems likely that this will not be necessary as rabbits tend to be hypercoagulable. Prothrombin times will be monitored to follow the effects of the anticoagulant and any added protamine. Because the apparatus is specifically designed to minimize platelet loss, we expect it to have few bleeding problems referable to this, particularly since the rabbits will only be perfused on one occasion.

Leakage of Sepharose beads from the apparatus will be prevented by inserting a nitrocellulose filter with 0.6 micron pores into the efflorent line. This filter will allow proteins to pass through it, but will retain the beads and any other particles that might cause embolization.

Because this is only a preliminary study, and future perfusion apparatus will likely have a different design, we will not routinely test the column effluent for pyrogenicity or sterility, although all apparatus will be sterilized by heat, ethylene oxide and/or merthiolate prior to use. Should a problem develope in the studies that are referable to a failure in sterility or to pyrogenicity, appropriate studies will then be conducted. In such a case, sterility would be determined by taking samples for bacterial cultures and pyrogenicity would be measured by the Limulus amebacyte lysate test.

PROGRESS DURING FY-80:

The nature of the rabbit immune response to BSA has been explored. I found that rabbits responded to an injection of BSA in Freund's adjuvant by producing antibodies and immune complexes. Both of these were detected by radioimmunoassays.

The response to BSA was determined by a double antibody RIA using iodinated BSA. Antibody was detected in six rabbits within 3-5 days. Antibody levels rose rapidly at first, and then more slowly for a period of five months. After a booster injection, antibody levels rose still further, followed by a small decrease.

Immune complexes detected by a C1q binding assay appeared within 3 days after primary immunization. They reached a peak within 14 days, and changed little after this. Three of the six rabbits received a booster injection of BSA, but this did not affect the level of immune complexes.

It became necessary to determine whether the immune complexes were derived from the injection of BSA or from constiuents of the Freund's adjuvant. Complete Freund's adjuvant contains mycobacteria in oil, while incomplete Freund's adjuvant contains only oil.

Three rabbits were injected with complete Freund's adjuvant, while two were injected with incomplete adjuvant. After six weeks the rabbits were boosted with incomplete adjuvant. The animals were bled once per week for three weeks. These will be analyzed for IC in the near future.

Pathology studies of tissues from sacrificed animals revealed lymphocytic infiltrates in the lungs and kidneys. These were not intense, however, and were suggestive of a chronic protozoal infection. This had been anticipated since many rabbits in the WRAIR colony show similar lesions. No severe signs of serum sickness appeared in the rabbits.

CONCLUSIONS:

Initial studies suggest that immune complexes appearing after injecting BSA and Freund's adjuvant may be predominantly composed of antigen and antibodies related to Freud's adjuvant, rather than to BSA. In order to remove specific immune complexes, as required by the protocol, it must be determined whether these complexes result from the BSA or the adjuvant. After analyzing the results of immunizing rabbits with only the complete or incomplete adjuvant, it will become apparent whether we should direct our efforts to removing complexes containing BSA or to removing those with adjuvant constituents. Thus, the future direction of this work depends upon the resulting of these studies now being performed.

CLINICAL INVESTIGATION PROGRAM

Work Unit No.: 3159-R

Funds Utilized, FY-80:

Funding Requirements, FY-81:

Personnel: An additional person is needed to complete Phase II. This person would spend 50% of time on this protocol, as follows:

| | |
|---|---|
| Rabbit bleeding and serum shortage | 5 hrs/wk |
| Preparing immunosorbents | 5 hrs/wk |
| Performing radioimmunoassays | 10 hrs/wk |
| TOTAL TIME | 20 hrs/wk |

Equipment: None

Supplies:

| | |
|---|---|
| Metabolic animal cages | 500.00 |
| Radioisotopes for immunoassays (125-I Bolton-Hunter Reagent; 5 orders per year at $200 per order) | 1,000.00 |
| Chemicals (Cyanogen bromide-activated Sepharose, antisera, anesthetics, buffers, antigens, others) | 2,000.00 |
| Chromatography colums | 500.00 |
| Glassware, Plastiware and pipette tips for immunoassays (1000) and general use | 1,500.00 |
| Miscellaneous supplies | 1,000.00 |
| TOTAL | 6,500.00 |

Travel: 400.00

Publication Costs: 400.00

Other:

| | |
|---|---|
| Rabbits - Purchase: 30 rabbits @ $25.00 | 750.00 |
| 1000 rabbit days @ $0.55 | 550.00 |
| TOTAL | $ 8,600.00 |

| Date: 11-25-80 | Protocol No: 3160-R | Status: Interim X / Final |
|---|---|---|

Title of Project: Study of Rheumatoid Arthritis and Sjogren's Syndrome Precipitins in Rheumatic Diseases.

| Starting Date: Summer, 1979 | Estimated Completion Date: June, 1981 |
|---|---|

Principal Investigator: Joseph T. Tesar, MD

| Associate Investigators: Oliver Lawless, MD | Facility: Walter Reed Hospital |
|---|---|
| | Dept/Svc Medicine-Rheumatology |

Key Words: Rheumatoid Factor
Rhematoid Arthritis Precipitins, Sjogren's Syndrome precipitins

| Accumulative MEDCASE Cost: $1,430.38 | Accumulative Contract Cost: | Accumulative Supply Cost: $6,499.27 |
|---|---|---|

| FY-80 MEDCASE Cost: $1,430.38 | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective:
Investigation of rheumatoid arthritis and Sjogren's syndrome precipitins.

Technical Approach:
Examination of rheumatoid and Sjogren's disease sera by agar gel precipitin technique using antigens obtained from thymus. Sera from patients with other rheumatic diseases used as controls.

Progress during FY-80: Clinical and immunological data from 65 patients were obtained. It was demonstrated that certain rheumatoid arthritis sera form an additional precipitin line with a thymus antigen. This is probably a RF with dual specificity, i.e. toward AHs and IgG.

Number of subjects to be studied before completion of study: 35

Serious/unexpected side effects in subjects participating in project:
None

Conclusions:
These data suggest a diagnostic application of these precipitins in rheumatoid arthritis and Sjogren's syndrome.

Publications or Abstracts, FY-80:
See annual progress report.

CLINICAL INVESTIGATION PROGRAM

Work Unit No.: 3160-R

Funds Utilized, FY-80: $3000

Funding Requirements, FY-81: TOTAL: $4490

Personnel: (name and grade)

Equipment: (describe in detail including cost) $990
Sonicator

Supplies: (consumable, animal purchase) $2500

Travel: (mission oriented, training and presentation) $500

Other: (equipment rentals, contracts for service, animal care and reprints)
Scientific publications $500

Work Unit No.: 3160-R

Title: Study of Rheumatoid Arthritis and Sjogren's Syndrome Precipitins in Rheumatic Diseases.

Investigators:

Principal: Joseph T. Tesar, M.D., Staff Rheumatologist

Associate: Oliver Lawless, M.D.,Section of Rheumatology

Starting Date: Summer, 1979

Objectives: The study was designed to evaluate the diagnostic value and the biological properties of rheumatoid arthritis and Sjogren's syndrome precipitins.

Technical Approach: Reference antisera with known precipitating antibodies to RAP and SS-A/B antigens are used for the identification of precipitin lines present in sera of patients with rheumatic diseases. The antigen used is a thymus or B-lymphocyte (tissue culture line) extract. No modification of protocol has been made.

Progress Report: Since the start of investigation we have examined approximately 65 sera of patients with rheumatoid arthritis, Sjogren's syndrome and appropriate rheumatic disease controls.

We have reference sera for RAP and Sjogren's syndrome precipitin determination. We have made the observation that certain IgM rheumatoid factors induce and additional precipitin line using the method for demonstration of RAP precipitins.

Publications:

M. Floyd and J.T. Tesar: The role of IgM rheumatoid factor in experimental vasculitis. Clin Exp. Immunol 36: 165, 1979.

R. Raskin, J.T. Tesar and O.Lawless: Sjogren's syndrome and hypokalemic paralysis. Accepted for publication, Arch Int. Med. 1980.

| Date: 20 October 1980 | Protocol No: 3161 | Status: Interim X<br>Final |
|---|---|---|

**Title of Project:** Evaluation of Immediate Hypersensitivity Skin Tests in Uremic Patients

| Starting Date: June 1979 | Estimated Completion Date: December 1980 |
|---|---|

**Principal Investigator:** Roghava V. Charya, M.D.

| **Associate Investigators:**<br>Richard Evans III, COL MC<br>Jim Baker, CPT MC | **Facility:** Walter Reed Army Medical Center<br>**Dept/Svc** Allergy-Immunology |
|---|---|

**Key Words:**

| Accumulative MEDCASE Cost:_____ | Accumulative Contract Cost:_____ | Accumulative Supply Cost:_____ |
|---|---|---|

| FY-80 MEDCASE Cost:_____ | Periodic Review Results:_____<br>(to be filled in by DCI) |
|---|---|

**Study Objective:** To determine whether immediate hypersensitivity as assessed by wheal and flare skin testing is a reliable method of determining potential IgE mediated allergic reactions in patients who are uremic.

**Technical Approach:** Evaluation of immediate hypersensitivity skin tests by prick tests to inhalant allergens in uremic patients. Histamine and morphine are to be used as positive controls.

**Progress during FY-80:** So far 5 uremic patients have been studied. Two patients had positive skin tests to inhalant allergen. There was only one patient who had both positive skin tests and allergic rhinitis history.

Number of subjects to be studied before completion of study: 50

Serious/unexpected side effects in subjects participating in project:
The other three patients had negative histories and skin tests.

**Conclusions:** None can be drawn at this time.

**Publications or Abstracts, FY-80:** None

CLINICAL INVESTIGATION PROGRAM

Work Unit No.: 3161

Funds Utilized, FY-80: None

Funding Requirements, FY-81: $2500.00

Personnel: (name and grade)

Equipment: (describe in detail including cost)

Supplies: (consumable, animal purchase)

Travel: (mission oriented, training and presentation) $1,000.00

Other: (equipment rentals, contracts for service, animal care and reprints)

IgE Prist test and Rast for each patient $1,500 (probably more than once)

# DISPOSITION FORM

For use of this form, see AR 340-15, the proponent agency is TAGCEN.

| REFERENCE OR OFFICE SYMBOL | SUBJECT |
|---|---|
| HSWP-MR | Clinical Investigation Protocol, Work Unit #3162-R |

TO C, Dept of Clin Invest FROM C, Rheumatology Svc DATE 3 December 1980 CMT 1

1. In response to your DF dated 22 August 1979, the protocol has been modified in the following manner.

2. The normal range will be defined using sera from Rheumatology Service Staff and from apparently normal patients evaluated in the Rheumatology Clinic. Consent will be obtained from normal subjects.

3. The consent form has been modified. The new consent form is attached.

Oliver J. Lawless

OLIVER J. LAWLESS, MD
Colonel, MC
Chief, Rheumatology & Clinical
Immunology Service

DA FORM 1 FEB 67 2496 REPLACES DD FORM 96, WHICH IS OBSOLETE.

| Date: 13 October 1980 | Protocol No: 3162-R | Status: Interim X<br>Final |
|---|---|---|

Title of Project:

Serial Studies of Serological Parameters in Systemic Lupus Erythematosus

| Starting Date: 22 August 1979 | Estimated Completion Date: 30 September 1982 |
|---|---|

Principal Investigator: Col Oliver J. Lawless, Maj Richard C. Welton

| Associate Investigators: | Facility: WRAMC |
|---|---|
| Bernard H. Berne, MD, PhD. | Dept/Svc: Medicine/Rheumatology Service |

Key Words:
Systemic lupus erythematosus, DNA binding, immune complexes

| Accumulative MEDCASE Cost: 0 | Accumulative Contract Cost: 0 | Accumulative Supply Cost: $13,820.18 |
|---|---|---|

| FY-80 MEDCASE Cost: | Periodic Review Results:<br>(to be filled in by PCI) |
|---|---|

Study Objective:

See attached sheet.

Technical Approach:

See attached sheet.

Progress during FY-80:

See attached sheet.

Number of subjects to be studied [illegible]: 500

Serious/unexpected side effects in subjects [illegible] project:

none

Conclusions:

See attached sheet.

Publications or Abstracts, FY-80. Berne BH and Lawless OJ: Re-evaluation of anti-DNA Antibody Levels Detected by the Farr Technique and FIAX Immunofluorescence Assay.

Clinical Chemistry 26:1072, 1980.

3. OBJECTIVES:

1) To assess the value of serial testing of DNA bindings and immune complex determinations by C1q bindings in systemic lupus erythematosus (SLE).

2) To ascertain in a prospective study whether rapid improvement in the above parameters can be found in the first weeks of steroid therapy in nephritis, and whether they can be used to regulate steroid dosage.

3) In a retrospective study, to relate changes in these parameters to the long-term course and prognosis in SLE.

4) To correlate the DNA binding and C1q binding assays with complement levels (C3, C4) and determine which of these tests are the best for short-term and long-term follow-up in SLE and related diseases.

5) To maintain the DNA binding assay as a routine procedure on the Rheumatology and Clinical Immunology Service and to standardize it to meet the requirements of the Joint Commission on the Accreditation of Hospitals (JCAH).

4. MEDICAL APPLICATION AND STATUS: Several investigators have shown that DNA binding levels correlate well with disease activity in SLE with diffuse proliferative glomerulonephritis (1-4). The correlation in other forms of SLE appears weaker. Recently, studies with several different assays for immune complexes, including C1q binding activity, have suggested that these also can serve as useful parameters in SLE, although their actual prognostic role has not yet been defined (5-7).

Measurements of DNA binding and immune complexes reported in the literature are usually performed on a monthly basis with occasional studies utilizing weekly measurements. At present, most physicians treat SLE complicated by diffuse proliferative glomerulonephritis with approximately 60mg of prednisone per day for at least three months, before making a final assessment of the degree of steroid responsiveness in each patient. Improved assays may be able to reduce this time. Few studies of DNA binding and immune

[illegible] will also be performed by the assay [illegible] depends upon both scintillation counting and [illegible] fluorescent technique.

The mean and standard deviations will be determined at each level. Quality control sera at each level will be placed in one or more positions on each run depending upon its length. If the quality control sera show a greater than 2SD deviation from the expected between-run mean at a given level, all assays near that level will be discarded.

If the Clq binding assay for IC proves to be useful and can be standardized, it will also be upgraded to meet JCAH criteria. Until that time, it will not be used in patient management, but will be utilized in research studies with appropriate cautions and controls used for interpreting data.

Phase II.

After quality control standards for DNA binding are established, we will begin Phase II of this study. In this phase, we will determine whether rapid changes in DNA and Clq binding occur during therapy of SLE.

If rapid changes are found, we will attempt to correlate these with changes in clinical status, with particular emphasis on diffuse proliferative glomerulonephritis, one of the most serious manifestations of SLE. We shall also determine whether these are better markers for acute changes than are C3 and C4 levels. Correlations with skin test reactivity (intermediate PPD, Candida, SKSD, mumps, Trichophyton) will also be determined, as will be changes in fluorescent antinuclear antibody titers.

Patients admitted to WRAMC with SLE and active nephritis will be entered into this study, provided that they have not been previously treated acutely with steroids or immunosuppressive agents. These patients will fulfill four or more American Rheumatism Association Preliminary Classification Criteria for SLE (including nephritis) and must give their informed consent for participation in this study which will entail no more than minimal risks.

We estimate that 20 patients fulfilling requirements outlined above will be available for this study during the first year of this project, including 12 whose sera has already been stored but not tested for all necessary components. All patients entered into this study will have 15 ml of blood drawn once every 2-3 days.

Sera will be stored in 500 ul aliquots at -20°C until tested. Each aliquot will be frozen and thawed only once. DNA bindings will be performed by the Farr assay. This test consists of: (1) Incubating sera with a standard preparation of tritiated double stranded DNA, with denatured DNA previously removed by endonuclease treatment. This preparation has been used in the Rheumatology Laboratory for two years; (2) Precipitation of complexed DNA by ammonium sulfate at 50% saturation; (3) Centrifugation at 3000 RPM at 4°C; (4) Removal of half of the supernatant; (5) Transfer of both halves of the reaction mixture to scintillation vials; (6) Counting of radioactivity in a beta scintillation [illegible]

(7) Calculation of percentage of DNA bound and the precision of the assay; (8) Where the percentage of DNA bound exceeds 50%, sera are diluted and tested to determine the concentration that gives a 50% binding. The "DNA binding capacity" of the serum, expressed as grams of DNA bound per liter of serum is then calculated. Binding capacities at 50% DNA binding are used for high binding sera because assay precisions vary inversely with DNA binding percentage above this level.

An aliquot of each specimen will be tested for Clq binding capacity. This measures levels of immune complexes and aggregated immunoglobulins. Patients with SLE often have elevated Clq binding levels, but the correlation with disease activity is not yet clear. The Clq binding assay is performed with the following steps:

(1) Clq, the first component of complement, is isolated from pooled human plasma, obtained from outdated whole blood in the WRAMC Blood Bank. Three units (1500 ml) of blood yield sufficient Clq for approximately 10,000 tests.

(2) The Clq is aliquoted and stored at -70°C. It is frozen and thawed only once.

(3) When ready for use, an aliquot is thawed and iodinated with 125-I. Either the Bolton-Hunter or Cloramine T method is used for iodinations, depending upon availability of reagents and efficiency of binding.

(4) Unbound iodine is removed by dialysis.

(5) 125-I Clq is incubated with serum in the presence of EDTA.

(6) The Clq binds to immune complexes and aggregated IgG.

(7) The total radioactivity added is determined in a gamma scintillation cocktail.

(8) Bound 125I Clq is precipitated by 25 g/liter of polyethylene glycol, molecular weight 6,000.

(9) Reaction tubes are centrifuged at room temperature at 3000 RPM.

(10) The supernatant is poured off and discarded.

(11) The radioactivity in the precipitate is counted.

(12) The percentage of Clq bound and the assay precision is calculated.

(13) Using a standard curve with aggregated human gamma globulin (HGG), the gram equivalents of aggregated HgG precipitated in each serum is calculated.

The Clq binding assay has been performed in this service for over a year. Although within-run precisions are within an acceptable level, run-to-run

variations are still too great to allow samples tested in different runs to be routinely compared. Therefore, ten normal sera are included in each run to give a normal range. All tests are done in duplicate. In serial studies on single patients, all samples are tested on the same run, or divided between no greater than two runs.

As we gain more experience with the Clq binding assay, we may be able to reduce run-to-run variation to a small enough level to allow exclusion of the 10 normal sera, now placed in each run. When this occurs, we will test the assay to determine whether it can fulfill JCAH criteria. In addition to the tests outlined above, the following tests will be performed as part of the routine care given to SLE patients:

Pre-Study:

1) CBC with platelet and reticulocyte counts
2) Westergren sedimentation rates
3) SMAC-20
4) Serum protein electrophoresis
5) Rh factor
6) Urinalysis
7) 24 hour urine for creatinine clearance and protein
8) Chest x-ray
9) Electrocardiogram
10) Renal biopsy where clinically indicated.

The following parameters will be followed on a routine basis:

1) Clinical parameters for classification of SLE - see flow sheet #1
2) Serial lab data: See flow sheet #2; these include:

   a) DNA binding and Clq binding - once every 2-3 days for four weeks or more until stable, then weekly.
   b) Urinalysis every 2-3 days for protein (Dipstick) and sediment.
   c) Creatinine clearance, serum creatinine, BUN and 24 hour urine protein twice weekly for 2 weeks, then once per week.
   d) Weekly CBC with Westergren erythrocyte sedimentation rate.
   e) FANA with titers weekly.
   f) C3, C4 weekly or more often if indicated.
   g) Weekly skin tests if negative at outset.

CRITERIA FOR THE CLASSIFICATION OF [illegible]

| CRITERIA | (+) IN PAST | (+) NOW | SEVERITY SCORE (CHECK ONE) 1 | 2 | 3 | 4 | 5 | 6 | 1 | 2 |
|---|---|---|---|---|---|---|---|---|---|---|
| 1. Facial erythema (butterfly rash) | | | | | | | | | | |
| 2. Discoid Lupus | | | | | | | | | | |
| 3. Raynaud's phenomenon | | | | | | | | | | |
| 4. Alopecia | | | | | | | | | | |
| 5. Photosensitivity | | | | | | | | | | |
| 6. Oral +/or nasopharyngeal ulcers | | | | | | | | | | |
| 7. Arthritis without deformity | | | | | | | | | | |
| 8. LE Cells (2 or more) (FANA > 1/160) | | | | | | | | | | |
| 9. Chronic false-positive (+) STS 6 months | | | | | | | | | | |
| 10. Profuse proteinuria 3.5 gm/day | | | | | | | | | | |
| 11. Cellular casts in urine | | | | | | | | | | |
| 12. Pleuritis +/or Pericarditis | | | | | | | | | | |
| 13. Psychosis +/or convulsions in the absence of uremia | | | | | | | | | | |
| 14. Hemolytic anemia, +/or leukopenia ( < 4,000), +.or thrombocytopenia ( < 100,000) | | | | | | | | | | |
| 15. Miscellaneous | | | | | | | | | | |

Scale: 0 = absent
1-5 = mild to severe
List numbers for lab results

NAME: _____

[illegible]: _____

| TEST | BASE | ST | D 2 P/S | D 4 P/S | 5 | 8 | 10 | 12 | 14 | 18 | 21 | 25 | 28 | DAY 35 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1) DNA Binding % | | | | | | | | | | | | | | |
| 2) DNA Binding Capacity | | | | | | | | | | | | | | |
| 3) Clq Binding | | | | | | | | | | | | | | |
| 4) FAT | | | | | | | | | | | | | | |
| 5) Serum C'3 | | | | | | | | | | | | | | |
| 6) " C'4 | | | | | | | | | | | | | | |
| 7) U/A - WBC's/ | | | | | | | | | | | | | | |
| 8) U/A - RBC's/ | | | | | | | | | | | | | | |
| 9) U/A - CASTS | | | | | | | | | | | | | | |
| 10) U/A - PROTEIN | | | | | | | | | | | | | | |
| 11) 24 HR. Protein | | | | | | | | | | | | | | |
| 12) Creat. Cl. | | | | | | | | | | | | | | |
| 13) Serum - BUN | | | | | | | | | | | | | | |
| 14) " - CR | | | | | | | | | | | | | | |
| 15) Hematology - WBC | | | | | | | | | | | | | | |
| 16) % Polys/ % Lymphs | | | | | | | | | | | | | | |
| 17) Hct/Hgb | | | | | | | | | | | | | | |
| 18) Sed Rate | | | | | | | | | | | | | | |
| 19) Prednisone Dose | | | | | | | | | | | | | | |
| 20) MISCELLANEOUS | | | | | | | | | | | | | | |
| 1) | | | | | | | | | | | | | | |
| 2) | | | | | | | | | | | | | | |
| 3) | | | | | | | | | | | | | | |
| 4) | | | | | | | | | | | | | | |
| 5) | | | | | | | | | | | | | | |

[illegible] parameter are already part of the [illegible] The [illegible] their performance as part of this study will therefore place no additional workload on the Brin Laboratory or other Services. They are essential to monitoring the course of SLE for both research and [illegible] care.

It is expected that the above study will take one year to complete. At its termination we shall know whether the Clq and DNA binding assays are useful adjuncts to clinical management of SLE on more than an occasional basis, and if either of these is a better parameter than those routinely followed in cases where nephritis appears.

Since SLE is a variable disease with many patterns of symptomatology, it is possible that we may determine that serial studies of Clq binding are most useful in some types of disease, DNA binding in other, and routine testing in still other cases. The elucidation of such types of disease may lead to important insights into the pathogenesis of SLE and related disorders.

Phase III

Phase III of this study will at first be performed concurrently with Phase II, but will last longer. This will be a retrospective investigation of DNA and Clq bindings in SLE patients and their correlation with long term prognosis. Few such studies exist in the literature because of the relative newness of these techniques (4), and those studies that have been done suggest that the correlation is not perfect. Since we use a different DNA preparation than do other investigators, our results for this assay may differ from theirs.

Our serum bank currently contains over 3000 specimens from SLE patients. More than 100 patients have been followed for a year, with some being followed for five years. We shall select for our analysis at least 30 patients who have shown at least one exacerbation and who have been followed for at least three years.

All sera from each of the selected patients will be tested for DNA and Clq binding. A sera from an individual will be tested on a single run to minimize assay variation. Sera will also be tested for C3 and C4 by radial immunodiffusion with appropriate quality controls.

Results will be correlated with the clinical course of each patient, as determined by chart review by a Rheumatology fellow. Where the clinic's charts are incomplete, we will attempt to retrieve the permanent inpatient chart and outpatient charts from the Walter Reed Patient Administration Division, from another military installation, or from the patient. Only those cases that can be completely documented will be analyzed. No test will be performed until the fellow is satisfied that the patients records are adequate for use in a publication. While it is not possible at this time to determine the number of patients with adequate retrievable records that can be used in this study, we expect it to be more than 30. Such a number would make possible a much larger study than has yet been published.

Risk

This study will involve taking an additional 30 ml of blood on 1 occasion from healthy people donating 500 ml for medical purposes. No additional venipunctures will be required. Donors will be identified only by age and sex. Informed consent will be obtained from donors, who will obtain no direct benefit from this study.

Patients with SLE and other diseases seen in the Rheumatology Clinic and on the medical wards will be asked to donate up to 30 ml on up to three occasions per week during acute phases of their illnesses and less for an indefinite period thereafter. Some of these patients may be anemic. This study must utilize anemic patients, since this is one of the common complications of SLE. Where the hematocrit is below 35, reduced amounts of blood will be obtained. Because the requirement for the use of an anemic patient, this protocol carries more than a low risk, as defined by WR 70-1, 8 January 1979.

All adult patients, and persons responsible for minor patients and for those incapable of consenting themselves, will be asked to give full informed consent. Children under legal age will be asked to give assent in writing if capable of understanding the risks and benefits involved.

This protocol may benefit some patients who are part of this study. The results of DNA binding assays and Clq binding assays may be used in making therapeutic decisions concerning individuals participating in this study. Within WRAMC, these assays will only be available to persons participating in this protocol. The tests will not be offered to WRAMC patients who have not given their consent to participate, as there are no funds allocated for performing the test on a routine basis.

Copies of consent forms are attached. There are three forms:

1) Blood donor form.
2) WRAMC patient form.
3) Guardian form for WRAMC patients not competent to consent or under legal age.

These forms are appended at the end of the protocol.

Data Analysis Plan: DNA and Clq binding levels in SLE patients will be compared with those in normals and in other diseases. Changes in levels in individual patients will be displayed graphically in longitudinal studies. All parameters measured (clinical, therapeutic and serological) will be plotted on the same graph.

Correlations of levels of different constituents in the same individual will be statistically analyzed by the Pearson correlation coefficient, including p values for their significance. It is recognized that correlations obtained in longitudinal studies are often imprecise, because trends of one parameter can change while those of another do not until a later time. To obtain a significant number of data points in such studies, one must compare the same parameters at the same times in more than two individuals, or one must group similar data points obtained at different times in the same individual, providing all of these points are following the same trends.

Significance of differences between normal and disease groups, and differences before and after therapy, will be analyzed by the Student t test. A $p < 0.01$ will be considered as the minimum significant level. The normal range will be defined as $\pm$ 2 standard deviations from the mean.

If data points in any group appear to be abnormally distributed, non-parametric statistics will be used. These will include the Wilcoxan matched pairs test, the Mann-Whitney U test for significance of differences of ungrouped data, and the Spearmann rank correlation test to find the correlation coefficient. Appropriate adjustments will be made for groups with large numbers of ties obtained in ranking data.

PROGRESS DURING FY-80:

We directed our efforts toward refining and evaluating methodology for measuring immune complexes and antibodies to DNA. These are involved in the pathogenesis of SLE.

Our present assay for immune complexes utilizes the precipitation of $125_I$ labelled C1q (part of the first complement component) by immune complexes in the presence of polyethylene glycol. This assay detects a high percentage of patients with SLE, but is subject to inferfering substances and the hazards of radioactivity. To avoid the use of radioactivity, we tried to develop an immune complex assay using anti-antibody. This unique IgM is found in occasional normal and diseased people. It reacts with the antibody in immune complexes present in several diseases, but not with unbound antibody. Using the anti-antibody, we attempted to devise a hemagluttination-inhibition technique to detect immune complexes. The results of these trials were not definitive, however, and the attempt was temporarily postponed until further background studies could be conducted.

Our assay for antibodies to DNA, the Farr technique, involves the precipitation of tritiated DNA by ammonium sulfate after it has bound to anti-DNA antibodies in patient sera. In 3,000 tests, we showed that SLE could be monitored with this assay. However, the assay is not very reproducible, involves the use of radioactivity and toxic chemicals (xylene), and is very time consuming.

We therefore tested a recently marketed fluorescent immunoassay system (FIAX) for antibodies to DNA. Over 1,000 tests were performed with this system. We found that the FIAX system while not exceedingly reproducible was equally reliable as the Farr assay, and had the same specificity for SLE. Further, results could be obtained within 3 hours of the receipt of a specimen with a smaller technician time than the Farr assay. Unlike the Farr assay, the FIAX method has no radioactive or chemical hazards.

If funds become available to purchase the FIAX system, we plan to replace our Farr assay with the FIAX method. This would add an important new capability to our laboratory, and the FIAX method could be extended to other assays involved in the diagnosis and management of SLE.

Clinical parameters and serial laboratory testing as outlined in the protocol have been collected on 27 patients over the past one year.

Through Tri-service Medical Information System, the computer program, "Clinflow" was used to enhance the evaluation of the large amount of data collected. Approximately 65,000 bits of data were entered and analyzed through various worksheet panels. The computer analysis has been completed and the information derived is presently being organized and will be placed in written form for publication and American Rheumatism Association National Meeting submission by mid January 1981.

Since normal blood bank donors could not be used in this study, the normal range was determined using sera from normal hospital staff and patients without significant disease that were referred to the Rheumatology Clinic.

A revised consent form was prepared to meet requirements of HSC. This is appended to this report.

CONCLUSIONS DURING FY-80:

We have validated the Farr and FIAX assays for antibodies to DNA to conform to JCAH standards. Because of its simplicity, speed and safety, we found the FIAX method to be superior to the Farr assay. It seems to be the best method currently available to measure these antibodies, although its reproducibility needs improvement.

We are continuing to evaluate new assays for immune complexes and anti-DNA antibodies. We are also currently using these to determine the significance of these substances in SLE and related disorders.

Publications or Abstracts, FY-80: (Continued)

Lindsey SM, Berne BH, Snyder KL, Lawless OJ: Circulating Immune Complexes (CIC) Response to Standard Steroid Therapy in Acute Systemic Lupus Erythematosus. 43rd Annual Meeting of the American Rheumatism Association. 1979.

Lawless OJ, Lindsey S, Snyder K and Berne B: Circulating Immune Complexes (CIC) Response to Standard Steroid Therapy in Acute Systemic Lupus Erythematosus Nephritis. IXth European Congress of Rheumatology, 1979, Wiesbaden.

CLINICAL INVESTIGATION PROGRAM

Work Unit No.: 3162-R

Funds Utilized, FY-80:

Funding Requirements, FY-81:

Personnel: One full time military (Sp 4) or civilian (GS-09) technician is required for this project. There is no Clinical Investigational personnel currently available for this protocol. We request the assignment of a CIS technician to complete this project. This additional person was authorized by the most recent manpower survey, but has not been assigned to the Rheumatology Service.

Equipment: FIAX Fluorometric System (Medcase Request)
Beckman Refrigerated Centrifuge (Medcase Request)

Supplies:

| | | |
|---|---|---|
| Radioimmunoassay: | | |
| Isotopes (125-I Bolton Hunter Reagent) 6 Orders at $200.00 per order | 1,200.00 | |
| Scintillation Cocktails (for 5000 assays) | 1,500.00 | |
| Scintillation Vials (for 5000 assays) | 1,000.00 | |
| Polystyrene Tubes (for 10,000 assays) | 2,000.00 | |
| Pipette Tips | 1,500.00 | |
| Serum vials for storage (1500 vials) | 500.00 | |
| Other Glassware and Plasticware | 1,000.00 | |
| Chemicals (buffers, radiac wash, etc) | 500.00 | |
| Miscellaneous Supplies | 1,000.00 | |
| TOTAL SUPPLIES | | $10,200.00 |

Travel: 500.00

Publication Costs: 500.00

| Date: 11-26-80 | Protocol No: 3163-R | Status: Interim X / Final |
|---|---|---|

Title of Project:
Histocompatibility Antigens in Acute Uveitis.

| Starting Date: September, 1979 | Estimated Completion Date: April-May 1981 |
|---|---|

Principal Investigator: Joseph T. Tesar, M.D.

| Associate Investigators: D.M. Strong, Chief, Histocomp. Lab. Paul Killian, Rheumatologist, F. Wergeland, Chief, Opth. Serv. | Facility: Walter Reed Hospital |
|---|---|
| | Dept/Svc Medicine-Rheumatology |

Key Words: Hla, Acute Anterior uveitis

| Accumulative MEDCASE Cost: $5,587.38 | Accumulative Contract Cost: $5,587.38 | Accumulative Supply Cost: $849.10 |
|---|---|---|

| FY-80 MEDCASE Cost: | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective:
To determine the frequency of HLA-C series antigens and HLA-B7 crossreactive antigen (B-7, B-27, B-22, B-40, B-42) in acute anterior uveitis.

Technical Approach:
Complete histocompatibility typing of all patients presenting in the opthalmology clinic with the diagnosis of acute non-granulomatous uveitis. See also the protocol annual progress report appended.

Progress during FY-80:
See annual progress report.

Number of subjects to be studied before completion of study: 12-15

Serious/unexpected side effects in subjects participating in project:
None

Conclusions:
See annual progress report.

Publications or Abstracts, FY-80:
See Annual progress report.

Work Unit No.: 3163-R

Title: Histocompatibility Antigens in Acute Uveitis (AAU)

Investigators:

Principal: Joseph T. Tesar, MD, Staff Rheumatologist WRAMC

Associate: Paul J. Killian, MD. Formerly Asst Chief Rheumatology Svc
D. Strong, MD, Chief, Histocompatibility Laboratory
F. Wergeland, MD, Chief, Ophthalmology Svc

Starting Date: September 1979

Completion Date: April 1981

Objective: To determine the frequency of HLA-C Series of antigens and HLA-B7 Crossreactive antigens (B-27, B-7, B-40, B-42, B-22) in acute anterior uveitis.

Key words: HLA-C1, HLA C-2, B-7 CREG antigens, acute anterior uveitis.

Technical Approach: No modifications

Progress Reports (Conclusions):

1) The HLA-C2 an antigen whose association with uveitis has not yet been described was found to be present in this study in 70% of 34 patients with acute anterior (non-granulomatous) uveitis (AAU). This is in contrast with a 39% incidence of HLA-B27 antigen in the same population (nl population = 8% HLA-B27, 10% HLA-C2.)

2) The relative risk for occurrence of AAU in persons with HLA-C2 antigen was calculated to be 27.0 and those with B-27 antigen 7.1.

3) The incidence of rheumatic disease (ankylosing spondylitis and Reiter's Syndrome) was 17.6% in this population (6/34).

Publications: Joseph T. Tesar, MD, Paul Killian MD, David Strong PhD et al: Acute anterior uveitis, strong association with a new histocompatibility antigen, HLA-C2. In Preparation, 1980

J. T. Tesar et al: Histocompatiblity antigens in acute anterior uveitis. Submitted to the Am. Transplant Soc. meeting 1981.

ork Unit No.: 3163-R

unds Utilized, FY-80: $2000

unding Requirements, FY-81: $1800 (including supplies, travel and publications).

Personnel: (name and grade)

Equipment: (describe in detail including cost) None

Supplies: (consumable, animal purchase) $1300

Travel: (mission oriented, training and presentation) $500

Other: (equipment rentals, contracts for service, animal care and reprints) None

| Date: 10/9/80 | Protocol No: 3164 | Status: Interim X<br>Final |
|---|---|---|

Title of Project:

The Comparison of Zaditen® and Theophylline in the Prophylaxis of Bronchial Asthma

| Starting Date: 1/18/80 | Estimated Completion Date: 12/81 |
|---|---|

Principal Investigator: Dr. Anthony J. Deutsch

| Associate Investigators: | Facility: WRAMC |
|---|---|
| Dr. Ana Ortiz<br>Dr. Richard Summers<br>Dr. Richard Evans | Dept/Svc Dept. of Allergy |

Key Words: Prophylactic Therapy in Asthma; Ketotifen

| Accumulative MEDCASE Cost: 0 | Accumulative Contract Cost: 0 | Accumulative Suppl Cost: 0 |
|---|---|---|

| FY-80 MEDCASE Cost: 0 | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective:

To evaluate the long term safety and efficacy of Zaditen® in the prophylaxis of asthma; to compare its effects to theophylline.

Technical Approach:

See original protocol.

Progress during FY-80: Fifteen patients entered (12 male, 3 female); one female patient terminated study at third month. Reason for discontinuation: recurrence of pre-study medical problem.

Number of subjects to be studied before completion of study: 30

Serious/unexpected side effects in subjects participating in project: None

Conclusions: Satisfactory progress; no complications to date.

Publications or Abstracts, FY-80: None

| Date: 15 October 1980 | Protocol No: 3165 | Status: Interim X<br>Final |
|---|---|---|

Title of Project: Clinical Trial of Skin Testing with Major and Minor Penicillin Derivatives in Hospitalized Patients.

| Starting Date: June 1980 | Estimated Completion Date: July 1982 |
|---|---|

Principal Investigator: Richard Evans III, COL MC

| Associate Investigators:<br>Lelia T. Gaines, MAJ MC | Facility: Walter Reed Army Medical Center<br>Dept/Svc Allergy-Immunology |
|---|---|

Key Words:

| Accumulative MEDCASE Cost: 0 | Accumulative Contract Cost: 0 | Accumulative Supply Cost: 0 |
|---|---|---|

| FY-80 MEDCASE Cost: | Periodic Review Results:<br>(to be filled in by DCI) |
|---|---|

Study Objective: To determine whether current penicillin determinants are adequate to predict patient's response to penicillin and derivatives.

Technical Approach: Skin test history positive and negative patients who will be given penicillin and record reactions, if any.

Progress during FY-80: To date, we have tested 12 patients with a history of penicillin allergy. Two patients had positive skin tests and were not given penicillin. The remainder were given penicillin or derivatives without reaction. We have begun to test history negative patients.

Number of subjects to be studied before completion of study: 200

Serious/unexpected side effects in subjects participating in project: None

Conclusions: None can be drawn at this time.

Publications or Abstracts, FY-80: None

Work Unit No.: 3165

Funds Utilized, FY-80: None

Funding Requirements, FY-81: $1500.00

Personnel: (name and grade) No additional requirements 10 hours week/med tech

Equipment: (describe in detail including cost) No additional requirements

Supplies: (consumable, animal purchase) No additional requirements

Travel: (mission oriented, training and presentation) $1500.00

Other: (equipment rentals, contracts for service, animal care and reprints) No additional requirements

| Date: 8 September 1980 | Protocol No: 3166 | Status: Interim x<br>Final |
|---|---|---|

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

| Starting Date: 25 March 1980 | Estimated Completion Date: Fall 1981 |
|---|---|

Principal Investigator: Richard J. Summers, LTC MC
H. S. Nelson, COL MC
~~Michael Schatz, M.D.~~

Associate Investigators:
Richard Evans III, COL MC
Bonnie Baswell, MAJ MC
Richard Weber, LTC MC
Clarence Virtue, COL MC

Facility: WRAMC

Dept/Svc Allergy-Clinical Immunology Service

Key Words: Local Anesthetic; Skin Tests; Challenge; Adverse Reaction

| Accumulative MEDCASE Cost: N/A | Accumulative Contract Cost: N/A | Accumulative Supply Cost: N/A |
|---|---|---|

| FY-80 MEDCASE Cost: N/A | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective: Evaluation of local anesthetic skin testing and progressive challenge in patients with previous adverse reaction to local anesthetic.

Technical Approach: Skin testing to local anesthetic to which the patient has reacted (by history) is performed at low concentrations. The concentration is gradually increased until either a positive skin test occurs or full strength local anesthetic has been tolerated.

Progress during FY-80: To date 2 patients have been completely tested and found to be negative at full strength.

Number of subjects to be studied before completion of study: 500 patients at 4 major medical centers.

Serious/unexpected side effects in subjects participating in project: None so far

Conclusions: Insufficient data at present

Publications or Abstracts, FY-80: None

CLINICAL INVESTIGATION PROGRAM

Work Unit No.: 3166

Funds Utilized, FY-80: N/A

Funding Requirements, FY-81: N/A

Personnel: Richard J. Summers, LTC MC and Associate Investigators

Equipment: N/A

Supplies: Consumable supplies utilized are those utilized in normal patient care

Travel: Presentation of paper at one national meeting - $800.

Other: N/A

| Date: 7 October 1980 | Protocol No: 4113 | Status: Interim XX<br>Final |
|---|---|---|

Title of Project: "Cooperative Gynecologic Oncology Group"

| Starting Date: N/A | Estimated Completion Date: N/A |
|---|---|

Principal Investigator: Robert C. Park, COL, MC, USA

| Associate Investigators: | Facility: Walter Reed Army Medical Center, Ward 67, Outpatient Clinic |
|---|---|
| Paul B. Heller, LTC, MC, USA<br>Terrel J. Michel, LTC, MC, USA<br>Geoffrey Weisbaum, LTC, MC, USA<br>William Neglia, MAJ, MC, USA | Dept/Svc: Department of OB-GYN, GYN Oncology Service |

Key Words: N/A

| Accumulative MEDCASE Cost: N/A | Accumulative Contract Cost: N/A | Accumulative Supply Cost: N/A |
|---|---|---|

| FY-80 MEDCASE Cost: N/A | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective: The Walter Reed section of Gynecologic Oncology is involved with nationally organized Gynecologic Oncology Group which contains 33 of the major medical centers in the country which are interested in the area of gynecologic tumors and treatment. GOG is recognized and funded through the National Cancer Institute.

Technical Approach: Walter Reed is active in 23 GOG protocols. Presently, there are 36 protocols either continuing to collect data or active. These protocols involve treatment of ovarian carcinoma, cervical carcinoma, [illegible] of the endometrium and uterine sarcoma. To date over 316 patients have been registered in this group from Walter Reed. About 292 have been placed in specific protocol studies.

Progress during FY-80: About 292 patients have been placed in GOG protocols from Walter Reed.

Number of subjects to be studied before completion of study: Unknown

Serious/unexpected side effects in subjects participating in project: Detailed in previous reports.

Conclusions: Detailed in previous reports.

| Date: 17 Dec 80 | Protocol No: 4151 / 4116 | Status: Interim X<br>Final |
|---|---|---|

**Title of Project:** The Evaluation of Fetal Systolic Time Intervals and Beat to Beat Interval Variations in Fetal Heart Rate as Early Indications of Fetal Maturity and Fetal Distress.

| Starting Date: FY 75 | Estimated Completion Date: undetermined |
|---|---|

**Principal Investigator:** JAMES HADDOCK

| **Associate Investigators:**<br>H. KLAPHOLZ<br>H. SKIBA-POWELL | **Facility:** WRAMC<br>**Dept/Svc** OB ob |
|---|---|

**Key Words:**

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: |
|---|---|---|

| FY-80 MEDCASE Cost: | Periodic Review Results:<br>(to be filled in by DCI) |
|---|---|

**Study Objective:** To determine fetal condition by evaluating cardiac function by fetal systolic time intervals

**Technical Approach:** Systolic time intervals is determined by EKG and phono cardiography.

**Progress during FY-80:** This project has been inactive since our initial report. With development of protocol 4151 we hope to be able to do this accurately by totally non invasive means antepartum by an abdominally derived fetal EKG signal. Hopefully, we'll have this technology by late April or Early May and could consider doing this.

Number of subjects to be studied before completion of study: 60

Serious/unexpected side effects in subjects participating in project:

Conclusions:

The additional new feature of the technology is to derive the fetal EKG signal by a non invasive means, namely from the maternal abdomen rather than from a fetal scalp lead. This is being done under an approved research protocol. An amendment to 4116 is in order but we would prefer to submit this at a time when we have this ability in hand and have a specific procedure in mind.

Date: 17 Dec 80 | Protocol No: 4124 | Status: Interim X / Final

Title of Project: Fetal Intensive Care Monitoring in a Long-Range Continuing Project

Starting Date: 1973 | Estimated Completion Date: On going

Principal Investigator: JAMES B. HADDOCK

Associate Investigators:
T. FRANK
A. PRESBYLICK
H. SKIBA-POWELL

Facility: WRAMC

Dept/Svc 08

Key Words:

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: |
|---|---|---|
| $435 | | |

FY-80 MEDCASE Cost:

Periodic Review Results: (to be filled in by DCI)

Study Objective: To accumulate a data base on perinatal outcome in relation to fetal heart rate abnormalities and labor curve abnormalities.

Technical Approach: Each fetal heart rate tracing and labor curve is reviewed and classified. We currently have available technology to put this infomration on a disk or computer tape for reference.

Progress during FY-80: as above

Number of subjects to be studied before completion of study: 1400 per year

Serious/unexpected side effects in subjects participating in project:
none

Conclusions:

Currently we have collected and catagorized over 6,500 FHR Tracings since initiation of this protocol. Review of these currently is time consuming and difficult. Shortly, we will have the ability to put these directly into a computer memory system. This will provide an invaluable data base for analysis.

| Date: 17 Dec 80 | Protocol No: 4129 | Status: Interim x<br>Final |
|---|---|---|

**Title of Project:** Antepartum Fetal Evaluation of Noise Evolved Heart Rate Response as an Indicator of Fetal Well-being.

| Starting Date: 1976 | Estimated Completion Date: May 82 |
|---|---|

**Principal Investigator:** JAMES HADDOCK

| **Associate Investigators:**<br>H. KLAPHOLZ<br>T. FRANK<br>A. PRESBYLICK<br>H. SKIBA-POWELL | **Facility:** WRAMC<br>**Dept/Svc** OB |
|---|---|

**Key Words:**

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: |
|---|---|---|
| FY-80 MEDCASE Cost: | Periodic Review Results: (to be filled in by DCI) | |

**Study Objective:** To test the validity of the concept that Fetal Heart Rate accelerations in response to an external stimulus are as good a predictor of fetal well being as are those associated with spontaneous fetal movement and accelerations.

**Technical Approach:** Fetal heart rate is recorded by standard techniques a five-second tone pulse 90 to 121 decibels is used to arouse the fetus and response noted. This has proven to be an excellent technique as shown by others as well. When we have a computer program to examine spectral frequency analysis of fetal heart rate variability. We plan to incorporate this technique into the project.

**Progress during FY-80:**

Number of subjects to be studied before completion of study: 100

Serious/unexpected side effects in subjects participating in project:
none

Note additional Co Investigator on this protocol is John Read. Initial work accomplished on this protocol in 1976 was promising. However, the initial investigator left and in the interim several papers were published on this technique which is now accepted as standard practice in current ante partum testing. We are developing a computer technology to accomplish spectral frequency analysis of FHR variability under an approved protocol. We intend to use the same set up as proposed but - simply analyze the data obtained with a computer program.

Date: 7 October 1980 | Protocol No: 4134 | Status: Interim XX Final

Title of Project: "Treatment of Women with Cervical Cancer, Stage IIB, IIIB, IVA, Confined to the Pelvis And/Or Para-Aortic Nodes With Radiotherapy Alone Versus Radiotherapy Plus Immunotherapy (Intravenous C-Parvum) (Phase III) GOG #24.

Starting Date: | Estimated Completion Date: Unknown

Principal Investigator: Robert C. Park, COL, MC, USA

Associate Investigators:
Paul B. Heller, LTC, MC, USA
Terrel J. Michel, LTC, MC, USA
William Neglia, MAJ, MC, USA

Facility: Walter Reed Army Medical Center

Dept/Svc Department of OB-GYN, GYN Oncology Service

Key Words: Cervical cancer, radiotherapy, and immunotherapy

| Accumulative MEDCASE Cost: None | Accumulative Contract Cost: None | Accumulative Supply Cost: None |
|---|---|---|

FY-80 MEDCASE Cost: None | Periodic Review Results: (to be filled in by TSO)

Study Objective: Radiotherapy is the standard treatment for patients with advanced cervical carcinoma. The goal of this project is determined if the addition of immunotherapy will enhance the radiation response rate.

Technical Approach: The patients are randomized to one of [illegible] treatment regimens: 1) Radiotherapy alone, or 2) Radiotherapy plus C-Parvum. Amendment to the protocol states that patients who have clinical Stage IB found to have disease extending out to the pelvic side walls at surgery are eligible.

Progress during FY-80: One hundred and ninety-two patient group-wide have been evaluated as eligible. Ten patients have been submitted from Walter Reed.

Number of subjects to be studied before completion of study: Annual accrual: 150 patients

Serious/unexpected side effects in subjects participating in project: Adverse effects that were seen were basically those expected.

Conclusions: It is too early to draw any conclusions with regard to improve survival.

Date: 7 October 1980 | Project No: 4135 | Status: XX

Title of Project: "A Randomized Comparison of Melphalan Alone Versus Adriamycin and Cyclophosphamide Versus Hexamethylmelamine and Melphalan in Patients with Ovarian Adenocarcinoma, Suboptimal Stage III, Stage IV, or Recurrent Equivalent to Stage III or IV (Phase III) GOG #22.

Starting Date: | Estimated Completion Date: Closed to patient entry as of 4 June 1979.

Principal Investigator: Robert C. Park, COL, MC, USA

Associate Investigators:
Paul B. Heller, LTC, MC, USA
Terrel J. Michel, LTC, MC, USA

Facility: Walter Reed Army Medical Center, Ward 67, and GYN Outpatient Clinic

Dept/Svc: Department of OB-GYN, GYN Oncology Service

Key Words: Melphalan versus Adriamycin & Cytoxan, versus Hexamethylmelamine and Melphalan in Ovarian carcinoma

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: |
|---|---|---|
| None | None | None |

FY-80 MEDCASE Cost: N/A

Periodic Review Results: (to be filled in by DCI)

Study Objective: Single alkylating chemotherapy agents produced 30% response rate in patients with epithelial ovarian cancer. The objective of this study is to determine if adding Adriamycin or hexamethylmelamine will enhance the response rate.

Technical Approach: Patients are randomized into one of three treatment arms. 1) Alkeran; 2) Alkeran plus hexamethylmelamine; and 3) Cytoxan plus Adriamycin.

Progress during FY-80: The total number of patients entered into this study was 432. The total number of patients from Walter Reed was 22.

Number of subjects to be studied before completion of study: Approximately 430.

Serious/unexpected side effects in subjects participating in project: There were no serious side effects in any Walter Reed patients.

Conclusions: The combination regimens appear to be more active than Melphalan alone in producing complete responses in these stages of ovarian cancer. Adriamycin and Cytoxan has a slightly higher response rate. Melphalan and hexamethylmelamine is oral and avoids cardiac risk and alopecia.

Publications or abstracts, FY-80:

| Date: 7 October 1980 | Protocol No: 4136 | Status: Interim XX<br>Final |
|---|---|---|

Title of Project: "A Randomized Comparison of Melphalan Alone Versus Melphalan Therapy Plus Immunotherapy in the Treatment of Women with Stage III (Optimal) Epithelial Carcinoma of the Ovary (Phase III)" GOG #25.

| Starting Date: | Estimated Completion Date: Unknown |
|---|---|

Principal Investigator: Robert C. Park, COL, MC, USA

| Associate Investigators: | Facility: Walter Reed Army Medical Center, Ward 67, and GYN Outpatient Clinic |
|---|---|
| Paul B. Heller, LTC, MC, USA<br>Terrel J. Michel, LTC, MC, USA | Dept/Svc: Department of OB-GYN, GYN Oncology Service |

Key Words: Epithelial ovarian carcinoma treated by Melphalan and immunotherapy

| Accumulative MEDCASE Cost: None | Accumulative Contract Cost: None | Accumulative Supply Cost: None |
|---|---|---|

| FY-80 MEDCASE Cost: None | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective: Melphalan alone produces a 30% response rate in patients with epithelial cancer. The objective of this study is to determine if the addition of an immunotherapy agent will enhance the response rate.

Technical Approach: Patients with optimal Stage III epithelial carcinoma of the ovary are randomized to one of two treatment regimens. Regimen 1 is Melphalan alone and Regimen 2 is Melphalan plus C-Parvum.

Progress during FY-80. One hundred and ninety-four patients have been entered into this protocol in the entire GOG. Walter Reed has entered three patients in this protocol.

Number of subjects to be studied before completion of study: 150 patients annual accrual.

Serious/unexpected side effects in subjects participating in project: No severe reactions have been noted in either of the treatment arms.

Conclusions: None at this time.

| Date: 7 October 1980 | Protocol No: 4137 | Status: Active: XX<br>Final: |
|---|---|---|

Title of Project: "A Randomized Comparison of Pelvic and Abdominal Radiation Therapy Versus Pelvic Radiation and Melphalan Versus Melphalan Alone in Stage II Carcinoma of the Ovary (Phase III)" GOG #29

Starting Date: 11 February 1977 Estimated Completion Date: November 1978

Principal Investigator: Robert C. Park, COL, MC, USA

| Associate Investigators: | Facility: | Walter Reed Army Medical Center, Ward 67, and GYN Outpatient Clinic |
|---|---|---|
| Paul B. Heller, LTC, MC, USA<br>Terrel J. Michel, LTC, MC, USA<br>William Neglia, MAJ, MC, USA | Dept/Svc | Department of OB-GYN, GYN Oncology Service |

Key Words: Stage II ovarian carcinoma, pelvic radiation, Alkeran

| Accumulative MEDCASE Cost: None | Accumulative Contract Cost: None | Accumulative Supply Cost: None |
|---|---|---|
| FY-80 MEDCASE Cost: None | Periodic Review Results: (to be filled in by DCI) | |

Study Objective: The standard treatment for patients with Stage II ovarian carcinoma has been postoperative irradiation to the abdomen and the pelvis. Recent data supports that single alkylating chemotherapy is equally effective. The objective of this study is to determine if radiation alone, chemotherapy alone, or the combination of the two are the best treatment methods for this disease.

Technical Approach: Patients are randomized to one of three treatment arms after a total abdominal hysterectomy and bilateral salpingo-oophorectomy plus evaluation of the endocervix, the diaphragm, the iliac, and para-aortic nodes. The patients then are randomized to 1) Pelvic and abdominal radiation therapy, 2) Pelvic irradiation and Melphalan, or 3) Melphalan alone.

Progress during FY-80: Patients are continuing to be followed who have received treatment. However, the GOG withdrew from this protocol as of November 1978. Therefore, no firm conclusions have been drawn from this study.

Number of patients [illegible] 245 were hopefully studied.

Nature of unexpected [illegible] participating in project: There were no serious or unexpected side effects in subjects participating in the project.

Conclusions: None.

| Date: 7 October 1980 | Protocol No: 4139 | Status: Interim XX Final |
|---|---|---|

Title of Project: "A Randomized Comparison of Melphalan, 5FU, and Megace Versus Adriamycin, Cytoxan, 5FU, and Megace in the Treatment of Patients with Primary Stage III, or IV Recurrent or Residual Endometrial Carcinoma (Phase III)" GOG # 28.

| Starting Date: 4 January 1977 | Estimated Completion Date: Closed to further entry on 15 October 1979. |
|---|---|

Principal Investigator: Robert C. Park, COL, MC, USA

| Associate Investigators: | Facility: Walter Reed Army Medical Center, Ward 67, GYN Outpatient Clinic |
|---|---|
| Paul B. Heller, LTC, MC, USA<br>Terrel J. Michel, LTC, MC, USA | Dept/Svc: Department of OB-GYN, GYN Oncology Service |

Key Words: Endometrial carcinoma, Stage III and IV, treated with chemotherapy.

| Accumulative MEDCASE Cost: None | Accumulative Contract Cost: None | Accumulative Supply Cost: None |
|---|---|---|
| FY-80 MEDCASE Cost: None | Periodic Review Results: (to be filled in by DCI) | |

Study Objective: To determine the efficacy of multi-drug preparations and to see if one of two programs previously shown to be effective by pilot studies is superior.

Technical Approach: Patients with advanced or recurrent endometrial carcinoma are randomized to one of two treatment regimens: 1) Melphalan, 5FU, and Megace, and 2) Adriamycin, Cytoxan, 5FU, and Megace.

Progress during FY-80: Three hundred and fifty-eight patients were entered into this protocol. Two were entered from Walter Reed.

Number of subjects to be studied before completion of study: 358

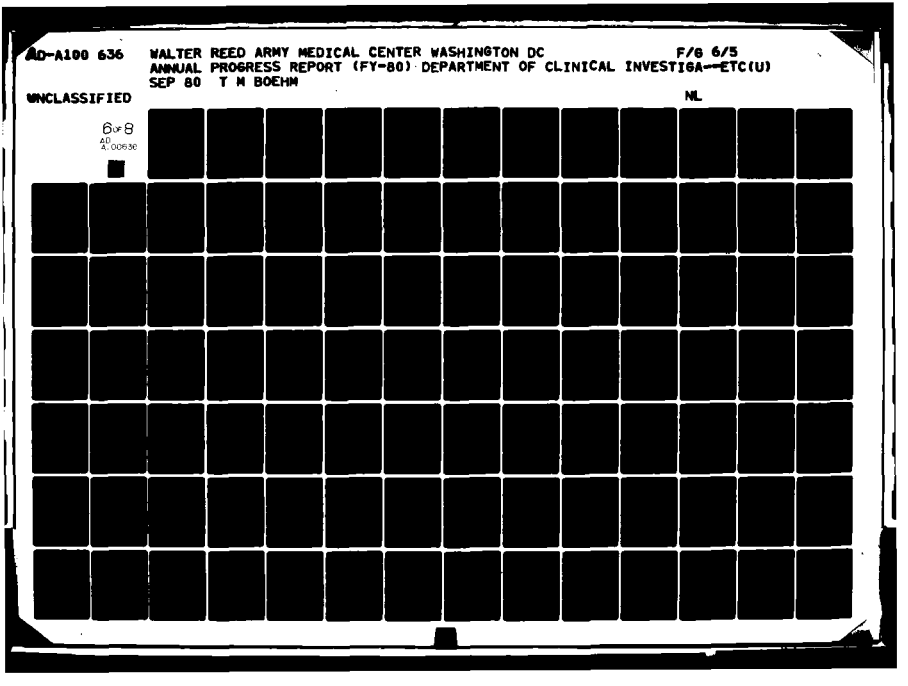
Serious/unexpected side effects in subjects participating in project: There were some hemotologic toxicities in ten patients and three drug-related deaths.

Conclusions: The overall objective response rate was 36.8%. The activity of Melphalan and 5FU for the first time the treatment of this disease has been established. There is suggestion that there is a better response to combination chemotherapy in patients with poor prognosis endometrial carcinoma in comparison to a single agent therapy. They will continue follow-up on patients entered in this study.

AD-A100 636 WALTER REED ARMY MEDICAL CENTER WASHINGTON DC F/G 6/5
ANNUAL PROGRESS REPORT (FY-80) DEPARTMENT OF CLINICAL INVESTIGA--ETC(U)
SEP 80 T M BOEHM

UNCLASSIFIED NL

6 OF 8
AD
A100636



| Date: 7 October 1980 | Protocol No: 4140 | Status: Interim XX Final |
|---|---|---|

Title of Project: "A Clinical-Pathologic Study of Stage I and II Carcinoma of the Endometrium," COG #33.

| Starting Date: 25 November 1980 | Estimated Completion Date: Unknown |
|---|---|

Principal Investigator: Robert C. Park, COL, MC, USA

| Associate Investigators: | Facility: Walter Reed Army Medical Center, Ward 67, GYN Outpatient Clinic |
|---|---|
| Paul B. Heller, LTC, MC, USA<br>Terrel J. Michel, LTC, MC, USA | Dept/Svc: Department of OB-GYN, GYN Oncology Service |

Key Words: Endometrial carcinoma, Stage I and II, surgical investigation

| Accumulative MEDCASE Cost: None | Accumulative Contract Cost: None | Accumulative Supply Cost: None |
|---|---|---|

| FY-80 MEDCASE Cost: None | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective: To determine the incidence of pelvic and aortic lymph node metastasis and the relationship of these node metastasis to other prognostic factors in Stage I and II carcinoma of the endometrium. All patients with Stage I and II endometrial carcinoma can be admitted to this protocol which will involve a surgical procedure and pathologic follow-up.

Technical Approach: The patient will have a total abdominal hysterectomy, bilateral salpingo-oophorectomy, selective pelvic and para-aortic lymphadenectomy and peritoneal cytology sampling. Thereafter, the patient will be followed up or entered onto an additional Gynecologic Oncology Group Protocol. Patients with Stage I, Grade 1 disease are not eligible for this protocol. All patients are to be entered to the protocol after the surgery has been performed.

Progress during FY-80: There have been 673 entries to this protocol. Walter Reed has entered 46 patients into this protocol.

Number of subjects to be studied before completion of study: Unknown

Serious/unexpected side effects in subjects participating in project: Four patients had pulmonary emboli. One patient was noted to have died. Seventeen patients had hemorrhage greater than 1000 cc.

Conclusions: It would appear that this study could define the surgical procedure required for optimal evaluation of this stage or stages of endometrial carcinoma.

| Date: 7 October 1980 | Protocol No: 4141 | Status: Interim XX<br>Final |
|---|---|---|

Title of Project: "A Randomized Study of Adriamycin as an Adjuvant After Surgery and Radiation Therapy in Patients with High-Risk Endometrial Carcinoma, Stage I and Occult Stage II." GOG #34.

| Starting Date: 22 August 1978 | Estimated Completion Date: Unknown |
|---|---|

Principal Investigator: Robert C. Park, COL, MC, USA

| Associate Investigators: | Facility: Walter Reed Army Medical Center, Ward 67, GYN Outpatient Clinic, OR |
|---|---|
| Paul B. Heller, LTC, MC, USA<br>Terrel J. Michel, LTC, MC, USA | Dept/Svc: Department of OB-GYN, GYN Oncology Service |

Key Words: Stage I and Occult Stage II endometrial carcinoma treated by Adriamycin

| Accumulative MEDCASE Cost: None | Accumulative Contract Cost: None | Accumulative Supply Cost: None |
|---|---|---|

| FY-80 MEDCASE Cost: None | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective: To study the differences in morbidity in patient's survival as functions of various tumor growth patterns in a patient with poor risk endometrial carcinoma.

Technical Approach: Patients are selected for this protocol by extent of disease determined at surgery. Those who have greater than 1/2 myometrial invasion or pelvic or para-aortic node involvement or microscopic evidence of cervical involvement will receive radiation therapy. Following this, there will be randomization to Adriamycin or no further treatment.

Progress during FY-80: To date, 83 patients have been entered to the entire Gynecologic Oncology Group. Five have been entered from Walter Reed.

Number of subjects to be studied before completion of study: Approximately 75/year for four years.

Serious/unexpected side effects in subjects participating in project: There has been evidence of bowel obstruction in one case. One patient died after surgery for relief of bowel obstruction, possibly due to radiation therapy.

Conclusions: None at present.

Publications or Abstracts, FY-80: None.

| Date: 7 October 1980 | Protocol No: 4142 | Status: Interim XX<br>Final |
|---|---|---|

Title of Project: "A Phase II Trial of ICRF in Patients With Advanced Pelvic Malignancies." GOG #26-G.

| Starting Date: 27 September 1978 | Estimated Completion Date: Unknown |
|---|---|

Principal Investigator: Robert C. Park, COL, MC, USA

| Associate Investigators: | Facility: | Walter Reed Army Medical Center, Ward 67, GYN Outpatient Clinic |
|---|---|---|
| Paul B. Heller, LTC, MC, USA<br>Terrel J. Michel, LTC, MC, USA | Dept/Svc | Department of OB-GYN, GYN Oncology Service |

Key Words: ICRF-159 in advanced pelvic malignancies.

| Accumulative MEDCASE Cost: None | Accumulative Contract Cost: None | Accumulative Supply Cost: None |
|---|---|---|

| FY-80 MEDCASE Cost: None | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective: To determine the efficacy of ICRF-159 in the treatment of advanced pelvic malignancies.

Technical Approach: Patients with histologically advanced and recurrent and persistent metastatic or local gynecologic cancer with documented disease progression will be entered into this treatment.

Progress during FY-80: Sixty patients have been entered to this protocol in the entire GOG. Five patients have been entered from Walter Reed. The patients with squamous cell carcinoma of the cervix as of November 1978 are no longer eligible for entry. Patients with epithelial carcinoma of the ovary as of June

Number of subjects to be studied before completion of study: 25 patient per site.

Serious/unexpected side effects in subjects participating in project: No serious or unexpected side effects have been noted.

Conclusions: ICRF appears to have a moderate activity in squamous cell carcinoma of the cervix at the dose and schedule tested, despite significant myelosuppression.

Publications or Abstracts, FY-80: None

PROGRESS DURING FY-80: 1980, are no longer eligible for entry.

| Date: 7 October 1980 | Protocol No: 4143 | Status: Interim XX / Final |
|---|---|---|

Title of Project: "A Randomized Comparison of Local Excision Versus Cryosurgery in Patients with Limited Grade 1, 2 or 3 Cervical Intraepithelial Neoplasia." GOG #31.

| Starting Date: 1 November 1978 | Estimated Completion Date: 1982 |
|---|---|

Principal Investigator: Robert C. Park, COL, MC, USA

| Associate Investigators: | Facility: Walter Reed Army Medical Center, GYN Outpatient Clinic |
|---|---|
| Paul B. Heller, LTC, MC, USA<br>Terrel J. Michel, LTC, MC, USA<br>Geoffrey Weisbaum, LTC, MC, USA | Dept/Svc: Department of OB-GYN, GYN Oncology Service |

Key Words: Local excision, cryotherapy, CIN-1, 2, 3.

| Accumulative MEDCASE Cost: None | Accumulative Contract Cost: None | Accumulative Supply Cost: None |
|---|---|---|

| FY-80 MEDCASE Cost: None | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective: To evaluate and compare the immediate and long-term effectiveness of outpatient cryosurgery and outpatient local excision in the treatment of limited cervical intraepithelial neoplasia (CIN) Grade 1, 2, or 3. Patients are then randomized to prospective studies.

Technical Approach: Patients are randomized to one of two treatment arms: 1) Outpatient cryosurgery, or 2) Outpatient surgical excision.

Progress during FY-80: To date there have been 296 patients entered from the entire GOG. Twenty-three patients have been entered from Walter Reed. It is too early to draw any statistical conclusions.

Number of subjects to be studied before completion of study: 300 annually. 660 total

Serious/unexpected side effects in subjects participating in project: At this point, none have been noted.

Conclusions: None.

Publications or Abstracts, FY-80: None.

2

| Date: 7 October 1980 | Project No.: 4144 | Status: Interim XX / Final |
|---|---|---|

Title of Project: "A Randomized Comparison of Surgical Conization Versus Cryosurgery in Patients With Extensive Grade 3 Cervical Intra-Epithelial Neoplasia (CIN)." GOG #32.

| Starting Date: September 1978 | Estimated Completion Date: 1981 |
|---|---|

Principal Investigator: Robert C. Park, COL, MC, USA

| Associate Investigators: | Facility: Walter Reed Army Medical Center, GYN Outpatient Clinic |
|---|---|
| Paul B. Heller, LTC, MC, USA<br>Terrel J. Michel, LTC, MC, USA<br>Geoffrey Weisbaum, LTC, MC, USA | Dept/Svc: Department of OB-GYN, GYN Oncology Service |

Key Words: Surgical conization, cryosurgery, CIN-3

| Accumulative MEDCASE Cost: None | Accumulative Contract Cost: None | Accumulative Supply Cost: None |
|---|---|---|

| FY-80 MEDCASE Cost: None | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective: Standard treatment for patients with cervical intraepithelial neoplasia Grade 3 would be in-hospital conization or in-hospital surgical hysterectomy. The purpose of this study is to evaluate and compare the immediate and long-term effectiveness of outpatient cryosurgery to the standard cold-knife conization in the treatment of extensive surgical intraepithelial neoplasia (CIN) Grade 3 in a randomized prospective study.

Technical Approach: The patient is randomized to one of two treatment arms. 1) Outpatient cryosurgery, or 2) Inpatient surgical conization.

Progress during FY-80: The GOG has accrued a total of 73 patients. Total evaluable are 33. Four have been entered from Walter Reed. It is too early for analysis at this point.

Number of subjects to be studied before completion of study: Approximately 310

Serious/unexpected side effects in subjects participating in project: None.

Conclusions: It is too early to draw conclusions. The patient accession will continue.

Publications or Abstracts, FY-80: None.

| Date: 7 October 1980 | Protocol No. 4145 | Status: Interim XX<br>Final |
|---|---|---|

Title of Project: "A Randomized Comparison of Melphalan Versus No Treatment in the Treatment of Patients with Selected Stage IAi, ii; IIBi Ovarian Cancer (Well to Moderately Differentiated)." NCI Protocol #7601.

| Starting Date: 22 August 1978 | Estimated Completion Date: 1983 |
|---|---|

Principal Investigator: Robert C. Park, COL, MC, USA

| Associate Investigators: | Facility: Walter Reed Army Medical Center, Ward 67, GYN Oncology Service |
|---|---|
| Paul B. Heller, LTC, MC, USA<br>Terrel J. Michel, LTC, MC, USA<br>Geoffrey Weisbaum, LTC, MC, USA<br>Geoffr | Dept/Svc: Department of OB-GYN, GYN Oncology Service |

Key Words: Early ovarian carcinoma, Melphalan versus no treatment

| Accumulative MEDCASE Cost: None | Accumulative Contract Cost: None | Accumulative Supply Cost: None |
|---|---|---|

| FY-80 MEDCASE Cost: None | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective: Scatterred non-randomized studies employing alkylating agents, chemotherapy. Have reported five-year survivals as high as 90% in patients with Stage I ovarian carcinoma. Unfortunately, the non-randomized nature, the small numbers, and the unavailability of detailed pathologic information make the definitive conclusions of these studies impossible. It is the purpose of the present study to determine the value of chemotherapeutic prophylactic therapy after surgery in definitive staging in patients with Stage IAi and IBi ovarian adenocarcinoma.

Technical Approach: Staging laparotomy and total abdominal hysterectomy and bilateral salpingo-oophorectomy is performed after which the patients are randomized to one of two schema. 1) Observation or 2) Melphalan.

Progress during FY-80: A total of nine patients have been randomized from Walter Reed. It is too early for specific statistical analysis.

Number of subjects to be studied before completion of study: Approximately 110.

Serious/unexpected side effects in subjects participating in project: There have been none noted.

Conclusions: None.

Publications or Abstracts, FY-80. None.

| Date: 7 October 1980 | Protocol No: 4146 | Marks Index: XX Dept |
|---|---|---|

Title of Project: "A Randomized Comparison of Melphalan Versus Radio-Isotopes in the Treatment of Patients with No Microscopic Residual Disease, Having all Stages IC and II (A, B and C), and of Selected Stages IAii, and IBii Ovarian Cancer." NCI Protocol #7602.

Starting Date: 22 August 1978 Estimated Completion Date: 1981 or 1982

Principal Investigator: Robert C. Park, COL, MC, USA

| Associate Investigators: | Facility: Walter Reed Army Medical Center, Ward 67, GYN Outpatient Clinic |
|---|---|
| Paul B. Heller, LTC, MC, USA<br>Terrel J. Michel, LTC, MC, USA<br>Geoffrey Weisbaum, LTC, MC, USA | Dept/Svc: Department of OB-GYN, GYN Oncology Service |

Key Words: Melphalan versus radio-isotopes in selected early ovarian cancer.

| Accumulative MEDCASE Cost: None | Accumulative Contract Cost: None | Accumulative Supply Cost: None |
|---|---|---|
| FY-80 MEDCASE Cost: None | Periodic Review Results: (to be filled in by DCI) | |

Study Objective: Mean five-year survivals of 39% with operation plus radiation. Twenty four percent survival for those treated with operation alone in Stage II and poor prognosis Stage I patients with minimal residual disease. In some successful series, 30-40 percent of the patients die of recurrent ovarian carcinoma despite surgery and subsequent radiotherapy. The purpose of this study is to compare the usefulness of Melphalan chemotherapy in intra-abdominal radioactive phosphorus in resectable Stage II and poor prognosis Stage I patients,

Technical Approach: Patients who have had staging laparotomy including total abdominal hysterectomy and bilateral salpingo-oophorectomy if there is no microscopic residual disease, randomization will be to 1) Melphalan or 2) Radioisotope. In the case of residual disease in Stage IIB and IIC lesions, the patients will be randomized to 1) Pelvic radiotherapy and Melphalan or 2) Melphalan alone.

Progress during FY-80: A total of two patients have been entered from Walter Reed. It is too early for specific statistical analysis.

Number of subjects to be studied before completion of study: Approximately 200-240.

Serious/unexpected side effects in subjects participating in project: There have been no severe toxic reactions at this time.

Conclusions: None.

Publications or Abstracts, FY-80: None.

STUDY OBJECTIVE: and to determine if an addition of pelvic radiotherapy to standard surgical and chemotherapeutic treatment of incompletely resected Stage II improves survival.

| Date: 7 October 1980 | Protocol No: 4147 | Status: Interim XX<br>Final |
|---|---|---|

Title of Project: "Surgical Pathological Study of Women With Squamous Cell Carcinoma of the Vulva." COG #36.

Starting Date: 15 November 1978 Estimated Completion Date: 1983

Principal Investigator: Robert C. Park, COL, MC, USA

| Associate Investigators: | Facility: Walter Reed Army Medical Center, Ward 67, GYN Outpatient Clinic |
|---|---|
| Paul B. Heller, LTC, MC, USA<br>Terrel J. Michel, LTC, MC, USA<br>Geoffrey Weisbaum, LTC, MC, USA | Dept/Svc: Department of OB-GYN, GYN Oncology Service |

Key Words: Surgical pathologic study, squamous cell carcinoma of vulva

| Accumulative MEDCASE Cost: None | Accumulative Contract Cost: None | Accumulative Supply Cost: None |
|---|---|---|
| FY-80 MEDCASE Cost: None | Periodic Review Results: (to be filled in by DCI) | |

Study Objective: To determine the validity of current FIGO staging to the pathologic prognosis factors of size of lesion, location of lesion, depth of invasion of tumor in mm., histologic rate, site, and number of positive lymph nodes in Stage I-IV carcinoma of the vulva. To rapidly accumulate prospective surgical pathologic data for development of further protocols. To determine the morbidity of primary radical surgery in vulvar carcinoma.

Technical Approach: All patients with primary previously untreated histologically confirmed invasive squamous cell carcinoma of the vulva, clinically determined to be Stage I-IV, that radical vulvectomy suffices to remove all of the lesion. Patients will have radical vulvectomy plus bilateral groin node dissection and will be randomized depending upon whether they have negative groin nodes to follow-up alone or positive groin nodes to more advanced protocol involving radiation therapy.

Progress during FY-80: There have been 122 patients entered from the entire GOG to date. It is too early to draw any statistical evaluation from this study.

Number of subjects to be studied before completion of study: Approximately 200.

Serious/unexpected side effects in subjects participating in project: None.

Conclusions: None at this time.

Publications or Abstracts, FY-80: None.

| Date: 7 October 1980 | Protocol No: 4148 | Status: Series XX<br>Type: |
|---|---|---|

Title of Project: "A Randomized Study of Radiation Therapy Versus Pelvic Node Resection For Patients With Invasive Squamous Cell Carcinoma of the Vulva Having Positive Groin Nodes." COG #37.

Starting Date: 15 November 1978 Estimated Completion Date: 1983

Principal Investigator: Robert C. Park, COL, MC, USA

| Associate Investigators:<br>William Neglia, MAJ, MC, USA<br>Paul B. Heller, LTC, MC, USA<br>Terrel J. Michel, LTC, MC, USA<br>Geoffrey Weisbaum, LTC, MC, USA | Facility: Walter Reed Army Medical Center, Ward 67, Radiation Therapy Dept.<br>Dept/Svc: Department of OB-GYN, GYN Oncology Service |
|---|---|

Key Words: Randomized study, squamous cell, vulva carcinoma, positive groin nodes.

| Accumulative MEDCASE Cost: None | Accumulative Contract Cost: None | Accumulative Supply Cost: None |
|---|---|---|

| FY-80 MEDCASE Cost: None | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective: To determine the benefit and morbidity of adding adjunctive radiotherapy to pelvis and groin in patients with positive groin nodes at radical vulvectomy and bilateral groin dissection.

Technical Approach: All patients with primary previously untreated histologically confirmed invasive squamous cell carcinoma of the vulva, such that radical vulvectomy suffices to remove all the local lesion and whose surgery revealed nodes in the groin on one or both sides containing metastatic carcinoma. Patients will be randomized after a radical vulvectomy plus bilateral groin nodes dissection to one of two regimens. Negative nodes - the patient will taken off the study. Positive nodes - the patient is to be randomized to regimen 1 including pelvic

Progress during FY-80: During FY-80, a total of 33 patients have been entered to this study. Analysis has not taken place because of small numbers entered.

Number of subjects to be studied before completion of study: Approximately 200

Serious/unexpected side effects in subjects participating in project: Bowel obstruction in six patients. Fistula from the bladder or bowel in one patient.

Conclusions: No definitive conclusions have been made.

Publications or Abstracts, FY-80: None.

TECHNICAL APPROACH: node dissection or regimen 2 including bilateral groin and pelvic node irradiation.

| Date: 17 Dec 80 | Protocol No: 4149 | Status: Interim X<br>Final |
|---|---|---|

Title of Project: Automated Detection of Fetal Heart Pattern Abnormalities

| Starting Date: 1979 | Estimated Completion Date: Undetermined |
|---|---|

Principal Investigator: HADDOCK, James

| Associate Investigators:<br>A. PRESBYLICK<br>T. FRANK<br>H. SKIBA-POWELL | Facility: WRAMC<br>Dept/Svc OB |
|---|---|

Key Words:

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: |
|---|---|---|
| FY-80 MEDCASE Cost: | Periodic Review Results: (to be filled in by DCI) | |

Study Objective: To develop a computer program to recognize fetal heart rate pattern anomalies and flag them for medical staff.

Technical Approach: Same as above

Progress during FY-80: This has been a low priority item since we hired a part-time consultant this year because (1) other items have been more important (2)connection to the research computer still has not been made (3) others have developed these at a sophisticated level. Modifications of existing technology and application of these techniques are still potentially important

Number of subjects to be studied before completion of study: 1400 per year

Serious/unexpected side effects in subjects participating in project:

none

Progress Cont'd

The technology to read FHR Traces is still in its infancy No program developed to date is at all satisfactory. Any application here would involve further development and modification. I believe this can be done with local personnel.

| Date: 17 Dec 80 | Protocol No: 4150 | Status: Interim X<br>Final |
|---|---|---|

**Title of Project:** On-Line Interpretation of Labor Curve Abnormalities

| Starting Date: Sep 80 | Estimated Completion Date: Mar 81 |
|---|---|

**Principal Investigator:** HADDOCK, James

| Associate Investigators:<br>A. PRESBYLICK<br>T. FRANK<br>H. SKIBA-POWELL | Facility: WRAMC<br>Dept/Svc OB |
|---|---|

**Key Words:**

| Accumulative MEDCASE Cost: $1435 | Accumulative Contract Cost: | Accumulative Supply Cost: |
|---|---|---|

| FY-80 MEDCASE Cost: $1435 | Periodic Review Results:<br>(to be filled in by DCI) |
|---|---|

**Study Objective:** To correlate labor curve abnormalities with uterine activity and to investigate the effect of therapy where uterine activity has been normal or abnormal.

**Technical Approach:** Uterine activity, pelvic exams, and therapies are entered automatically and by hand on line to the OB Research Computer. The computer is to be programmed to perform the above functions.

**Progress during FY-80:** The development of the program has been the chief task of Mr. Presbylick for the past 2 months. Computer connections will be made shortly.

Number of subjects to be studied before completion of study: 700

Serious/unexpected side effects in subjects participating in project:

None

| Date: 17 Dec 80 | Protocol No: 4141 | Status: Interim X / Final |
|---|---|---|

Title of Project: Early Reliable Detection of Fetal Heart Rate Variability by Adaptive Digital Filtering

| Starting Date: JAN 80 | Estimated Completion Date: JUN 82 |
|---|---|

Principal Investigator: JAMES HADDOCK

| Associate Investigators: | Facility: WRAMC |
|---|---|
| T. FRANK<br>A. PRESBYLICK<br>H. SKIBA-POWELL | Dept/Svc OB |

Key Words:

| Accumulative MEDCASE Cost: $870 | Accumulative Contract Cost: | Accumulative Supply Cost: |
|---|---|---|

| FY-80 MEDCASE Cost: | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective: To develop a computer program to extract a fetal EKG from a maternal abdominal wall EKG signal. This will then be used to compute beat-to-beat variability and evaluate fetal condition by noninvasive antepartum testing

Technical Approach:

As above

Progress during FY-80: ..Considerable progress has been made in the development of the programming above noted

Number of subjects to be studied before completion of study: See attached

Serious/unexpected side effects in subjects participating in project:
None

Conclusions:

(a) Initially 30 - 50
(b) If technically feasible, to be evaluated for broader application of testing fetal condition

| Date: 7 October 1980 | Protocol No: 4152 | Status: Interim XX / Final |
|---|---|---|

Title of Project: "A Phase II Trial of Maytansine in Patients With Advanced Pelvic Malignancies." GOG #26-H.

| Starting Date: 21 November 1978 | Estimated Completion Date: Unknown |
|---|---|

Principal Investigator: Robert C. Park, COL, MC, USA

| Associate Investigators: | Facility: | WalterReed Army Medical Center, Ward 67, GYN Outpatient Clinic |
|---|---|---|
| Paul B. Heller, LTC, MC, USA<br>Terrel J. Michel, LTC, MC, USA | Dept/Svc | Department of OB-GYN, GYN Oncology Service |

Key Words: Phase II, Maytansine, pelvic malignancies

| Accumulative MEDCASE Cost: None | Accumulative Contract Cost: None | Accumulative Supply Cost: None |
|---|---|---|

| FY-80 MEDCASE Cost: None | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective: To determine the efficiency of chemotherapy agents in patients whose advanced malignancies have been resistent to high priority methods of treatment. A rejection type of design will be used involving a fixed sample size of 25 evaluable patients per disease site per drug studied. The design allows replacement of ineffective regimens by newer agents or combinations.

Technical Approach: Maytansine appears to be similar to the vinca alkaloids, affecting DNA synthesis in arresting cells in metaphase of mitosis by inhibition of tubulin prolimerization. Maytansine has shown activity against many animal tumor models. Three schedules have been studies in Phase I trials. Single bolus every three weeks is convenient dose for patients. Only one gynecologic maligancy was included in the 20 patients. This was an ovarian carcinoma in which one response was seen in five patients. Other responses were confined to

Progress during FY-80: Sixty-nine patients have been entered onto this protocol from the entire GOG.

Technical Approach: (continued) non-gynecologic malignancies.

Number of subjects to be studied before completion of study: 25 patients in each categor
Serious/unexpected side effects in subjects participating in project: None. of disease

Conclusions: Maytansine is insignificant against squamous cell carcinoma of the cervix and epithelial tumors of the ovary. Other areas have yet to be evaluated.

Publications or Abstracts, FY-80: None.

| Date: 7 October 1980 | Protocol No: 4153 | Project: Inter'n XX Iject |
|---|---|---|

Title of Project: "A Phase II Trial of Baker's Antifol in Patients With Advanced Pelvic Malignancies." COG #26-F.

| Starting Date: 21 November 1978 | Estimated Completion Date: Unknown |
|---|---|

Principal Investigator: Robert C. Park, COL, MC, USA

| Associate Investigators: | Facility: | Walter Reed Army Medical Center, Ward 67, GYN Outpatient Clinic |
|---|---|---|
| Paul B. Heller, LTC, MC, USA<br>Terrel J. Michel, LTC, MC, USA | Dept/Svc | Department of OB-GYN, GYN Oncology Service |

Key Words: Phase II, Baker's antifol, advanced pelvic malignancy

| Accumulative MEDCASE Cost: None | Accumulative Contract Cost: None | Accumulative Supply Cost: None |
|---|---|---|

| FY-80 MEDCASE Cost: None | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective: To determine the efficacy of Baker's Antifol in patients whose advanced malignancies have been resistent to high priority methods of treatment. A rejection type of desigu will be used involving six sample size of 25 evaluable patients per disease site per drug.

Technical Approach: Baker's antifol, also known as triazinate, is an antagonist of folate metabolism which acts by blocking dihydrofolate reductase. This drug is believed to diffuse passively into the cells by active transport mechanism. The drug is able to penetrate the CNS in quantities reaching CNS levels of 1-5% of blood levels following IV administration. It is excreted mainly by the liver and much lesser extent by the kidney. Toxicities include myocutaneous and gastro intestinal effects. Moderate myelosuppression has been observed. Responses have

Progress during FY-80: Sixty-nine patients have been entered into this protocol from the entire COG.

Number of subjects to be studied before completion of study: 25 patients per disease site

Serious/unexpected side effects in subjects participating in project: Some Grade 3 mucocytis has been observed in two of the patients.

Conclusions: There is some limited activity noted in the sites studies. This drug is probably not as useful as more conventional drugs.

Publications or Abstracts, FY-80: None.

TECHNICAL APPROACH: been observed in adenocarcinoma in the lung, breast, and sarcomas, and acute myelogenous leukemia. Patients not eligible for higher priority studies who have advanced pelvic malignancies will be entered into this protocol when the drug is suggested by the COG office. The drug will be given as 500 mg/m$^2$ and 500 cc. of D-5 and normal saline as an infusion every 30-60 minutes. This drug will be repeated weekly as toxicity permits. The patient will be followed to progression of disease.

82

/

| Date: 7 October 1980 | Protocol No: 4154 | Status: Interim XX<br>Final |
|---|---|---|

Title of Project: "A Randomized Comparison of Cis-platinum, 50 mg/m$^2$ Every Three Weeks Versus Cis-platinum, 100 mg/m$^2$ Versus Cis-platinum, 20 mg/m$^2$/Day X Five in the Treatment of Patients With Advanced Carcinoma of the Cervix (Phase III)." GOG #43.

Starting Date: 9 February 1979 | Estimated Completion Date: 1984

Principal Investigator: Robert C. Park, COL, MC, USA

| Associate Investigators: | Facility: Walter Reed Army Medical Center, Ward 67, GYN Outpatient Clinic |
|---|---|
| Paul B. Heller, LTC, MC, USA<br>Terrel J. Michel, LTC, MC, USA | Dept/Svc: Department of OB-GYN, GYN Oncology Service |

Key Words: Cis-platinum in advanced carcinoma of cervix, Stage III

| Accumulative MEDCASE Cost: None | Accumulative Contract Cost: None | Accumulative Supply Cost: None |
|---|---|---|

| FY-80 MEDCASE Cost: None | Periodic Review Results: (to be filled in by DCI) |
|---|---|

*Study Objective: To confirm the effectiveness of Cis-platinum in advanced and recurrent squamous cell carcinoma of the cervix, no longer responding to radiation therapy or surgery. To compare the frequency and duration of response, and adverse effect of DDP therapy using three different doses and treatment schedules. To evaluate the roles of serial determination of serum carcinoembryonic antigen (CEA) levels and determining extent of disease, response of treatment, and in predicting treatment failure. To access re-treatment with Cis-platinum of patients

*Technical Approach: Patients who have histologically confirmed local, advanced, recurrent, persistent, or metastatic squamous cell carcinoma of the cervix which is resistent to curative treatment with surgery or radiotherapy are eligible. All patients must have lesions which are measurable or evaluable by a physical exam. For patients who are being re-treated with Cis-platinume, the patient must have a measurable recurrent or progressive disease noted during follow-up after completion of initial therapy. Patients must demonstrate a 50% or greater increase

*Progress during FY-80: Two hundred and sixty-one patients were entered to this protocol. One hundred and sixty-two patients were considered evaluable.

Number of subjects to be studied before completion of study: Approximately 135

Serious/unexpected side effects in subjects participating in project: None known.

Conclusions: There are no significant differences in response when three regimens are compared. The study is progressing satisfactorily and it is anticipated that additional patient entries will be acquired to meet the objectives of this study.

Publications or Abstracts, FY-80: None.

TECHNICAL APPROACH: of the tumor size over the size of completion of initial therapy. Patients must admit all previous Cis-platinum therapy for at least three weeks. These patients will be randomized depending upon treatment status to Regimen 1: 50 mg/m$^2$ IV every three weeks X eight courses. Regimen 2: 100 mg/m$^2$ IV every three weeks X four course. Regimen 3: 20 mg/m$^2$ IV for five days every three weeks X four courses. The patients will be followed up every four weeks after the courses are completed. If progression occurs, the patients will be re-treated until progression after the re-treatment begins.

| Date: 7 October 1980 | Protocol No: 4155 | Status: Interim XX<br>Final |
|---|---|---|

Title of Project: "Evaluation of Adjuvant Vincristine, Dactinomycin, and Cyclophosphamide Therapy in Malignant Germ Cell Tumors of the Ovary After Resection of all Gross Tumor (Phase III)." GOG #44.

| Starting Date: 9 February 1979 | Estimated Completion Date: 1982 |
|---|---|

Principal Investigator: Robert C. Park, COL, MC, USA

| Associate Investigators: | Facility: Walter Reed Army Medical Center, Ward 67, GYN Outpatient Clinic |
|---|---|
| Paul B. Heller, LTC, MC, USA<br>Terrel J. Michel, LTC, MC, USA | Dept/Svc: Department of OB-GYN, GYN Oncology Service |

Key Words: Vincristine, Actinomycin-D, Cyclophosphamide, germ cell tumors of ovary

| Accumulative MEDCASE Cost: None | Accumulative Contract Cost: None | Accumulative Supply Cost: None |
|---|---|---|

| FY-80 MEDCASE Cost: None | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective: To evaluate the effect of combined profilactic Vincristine, Dactinomycin and Cyclophosphamide (VAC) chemotherapy in patients with endodermal sinus tumor, embryonal carcinoma, immature teratoma (Grade 2 and 3), choriocarcinoma, and malignant mixed germ cell tumors of the ovary, Stages I and II after removal of all gross tumor. To evaluate the role of serum markers, especially alphafetoprotein (AFP) and human chorionic gonadotrophin (beta HCG) when these are present in predicting response and relapse. To

Technical Approach: Histologically confirmed malignant germ cell tumors of the ovary, Stages I or II, if previously untreated and completely resected, excluding patients with pure dysgerminoma are eligible. Patients with early Stage III disease will be accepted if all gross tumor is resected. After gross resection of all tumor, negative biopsy of omentum, negative peritoneal washings, patients will be placed on Vincristine, Actinomycin, and Cytoxan as described by protocol. At the end of 24 weeks of therapy, the patient will have a second-

Progress during FY-80: There have been 27 entries to this protocol. Of 10 patients who have had second-look operations, six were negative. All patients, whether negative or positive at second-look laparotomy are presently alive.

Number of subjects to be studied before completion of study: 15-20 per year.

Serious/unexpected side effects in subjects participating in project: There have been three Grade 3 WBC toxocities, three Grade 3 GI toxicities, and nine Grade 3 neurologic toxicities.

Conclusions: It is too early for any conclusions.

Publications or Abstracts, FY-80: None.

STUDY OBJECTIVE: determine the role of re-staging laparotomy in determining response, predicting relapse, and planning further therapy.

TECHNICAL APPROACH: look laparotomy performed. If there is no evidence of disease, the patient will have three more cycles of VAC. If no progression, VAC will be stopped. If progression, the patient will be entered in a protocol for recurrent disease. If at re-staging laparotomy the recurrence is noted, the patient will be entered in a protocol for recurrent disease.

4

Title of Project: "Evaluation of Vinblastine, Bleomycin, and Cis-platinum in Stage III and IV and Recurrent Malignant Germ Cell Tumors of the Ovary (Phase III)." GOG #45.

Fiscal

Starting Date: 29 June 1979 | Estimated Completion Date: July 1982

Principal Investigator: Robert C. Park, COL, MC, USA

Associate Investigators:

Paul B. Heller, LTC, MC, USA
Terrel J. Michel, LTC, MC, USA

Facility: Walter Reed Army Medical Center, Ward 67, GYN Outpatient Clinic

Dept/Svc: Department of OB-GYN, GYN Oncology Service

Key Words: Advanced germ cell tumors of the ovary treated with Vinblastine, Bleomycin, and Cis-platinum

| Accumulative MEDCASE Cost: None | Accumulative Contract Cost: None | Accumulative Supply Cost: None |
|---|---|---|

FY-80 MEDCASE Cost: None

Periodic Review Results: (to be filled in by DCI)

Study Objective: To evaluate the effect of four cycles of combined Vinblastine, Bleomycin, and Cis-platinum (VBP) chemotherapy in the management of patients with endodermal sinus tumor, embryonal carcinoma, immature teratoma (all grades), choriocarcinoma, and malignant mixed germ cell tumors of the ovary with advanced or recurrent disease, incompletely resected. To evaluate the role of serum markers, especially alphafetoprotein and human chorionic gonadotrophin when these are present in predicting response and relapse. To determine the role

Technical Approach: Histologically confirmed malignant germ cell tumors of the ovary with advanced (Stage III or IV) or recurrent disease, incompletely resected, excluding patients with pure dysgerminoma (mature anaplastic) are eligible. Patients with incompletely resected Stage II disease are eligible. Patients previously treated with VAC are eligible. After the surgery, the patients are placed upon four course of Velban, Bleomycin, and Cis-platinum. With progression of the disease, the patients are switched to 12 cycles of

Progress during FY-80: There have been 21 patients entered to this protocol from the entire GOG.

Number of subjects to be studied before completion of study: Approximately 15 per year.

Serious/unexpected side effects in subjects participating in project: There has been one Grade 4 WBC toxicity, six Grade 3 WBC toxicities, and three Grade 3 GI toxicities.

Conclusions: As expected, toxicities are considered manageable. Early results are encouraging.

Publications or Abstracts, FY-80: None.

STUDY OBJECTIVE: of re-staging laparotomy in patients in clinical remission in assessing completeness of response and then planning further therapy. To evaluate and compare the effect of Vincristine, Dactinomycin, and Cyclophosphamide (VAC) chemotherapy in patients found to have persistent disease at the time of re-staging laparotomy. To determine the need for maintenance Vinblastine therapy in patients found free of disease at re-staging laparotomy.

TECHNICAL APPROACH: Vincristine, Actinomycin-D, and Cytoxan. With complete or partial response, the patient will have a re-staging laparotomy. If there is no evidence of disease, the patient will be placed on Vinblastine for 18 months. If there is persistence of the disease, the patient will be placed on Vincristine, Actinomycin-D, and Cytoxan.

| Date: 26 Nov 80 | Protocol No: 4157 | Status: Interim X<br>Final |
|---|---|---|

Title of Project:

Prophylactic Antibiotics in Abdominal Hysterectomy

| Starting Date: Apr 79 | Estimated Completion Date: Mar 80 |
|---|---|

Principal Investigator: Patrick Duff, M.D., LTC, MC

| Associate Investigators:<br>None | Facility: WRAMC<br>Dept/Svc OB-GYN |
|---|---|

Key Words:
Antibiotic Prophylaxis

| Accumulative MEDCASE Cost: None | Accumulative Contract Cost: None | Accumulative Supply Cost: None to date |
|---|---|---|

| FY-80 MEDCASE Cost: | Periodic Review Results:<br>(to be filled in by DCI) |
|---|---|

*Study Objective:

The objective of the study is to determine whether prophylactic antibiotics can reduce the incidence of operative site infection following abdominal hysterectomy.

*Technical Approach:

The study design is outlined in the complete protocol on file with CIS., Prospective, randomized, double-blinded.

*Progress during FY-80: 85 patients have been enrolled in the study to date.

Number of subjects to be studied before completion of study: 100

Serious/unexpected side effects in subjects participating in project:
No adverse reactions to administration of Cefoxitin

Conclusions:
Data not yet analyzed.

Funds utilized, FY-80: None

Publications or Abstracts, FY-80: None to date

| Date: 26 Nov 80 | Protocol No: 4158 | Status: Interim / Final XX |
|---|---|---|

Title of Project:

Antibiotic Prophylaxis in Low Risk Cesarean Section

| Starting Date: Apr 79 | Estimated Completion Date: Jun 80 |
|---|---|

Principal Investigator: LTC Patrick Duff, MC

| Associate Investigators:<br>CPT Paul N. Smith<br>John Keiser<br>Susan Strong | Facility: WRAMC<br><br>Dept/Svc OB-GYN |
|---|---|

Key Words:
Antibiotic Prophylaxis in Cesarean Section

| Accumulative MEDCASE Cost: None | Accumulative Contract Cost: None | Accumulative Supply Cost: $450.00 |
|---|---|---|

| FY-80 MEDCASE Cost: None | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective:

Please see attached manuscript

Technical Approach:

Progress during FY-80: Investigation Completed

Number of subjects to be studied before completion of study: 82

Serious/unexpected side effects in subjects participating in project: NONE

Conclusions:

Manuscript has been written.

Work Unit No.: 4158

Funds Utilized, FY-80: $450.00

Funding Requirements, FY-81: None

| Date: 7 October 1980 | Protocol No: 4159 | Status: Interim XX<br>Final |
|---|---|---|

Title of Project: "Treatment of Recurrent or Advanced Uterine Sarcoma. A Randomized Comparison of Adriamycin Versus Adriamycin and Cyclophosphamide (Phase III)." GOG #42.

| Starting Date: 6 April 1979 | Estimated Completion Date: Unknown |
|---|---|

Principal Investigator: Robert C. Park, COL, MC, USA

| Associate Investigators: | Facility: Walter Reed Army Medical Center; Ward 67, GYN Outpatient Clinic |
|---|---|
| Paul B. Heller, LTC, MC, USA<br>Terrel J. Michel, LTC, MC, USA | Dept/Svc: Department of OB-GYN, GYN Oncology Service |

Key Words: Chemotherapy for recurrent or advanced uterine sarcoma.

| Accumulative MEDCASE Cost: None | Accumulative Contract Cost: None | Accumulative Supply Cost: None |
|---|---|---|

| FY-80 MEDCASE Cost: None | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective: To determine if Adriamycin alone is more effective than Adriamycin and Cyclophosphamide in producing reponses in advanced or recurrent uterine sarcoma. The second objective is to determine if the duration of response for each treatment arm is different.

Technical Approach: Patients with primary Stage III, primary Stage IV, or recurrent uterine sarcoma are eligible. Both patients with non-measurable and measurable disease are eligible but they may be analyzed separately. Patients with all cell types of uterine sarcoma are eligible. Patients previously treated with radiotherapy to the pelvic bed are eligible but they must have completed this radiation more than three months prior to entry on this study. The patients will have an exploratory laparotomy, TAH/BSO, omentectomy if feasible. The patient

Progress during FY-80: A total of 56 patients have been entered into this protocol.

Number of subjects to be studied before completion of study: 75 patients

Serious/unexpected side effects in subjects participating in project: There have been none.

Conclusions: Regimens are well tolerated by patients entered. There is not enough accrual at this point to draw any permanent conclusions. To date there have been no complete responses. There has been one partial response and several progressions.

Publications or Abstracts, FY-80: None.

TECHNICAL APPROACH: will then either have radiation or not. After that, they will be stratified by regimen 1 to receive Adriamycin, 60 mg/m$^2$ IV every three weeks, or regimen 2 to receive Adriamycin, 60 mg/m$^2$ IV plus Cyclophosphamide, 500 mg/m$^2$ IV, both every three weeks.

| Date: 7 October 1980 | Protocol No: 4160 | Status: Interim xx<br>Final |
|---|---|---|

Title of Project: "A Clinical Pathologic Study of Stage I and II Uterine Sarcomas." GOG #40.

Starting Date: 6 August 1979 | Estimated Completion Date: Unknown

Principal Investigator: Robert C. Park, COL, MC, USA

| Associate Investigators: | Facility: Walter Reed Army Medical Center, Ward 67, GYN Outpatient Clinic |
|---|---|
| Paul B. Heller, LTC, MC, USA<br>Terrel J. Michel, LTC, MC, USA | Dept/Svc: Department of OB-GYN, GYN Oncology Service |

Key Words: Clinical pathologic study, Stage I and II, uterine sarcoma

| Accumulative MEDCASE Cost: None | Accumulative Contract Cost: None | Accumulative Supply Cost: None |
|---|---|---|
| FY-80 MEDCASE Cost: None | Periodic Review Results: (to be filled in by DCI) | |

Study Objective: The purpose of this study is to determine the incidence of pelvic and aortic lymph node metastasis associated with Stage I and II uterine sarcomas. The relationship of these node metastasis to other important prognostic factors such as mytotic indexes, tumor, and the complication rate of the procedures.

Technical Approach: All patients with histologically proven uterine sarcoma, clinical Stage I and II who are medically suitable for hysterectomy and lymphadenectomy are eligible for this study. All patients will undergo, at a minimum, a simple extrafacial abdominal hysterectomy, bilateral salpingo-oophorectomy, selective pelvic and para-aortic lymphadenectomy. Peritoneal cytology will be obtained. Omental biopsy is recommended as an optional procedure. All histologic types of uterine sarcomas are acceptable.

Progress during FY-80: Fifty-five patients have been entered into the protocol to the entire GOG.

Number of subjects to be studied before completion of study: Unknown.

Serious/unexpected side effects in subjects participating in project: None

Conclusions: There are no conclusions at this time.

Publications or Abstracts, FY-80: None.

Report Control XX
Final

Title of Project: "Surgical Staging of Ovarian Carcinoma." GOG #41.

Starting Date: 6 April 1979 Estimated Completion Date: Unknown

Principal Investigator: Robert C. Park, COL, MC, USA

Associate Investigators:
Paul B. Heller, LTC, MC, USA
Terrel J. Michel, LTC, MC, USA

Facility: Walter Reed Army Medical Center, Ward, 67, GYN Outpatient Clinic

Dept/Svc: Department of OB-GYN, GYN Oncology Service

Key Words: Surgical staging, ovarian carcinoma

| Accumulative MEDCASE Cost: None | Accumulative Contract Cost: None | Accumulative Supply Cost: None |
|---|---|---|
| FY-80 MEDCASE Cost: None | Periodic Review Results: (to be filled in by DCI) | |

Study Objective: To determine the spread of ovarian carcinoma to intraperitoneal structures and retroperitoneal lymph nodes by direct examination, cytologic sampling, and biopsy. To establish a surgical protocol for patients entered into Gynecologic Oncology Group ovarian cancer treatment protocols. To determine the complication rate of procedures outlined.

Technical Approach: All patients explored in the investigator's institution and found to have Stages I, II or III (optimal) ovarian carcinoma are eligible. All histologic types of ovarian carcinoma and differentiation are acceptable for entry into this protocol. Patients whose procedures were performed at referral institutions are eligible for entry provided that the eligibility criteria are met. Patients with all histologic types of primary ovarian cancer are eligible including epithelial tumors, germ cell tumors, stromal tumors, and

Progress during FY-80: Fifty-seven entries have been made from the entire GOG into this protocol. No analysis has been made of this data yet.

Number of subjects to be studied before completion of study: unknown

Serious/unexpected side effects in subjects participating in project: None of note.

Conclusions: None.

Publications or Abstracts, FY-80: None.

TECHNICAL APPROACH: all others. Tumors metastatic to the ovary are not eligible for inclusion. A total abdominal hysterectomy, bilateral salpingo-oophorectomy, except in young patients with a unilateral disease, are performed. Selective pelvic and para-aortic lymphadenectomy are performed. Omental biopsy and peritoneal cytology sampling in addition are performed. The diaphragm is examined and a Pap smear and biopsy are performed in this area. The patient then would be entered into an appropriate treatment protocol and followed for five years.

| Date: 7 October 1980 | Protocol No: 4162 | Status: Interim XX Final |
|---|---|---|

Title of Project: "A Randomized Comparison of Melphalan Versus Intraperitoneal Chromic Phosphate in the Treatment of Women with Stage I (Exclusive of Stage IAi, G1; and IBi, G1) Epithelial Carcinoma of the Ovary (Phase III)." GOG #46.

| Starting Date: 21 August 1979 | Estimated Completion Date: December 1983 |
|---|---|

Principal Investigator: Robert C. Park, COL, MC, USA

| Associate Investigators: | Facility: Walter Reed Army Medical Center Ward 67, GYN Outpatient Clinic |
|---|---|
| Paul B. Heller, LTC, MC, USA<br>Terrel J. Michel, LTC, MC, USA | Dept/Svc: Department of OB-GYN, GYN Oncology Service |

Key Words: Melphalan, ICP-32, epithelial carcinoma of ovary

| Accumulative MEDCASE Cost: None | Accumulative Contract Cost: None | Accumulative Supply Cost: None |
|---|---|---|

| FY-80 MEDCASE Cost: None | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective: The purpose of this study is to evaluate the relative effectiveness of Melphalan versus peritoneal radioactive chromic phosphate as adjuvant therapy in Stage I, exclusive of IAi, G1 and IBi, G1 epithelial cancers of the ovary in a randomized prospective study. Patients who are eligible are those with surgical Stage IAi, G2, G3; IAii; IBi, G2, G3; IBii; and IC epithelial cancer of the ovary, FIGO classification, who have undergone optimal staging. The surgery performed will be total abdominal hysterectomy, bilateral salpingo-oophorectomy, partial

Technical Approach: Patients with Stage IAi, G2, G3; IAii; IBi, G2, G3; or IBii or IC epithelial cancer of the ovary are eligible for this protocol and those who have undergone optimal staging.

Progress during FY-80: Six patients have been entered into this protocol. It is too early to analyze this protocol.

Number of subjects to be studied before completion of study: 93 to each treatment arm.
Serious/unexpected side effects in subjects participating in project: None.

Conclusions: It is too early to form any conclusions.

Publications or Abstracts, FY-80: None.

STUDY OBJECTIVE: omentectomy, and staging examination. These patients will then be randomized to either Regimen 1: Melphalan, 7 mg/m$^2$/day X five days every four weeks for 10 course or 18 months. Or Regimen 2: chromic phosphate 15 millicuries intraperitoneally as a single dose.

Date: 7 October 1980 | Protocol No: 4163 | Status: Interim XX / Final

Title of Project: "A Phase II Trial of Cis-Platinum in the Treatment of Advanced Gynecologic Cancer." GOG #26-C.

Starting Date: 6 April 1979 | Estimated Completion Date: Unknown

Principal Investigator: Robert C. Park, COL, MC, USA

Associate Investigators:

Paul B. Heller, LTC, MC, USA
Terrel J. Michel, LTC, MC, USA

Facility: WalterReed Army Medical Center, Ward 67, GYN Outpatient Clinic

Dept/Svc: Department of OB-GYN, GYN Oncology Service

Key Words: Phase II, Cis-platinum, advanced gynecologic malignancy

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: |
|---|---|---|
| None | None | None |

FY-80 MEDCASE Cost: None

Periodic Review Results: (to be filled in by DCI)

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 a fixed sample size of 25 evaluable patients per disease site per drug or a combination of drugs studies. 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. Cis-platinum has demonstrated activity in animals studies against transitional cell carcinoma in mice. Toxicity trials in animals reveals myelosuppression, lymphoid atrophy, hemorrhagic introcolitis, renal tubular necrosis, and cochlear damage, as well as some degree of immunosuppression. Reports have been made on Phase 1 and broad Phase II studies with this agent. Responses have been noted in testicular tumors including germ cell tumors. Ovarian carcinoma, bladder carcinoma, squamous cell carcinoma of the head and neck, and squamous cell carcinoma of the cervix. Patients with histologically confirmed gynecologic cancer, either recurrent or advanced, on initial presentation are eligible. Cis-platinum will be given as 50 mg/m$^2$ IV every three weeks. Hydration will be given at each course. Once enough patients in any disease category have been treated with Cis-platinum, the entire group will move on to the next drug recommended in this GOG protocol.

Progress during FY-80: Two hundred and one patients have been accessed to this protocol. Combinations of Cis-platinum and other regimens will be tested in future trials. Tumor categories, except epithelial ovarian carcinoma and squamous cell carcinoma of the cervix continue to accrue cases for consideration.

Number of subjects to be studied before completion of study: 25 cases per disease site.

Serious/unexpected side effects in subjects participating in project: There have been some Grade 3 GI toxicity and some Grade 3 hypokalemia noted.

Conclusions: Cis-platinum has marked activity as a first-line chemotherapeutic in squamous cell carcinoma of the cervix and is active as a second-line therapy for advanced adenocarcinoma of the ovary. The drug appears to be active against endometrial carcinoma but may have limited activity in therapy of sarcomas and cervical adenocarcinoma.

Publications or Abstracts, FY-80:

None.

| Date: 7 October 1980 | Protocol No. 4165 | Grade: Inter n. XX<br>Fac: |
|---|---|---|

Title of Project: "A Phase II Trial of AMSA in Patients With Advanced Pelvic Malignancies." GOG #26-I.

Started: 21 August 1979 | Completion Date: Unknown

Principal Investigator: Robert C. Park, COL, MC, USA

| Associate Investigators: | Facility: | Walter Reed Army Medical Center, Ward 67, GYN Outpatient Clinic |
|---|---|---|
| Paul B. Heller, LTC, MC, USA<br>Terrel J. Michel, LTC, MC, USA | Dept/Svc | Department of OB-GYN, GYN Oncology Service |

Key Words: Phase II, AMSA, advanced pelvic malignancies

| Accumulative MEDCASE Cost: None | Accumulative Contract Cost: None | Accumulative Supply Cost: None |
|---|---|---|
| FY-80 MEDCASE Cost: None | Periodic Review Records: (to be filled in by DCI) | |

Study Objective: To determine the efficacy of AMSA in patients whose advanced malignancies have been resistent to high priority methods of treatment. A rejection type design will be used involving a fixed sample size of 25 evaluable patients per disease site per drug.

Technical Approach: AMSA is acridine derivitive with significant activity in several animal tumors. The drug inhibits DNA synthesis but has little effect upon RNA synthesis. It binds the DNA through intercalation and external binding. It has particular affinity for adenine-thyamine pairs. In a Phase I trial responders were observed in a case of lymphangiosarcoma and in a case of ovarian carcinoma. AMSA is attractive because its activity is about the same as Adriamycin but is has less larger producing effects. The drug is to be administered

Progress during FY-80: There have been a total of 11 entries to this protocol.

Number of subjects to be studied before completion of study: 25 patients per disease

Serious/unexpected side effects in subjects participating in project: Essentially none.

Conclusions: It is too early for any definitive conclusions.

Publications or Abstracts, FY-80: None.

TECHNICAL APPROACH: as a dose of 120 mg/m$^2$ intravenously, repeated every four weeks as toxicity permits. Patients who have received pelvic and/or abdominal radiation previously will get 90 mg/m$^2$ at the same interval.

| Date: 7 October 1980 | Protocol No: 4166 | Status: Interim XX / Final |
|---|---|---|

Title of Project: "A Phase II Trial of Yoshi-864 in Patients With Advanced Pelvic Malignancies." COG # 26-J.

| Starting Date: 21 August 1979 | Estimated Completion Date: Unknown |
|---|---|

Principal Investigator: Robert C. Park, COL, MC, USA

| Associate Investigators: | Facility: Walter Reed Army Medical Center, Ward 67, GYN Outpatient Clinic |
|---|---|
| Paul B. Heller, LTC, MC, USA<br>Terrel J. Michel, LTC, MC, USA | Dept/Svc: Department of OB-GYN, GYN Oncology Service |

Key Words: Phase II, Yoshi-864, advanced pelvic malignancy

| Accumulative MEDCASE Cost: None | Accumulative Contract Cost: None | Accumulative Supply Cost: None |
|---|---|---|

| FY-80 MEDCASE Cost: None | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective: To determine the efficacy of Yoshi-864 in patients whose advanced malignancies have been resistent to high priority methods of treatment. A rejection type design will be used involving a fixed sample size of 25 evaluable patients per disease site per drug.

Technical Approach: Yoshi-864 is a sulfonic acid estor of aminoglycol synthesized by EL-merzabinisakurai as an alkylating agent active against experimental tumors resistent to nitrogen mustard derivitives. Structurally it is similar to busulfan but it is active against the L1210 system in mice where busulfan is not active. Exact mechanism of action has bet been elucidated. It may have alkylating activity. The drug shows no cross resistance to natural-occurring alkylating agent-resistent animal tumors. First clinical studies with Yoshi-864 were conducted in Japan

Progress during FY-80: There have been six entries to this protocol.

Number of subjects to be studied before completion of study: 25 per disease site.

Serious/unexpected side effects in subjects participating in project: None.

Conclusions: It is too early to draw any conclusions.

Publications or Abstracts, FY-80: None.

TECHNICAL APPROACH: with encouraging results in chronic myelogenous leukemias at doses of 5-100 mg/ per day. In a COG study, there have been six partial responses reported in 16 patients with ovarian cancer. Patients who have histologically confirmed advanced recurrent resistent metastatic or local gynecologic cancer with documented disease progression are eligible for this study. Yoshi-864 will be administered at 2.0 mg/kg/day for 5 days intravenously and repeated every six weeks as toxicity permits.

| Date: 7 October 1980 | Protocol No: 4167 | Status: Interim XX<br>Final |
|---|---|---|

Title of Project: "A Phase II Randomized Study of Adriamycin Plus Cyclophosphamide Versus Adriamycin Plus Cyclophosphamide Plus Cis-platinum in Patients with Advanced Ovarian Adenocarcinoma, Suboptimal Stage III, Stage IV, and Recurrent." COG #47.

Project Date: 21 August 1979 Estimated Completion Date: 1982

Principal Investigator: Robert C. Park, COL, MC, USA

| Associate Investigators: | Facility: | Walter Reed Army Medical Center, Ward 67, GYN Outpatient Clinic |
|---|---|---|
| Paul B. Heller, LTC, MC, USA<br>Terrel J. Michel, LTC, MC, USA | Dept/Svc | Department of OB-GYN, GYN Oncology Service |

Key Words: Adriamycin, Cytoxan, Cis-platinum treatment in advanced adenocarcinoma of the ovary.

| Accumulative MEDCASE Cost: None | Accumulative Contract Cost: None | Accumulative Supply Cost: None |
|---|---|---|

| FY-80 MEDCASE Cost: None | Periodic Review Results:<br>(to be filled in by DCI) |
|---|---|

Study Objective: To determine if the addition of Cis-platinum to Adriamycin, plus Cyclophosphamide improves remission rate, remission duration, or survival in Stage IV, suboptimal Stage III, and recurrent ovarian adenocarcinoma. To determine the frequency and duration of true complete remission using these regimens as judged at a second-look laparotomy.

Technical Approach: Patients who have been diagnosed as Stage IV and suboptimal Stage III primary cases or recurrent cases are eligible. Suboptimal Stage III is defined as those Stage III patients with at least one residual lesion at the time of surgery equal to or greater than 3 cm. in the largest diameter in the abdomen or pelvis. Histologic types eligible are serous adenocarcinoma, mucinous adenocarcinoma, clear cell adenocarcinoma, endometroid adenocarcinoma, undifferentiated carcinoma, or mixed epithelial carcinoma. Patients with measurable

Progress during FY-80: Two hundred and eight patients have been entered into this study.

Number of subjects to be studied before completion of study: 400

Serious/unexpected side effects in subjects participating in project: Renal toxicity was was observed in 42.6 patients in cases who received Cis-platinum; all were mild toxicities except for one case. Fourteen WBC and 3 platelet toxicities of severe grade

Conclusions: None.

Publications or Abstracts, FY-80: None.

TECHNICAL APPROACH: disease and patients without measurable disease is a separate category and will be evaluated. The patients will be stratified by performance and measurable versus non-measurable disease entered into the protocol and then randomized to Regimen 1: including Adriamycin, 50 mg/m$^2$ IV, Cyclophosphamide, 500 mg/m$^2$ IV every two weeks for eight courses versus Regimen 2: Adriamycin, 50 mg/m$^2$, Cyclophosphamide, 500 mg/m$^2$, and Cis-platinum, 50 mg/m$^2$, all given IV every three weeks for eight courses. After these course, a second-look laparotomy will be performed. Patients with complete response will be maintained on Cyclophosphamide, 500 mg/m$^2$ every three weeks for an addition of 12 months. Patients with partial response or stable disease will be taken off the study.

| Date: 26 Nov 80 | Protocol No: 4168 | Status: Interim X<br>Final |
|---|---|---|

Title of Project:

Comparison of Two Antibiotic Regimens for the Treatment of Soft Tissue Pelvic Infections

| Starting Date: Apr 79 | Estimated Completion Date: Apr 80 |
|---|---|

Principal Investigator: Patrick Duff, M.D., LTC, MC

| Associate Investigators: None | Facility: WRAMC |
|---|---|
| | Dept/Svc OB-GYN |

Key Words: Antibiotic Treatment of Pelvic Infections

| Accumulative MEDCASE Cost: None | Accumulative Contract Cost: None | Accumulative Supply Cost: None to Date |
|---|---|---|

| FY-80 MEDCASE Cost: None | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective:

The purpose of the study is to compare the efficacy of Cefoxitin versus the combination of Penicillin and Gentamicin for treating a variety of pelvic infections.

Technical Approach:

The entire treatment protocol is on file with CIS.

Progress during FY-80: 75 patients have been enrolled in the study to date.

Number of subjects to be studied before completion of study: 100

Serious/unexpected side effects in subjects participating in project:

Conclusions: At the present time, there is no statistically significant difference between the two regimens.

Publications or Abstracts, FY-80: None to date

Work Unit No.: 4168

Funds Utilized, FY-80: None

Funding Requirements, FY-81:

Personnel: (name and grade)

Equipment: (describe in detail including cost)

Supplies: (consumable, animal purchase)

Travel: (mission oriented, training and presentation) $500

Other: (equipment rentals, contracts for service, animal care and reprints)

| Date: 17 October 1980 | Protocol No: 4169 | Status: Interim X<br>Final |
|---|---|---|

Title of Project:

Effectiveness of Heat Lamps and Surgigators in Promoting Comfort and Healing of Median Episiotomies.

| Starting Date: Oct 1979 | Estimated Completion Date: Dec 1980 |
|---|---|

Principal Investigator: MAJ Clifford Simons, ANC

| Associate Investigators: | Facility: WRAMC, Units 43,44 |
|---|---|
| LTC Reuben B. Bowie, ANC<br>CPT Marcia Kossman, ANC | Dept/Svc Nursing Research Service |

Key Words:
Median Episiotomies, Healing

| Accumulative MEDCASE Cost: 0 | Accumulative Contract Cost: 0 | Accumulative Supply Cost: 0 |
|---|---|---|

| FY-80 MEDCASE Cost: 0 | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective:
To determine whether there is any difference in the rate of healing and/or the patient's expression of comfort depending upon the post episiotomy care regime used.

Technical Approach:

No change from protocol submitted.

Progress during FY-80:

88 subjects accured.

Number of subjects to be studied before completion of study: ~~100 were desired~~

Serious/unexpected side effects in subjects participating in project:

None

Conclusions:
None at this time. Data analysis is being conducted.

# DISPOSITION FORM

For use of this form, see AR 340-15; the proponent agency is The Adjutant General's Office.

| REFERENCE OR OFFICE SYMBOL | SUBJECT |
|---|---|
| HSWP-NR | Response to reviewer comments on FY 80 ADR for work Unit # 4169 |

| TO | FROM | DATE | CMT 1 |
|---|---|---|---|
| C, Dept Clin Invest | C, Nsg Rsh Svc | 8 Dec 1980<br>MAJ Southby/ab/2026 | |

1. It is understood that no money was spent on this work unit in FY80.

2. The original budget request of $800 ($300 for data analysis and $500 for presentation and reprints) was insufficient considering current costs.

3. The funding request for FY81 added the following to the original budget request:

   a. $100 for consumable supplies
   b. $150 for reprints (Reprints may be a separate charge for example $200 for Milt Med).
   c. $500 for travel for an additional investigator (3 people are conducting the study).

4. This request is $750 above the orginal amount requested.

Janet R. Southby

JANET R. SOUTHBY
MAJ(P), ANC
C, Nursing Research Service
WRAMC

DA FORM 1 FEB 62 2496 REPLACES DD FORM 96, EXISTING STOCKS OF WHICH WILL BE ISSUED AND USED UNTIL 1 FEB 63 UNLESS SOONER EXHAUSTED.

☆ U.S. GPO: 1971—853-13/8059

# CLINICAL INVESTIGATION PROGRAM

| | |
|---|---|
| ORK UNIT NO.: 4169 | TITLE: Effectiveness of Heat Lamps and Surgigators in Promoting Comfort and Healing of Median Episiotomies. |
| | PRINCIPAL INVESTIGATOR: MAJ Clifford M.B. Simons |
| | Co-investigators: MAJ Bowie, CPT Kossman |

| MENT OF NSE | | FY 81 | FY 82 | REMARKS |
|---|---|---|---|---|
| - 1200 | Personnel: | | | |
| 00 | Travel: | | | |
| | Mission | | | |
| | Conference | 1000.00 | | 2 persons |
| | Patient | | | |
| 19 | Rental Equip: | | | |
| 00 | Printing and Reproduction: | 150.00 | | |
| 72 | Contractual Svc Lab Contracts: | | | |
| 00 | Consumable Supplies and Experimental Animals | 100.00 | | |
| ng: | Data Analysis | 300.00 | | |
| al: | | 1550.00 | | |
| Requirement Ranks | | No | No | WORK UNITS: |

| Date: 7 October 1980 | Protocol No: 4170 | Status: Interim XX<br>Final |
|---|---|---|

Title of Project: "A Phase II Trial of Chlorozotocin in Patients with Advanced Pelvic Malignancies." GOG #26-K.

| Starting Date: | Estimated Completion Date: Unknown |
|---|---|

Principal Investigator: Robert C. Park, COL, MC, USA

| Associate Investigators: | Facility: Walter Reed Army Medical Center, Ward 67, GYN Outpatient Clinic |
|---|---|
| Paul B. Heller, LTC, MC, USA<br>Terrel J. Michel, LTC, MC, USA | Dept/Svc: Department of OB-GYN, GYN Oncology Service |

Key Words: Phase II Chlorozotocin, advanced pelvic malignancies.

| Accumulative MEDCASE Cost: None | Accumulative Contract Cost: None | Accumulative Supply Cost: None |
|---|---|---|

| FY-80 MEDCASE Cost: None | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective:

Technical Approach:

Progress during FY-80: To date, no patients have been placed in this protocol from the entire GOG.

Number of subjects to be studied before completion of study:

Serious/unexpected side effects in subjects participating in project:

Conclusions:

Publications or Abstracts, FY-80:

Date: 7 October 1980 Protocol No. 4171 Status: Interim X
Final

Title of Project: "A study of Progestin Therapy in a Randomized Comparison of Adriamycin Versus Adriamycin Plus Cyclophosphamide in Patients with Advanced Endometrial Carcinoma After Hormonal Failure." GOG #48.

Starting Date: 10 July 1980 Estimated Completion Date: 1983

Principal Investigator: Robert C. Park, COL, MC, USA

Associate Investigators:
Paul B. Heller, LTC, MC, USA
Terrel J. Michel, LTC, MC, USA

Facility: Walter Reed Army Medical Center, Ward 67, GYN Outpatient Clinic

Dept/Svc: Department of OB-GYN, GYN Oncology Service

Key Words: Advanced endometrial carcinoma, hormonal failure, Adriamycin, Cytoxan.

| Accumulative MEDCASE Cost: None | Accumulative Contract Cost: None | Accumulative Supply Cost: None |
|---|---|---|

FY-80 MEDCASE Cost: None

Periodic Review Results: (to be filled in by DCI)

Study Objective: To evaluate the response of advanced or recurrent endometrial carcinoma to oral progestins in patients who have received no prior hormonal therapy. To compare a combination of Adriamycin, and Cyclophosphamide or Adriamycin alone as therapy for advanced or recurrent endometrial carcinoma which no longer responds to or has failed to respond to progestins in patients who have received no prior cytotoxic drugs. Confirmation of the report at 37% response rate of advanced or recurrent endometrial carcinoma to Adriamycin.

Technical Approach: Patients must have documented primary Stage III, primary Stage IV recurrent or residual endometrial adenocarcinoma, adenocanthoma, or adenosquamous carcinoma. Those patients with positive cytology as evidence of spread are eligible as non-measurable disease cases. Those patients with prior hormonal therapy will be entered directly. Those patients with no prior hormonal therapy will receive Provera, 50 mg t.i.d. until progression of disease. Patients then must be off therapy for three weeks. They will then be randomized to

Progress during FY-80: There have been 39 entries to this protocol.

Number of subjects to be studied before completion of study: 100 per year

Serious/unexpected side effects in subjects participating in project: None of note.

Conclusions: It is too early for conclusions.

Publications or Abstracts, FY-80: None.

STUDY OBJECTIVE: Confirmation of survival benefits responders to cytotoxic drugs.

TECHNICAL APPROACH: Regimen 1: Adriamycin, 60 mg/m$^2$ IV every three weeks for eight courses or Regimen 2: Adriamycin, 60 mg/m$^2$ IV every three weeks for eight courses plus Cyclophosphamide, 500 mg/m$^2$ IV every three weeks for eight courses. Responders will be followed up at the completion of therapy. Patients with progression will be placed on another protocol.

| Date: 18 SEPT 80 | Protocol No: 4514 | Status: Interim X<br>Final |
|---|---|---|

Title of Project: Clinical Evaluation of Indium 111 DTPA

| Starting Date: 25 JUN 74 | Estimated Completion Date: Indeterminate |
|---|---|

Principal Investigator: DOUGLAS VAN NOSTRAND, M.D., MAJ, MC

| Associate Investigators: | Facility: Walter Reed Army Medical Center |
|---|---|
| Asaf Durakovic, M.D., MAJ, MC<br>James Corley, MAJ, MSC<br>Richard Stotler, MAJ, MSC | Dept/Svc Nuclear Medicine Service |

Key Words:

| Accumulative MEDCASE Cost: NONE | Accumulative Contract Cost: NONE | Accumulative Supply Cost: NONE |
|---|---|---|

| FY-80 MEDCASE Cost: NONE | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective: The purpose of this study is to evaluate the efficacy and safety of the radiopharmaceutical Indium 111 DTPA in the evaluation of cerebral spinal fluid flow.

Technical Approach: No modifications have been made to the original protocol.

Progress during FY-80: During the period of 1 October 1979 through 18 September 1980, a total of 14 patients were studied.

Number of subjects to be studied before completion of study: 40

Serious/unexpected side effects in subjects participating in project:

(See attached sheet)

Conclusions: (See attached sheet.)

# DISPOSITION FORM

For use of this form, see AR 340-15, the proponent agency is TAGCEN.

| REFERENCE OR OFFICE SYMBOL | SUBJECT |
|---|---|
| HSWP-XN | Annual Progress Report - Work Unit #4514 |

TO Clinical Investigation, WRAMC

FROM C, Nuclear Medicine Svc., WRAMC

DATE 5 DEC 80

CMT 1

MAJ Van Nostrand/msm/61186

1. No other conclusions can be obtained from the 14 patients who have been studied to date.

2. It is important to emphasize that the purpose of this protocol is two fold. (a) A protocol must be in effect in order for Walter Reed Army Medical Center to obtain FDA Phase III IND radiopharmaceuticals. (b) The objective of the Phase III study is for evaluation of the safety of the radiopharmaceutical Indium 111 DTPA as noted in the Annual Progress Report.

DOUGLAS VAN NOSTRAND, M.D.
MAJ, MC
C, NUCLEAR MEDICINE SERVICE

DA FORM 2496 REPLACES DD FORM 96, WHICH IS OBSOLETE.

# DISPOSITION FORM

For use of this form, see AR 340-15, the proponent agency is TAGCEN.

| REFERENCE OR OFFICE SYMBOL | SUBJECT |
|---|---|
| HSWP-XN | REQUEST FOR EXTENSION OF PROTOCOL #4514 |

TO CLINICAL INVESTIGATION COMM. WRAMC
FROM C, NUCLEAR MEDICINE SVC. WRAMC
DATE 18 SEPT 80
CMT 1
msm/61186

1. TITLE OF PROJECT: Clinical Evaluation of Indium 111 DTPA.

2. INVESTIGATORS: Douglas Van Nostrand, M.D., MAJ, MC

3. STATUS: The present protocol is subject to termination on 30 September 1980 since it has been in effect for three years. This request is to continue this protocol for an additional extension of 3 years. Indium 111 DTPA is still under Phase III investigation with the Food and Drug Administration. Presently, it is still considered the radiopharmaceutical of choice for studying the physiology of cerebrospinal fluid flow. The progress report to date is as noted on appendix C. Only one adverse reaction has been noted in the last year. As noted, the conclusion was the reaction was not due to the product.

4. IMPACT: As previously, there is no impact on any other service or department.

5. FUNDING: There is no requirement for funding. The radiopharmaceutical is purchased from the Nuclear Medicine supply funds.

Douglas Van Nostrand

DOUGLAS VAN NOSTRAND, M.D.
MAJ, MC
C, NUCLEAR MEDICINE SERVICE

DA FORM 2496 REPLACES DD FORM 96, WHICH IS OBSOLETE.

RIOUS/UNEXPECTED SIDE EFFECTS IN SUBJECT PARTICIPATING IN PROJECT:

adverse reaction was reported. A meningitis type reaction 24 hours post-injection in a 5 year old female patient was noted by the attending physician. injection was difficult with several attempts made to place the spinal dle intrathecally. Subsequent evaluation revealed negative cultures of the rebrospinal fluid. The pyrogen test (limulus lysate 0.125 ng/ml level) of e product was negative. Blood agar plates of the product were negative. e reaction was felt not to be due to the product, however, the specific tiology was undetermined. Another patient received a dose from the same lot awn at the same time and injected within 30 minutes of this patient. This tter patient experienced no adverse reactions.

ne results of the 14 patients studied over the above interim are described s follows:

a. 8 normal studies.
b. 1 suboptimal.
c. 1 normal pressure hydrocephalus.
d. 3 abnormal tracer distribution with blockage of CSF flow.
e. 1 communicating hydrocephalus.

INVESTIGATIONAL PROGRESS REPORT/RCS MED-254

1. The following is an interim progress report for investigational drugs according to Paragraph 7, AR 40-7.

2. IDENTIFICATION OF STUDY: Clinical Evaluation of Indium 111 DTPA.

3. INVESTIGATOR: Douglas Van Nostrand, M.D., MAJ, MC

4. LOCATION OF STUDY: Walter Reed Army Medical Center, Nuclear Medicine Service.

5. NUMBER OF SUBJECTS INVOLVED: 14

6. NARRATIVE OF PROGRESS: The results of the 14 patients studied over the above interim are described as follows:

a. 8 normal studies.
b. 1 suboptimal.
c. 1 normal pressure hydrocephalus.
d. 3 abnormal tracer distribution with blockage of CSF flow.
e. 1 communicating hydrocephalus.

7. ADVERSE REACTIONS: One adverse reaction was reported. A meningitis type reaction 24 hours post-injection in a 5 year old female patient was noted by the attending physician. The injection was difficult with several attempts made to place the spinal needle intrathecally. Subsequent evaluation revealed negative cultures of the cerebrospinal fluid. The pyrogen test (limulus lysate 0.125 ng/ml level) of the product was negative. Blood agar plates of the product were negative. The reaction was felt not to be due to the product, however, the specific etiology was undetermined. Another patient received a dose from the same lot drawn at the same time and injected within 30 minutes of this patient. This latter patient experienced no adverse reactions.

8. DISPOSITION OF UNUSED SUPPLIES: No supplies were unused.

| Date: 14 SEP 80 | Protocol No: 4521 | Status: Interim X<br>Final |
|---|---|---|

Title of Project: Technetium 99m Pyridoxylideneglutamate (99mTc PG) for Diagnosis of Hepatobiliary Disease.

| Starting Date: 7 NOV 78 | Estimated Completion Date: NOV 81 |
|---|---|

Principal Investigator: DOUGLAS VAN NOSTRAND, MAJ, USA, MC

| Associate Investigators:<br>Asaf Durakovic, MAJ, USA, MC | Facility: Walter Reed Army Medical Center |
|---|---|
| | Dept/Svc Nuclear Medicine Service |

Key Words:

| Accumulative MEDCASE Cost: NONE | Accumulative Contract Cost: NONE | Accumulative Supply Cost: NONE |
|---|---|---|

| FY-80 MEDCASE Cost: NONE | Periodic Review Results:<br>(to be filled in by DCI) |
|---|---|

Study Objective: The purpose of this study is to evaluate the clinical efficacy of Tc 99m PG as a diagnostic hepatobiliary and gallbladder agent.

Technical Approach: No modifications have been made to the original protocol in regard to technical approach.

Progress during FY-80: During the period of 1 Oct 79 through 14 Sep 80, a total of 28 Tc PG studies were performed.

Number of subjects to be studied before completion of study: 25

Serious/unexpected side effects in subjects participating in project: No adverse reactions have been noted in any of the above studies.

Conclusions: (See attached sheet)

CONCLUSIONS: A total of 28 Tc PG studies were performed. The distribution of studies were as follows:

(1) 16 Normal studies, (2) 3 studies with decreased liver function and dilated ducts, (3) 1 study with non-visualization of the gallbladder with prominent ducts [pancreatic carcinoma], (4) 7 studies with non-visualization of the gallbladder with acute cholecystitis, (5) 1 study with decreased liver function and normal ducts.

DOUGLAS [illegible] NOSTRAND, M.D.
MAJ, MC
CHIEF, NUCLEAR MEDICINE SERVICE

ANNUAL PROGRESS REPORT IN CONCORDANCE WITH PARAGRAPH 7 AR 40-7.

1. Study Title: Technetium 99m Pyridoxylideneglutamate (Tc99m PG) for Diagnosis of Hepatobiliary Disease.

2. Location of Study: Walter Reed Army Medical Center

3. Number of Subjects Studied: 28

4. Progress Report: A total of 28 patients have been studied with TcPG. No adverse reactions have been noted in any of the studies. The distribution of studies were as follows: (1) 16 normal studies, (2) 3 studies with decreased liver function and dilated ducts, (3) 1 study with non-visualization of the gallbladder with prominent ducts [pancreatic carcinoma], (4) 7 studies with non-visualization of the gallbladder with acute cholecystitis, (5) 1 study with decreased liver function and normal ducts. This information was reported to the IND holder who is Dr. Robert Lull at Letterman Army Medical Center.

5. Project Future: It is anticipated an additional 5 patients will be studied before the protocol is completed.

6. No unused supplies of investigational drug require disposition.

DOUGLAS VAN NOSTRAND, M.D.
MAJ, MC
C, NUCLEAR MEDICINE SERVICE

| Date: 13 Oct 1980 | Protocol No: 4522 | Status: Interim X<br>Final |
|---|---|---|

Title of Project: Determination in Humans of the Effective Half-Life of Botulism Immune Plasma (Human) IND #1332 Administered Intravenously.

| Starting Date: Nov 1979 | Estimated Completion Date: Nov 1981 |
|---|---|

Principal Investigator: MAJ James H. Anderson, USAMRIID, Ft Detrick

| Associate Investigators:<br>MAJ George E. Lewis<br>COL Joseph F. Metzger<br>LTC Clarence J. Peters<br>Peter B. Jahrling<br>LTC Robert J. Kaminski, WRAMC<br>James E. Roggers, USAMC | Facility:<br>USAMRIID, Ft Detrick<br><br>Dept/Svc |
|---|---|

Key Words:
Botulism, Immune Plasma, Antitoxin, BW

| Accumulative MEDCASE Cost: None | Accumulative Contract Cost: None | Accumulative Supply Cost: $500 |
|---|---|---|

| FY-80 MEDCASE Cost: None | Periodic Review Results:<br>(to be filled in by DCI) |
|---|---|

Study Objective: To obtain data that will contribute to the determination of both a therapeutic and a prophylactic dosage of Botulism Immune Plasma (Human).

Technical Approach: Administration of 300 ml of Botulism Immune Plasma (Human) Intravenously. Routine blood volume determination using standard radioisotopic technique, assay of sequential blood samples for the detection of aquired antibodies to botulinal toxins.

Progress during FY-80: The relationship between the quantity and titer of immune plasma administered, the predicted recipient titer and the passively aquired titers has been determined in five human volunteers.

Number of subjects to be studied before completion of study: ten

Serious/unexpected side effects in subjects participating in project: None

Conclusions: Half-life values for the neutralizing activity of infused BIP averaged 21-27 days. In 4 of 5 volunteers, the actual period of "protection" equaled or exceeded the predicted period of "protection", indicating the feasibility of making such predictions.

Publications or Abstracts, FY-80:

Work Unit No.: 4522

Funds Utilized, FY-80: None

Funding Requirements, FY-81: Yes

Personnel: (name and grade) None

Equipment: (describe in detail including cost) None

Supplies: (consumable, animal purchase) Supplies for 5 blood volume determinations

Travel: (mission oriented, training and presentation) None

Other: (equipment rentals, contracts for service, animal care and reprints) None

| Date: | Protocol No: 4523 | Status: Interim XX<br>Final |
|---|---|---|

Title of Project: Determination of Glomerular Filtration Rate Using Radiotracer Techniques.

| Starting Date: Indefinite | Estimated Completion Date: |
|---|---|

Principal Investigator:

| Associate Investigators:<br>MAJ D. Van Nostrand, MC<br>COL J. Light, MC | Facility: WRAMC<br>Dept/Svc Nuclear Medicine Service |
|---|---|

Key Words:

| Accumulative MEDCASE Cost: 0 | Accumulative Contract Cost: 0 | Accumulative Supply Cost: 0 |
|---|---|---|

| FY-80 MEDCASE Cost: 0 | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective:

Technical Approach:

Progress during FY-80: This study requires certain equipment as described in the protocol. Funds to purchase this equipment are being sought, and the project is expected to be activated upon their acquisition.

Number of subjects to be studied before completion of study: 50 - 75

Serious/unexpected side effects in subjects participating in project: None

Conclusions:

Publications or Abstracts, FY-80:

Work Unit No. :4601

Title of Project : Participation in the National Cooperative Study of Early Hodgkin's Disease.

Investigators :

Principal Investigator : George B. Hutchison, M. D.
Project coordinator at Harvard School of Public Health.

Associate Investigator : Jeffrey Berenberg, M. D. and William Neglia, M. D. at Walter Reed Army Medical Center.
29 associate investigators at other collaborating centers.

Objectives : To determine the effects on survival, disease extension, and complications of therapy of differing irradiation volumes in treatment of early staged Hodgkin's disease.

Technical Approach : This clinical trial study was randomized and prospective, comparing localized irradiation to clinically involved region with extended field irradiation to clinically involved region plus regions suspected of being sites of sub-clinical disease.

Progress and Results : An interim report was distributed August, 1970. Localized recurrences have appeared in significantly greater frequency in patients receiving localized treatment than in those given extended field therapy. Extensions to extra-nodal sites on the same side of the diaphragm as the initial disease are also more frequent with localized treatment, but the excess is smaller, and transdiaphragmatic extensions are only slightly reduced by extended field therapy. There is no significant survival difference between the two therapy groups for the total collaboration, and for the Walter Reed series there is a non-significant reduction in mortality in the group given localized therapy.

Entry of patients into this study was terminated in 1971 at Walter Reed and in 1973 for the entire collaboration. At a meeting of all participating institutions held in Chicago, July, 1976, it was decided that follow-up of 10 years or more might be needed to conclude the study. The survival of both groups is substantially better than projected in 1967, at the outset of the study and based on reports available at that time.

Conclusions : To date, comparison of localized fields with extended fields of therapy of early Hodgkin's disease has not shown a clear superiority of either technique within 11 years of follow-up. The study suggests that extensions following extended field therapy may routinely carry a poor prognosis but that local extensions following local field therapy may be followed by cure in a substantial proportion of cases.

Publications :

1. Hutchison, G. B. Progress report. Hodgkin's Clinical Trial, 1972. National Cancer Institute Monograph No. 36:387-395. 1973.

2. Nickson, J. J. and Hutchison, G. B. Hodgkin's disease clinical trial. Sixth National Cancer Conf. Proc. 1968. Pages 77-81. Lippincott Philadelphia. 1970.

3. Nickson, J. J. and Hutchison, G. B. Extension of disease, complications of therapy, and deaths in localized Hodgkin's disease; preliminary report of a clinical trial. Am. J. Roentg., Rad. Th., Nuc. Med. 114:564-573. 1972.

4. A collaborative study. Report prepared by Hutchison, G. B. on behalf of Steering Committee. Survival and complications of radiotherapy following involved and extended field therapy of Hodgkin's disease, stages 1 and 2. Cancer 38: 288-305. 1976.

Funding requirements :

Estimated January to December, 1980

Travel : $1,200

| Date: 27 Oct 80 | Protocol No: 4709 | Status: Interim X<br>Final |
|---|---|---|

Title of Project: Eye Tracking in Radiologists

| Starting Date: | Estimated Completion Date: |
|---|---|

Principal Investigator: Sherry L. Brahman, MD, LTC, MC

| Associate Investigators: | Facility: Walter Reed General Hospital |
|---|---|
| | Dept/Svc Radiology/Diagnosis |

Key Words:

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: |
|---|---|---|

| FY-80 MEDCASE Cost: | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective:

No work on this protocol to date.

Project awaits decision concerning funding for equipment which may be procured in 80-81.

Funding requirements: Actual requirements for FY-81 uncertain as decision concerning funding for necessary equipment remains outstanding.

Site visit was performed by principal investigator. Funds were to be provided by the Chief, Dept. Radiology. These have not materialized due to many budget Constraints. The principal investigator is separating from service 1 October 1980. This protocol and further work lie in the hands of Chief, Dept. Radiology.

LTC MC

David J. Curtis, LTC, MC
30 September 1980

# DISPOSITION FORM

For use of this form, see AR 340-15, the proponent agency is TAGCEN.

| REFERENCE OR OFFICE SYMBOL | SUBJECT |
|---|---|
| HSWP-XD | Protocol No. 4701 Final Report |

TO THRU: C, Dept of Radiology FROM Robert Golden, M.S. DATE 10 Oct 1980 CMT 1
Thru: C, Diagnostic Svc Physicist

TO: C, Dept of Clinical Investigation, WRAMC

Timothy M. Boehm, LTC, MC

1. Attached is detail summary sheet (Appendix C) for protocol No. 4701 and a final report prepared for publication entitled "Patient Exposure Estimates using a Chest Phantom."

Robert Golden, M.S.

Robert Golden, M. S.
Physicist
Diagnostic Radiology Svc
Department of Radiology

DA FORM 1131 2496 REPLACES DD FORM 96, WHICH IS OBSOLETE.

| Date: 9 Oct 1982 | Protocol No: 4701 | Status: Interim |
|---|---|---|
| | | Final XX |

Title of Project: Comparison of Test Chest with Human Subjects on Radiographic Chest units.

| Starting Date: 26 Feb. 1980 | Estimated Completion Date: 1 Oct 1980 |
|---|---|

Principal Investigator: Robert Golden, M. S.

| Associate Investigators: | Facility: WRAMC |
|---|---|
| E. Thomas Pulaski, M. D.<br>Priscilla F. Butler, M. S.<br>(Bureau of Radiological Health) | Dept/Svc Diagnostic Radiology Svc. |

Key Words: Patient exposure, humanoid phantom, Automatic exposure control

| Accumulative MEDCASE Cost: None | Accumulative Contract Cost: None | Accumulative Supply Cost: None |
|---|---|---|

| FY-80 MEDCASE Cost: None | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective: to determine whether humanoid phantoms are reasonably analogous to human patients in terms of performance of automatic exposure controls of dedicated chest x-ray units.

Technical Approach: Measure for routine patient chest exposures, the exposure, KVP, milliamperes and time of exposure and compare to corresponding data for humanoid phantoms. Compare patient exposure data to humanoid phantom data, considering sex, weight, and patient thickness.

Progress during FY-80:

Please see attached report.

Number of subjects to be studied before completion of study: 26

Serious/unexpected side effects in subjects participating in project: None

Conclusions: Humanoid phantoms are reasonable patient analogs in terms of their AEC performance on one x-ray unit for a single technique for a small patient population.

Publications or Abstracts, FY-80:

To be submitted to Health Physics Journal for Pulication.

| Date: 27 Oct 80 | Protocol No: 4702 | Status: ( Interim ) Final |
|---|---|---|

Title of Project:
Video Transmission, Storage of Diagnostic Evaluation

| Starting Date: | Estimated Completion Date: |
|---|---|

Principal Investigator: Sherry L. Brahman, MD, LTC, MC

| Associate Investigators:<br>E. Thomas Pulaski, MD, LTC, MC<br>David J. Curtis, MD, (USUHS) | Facility: Walter Reed General Hospital<br>Dept/Svc Radiology/Diagnosis |
|---|---|

Key Words:

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: |
|---|---|---|

| FY-80 MEDCASE Cost: | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective:
Terminate this study. Equipment will not be procured.

The Microdose radiographic machine required for this project is on the property books of WRAMC, but is not serviceable at this time. Funds for refurbishment of the Microdose are in doubt and the fate of the project lies in the hands of the Chief, Dept. Radiology. The principle investigator is separating from service 1 October 1980.

LTCol

| Date: 20 October 1980 | Protocol No: 6018 | Status: ~~Interim~~ Final |
|---|---|---|

Title of Project: Newborn Host Defenses I: Developmental Aspects of Newborn Neutrophil Chemotaxis

| Starting Date: 20 June 77 | Estimated Completion Date: 20 June 80 |
|---|---|

Principal Investigator: Paul J. Thomas, MD, LTC, MC

| Associate Investigators: Frederick B. Ruymann,MD, COL, MC<br>Doris Burgess | Facility:<br>Dept/Svc |
|---|---|

Key Words: Newborn neutrophil, chemotaxis

| Accumulative MEDCASE Cost:_____ | Accumulative Contract Cost:_____ | Accumulative Supply Cost:_____ |
|---|---|---|

| FY-80 MEDCASE Cost:_____ | Periodic Review Results:_____ (to be filled in by DCI) |
|---|---|

Study Objective: Confirm and characterize the cellular chemotactic defect of the newborn neutrophil and to correlate this decrease with gestational age.

Technical Approach: Modified $^{51}Cr$ labelled neutrophil chemotaxis assay using Boyden chambers comparing cord blood neutrophils to normal adult volunteer neutrophils. Preliminary studies on the effect of chemotaxis of certain drugs such as vinblastin and the effect of concentration of the neutrophils on chemotaxis, also done using same technique.

Progress during FY-80: Due to difficulties in obtaining cord blood neutrophils, only 2 newbones were studied on this protocol. Because of the slow accrual and because of the higher priority of other studies on the newborn neutrophil, this study has been closed.

Number of subjects to be studied before completion of study: Projected: 100, Actual: 52

Serious/unexpected side effects in subjects participating in project: NONE

Conclusions: Decreased newborn neutrophil chemotaxis has been confirmed as statistically significant. The correlation with gestational age has yielded no statistical differences noted. The conclusions have been published in the following.

Publications or Abstracts, FY-80:

Mease, A.D., Fischer, C.W., Hunter, K.W., and Ruymann, F.B: Decreased phytohemagglutinin-induced aggregation and C5a-induced chemotaxis of human newborn neutrophils. Pediatr Res 14:142-146 (1980).

FUNDING REPORT
CLINICAL INVESTIGATION PROGRAM

Work Unit No.: 6018

Funds Utilized, FY-80: $2000

Funding Requirements, FY-81: NONE

Personnel: NONE

Equipment: NONE

Supplies: NONE

Travel: NONE

Other: NONE

1. Work Unit No.: 6021

2. Title of Project: The Role of Leutinizing Hormone Releasing Hormone (LHRH) in Evaluation of the Hypothalamic Pituitary Gonadal Axis in Children

3. Principal Investigator: LTC Chandra M. Tiwary, MC

4. Objective: To develop a test for assessing hypothalamo-hypophyseal-gonadal axis in children which can be used on an outpatient basis.

5. Progress and Results: 57 children were studied; of these 4 can not be included in the protocol because these receive only one injection of LHRH (the protocol requires 3 injection to be given to each child), the gonadotropin results on six children are not available yet. The conclusions based upon the analysis of 47 children are as follows.

A. Girls with precocious puberty can be differentiated from those with premature adrenarche.

B. The pool serum LH and serum FSH value is directly correlated with the mean and the peak serum LH and FSH value. This suggests that for most clinical purposes analysis of the gonadotropin in one serum sample may be sufficient. This would reduce the cost.

C. Gonadotropin response to LHRH is different in children with malignancy treated with chemotherapy and/or radiation. Thus the LHRH test can be used to detect subtle derangement of hypothalamo-hypophyseal-gonadal axis.

6. Funds requested for FY 1981:

| | |
|---|---|
| Paper publication | $200.00 |
| Travel for presentation of paper | 600.00 |
| TOTAL | $800.00 |

7. Publication: Three abstracts published

8. Type of report - Final

# DISPOSITION FORM

For use of this form, see AR 340-15, the proponent agency is TAGCEN.

| REFERENCE OR OFFICE SYMBOL | SUBJECT |
|---|---|
| HSWP-KOP | Reply to your comments on the protocol # 6021 |

TO THRU: C, Dept of Peds. FROM C, Peds Endoc. Section DATE 2 Feb. 1981 CMT 1

TO: C, Clinical Investigation

1. According to the protocol each child receives 3 injections of LHRH. Each of the four children received only one injection (non compliance) therefore, they are not included.

2. We did not observe any ill effects in any subjects due to participation in the study specifically LHRH injection did not produce any observable ill effects.

CHANDRA M. TIWARY, M.D.
LTC, MC
Chief, Pediatric Endoc. Section

DA FORM 2496 REPLACES DD FORM 96, WHICH IS OBSOLETE.

| Date: 20 Oct 80 | Protocol No: 6023 | Status: Interim / ~~Final~~ |
|---|---|---|

Title of Project: Newborn Host Defenses II: Studies of the Newborn Neutrophil Membrane Using Lectins as Molecular Probes.

| Starting Date: 24 January 78 | Estimated Completion Date: 24 June 81 |
|---|---|

Principal Investigator: Paul J. Thomas, MD, LTC, MC

| Associate Investigators:<br>Gerald W. Fischer, MD, LTC, MC<br>Frederick B. Ruymann, MD, COL, MC<br>Doris Burgess | Facility:<br><br>Dept/Svc |
|---|---|

Key Words: Newborn neutrophil, neurophil aggregation

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: |
|---|---|---|
| FY-80 MEDCASE Cost: | Periodic Review Results: (to be filled in by DCI) | |

Study Objective: Study of differences between adult and newborn neutrophils in ability to form aggregates in response to plant lectins, C5a, and Zymosan activated serum.

Technical Approach: Using a standard platelet aggregometer, study of aggregation of cord blood neutrophils and adult neutrophils at a standard concentration ($5X10^6$ cells/ml)using phytohemagglutinin (PHA), column purified C5a, and zymosan activated serum (ZAS). The effect of vinblastin and cytochalasin B on aggregation of both adult and newborn neutrophils were also studied.

Progress during FY-80: Only 2 newborns were studied due to the lack of cord blood available for study.

Number of subjects to be studied before completion of study: Projected: 100, Actual: 32

Serious/unexpected side effects in subjects participating in project: NONE

Conclusions: Newborns have statistically poorer aggregation of neutrophils in response to PHA, C5a, and ZAS. The addition of vinblastin decreased the adult aggregation but did not significantly change the newborn aggregation. The addition of cytochalasin B resulted in the disappearance of the normal adult neutrophil aggregation - deaggregation but did not significantly affect the newborn aggregation. Further study is warranted in working at the effect of concentration of C5a or ZAS on the aggregation since other investigators have reported different newborn aggregation problems with differing concentrations.

(Con't) #6023

Publications or Abstracts, FY-80:

Mease AD, Fischer CW, Hunter KW, Ruymann FB: Decreased phytohemagglutinin-induced aggregation and C5a-induced chemotaxis of human newborn neutrophils. Pediatr Res 14:142-146 (1980).

Mease AD, Burgess DP, Thomas PJ: Differences between neonatal and adult complement-induced neutrophil aggregation and cellular augmentation of neutrophil chemotaxis. Pediatr Res 14:549 (abstract #740), (1980). - Presented at the 1980 APS-SPR meeting, San Antonio, Texas, 2 May 1980.

Mease AD, Burgess DP, Thomas PJ: Neonatal differences in complement-induced neutrophil aggregation and cellular augmentation of neutrophil chemotaxis. (Submitted for publication)

FUNDING REPORT

CLINICAL INVESTIGATION PROGRAM

Work Unit No.: 6023

Funds Utilized, FY-80: $2000

Funding Requirements, FY-81: $500

Personnel: Doris Burgess, GS-9, 10%

Equipment: NONE

Supplies: $500

Travel: NONE

Other: NONE

| Date: 20 October 1980 | Protocol No: 6024 | Status: Interim ~~Final~~ |
|---|---|---|

Title of Project: Newborn Host Defenses III: Phagocytosis and Killing of Group B Streptococci

| Starting Date: 24 January 78 | Estimated Completion Date: 24 January 81 |
|---|---|

Principal Investigator: Paul J. Thomas, MD, LTC, MC

| Associate Investigators:<br>Gerald W. Fischer, MD, LTC, MC<br>George Lowell<br>Frederick B. Ruymann, MD, COL, MC<br>James W. Bass, MD, COL, MC | Facility:<br><br>Dept/Svc |
|---|---|

Key Words: Newborn neutrophil, group B streptocci

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: |
|---|---|---|

| FY-80 MEDCASE Cost: | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective: Study phagocytosis and killing of group B streptocci newborn neutrophils.

Technical Approach: Assay for 5 strains of group B streptococci using streptococci specific anti-streptococcal antibody, complement, and adult neutrophils been established and reported. Adult and newborn (cord ) neutrophils compared using this assay.

Progress during FY-80: No new newborns have been studied because of the low accural of newborn cord blood samples for all studies.

Number of subjects to be studied before completion of study: Projected: 25, Actual: 5

Serious/unexpected side effects in subjects participating in project: ---

Conclusions: None as yet. Recommend trying to complete study by 24 January 81.

Publications or Abstracts. FY-80: None.

FUNDING REPORT
CLINICAL INVESTIGATION PROGRAM

Work Unit No.: 6024

Funds Utilized, FY-80: NONE

Funding Requirements, FY-81: $1000

Personnel: Doris Burgess, GS-9, 10%

Equipment: NONE

Supplies: $500

Travel: $500

Other: NONE

a) Work Unit Number: 6025

b) Title: Role of surface tension measurement of amniotic fluid lipid extract in Prediction of RDS in the newborn.

c) Investigators:

Principal: Chandra M. Tiwary, M.D., LTC, MC.
Associates: James Haddock, M.D., LTC, MC
Dale Landes, M.D., LTC, MC
Doris Burgess

d) Starting date: The apparatus was not available till June 1979 and then the investigation was started.

e) Estimated date of completion December 1981

f) Objective: To measure surface tension of amniotic fluid lipid extract prior to and during labor, and to correlate it with the subsequent development of RDS in newborn.

g) Key words: None

h) Technical Approach: No changes

i) Progress and Results: We have studied the amniotic fluid from 43 patients. The results show that a high surface tension of the amniotic fluid lipid extract predicts (a) the development of RDS in the newborn or (b) an unusual course in the immediate newborn period requiring observation in the special care nursery. The analysis of the patients studied so far is given in the attached abstract.

j) Conclusion: We would like to confirm our data by analysing more patients (we had only one child with RDS); approximate number would be 300.

k) No complecation or side effect occured during the study.

l) Copy of the abstract submitted for presentation at the forthcoming pediatric triservice conference is enclosed.

FY 81:

| | |
|---|---|
| Chemicals and supplieds | $300.00 |
| Papers publication etc | 200.00 |
| Travel | 600.00 |
| TOTAL | $1,100.00 |

# Surface Tension of Amniotic Fluid Lipid Extract as a Predictor of Immediate Neonatal Course

Chandra M. Tiwary, D. Landes and James B. Haddock with the technical assistance of D. Burgess. Department of Pediatrics Obstetrics and Gynecology, Walter Reed Army Medical Center, Washington, D. C. 20012 and Uniformed Services University of the Health Sciences, Bethesda, Maryland.

Surface Tension (ST) of Amniotic Fluid (AF) lipid extract correlates with the AF L/S ratio and predicts the fetal pulmonic maturity. We measured the ST in AF to predict the development of RDS in the neonate. Serendipitously we observed that a high ST was associated with a variety of complications (other than RDS) during the immediate neonatal period. We report the value of ST measurement in AF.

Amniotic fluid was collected during the 24 hours period of delivery and was frozen at -70° C till analyzed. A chloroform methanol lipid extract was made of the AF and ST lowering property of the lipid extract was measured in an autotensiometer (Fisher Lab). The minimum amount of the lipid extract (in microliters) required to maximally lower the ST (dynes/cm) was recorded. These two values were added. This figure (the ST sum) was analyzed relative to clinical condition of the baby.

We studied 42 AF from 42 mothers, 27 delivered vaginally, 13 by Cesarean Section and 2 by forceps. The pregnancy was normal in 33 and complicated in 9 (pre eclamptic toxemia - 3, Diabetes Mellitus - 2, hypertension - 2, and one each with anemia, appendicitis). Twenty eight babies had a normal course, 14 had a complication(s) (Rh disease - 4, hypoglycemia - 3, meconium staining -3, ABO incompatability - 2, multiple congenital anomalies - 1, RDS -1). Thirty six babies were 2,500 gm or over and 6 were less than 2,500 gm,(3 were premature, less than 37 weeks gestation).

The ST sum was 45 or less in 28 babies and all but three (hypoglycemia - 1, meconium staining - 1, ABO incompatability - 1) had a normal course, in 14 babies the ST sum was > 45 and all but 3 had an abnormal course requiring close observation and/or treatment (RDS - multiple congenital anomalies - 1 meconium staining 2, Rh disease, multiple exchange transfusion - 4, sepsis and/or hypoglycemia - 2, ABO incompatability - 1). The Apgar score was normal ( < 5 at 1 min & 5 min) in all except 3 babies in the group with ST sum of >45, and it was abnormal in one baby in the < 45 ST sum group.

To determine the effect of prematurity on the surface tension we selected babies with gestational age of 37 weeks or less, or birth weight of 2,500 gm or less, in three babies the ST sum was less than 45 and in 8 it was greater than 45. Significantly, the highest ST sum of 87 was in a 2,769 gm, 37 weeks gestation and the lowest value of 31 was also in a 2,765 gm, 38 weeks gestation baby..

Conclusion:

1. A ST sum of more than 45 - particularly if it is more than 50 - predicts an abnormal course in the immediate neonatal period requiring dose observation and intervention.

2. A ST sum of less than 45 - especially if it is less than 40-is associated with an uncomplicated neonatal course.

3. Maternal conditions such as anemia, hypertension, pre eclampsia do not effect the ST.

4. The ST is effected by factors other than low birth weight or gestational age.

Speculation:

A raised ST sum signifies pulmonic immaturity which may be associated with immaturity of the other organs. This may explain the increased number of babies with nonpulmonic complications in the high ST sum group.

(a) Work Unit Number: 6026

(b) Title: Tracheal Aspirate surface tension as a prognostic indicator in infants with Respiratory Distress Syndrome (RDS)

(c) Investigators:

Principal: Chandra M. Tiwary, M.D., LTC, MC
Associates: Richard D. Landes, M.D., LTC, MC
Doris P. Burgess, Medical Technologist

(d) Starting date: September 1979

(e) Estimated date of completion: June 1982

(f) Objective: To measure the surface tension of the lipid extract of trachael aspirate at various periods and to use this data in evaluating the prognosis of newborn with respiratory distress syndrome (RDS).

(g) Key words: None

(h) Technical approach: No modifications

(i) Progress and results: We analysed 52 trachael aspirate samples from six babies. All these babies were intubated and had RDS. As the ST of the trachael aspirate decreased the respiratory status improved. In some cases the babies developed other complications ie. bleeding episodes, seizure disorder, renal failure or intestinal obstruction or heart failure etc and died. Respiratory status occasionally during the complication one but usually it remained unchanged Once the ST decreased, it did not rise again except transiently in a few samples.

(j) Conclusions: The preliminary data are very encouraging with respect to prediction in the improvement of respiratory status of intubated babies. We need to study more babies (about 30) to confirm the preliminary results.

(k) No unexpected or serious side effects in subjects participating in this study.

(l) Publications: No

| | | |
|---|---|---|
| FY 81: | Chemical and supplies | $500.00 |
| | Paper Publication | 120.00 |
| | Travel | 600.00 |
| | Total | $1,220.00 |

| Date: 20 October 1980 | Protocol No: 6027 | Status: ~~Interim~~ Final |
|---|---|---|

Title of Project: WRAMC #7808 - Combined Modality Therapy of Brain Tumors in Childhood

| Starting Date: 26 September 78 | Estimated Completion Date: October 1980 |
|---|---|

Principal Investigator: Frederick B. Ruymann, MD, COL, MC

| Associate Investigators: | Facility: |
|---|---|
| Paul J. Thomas, MD, LTC, MC | Dept/Svc |

Key Words: Brain tumor, high dose methotrexate

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: |
|---|---|---|

| FY-80 MEDCASE Cost: | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective. To determine if the addition of chemotherapy with dexamethasone, vincristine, high dose methotrexate, VP-16, CCNU, and procarbazine following surgery and radiation will increase survival time/quality of life in children with brain tumors.

Technical Approach: Stratification into high & standard risk with non-randomized induction phase followed by non-randomized maintenance.

Progress during FY-80: No additional patients have accrual. High dose methotrexate is no longer available through the NCI.

Number of subjects to be studied before completion of study: projected: 24, Actual: 3

Serious/unexpected side effects in subjects participating in project: None

Conclusions: 2/3 patients have expired because of tumor recurrence. There are not enough patients to evaluate effectiveness. Recommend closing this study because of unavailability of high dose methotrexate.

Publications or Abstracts. FY-80: None.

1. Work Unit N.: 6028

2. Title of Project: Application of Hb. $A_1C$ as an indicator of juvenile diabetes control.

3. Investigations: Chandra M. Tiwary, LTC, MC
R. Bongiovanni, CPT, MC

4. Objective: To determine if measurement of Hb. $A_1C$ is an effective means of assessing diabetic control and to determine the optimal time for its measurement. To determine if the HB $A_1C$ in obese children correlateswith the insulin level.

5. Progress and Results: We analysed Hb. $A_1C$ in approximately 20 children, most of the children had analysis performed more than once. From the analysis of the data we conclude that

A. Hb. $A_1C$ measurement is a good indicator of the degree of diabetic control during the previous 2-4 weeks.

B. The change in Hb. $A_1C$ is rapid in newly diagnosed diabetic as opposed to those with diabetes of long duration. In dew diabetic the fall in Hb. $A_1C$ can be monitored every week while in others the change is apparent in 3 weeks.

Conclusion: We suggest that in children with established diabetes mellitus, the Hb. $A_1C$ should be measured at 3-4 weeks interval to assess the degree of diabetic control. Hb. $A_1C$ is in normal range in obese patients and is not related to serum insulin level.

| | | |
|---|---|---|
| Funds utilized in FY 1980 | | $1,472.00 |
| Funds requested in FY 1981 | | |
| Paper publication | | $200.00 |
| Travel to meeting | | 600.00 |
| | TOTAL | 800.00 |

Publication: One abstract published

Type of Report: Final

Date: 20 OCT 80/19 JAN 81 | Protocol No: 6020 | Status: Interim

Title of Project: Newborn Host Defenses IV: Study of Newborn Neutrophil-Neutrophil Interaction.

Starting Date: 22 OCT 1979 | Estimated Completion Date: 22 OCT 1981

Principal Investigator: Paul J. Thomas, MD, LTC, MC

Associate Investigators:
Frederick B. Ruymann, MD, COL, MC
Doris P. Burgess

Facility:

Dept/Svc

Key Words: Newborn neutrophil, chemotaxis, neutrophil aggregation

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: |
|---|---|---|
| | | |

FY-80 MEDCASE Cost:

Periodic Review Results: (to be filled in by DCI)

Study Objective: Investigate differences between adult and newborn neutrophil by a. studying the effect of cell concentration on chemotaxis; b. studying the kinetics of concentration effect on chemotaxis; and, c. studying the C5a-induced aggregation of newborn and adult neutrophils.

Technical Approach: Using the established $^{51}$Cr-labelled neutrophil Boyden chamber chemotaxis assay and the neutrophil aggregation assay, the concentration of newborn and adult neutrophils is varied in the chemotaxis assay and the aggregation of newborn and adult neutrophils is evaluated using C5a as the aggregation stimulus. Preincubation of cells with vinblastin and cytochalsin-B is also done to study the contribution of the microtubules and microfilaments.

Progress during FY-80: 15 Newborn-adult neutrophil pairs were studied with varying concentrations of neutrophils. 8 newborn adult neutrophil pairs were studied with respect to C5a aggregation.

Number of subjects to be studied before completion of study: Projected: 50; Actual 15/8

Serious/unexpected side effects in subjects participating in project: None

Conclusions: Newborn neutrophils have augmented chemotaxis with increased cell concentration; however, the augmentation is only about half that seen with the adult. Newborn neutrophil aggregation appears to be irreversible, similar to that seen with adult aggregation after preincubation of the neutrophils with cytochalasin-B. Further study of the aggregation and chemotaxis is needed. New studies suggested by this study will be forthcoming.

The corrected portion of the study is amended. The lactoferrin possibility was only listed as an example of further studies suggested by this study. If this possibility turns out to have some merit, a new protocol will be written.

C-8

(Con't) #6029

Publications or Abstracts, FY-80:

Mease AD, Burgess DP , Thomas PJ: Differences between neonatal and adult complement-induced neutrophil aggregation and cellular augmentation of neutrophil chemotaxis. Pediatr Res 14:549 (Abstract #740) (1980). Presented at the 1980 APS-SPR meetings, San Antonio, Texas, 2 May 1980.

Mease AD, Burgess DP, Thomas PJ: Neonatal differences in complement-induced neutrophil aggregation and cellular augmentation of neutrophil chemotaxis (Submitted for publication).

## FUNDING REPORT
## CLINICAL INVESTIGATION PROGRAM

Work Unit No.: 6029

Funds Utilized, FY-80: $700

Funding Requirements, FY-81: $2000

Personnel: Doris Burgess, GS-9, 20%

Equipment: NONE

Supplies: $1500

Travel: $500

Other: NONE

| Date: 20 October 1980 | Protocol No: 6030 | Status: Interim XXXX Final |
|---|---|---|

Title of Project: Studies of Adult and Newborn Neutrophil Chemotaxis under Agarose

| Starting Date: 22 Oct 79 | Estimated Completion Date: October 81 |
|---|---|

Principal Investigator: Paul J. Thomas, MD, ITC, MC

| Associate Investigators:<br>Frederick B. Ruymann, MD, COL, MC<br>Doris P. Burgess | Facility:<br><br>Dept/Svc |
|---|---|

Key Words: Newborn neutrophil, chemotaxis under agarose

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: |
|---|---|---|

| FY-80 MEDCASE Cost: | Periodic Review Results:<br>(to be filled in by DCI) |
|---|---|

Study Objective: Comparison of newborn (cord) neutrophil and adult neutrophil chemotaxis under agarose.

Technical Approach: Using agarose technique of Nelson & Quie, study the amount of chemotaxis of adult and newborn neutrophils under varying conditions of stimuli, concentration of neutrophils, and presence of compounds such as vinblastin .

Progress during FY-80: The agarose technique was established in our laboratory with reproducible results with adult neutrophils obtained. Lack of the Tri-Simplex projector & the obtaining of only 1 cord blood for study have impeded progress of this protocol.

Number of subjects to be studied before completion of study: Projected: 50, Actual: 1

Serious/unexpected side effects in subjects participating in project: NONE.

Conclusions: Too early.

Publications or Abstracts. FY-80: None.

The listing of one patient studied was an error. Only one newborn was studied using the agarose technique; however, 35 adult samples were studied while attempting to firmly establish this technique in our laboratory. As of this time, the technique is still not reliably reproducible and an estimated 5-10 more adult studies will need to be done before any more newborns will be studied.

Work Unit No.: 6030

Funds Utilized, FY-80: $2500

Funding Requirements, FY-81: $2500

| | |
|---|---|
| Personnel: | Doris Burgess, GS-9, 20% |
| Equipment: | NONE |
| Supplies: | $2000 |
| Travel: | $500 |
| Other: | NONE |

| Date: 20 OCT 80 | Protocol No: 6101 | Status: Interim / Final |
|---|---|---|

Title of Project: SWOG PROTOCOL # 7834
Second Induction and Maintenance in Acute Lymphocytic Leukemia, Phase III.

| Starting Date: 2 MAY 80 | Estimated Completion Date: APR 81 |
|---|---|

Principal Investigator: Frederick B. Ruymann MD, COL MC

| Associate Investigators: | Facility: |
|---|---|
| Paul J. Thomas MD, LTC MC<br>Donald Karcher MD, LTC MC<br>William Neglia MD, LTC MC | Dept/Svc |

Key Words: Acute lymphocytic leukemia, relapse

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: |
|---|---|---|

| FY-80 MEDCASE Cost: | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective: To investigate the effectiveness of an induction with vincristine, adriamycin, and prednisone followed by intrathecal therapy with methotrexate, hydrocortisone, and cytosine arabinoside in relapse acute lymphocytic leukemia; to investigate the effectiveness of maintenance therapy with cycles of 6-thioguanine, cytosine arabinoside; cytoxan, vincristine, cytosine arabinoside, prednisone; & vincristine, adriamycin, prednisone.

Technical Approach: Standard induction with vincristine, adriamycin and prednisone with alternate induction with 6-thioguanine and cytosine arabinoside in case of induction failure with VAP; CNS prophylaxis with intrathecal three drug therapy; randomization between two maintenance arms.

Progress during FY-80: No WRAMC patients were entered on this study.

Number of subjects to be studied before completion of study: --

Serious/unexpected side effects in subjects participating in project: --

Conclusions: Because of high relapse rate on this treatment, this study was closed by the group to patients with marrow relapse only; the study remains open for systemic therapy in patients with extra-medullary relapse.

Publications or Abstracts. FY-80: --

The protocol was indeed properly amended. Reports from the group with respect to all group protocols are published twice per year and a copy will be furnished to your office should you desire them.

FUNDING REPORT
CLINICAL INVESTIGATION PROGRAM

Work Unit No.: 6101 - 6131

Funds Utilized, FY-80: NONE

Funding Requirements, FY-81: NONE

Personnel: NONE

Equipment: NONE

Supplies: NONE

Travel: NONE

Other: NONE

| Date: 20 OCT 80 | Protocol No: 6102 | Status: Interim / Final |
|---|---|---|

Title of Project: SWOG PROTOCOL # 7703
Radiation Therapy in Combination with BCNU, DTIC, or Procarbazine in Patients with Malignant Gliomas of the Brain, Phase III.

| Starting Date: 3 MAR 80 | Estimated Completion Date: JAN 81 |
|---|---|

Principal Investigator: Frederick B. Ruymann MD, COL MC

| Associate Investigators: | Facility: |
|---|---|
| Paul J. Thomas MD, LTC MC<br>William Neglia MD, LTC MC<br>Eugene George MD, COL MC | Dept/Svc |

Key Words: Malignant glioma

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: |
|---|---|---|

| FY-80 MEDCASE Cost: | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective: To study the effect of adding one of three chemotherapy drugs to radiation therapy after neurosurgery for malignant brain glioma.

Technical Approach: Randomized study between BCNU, DTIC, or procarbazine following surgery and radiation therapy.

Progress during FY-80: No WRAMC patients were entered on this study.

Number of subjects to be studied before completion of study: --

Serious/unexpected side effects in subjects participating in project: --

Conclusions: This is primarily an adult SWOG protocol and will be dropped by the pediatric group when the pediatric group becomes independent of SWOG in January 1981

Publications or Abstracts. FY-80: --

| Date: 20 OCT 80 | Protocol No: 6103 | Status: Interim / Final |
|---|---|---|

**Title of Project:** SWOG PROTOCOL # 7919
Evaluation of m-AMSA in Children with Acute Leukemia and Non-Hodgkin's Lymphoma in Relapse, Phase II.

| Starting Date: 3 MAY 80 | Estimated Completion Date: -- |
|---|---|

**Principal Investigator:** Frederick B. Ruymann MD, COL MC

| **Associate Investigators:** | **Facility:** |
|---|---|
| Paul J. Thomas MD, LTC MC | **Dept/Svc** |

**Key Words:** Acute leukemia, relapse; non-Hodgkin's lymphoma, relapse

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: |
|---|---|---|

| FY-80 MEDCASE Cost: | Periodic Review Results: (to be filled in by DCI) |
|---|---|

**Study Objective:** To study the effectiveness of m-AMSA as an inducing agent for acute leukemia and non-Hodgkin's lymphoma in relapse.

**Technical Approach:** Non-randomized study for non-Hodgkin's lymphoma and acute non-lymphocytic leukemia; randomized between two dosage schedules for acute lymphocytic leukemia.

**Progress during FY-80:** One patient with non-lymphocytic leukemia was placed on study and, after two courses, the patient had a transient peripheral blood blast count decrease but no detectable marrow response.

Number of subjects to be studied before completion of study: --

Serious/unexpected side effects in subjects participating in project: None for our patient but nationwide, severe cardiac arrythmias have been reported.

**Conclusions:** Study remains open with precautions of continuous cardiac monitoring during administration of m-AMSA

**Publications or Abstracts. FY-80:--**

Date: 20 OCT 80 | Protocol No: 5104 | Status: Interim / Final

Title of Project: SWOG PROTOCOL # 7818
Evaluation of Rubidazone in Children with Acute Lymphoblastic and Acute Myelogenous Leukemia, Phase II.

Starting Date: 14 JUL 80 | Estimated Completion Date: --

Principal Investigator: Frederick B. Ruymann MD, COL MC

Associate Investigators:
Paul J. Thomas MD, LTC MC

Facility:

Dept/Svc

Key Words: Acute leukemia, relapse

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: |
|---|---|---|
| | | |

FY-80 MEDCASE Cost:

Periodic Review Results: (to be filled in by DCI)

Study Objective: To study the effectiveness of Rubidazone in inducing remissions in children with acute leukemia in relapse.

Technical Approach: Randomized study of two dosage schedules of Rubidazone given intravenously over one hour.

Progress during FY-80: One patient with T-cell leukemia in florid relapse was placed on study; however, he expired within 12 hours of receiving the Rubidazone, cause of death not certain, autopsy results pending.

Number of subjects to be studied before completion of study: --

Serious/unexpected side effects in subjects participating in project: See progress- death may have been drug-related study coordinator notified.

Conclusions: Study remains open until supply of Rubidazone is exhausted

The one death within 12 hours was initially thought to be a possible drug related death. The child developed progressive coma and heart rate and rhythm disturbances culminating in a cardiac arrest. At autopsy, the child had massive leukemic infiltrations in the abdominal organs, the CNS, and the heart, including an infiltration of the heart around the A-V node. The pathologists were content to call the cause of death massive leukemic infiltration and it was their opinion that the drug played little or no role in the death.

| Date: 20 OCT 80 | Protocol No: 6105 | Status: Interim Final |
|---|---|---|

Title of Project: SWOG PROTOCOL # 7607P
Evaluation of Lithium Carbonate in the Amelioration of Hematopoietic Toxicity Following Cancer Chemotherapy in Children with Solid Tumors Treated with AD-CON-FU, Phase II

| Starting Date: 14 JUL 80 | Estimated Completion Date: -- |
|---|---|

Principal Investigator: Frederick B. Ruymann MD, COL MC

| Associate Investigators: Paul J. Thomas MD, LTC MC | Facility: |
|---|---|
| | Dept/Svc |

Key Words: Solid tumors, pediatric, chemotherapy

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: |
|---|---|---|

| FY-80 MEDCASE Cost: | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective: To study the effectiveness of lithium carbonate on the neutropenia caused by AD-CON-FU; to study the effectiveness of AD-CON-FU (adriamycin, cytoxan, vincristine, and 5-flurouracil) on various pediatric solid tumors in patients not eligible for other protocols of higher priority.

Technical Approach: Randomized study with respect to the addition or not of lithium carbonate to the four drug chemotherapy; stratified by tumor type.

Progress during FY-80: No WRAMC patients have been entered on this study.

Number of subjects to be studied before completion of study: --

Serious/unexpected side effects in subjects participating in project: --

Conclusions: Study remains open

Publications or Abstracts. FY-80: --

| Date: 20 OCT 80 | Protocol No: 6106 | Status: Interim X / Final |
|---|---|---|

Title of Project: SWOG PROTOCOL # 7604
Evaluation of Galactitol in Patients with Advanced Cancer, Phase II.

| Starting Date: 2 MAY 80 | Estimated Completion Date: OCT 80 |
|---|---|

Principal Investigator: Frederick B. Ruymann MD, COL MC

| Associate Investigators: Paul J. Thomas MD, LTC MC | Facility: |
|---|---|
| | Dept/Svc |

Key Words: galactitol, Phase II

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: |
|---|---|---|

| FY-80 MEDCASE Cost: | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective: To study the effect of Galactitol on advanced childhood malignancies and to evaluate toxicity.

Technical Approach: Non-randomized study with initial dosage modification for liver, kidney or bone marrow impairment.

Progress during FY-80: No WRAMC patients were entered on this study

Number of subjects to be studied before completion of study: --

Serious/unexpected side effects in subjects participating in project: Groupwide trials revealed serious hematological complications -- none in WRAMC patients

Conclusions: Study closed by Group because of serious side effects and overall lack of response.

Publications or Abstracts. FY-80: --

| Date: 20 OCT 80 | Protocol No: 6107 | Status: Interim Final |
|---|---|---|

**Title of Project:** SWOG PROTOCOL # 7810
Evaluation of Anguidine in Children with Acute Lymphoblastic and Non-lymphoblastic Leukemia in Relapse, Phase II.

| Starting Date: 14 JUL 80 | Estimated Completion Date: -- |
|---|---|

**Principal Investigator:** Frederick B. Ruymann MD, COL MC

| **Associate Investigators:** Paul J. Thomas MD, LTC MC | **Facility:** |
|---|---|
| | **Dept/Svc** |

**Key Words:** Acute leukemia, relapse

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: |
|---|---|---|

| **FY-80 MEDCASE Cost:** | **Periodic Review Results:** (to be filled in by DCI) |
|---|---|

**Study Objective:** To study the effectiveness of anguidine in inducing remissions in children with acute leukemia in relapse

**Technical Approach:** Non-randomized study of anguidine with dosage modification depending on degree of toxicity

**Progress during FY-80:** One patient with juvenile chronic granulocytic leukemia had a transient response but quickly relapsed.

**Number of subjects to be studied before completion of study** --

**Serious/unexpected side effects in subjects participating in project:** --

**Conclusions:** Study remains open for monocytic and monomyelocytic leukemia

**Publications or Abstracts. FY-80:** --

| Date: 20 OCT 80 | Protocol No: 6108 | Status: Interim / Final |
|---|---|---|

Title of Project: SWOG PROTOCOL # 7621
MOPP versus OPP in the Treatment of Children with Recurrent Brain Tumors, Phase III.

| Starting Date: 24 MAR 80 | Estimated Completion Date: -- |
|---|---|

Principal Investigator: Frederick B. Ruymann MD, COL MC

| Associate Investigators: | Facility: |
|---|---|
| Paul J. Thomas MD, LTC MC<br>Eugene George MD, COL MC | Dept/Svc |

Key Words: Brain tumor, recurrent

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: |
|---|---|---|

| FY-80 MEDCASE Cost: | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective: To study the comparative effect of vincristine, prednisone and procarbazine with or without nitrogen mustard in the treatment of childhood recurrent brain tumors.

Technical Approach: Randomized study for the addition of nitrogen mustard to vincristine, prednisone, and procarbazine.

Progress during FY-80: No WRAMC patients were entered on this study

Number of subjects to be studied before completion of study: --

Serious/unexpected side effects in subjects participating in project: --

Conclusions: Study remains open

Publications or Abstracts. FY-80: --

| Date: 20 OCT 80 | Protocol No: 6109 | Status: Interim / Final |
|---|---|---|

Title of Project: SWOG PROTOCOL # 7709
Evaluation of Compliance in Children with Malignant Disease Treated with Prednisone

| Starting Date: 24 MAR 80 | Estimated Completion Date: OCT 80 |
|---|---|

Principal Investigator: Frederick B. Ruymann MD, COL MC

| Associate Investigators: | Facility: |
|---|---|
| Paul J. Thomas MD, LTC MC | Dept/Svc |

Key Words: Compliance, prednisone

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: |
|---|---|---|

| FY-80 MEDCASE Cost: | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective: To evaluate the compliance of patients receiving prednisone for malignant diseases.

Technical Approach: Study of urine samples for presence of steroid metabloites.

Progress during FY-80: No WRAMC patients entered on this study

Number of subjects to be studied before completion of study: --

Serious/unexpected side effects in subjects participating in project: --

Conclusions: Study closed by Group because of adequate numbers of patients entered.

Publications or Abstracts. FY-80: --

| Date: 20 OCT 80 | Protocol No: 6110 | Status: Interim / Final X |
|---|---|---|

Title of Project: SWOG PROTOCOL # 7865
Acute Lymphoblastic Leukemia Classification Portion of ALinC 13

| Starting Date: 20 JAN 80 | Estimated Completion Date: -- |
|---|---|

Principal Investigator: Frederick B. Ruymann MD, COL MC

| Associate Investigators: | Facility: |
|---|---|
| Paul J. Thomas MD, LTC, MC<br>Donald Karcher MD, LTC MC<br>Barbara Detrick-Hooks | Dept/Svc |

Key Words: Acute Lymphoblastic leukemia, classification

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: |
|---|---|---|
| FY-80 MEDCASE Cost: | Periodic Review Results: (to be filled in by DCI) | |

Study Objective: To evaluate the classification of acute lymphoblastic leukemia by studying cytochemical staining and immunologic characteristics of the blasts

Technical Approach: Evaluation of the blasts in the bone marrow by the use of cytochemical stains and immunologic studies.

Progress during FY-80: 8 WRAMC patients have been entered on this study with 2 T-cell and 6 "non-T, non-B cell" leukemias identified. Techniques have been established and verified in the pathology lab

Number of subjects to be studied before completion of study: --

Serious/unexpected side effects in subjects participating in project: --

Conclusions: T-cell and B-cell leukemias separable from other acute lymphoblastic leukemias and separate treatment protocols are based on the ability to make these distinctions. Study remains open.

Publications or Abstracts, FY-80: ---

| Date: 20 OCT 80 | Protocol No: 6111 | Status: Interim XFinalXX |
|---|---|---|

**Title of Project:** SWOG PROTOCOL # 7812
Evaluation of Anguidine in the Treatment of Central Nervous System Tumors, Phase II.

| Starting Date: 3 MAR 80 | Estimated Completion Date: -- |
|---|---|

**Principal Investigator:** Frederick B. Ruymann MD, COL MC

| Associate Investigators: | Facility: |
|---|---|
| Paul J. Thomas MD, LTC MC<br>Eugene George MD, COL MC | Dept/Svc |

**Key Words:** CNS Tumors, recurrent

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: |
|---|---|---|

| FY-80 MEDCASE Cost: | Periodic Review Results: (to be filled in by DCI) |
|---|---|

**Study Objective:** To study the effect of intravenous anguidine given weekly in children with recurrent brain tumors.

**Technical Approach:** Non-randomized study with dosage adjustments for impaired liver, kidney, and bone marrow function.

**Progress during FY-80:** No WRAMC patients have been entered on this study

Number of subjects to be studied before completion of study: --

Serious/unexpected side effects in subjects participating in project: --

**Conclusions:** This study remains open for non-astrocytomas

Publications or Abstracts. FY-80 -

| Date: 20 OCT 80 | Protocol No: 6112 | Status: Interim / FinalX |
|---|---|---|

Title of Project: SWOG PROTOCOL # 7843
Evaluation of Rubidazone in the Treatment of Children with Solid Tumors, Phase II.

| Starting Date: 14 JUL 80 | Estimated Completion Date: -- |
|---|---|

Principal Investigator: Frederick B. Ruymann MD, COL MC

| Associate Investigators: | Facility: |
|---|---|
| Paul J. Thomas MD, LTC MC | Dept/Svc |

Key Words: Brain tumor, recurrent; solid tumor, recurrent

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: |
|---|---|---|

| FY-80 MEDCASE Cost: | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective: To study the effect of rubidazone on recurrent solid tumors and brain tumors in children.

Technical Approach: Non-randomized study with dosage adjustments for impaired liver, kidney, and bone marrow function.

Progress during FY-80: No WRAMC patients were entered on this study.

Number of subjects to be studied before completion of study: --

Serious/unexpected side effects in subjects participating in project: --

Conclusions: Study remains open until supply of rubidazone is exhausted

Publications or Abstracts, FY-80: ---

| Date: 20 OCT 80 | Protocol No: 6113 | Status: Interim XXXXX |
|---|---|---|

Title of Project: SWOG PROTOCOL # 7617
Combination Chemotherapy with Vinblastin Sulfate and Bleomycin in Children with Metastatic Solid Tumors, Phase II.

| Starting Date: 24 MAR 80 | Estimated Completion Date: -- |
|---|---|

Principal Investigator: Frederick B. Ruymann MD, COL MC

| Associate Investigators: | Facility: |
|---|---|
| Paul J. Thomas MD, LTC MC | Dept/Svc |

Key Words: Solid tumors, pediatric, metastatic

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: |
|---|---|---|

| FY-80 MEDCASE Cost: | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective: To study the effect of treatment of metastatic pediatric solid tumors with vinblastin and bleomycin.

Technical Approach: Non-randomized study with dosage adjustments for impaired liver, kidney, or marrow function.

Progress during FY-80: No WRAMC patients were entered on this study.

Number of subjects to be studied before completion of study: --

Serious/unexpected side effects in subjects participating in project: --

Conclusions: Study remains open

Publications or Abstracts. FY-80: --

| Date: 30 OCT 80 | Protocol No: 6114 | Status: Interim / Final |
|---|---|---|

Title of Project: SWOG PROTOCOL # 7831

| Starting Date: 24 MAR 80 | Estimated Completion Date: 1 OCT 80 |
|---|---|

Principal Investigator: Frederick B. Ruymann MD, COL MC

| Associate Investigators: Paul J. Thomas MD, LTC MC | Facility: |
|---|---|
| | Dept/Svc |

Key Words: Acute leukemia, neocarzinostatin

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: |
|---|---|---|

| FY-80 MEDCASE Cost: | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective: To study the effectiveness of Neocarzinostatin in inducing remissions in acute leukemia in relapse.

Technical Approach: Non-randomized study of Neocarzinostatin given intravenously daily for 5 days.

Progress during FY-80: No WRAMC patients were entered on this study.

Number of subjects to be studied before completion of study: --

Serious/unexpected side effects in subjects participating in project: Severe myelosuppression and thrombocytopenia (Not at WRAMC)

Conclusions: Study closed by group because of toxicity

Publications or Abstracts. FY-80: --

| Date: 20 OCT 80 | Protocol No: 6115 | Status: Interim / Final |
|---|---|---|

Title of Project: SWOG PROTOCOL # 7376
Evaluation of the Natural History of Histiocytosis X

| Starting Date: 21 MAR 80 | Estimated Completion Date: -- |
|---|---|

Principal Investigator: Frederick B. Ruymann MD, COL MC

| Associate Investigators: | Facility: |
|---|---|
| Paul J. Thomas MD, LTC MC<br>Donald Karcher MD, LTC MC | Dept/Svc |

Key Words: Histiocytosis X

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: |
|---|---|---|

| FY-80 MEDCASE Cost: | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective: To characterize the course of Histiocytosis X in children who have not been previously treated.

Technical Approach: Studies of extent of disease immunologic competence, effects of disease, and effects of therapy at yearly intervals.

Progress during FY-80: No WRAMC patients have been entered on this study.

Number of subjects to be studied before completion of study: --

Serious/unexpected side effects in subjects participating in project: --

Conclusions: Study remains open

Publications or Abstracts. FY-80: --

| Date: 20 OCT 80 | Protocol No: 6116 | Status: Interim / Final |
|---|---|---|

Title of Project: SWOG PROTOCOL # 7612
MOPP plus Bleomycin and A-COPP with Involved Field Radiation Therapy in Stage III Hodgkin's Disease in Children.

| Starting Date: 2 MAR 80 | Estimated Completion Date: -- |
|---|---|

Principal Investigator: Frederick B. Ruymann MD, COL MC

| Associate Investigators: | Facility: |
|---|---|
| Paul J. Thomas MD, LTC MC<br>Donald Karcher MD, LTC MC<br>William Neglia MD, LTC MC<br>Monroe Levine MD, LTC MC | Dept/Svc |

Key Words: Hodgkin's disease, stage III

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: |
|---|---|---|

| FY-80 MEDCASE Cost: | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective: To study the effect of radiation therapy after chemotherapy with MOPP-Bleo (mustargen-nitrogen mustard, oncovin-vincristine, prednisone, procarbazine, and bleomycin) versus ACOPP (adriamycin, cytoxan, oncovin-vincristine, prednisone, and procarbazine).

Technical Approach: Randomized study between two chemotherapy arms, MOPP-Bleo and ACOPP, followed by radiation therapy and further chemotherapy with the same drugs.

Progress during FY-80: Two patients were entered on study and both appear to have had a complete response to therapy.

Number of subjects to be studied before completion of study: --

Serious/unexpected side effects in subjects participating in project: --

Conclusions: Study remains open

Publications or Abstracts. FY-80: --

| Date: 20 OCT 80 | Protocol No: 6117 | Status: Interim / Final |
|---|---|---|

Title of Project: SWOG PROTOCOL # 7712
Comparison of Treatment Regimens for the First CNS Relapse in Children with Acute Lymphocytic Leukemia, Phase III.

| Starting Date: 14 JUL 80 | Estimated Completion Date: --- |
|---|---|

Principal Investigator: Frederick B. Ruymann MD, COL MC

| Associate Investigators: | Facility: |
|---|---|
| Paul J. Thomas MD, LTC MC<br>William Neglia MD, LTC MC | Dept/Svc |

Key Words: CNS leukemia

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: |
|---|---|---|

| FY-80 MEDCASE Cost: | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective: To study the effectiveness of radiation therapy and intra thecal therapy in the treatment of CNS leukemia; to study the effect of maintenance intrathecal therapy versus no maintenance in duration of response.

Technical Approach: Randomized study after successful therapy with radiation therapy to the skull and intrathecal therapy with methotrexate, hydrocortisone, and cytosine arabinoside. Randomization between no further therapy versus intrathecal triple drug therapy every 8 weeks. Requires systemic reinduction protocol in addition.

Progress during FY-80: No WRAMC patients have been entered on this study.

Number of subjects to be studied before completion of study: --

Serious/unexpected side effects in subjects participating in project: --

Conclusions: Study remains open

Publications or Abstracts. FY-80: --

| Date: 20 OCT 80 | Protocol No: 6118 | Status: Interim<br>Annual |
|---|---|---|

Title of Project: SWOG PROTOCOL # 7905
ACOP-plus for Non-Hodgkin's Lymphoma in Children, Phase III.

| Starting Date: 14 JUL 80 | Estimated Completion Date: -- |
|---|---|

Principal Investigator: Frederick B. Ruymann MD, COL MC

| Associate Investigators: | Facility: |
|---|---|
| Paul J. Thomas MD, LTC MC<br>Donald Karcher MD, LTC MC<br>William Neglia MD, LTC MC | Dept/Svc |

Key Words: Non-Hodgkin's lymphoma, therapy

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: |
|---|---|---|
| FY-80 MEDCASE Cost: | Periodic Review Results: (to be filled in by DCI) | |

Study Objective: To study the effectiveness of radiation therapy with ACOP-plus chemotherapy versus radiation therapy with $LSA_2$-$L_2$ chemotherapy in obtaining and maintaining remissions in childhood non-Hodgkin's lymphoma.

Technical Approach: Randomized study between chemotherapy regimens ACOP-plus (adriamycin, cytoxan, vincristine, prednisone, 6-mercaptopurine) and $LSA_2$-$L_2$ (daunomycin, BCNU, hydroxyurea, L-asparaginase, 6-thioguanine, cytosine arabinoside, vincristine, prednisone, cytoxan, methotrexate, intrathecal methotrexate)

Progress during FY-80: Two WRAMC patients were entered on this study and both have achieved satisfactory remissions on the ACOP-plus arm.

Number of subjects to be studied before completion of study: --

Serious/unexpected side effects in subjects participating in project: --

Conclusions: Study remains open

Publications or Abstracts. FY-80: --

| Date: 20 OCT 80 | Protocol No: 6119 | Status: Interim / Final |
|---|---|---|

Title of Project: SWOG PROTOCOL # 7796
Adjuvant Chemotherapy for Localized Unilateral Retinoblastoma, Reese-Ellsworth Group 5, Phase III.

| Starting Date: 14 JUL 80 | Estimated Completion Date: -- |
|---|---|

Principal Investigator: Frederick B. Ruymann MD, COL MC

| Associate Investigators:<br>Paul J. Thomas MD, LTC MC<br>Paul Whitmore MD, LTC MC | Facility:<br>Dept/Svc |
|---|---|

Key Words: Retinoblastoma, unilateral, chemotherapy

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: |
|---|---|---|

| FY-80 MEDCASE Cost: | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective: To study the effect of chemotherapy versus no chemotherapy after enucleation of unilateral retinoblastoma, Reese-Ellsworth Group 5.

Technical Approach: Randomized study between chemotherapy with vincristine and cytoxan versus no chemotherapy.

Progress during FY-80: No WRAMC patients have been entered on this study

Number of subjects to be studied before completion of study: --

Serious/unexpected side effects in subjects participating in project: --

Conclusions: Study remains open

Publications or Abstracts, FY-80: --

| Date: 20 OCT 80 | Protocol No: 6120 | Status: Interim / ~~Final~~ |
|---|---|---|

Title of Project: SWOG PROTOCOL # 7837
Evaluation of Systemic Therapy for Children with T-cell Acute Lymphocytic Leukemia, Phase III.

| Starting Date: 14 JUL 80 | Estimated Completion Date: -- |
|---|---|

Principal Investigator: Frederick B. Ruymann MD, COL MC

| Associate Investigators: | Facility: |
|---|---|
| Paul J. Thomas MD, LTC MC<br>Donald Karcher MD, LTC MC<br>Barbara Detrick-Hooks<br>~~William Voglia, MD, LTC MC~~ | Dept/Svc |

Key Words: T-cell leukemia

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: |
|---|---|---|
| | | |

| FY-80 MEDCASE Cost: | Periodic Review Results: (to be filled in by DCI) |
|---|---|
| | |

Study Objective: To evaluate "Duke" chemotherapy regimen versus $LSA_2$-$L_2$ regimen in the treatment of children with T-cell leukemia.

Technical Approach: Randomized study between "Duke" regimen (vincristine, prednisone, L-aspariginase, adriamycin, cranial radiation, cytosine arabinoside, 6-thioguanine, methotrexate, cytoxan, intrathecal therapy with methotrexate, hydrocortisone, and cytosine arabinoside (ARA-C)) versus $LSA_2$-$L_2$ regimen (cytoxan, vincristine, prednisone, L-asparaginase, daunomycin, cranial radiation, intrathecal methotrexate, ARA-C, 6-thioguanine, BCNU, hydroxyurea) in the treatment of t-cell leukemia.
Progress during FY-80: Two WRAMC patients were entered on study and both achieved a satisfactory remission; however, one developed a testicular relapse followed by a systemic relapse and died.

Number of subjects to be studied before completion of study: --

Serious/unexpected side effects in subjects participating in project: --

Conclusions: Study remains open

Publications or Abstracts. FY-80: --

| Date: 29 OCT 80 | Protocol No: 6121 | Status: Interim |
|---|---|---|

Title of Project: SWOG PROTOCOL # 7799
Rare Tumor Registry.

| Starting Date: 4 Feb 80 | Estimated Completion Date: -- |
|---|---|

Principal Investigator: Frederick B. Ruymann MD, COL MC

| Associate Investigators: | Facility: |
|---|---|
| Paul J. Thomas MD, LTC MC<br>Donald Karcher MD, LTC MC | Dept/Svc |

Key Words: Rare tumor registry

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: |
|---|---|---|

| FY-80 MEDCASE Cost: | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective: To accumulate data on unusual, uncommon, infrequent, and rare tumors of childhood

Technical Approach: Registry with pathology review of patients with rare tumors.

Progress during FY-80: No WRAMC patients have been registered on this study.

Number of subjects to be studied before completion of study: --

Serious/unexpected side effects in subjects participating in project: --

Conclusions: Study remains open

Publications or Abstracts. FY-80: --

| Date: 20 OCT 80 | Protocol No: 6122 | Status: Interim / Final |
|---|---|---|

Title of Project: SWOG PROTOCOL # 7829
A Comparison of Two Dose Regimens of Intrathecal Methotrexate for Treatment of CNS leukemia, Phase II.

| Starting Date: 14 JUL 80 | Estimated Completion Date: -- |
|---|---|

Principal Investigator: Frederick B. Ruymann MD, CCL MC

| Associate Investigators: Paul J. Thomas MD, LTC MC | Facility: |
|---|---|
| | Dept/Svc |

Key Words: Leukemia, CNS,

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: |
|---|---|---|

| FY-80 MEDCASE Cost: | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective: To evaluate the effectiveness and toxicity of two methotrexate dosages given intrathecally for the treatment of CNS leukemia.

Technical Approach: Randomized study between standard dose methotrexate and low dose methotrexate given intrathecally for the treatment of CNS leukemia.

Progress during FY-80: No WRAMC patients have been entered on this study.

Number of subjects to be studied before completion of study:

Serious/unexpected side effects in subjects participating in project: --

Conclusions: Study remains open

Publications or Abstracts, FY-80: --

| Date: 20 OCT 80 | Protocol No: 6123 | Status: Interim Final |
|---|---|---|

Title of Project: SWOG PROTOCOL # 7623
Evaluation of Systemic Regimens in the Treatment of Acute Leukemia of Childhood (ALinC 12)

| Starting Date: 14 JUL 80 | Estimated Completion Date: -- |
|---|---|

Principal Investigator: Frederick B. Ruymann, MD, COL MC

| Associate Investigators: | Facility: |
|---|---|
| Paul J. Thomas MD, LTC MC<br>Donald Karcher MD, LTC MC<br>Barbara Detrick-Hooks<br>William Neglia MD, LTC MC | Dept/Svc |

Key Words: Acute lymphoblastic leukemia

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: |
|---|---|---|
| FY-80 MEDCASE Cost: | Periodic Review Results: (to be filled in by DCI) | |

Study Objective: To investigate more intensive chemotherapy versus less intensive chemotherapy in the treatment of high risk and standard risk acute lymphocytic leukemia

Technical Approach: Randomized study between three arms
1) vincristine, prednisone, L-asparaginase, cranial radiation with intrathecal methotrexate, 6-mercaptopurine, methotrexate, drugs during maintenance adjusted to keep the WBC at 3000-4500;
2) same as 1) 4xcept maintenance WBC kept at 500-3000;
3) vincristine, prednisone, L-asparaginase, cytoxan, intrathecal therapy with methotrexate, hydrocortisone, and cytosine arabinoside, intravenous methotrexate, oral 6-mercaptopurine.

Progress during FY-80: 6 WRAMC patients entered on study, 1 died during induction of CNS bleed, 5 successfully in primary maintained remission.

Number of subjects to be studied before completion of study: --

Serious/unexpected side effects in subjects participating in project: --

Conclusions: Study remains open until the second generation study (ALinC 13) is activated in late 1980 or early 1981.

Publications or Abstracts, FY-80: --

| Date: 20 OCT 80 | Protocol No: 6124 | Status: Interim |
|---|---|---|

Title of Project: SWOG PROTOCOL # 8000
The National Wilms' Tumor Study - 3.

| Starting Date: 24 MAR 80 | Estimated Completion Date: -- |
|---|---|

Principal Investigator: Frederick B. Ruymann MD, COL MC

| Associate Investigators:<br>Paul J. Thomas MD, LTC MC<br>David McLeod MD, LTC MC<br>William Neglia MD, LTC MC | Facility:<br><br>Dept/Svc |
|---|---|

Key Words: Wilms' Tumor

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: |
|---|---|---|

| FY-80 MEDCASE Cost: | Periodic Review Results:<br>(to be filled in by DCI) |
|---|---|

Study Objective: To investigate the therapy of different stage and histology Wilms' tumor with surgery, radiation therapy, and chemotherapy.

Technical Approach: Randomized study by stage (I-IV) and histology (favorable or unfavorable). Stage I (fav) - chemotherapy with vincristine and actinomycin-D for 10 weeks versus 6 months. Stage II (fav) - 2000 R versus no radiotherapy; vincristine, actinomycin-D, adriamycin versus intensive vincristine and actinomycin-D. Stage III (fav)- 1000 R versus 2000 R radiotherapy; Chemotherapy same as II. Stage IV and all (unfav)- radiation therapy with vincristine, actinomycin-D, adriamycin, cytoxan.

Progress during FY-80: Two patients were entered on therapy and both have remained free of disease so far.

Number of subjects to be studied before completion of study: --

Serious/unexpected side effects in subjects participating in project: --

Conclusions: Study remains open

Publications or Abstracts. FY-80: --

| Date: 20 OCT 80 | Protocol No: 6125 | Status: Interim Final X |
|---|---|---|

Title of Project: SWOG PROTOCOL # 7909
Evaluation of MOPP Adjuvant Chemotherapy in the Treatment of Localized Medulloblastoma and Ependymoma, Phase III.

| Starting Date: 18 SEP 80 | Estimated Completion Date: -- |
|---|---|

Principal Investigator: Frederick B. Ruymann MD, COL MC

| Associate Investigators:<br>Paul J. Thomas MD, LTC MC<br>William Neglia MD, LTC MC<br>Eugene George MD, COL MC | Facility:<br><br>Dept/Svc |
|---|---|

Key Words: Medulloblastoma, ependymoma, chemotherapy

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: |
|---|---|---|

| FY-80 MEDCASE Cost: | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective: To evaluate radiation therapy alone versus radiation therapy plus MOPP (mustargen - nitrogen mustard, oncovin - vincristine, prednisone, and procarbazine) chemotherapy in the treatment of localized medulloblastoma and ependymoma.

Technical Approach: Randomized study between radiation therapy and radiaition therapy plus MOPP.

Progress during FY-80: No WRAMC patients have been entered on this protocol

Number of subjects to be studied before completion of study: --

Serious/unexpected side effects in subjects participating in project: --

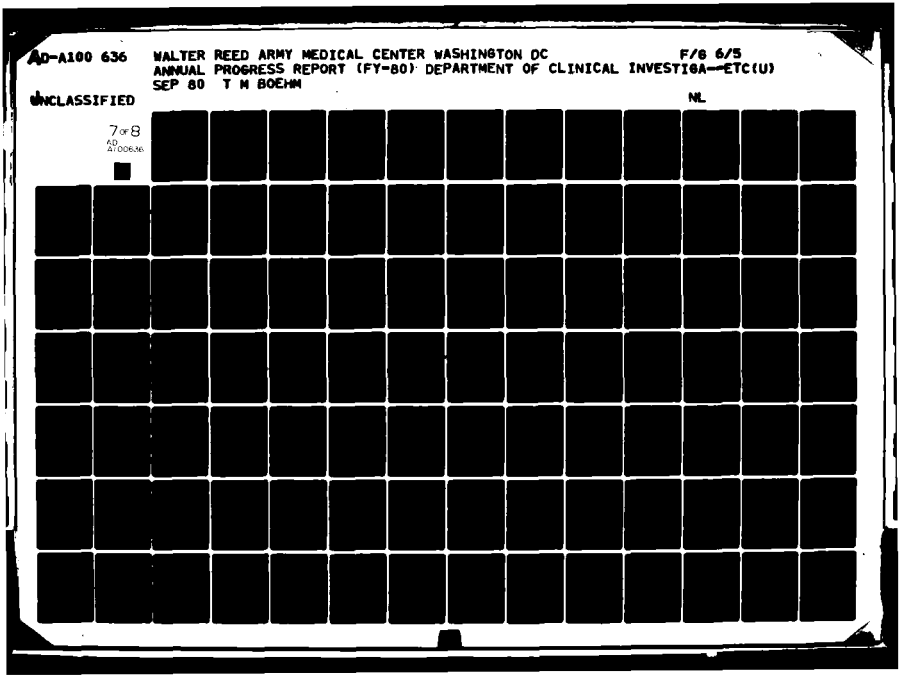
Conclusions: Study remains open

Publications or Abstracts. FY-80:
--

AD-A100 636 WALTER REED ARMY MEDICAL CENTER WASHINGTON DC F/G 6/5
ANNUAL PROGRESS REPORT (FY-80) DEPARTMENT OF CLINICAL INVESTIGA--ETC(U)
SEP 80 T M BOEHM

UNCLASSIFIED NL

7 of 8
AD
A 006.36



| Date: 20 OCT 80 | Protocol No: 6126 | Status: Interim / Final |
|---|---|---|

Title of Project: SWOG PROTOCOL # 7994
Therapy for Extra-ocular Retinoblastoma with Cyclophosphamide, Vincristine, Adriamycin and Irradiation.

| Starting Date: 14 JUL 80 | Estimated Completion Date: -- |
|---|---|

Principal Investigator: Frederick B. Ruymann MD, COL MC

| Associate Investigators: | Facility: |
|---|---|
| Paul J. Thomas MD, LTC MC<br>Paul Whitmore MD, LTC MC<br>William Neglia MD, LTC MC | Dept/Svc |

Key Words: Retinoblastoma, extra-ocular

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: |
|---|---|---|
| FY-80 MEDCASE Cost: | Periodic Review Results: (to be filled in by DCI) | |

Study Objective: To study the effect of chemotherapy and radiation therapy in the treatment of extra-ocular retinoblastoma by class (degree and type of spread)

Technical Approach: Non-randomized study with treatment regimen specified for each class (1-5). Class 1 - chemotherapy with vincristine and cytoxan; class 2 - chemotherapy with vincristine, cytoxan, adriamycin, intrathecal three drug therapy, and radiation therapy; class 3, 4, and 5 use the same treatments used in class 2 but vary the length of therapy and use the intrathecal therapy only if there is danger of spread to the spinal fluid.

Progress during FY-80: One patient has been entered on this study and is tolerating the therapy very well.

Number of subjects to be studied before completion of study: --

Serious/unexpected side effects in subjects participating in project: --

Conclusions: Study remains open

Publications or Abstracts. FY-80: --

| Date: 20 OCT 80 | Protocol No: 6127 | Status: Interim / Final X |
|---|---|---|

Title of Project: SWOG PROTOCOL # 7721
Evaluation of Induction, Remission Maintenance with and without Periodic Reinforcement, and CNS Prophylaxis in Acute Non-Lymphocytic Leukemia, Phase III.

| Starting Date: 2 MAY 80 | Estimated Completion Date: -- |
|---|---|

Principal Investigator: Frederick B. Ruymann, MD, COL MC

| Associate Investigators: | Facility: |
|---|---|
| Paul J. Thomas, MD, LTC MC<br>William Neglia, MD, LTC, MC<br>Donald Karcher, MD, MAJ MC | Dept/Svc |

Key Words: Acute Non-Lymphocytic leukemia

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: |
|---|---|---|
| FY-80 MEDCASE Cost: | Periodic Review Results: (to be filled in by DCI) | |

Study Objective: To investigate the induction rate in non-lymphocytic leukemia of vincristine, adriamycin, and prednisone (VAP); to investigate the effectiveness of CNS prophylaxis with radiation therapy and intrathecal therapy with methotrexate, hydrocortisone, and cytosine arabinoside; to investigate the effect of periodic reinforcement (VAP) on maintenance therapy.

Technical Approach: Standard VAP induction with alternate in duction with 6-thioguanine and cytosine arabinoside (ARA-C) if VAP induction fails. CNS prophylaxis with radiation therapy and triple intrathecal drug therapy. Randomized maintenance arms consisting of cycles of 6-thioguanine and ARA-C; cytoxan, vincristine, ARA-C, and prednisone; ± vincristine, adriamycin, prednisone.

Progress during FY-80: Two patients were entered on study. One patient died of overwhelming varicella infection during induction; the other has achieved a satisfactory remission and is on maintenance.

Number of subjects to be studied before completion of study: --

Serious/unexpected side effects in subjects participating in project: --

Conclusions: Study remains open

Publications or Abstracts. FY-80: --

| Date: 20 OCT 80 | Protocol No: 6128 | Status: Interim |
|---|---|---|

Title of Project: SWOG PROTOCOL # 7901
Rescue Therapy for Non-CNS Extra-medullary Disease in children with Acute Lymphoblastic Leukemia, Phase III

| Starting Date: 16 MAY 80 | Estimated Completion Date: -- |
|---|---|

Principal Investigator: Frederick B. Ruymann MD, COL MC

| Associate Investigators: | Facility: |
|---|---|
| Paul J. Thomas MD, LTC, MC<br>William Neglia MD, LTC MC | Dept/Svc |

Key Words: Extra-medullary leukemia

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: |
|---|---|---|
| FY-80 MEDCASE Cost: | Periodic Review Results: (to be filled in by DCI) | |

Study Objective: To determine the effectiveness of radiation therapy to local areas of extra-medullary, non-CNS leukemia.

Technical Approach: Non-randomized standard therapy for various site of extramedullary leukemia -- including kidneys, testes, mediastinum, ocular sites, and bone. Systemic therapy also required.

Progress during FY-80: One patient with T-cell leukemia with a testicular relapse responded well to the radiation therapy to the testes but suffered a systemic relapse and died.

Number of subjects to be studied before completion of study: --

Serious/unexpected side effects in subjects participating in project: --

Conclusions: Study remains open

Publications or Abstracts. FY-80: --

| Date: 20 OCT 80 | Protocol No: 6129 | Status: Interim Final XX |
|---|---|---|

Title of Project: SWOG PROTOCOL # 7906
Multidrug Adjuvant Chemotherapy in Non-metastatic Osteosarcoma, Comparison of CONPADRI-I with CONPADRI-V

| Starting Date: 30 MAY 80 | Estimated Completion Date: -- |
|---|---|

Principal Investigator: Frederick B. Ruymann, MD, COL MC

| Associate Investigators:<br>Paul J. Thomas MD, LTC MC<br>Monroe Levine, MD, LTC MC | Facility:<br>Dept/Svc |
|---|---|

Key Words: Osteosarcoma, chemotherapy

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: |
|---|---|---|

| FY-80 MEDCASE Cost: | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective: To compare two chemotherapy and surgery regimens in the treatment of osteosarcoma (non-metastatic).

Technical Approach: Randomized study between surgery followed by CONPADRI-I chemotherapy (cytoxan, vincristine, melphalan, and adriamycin) versus high dose methotrexate for 7 courses followed by surgery followed by cytoxan, vincristine, melphalan, and adriamycin.

Progress during FY-80: No WRAMC patients have been entered on this protocol

Number of subjects to be studied before completion of study: --
Serious/unexpected side effects in subjects participating in project: --

Conclusions: Study remains open

Publications or Abstracts, FY-80: --

| Date: 22 OCT 80 | Protocol No: 6130 | Status: Interim / Final XX |
|---|---|---|

Title of Project: SWOG PROTOCOL # 8002
Combination Chemotherapy with Adriamycin, Cis-diamminedichloroplatinum, Vincristine, and Cytoxan in Children with Metastatic Neuroblastoma, Stage IV.

| Starting Date: 1 OCT 80 | Estimated Completion Date: -- |
|---|---|

Principal Investigator: Frederick B. RUymann, MD, COL MC

| Associate Investigators: | Facility: |
|---|---|
| Paul J. Thomas, MD, LTC, MC | Dept/Svc |

Key Words: Neuroblastoma, Stage IV, chemotherapy

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: |
|---|---|---|
| FY-80 MEDCASE Cost: | Periodic Review Results: (to be filled in by DCI) | |

Study Objective: To investigate the effectiveness and toxicities of four drug chemotherapy on childhood metastatic neuroblastoma.

Technical Approach: Non randomized study using vincristine, cytoxan, Adriamycin, and cis-platinum in children with stage IV neuroblastoma. Patient must have a measurable lesion.

Progress during FY-80: No WRAMC patients have been entered on this protocol.

Number of subjects to be studied before completion of study: --

Serious/unexpected side effects in subjects participating in project: --

Conclusions: Study remains open

Publications or Abstracts. FY-80: --

| Date: 20 OCT 80 | Protocol No: 6131 | Status: Interim / Final X |
|---|---|---|

Title of Project: SWOG PROTOCOL # 8075
Circulating Immune complexes in Pediatric Malignancies

| Starting Date: 1 OCT 80 | Estimated Completion Date: -- |
|---|---|

Principal Investigator: Frederick B. Ruymann, MD, COL MC

| Associate Investigators:<br>Paul J. Thomas, MD, LTC MC<br>Barbara Detrick-Hooks | Facility:<br>Dept/Svc |
|---|---|

Key Words: Immune complexes, malignancy

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: |
|---|---|---|

| FY-80 MEDCASE Cost: | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective: To measure levels of circulating immune complexes before therapy, during the course of therapy, and after therapy in pediatric patients with acute lymphocytic leukemia, neuroblastoma, acute non-lymphocytic leukemia, and osteosarcoma.

Technical Approach: Serum samples analyzed in reference laboratory for presence of circulating immune complexes, and correlation with type of disease, therapy given, and success of therapy made with the immune complexes data.

Progress during FY-80: No WRAMC patients have yet been entered on this study.

Number of subjects to be studied before completion of study: -

Serious/unexpected side effects in subjects participating in project: --

Conclusions: Study remains open

Publications or Abstracts. FY-80:

| Date: 6 Oct 80 | Protocol No: 7111 | Status: ~~Interim~~ Final |
|---|---|---|

Title of Project: Interruption of Maintenance Neuroleptic Therapy

| Starting Date: 15 Oct 77 | Estimated Completion Date: 30 Sep 80 |
|---|---|

Principal Investigator: R. Harlan Bridenbaugh, COL, MC

| Associate Investigators:<br>James G. Hunter, MAJ, MC<br>Robert L. Bank, MAJ, MC | Facility:<br>Walter Reed Army Medical Center<br>Dept/Svc Psychiatry |
|---|---|

Key Words: Prolactin; Neuroleptic Therapy; Discontinuance

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: |
|---|---|---|
| FY-80 MEDCASE Cost: | Periodic Review Results: (to be filled in by DCI) | |

Study Objective: (1) To determine the immediate and long-term results of interrupting maintenance neuroleptic therapy; (2) to compare three and twelve week schedules for tapering neuroleptic therapy; and (3) to determine the relationship between serum prolactin and clinical status during reduction of neuroleptic therapy.

Technical Approach: Systematic evaluation of patient's mental status and psychological functioning by standardized rating scales. Monitoring of serum prolactin levels during tapering and after discontinuance of maintenance neuroleptic therapy.

Progress during FY-80: See attached continuation sheet.

Number of subjects to be studied before completion of study: See attached continuation sheet.

Serious/unexpected side effects in subjects participating in project:

Conclusions: No definitive conclusions can be made but it does appear that, for some patients, doses of maintenance neuroleptics too low to raise prolactin levels will maintain remission from psychosis.

Publications or Abstracts, FY-80:
None.

Protocol No: 7111 "Interruption of Maintenance Neuroleptic Therapy"

Progress during FY-80: Three (3) more patients were entered into the study during FY-80, bringing the total number of subjects to six (6). Two patients were unable to maintain remission without neuroleptics (one was hospitalized and the other was re-started on neuroleptic therapy as an outpatient). The third patient became hypomanic and responded to lithium carbonate. Prolactin levels for patients from FY-80 are pending on samples that had been kept frozen at -70° C. Values from patients studied in FY-78 were within the normal range but did show a small decline, within the normal range, in relationship to tapering doses of neuroleptics. The sample of subjects is too small to compare different rates of tapering medication. The project was of heuristic value in that prolactin level determinations are now routinely used within the department to assess patient compliance and/or degree of bioavailablility of prescribed neuroleptics.

Number of subjects to be studied before completion of study: NA; project terminated due to reassignment of Principal Investigator.

| Date: 6 Oct 80 | Protocol No: 7214 | Status: Interim / Final |
|---|---|---|

Title of Project: Pre- and Post-Discharge Assessment of Psychiatric Patients

| Starting Date: Jan 77 | Estimated Completion Date: Sep 80 |
|---|---|

Principal Investigator: Donald W. Morgan, COL, MC

| Associate Investigators:<br>R. Harlan Bridenbaugh, COL, MC<br>Emmanuel G. Cassimatis, LTC, MC<br>Charles R. Privitera, LTC, MC | Facility:<br>Walter Reed Army Medical Center<br><br>Dept/Svc Psychiatry |
|---|---|

Key Words: psychiatric patients; MEB; follow-up

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: |
|---|---|---|
| FY-80 MEDCASE Cost: | Periodic Review Results: (to be filled in by DCI) | |

Study Objective: To establish, with the Department of Psychiatry, WRAMC, a structured method of assessing pre- and post-discharge levels of psychosocial function of psychiatric patients seen by a Medical Evaluation Board (MEB); to compare pre-discharge morbidity with post-discharge function of psychiatric patients seen by an MEB.

Technical Approach: From Jan 77 to Aug 77, 200 consecutive patients seen by an MEB were entered into the study. Baseline psychological and demographic data were obtained while still on an inpatient status. Patients have been followed every three months by mailed questionnaires to monitor emotional and social-vocational functioning. Follow-up for each participant was terminated two years after departing WRAMC.

Progress during FY-80: See attached continuation sheet.

Number of subjects to be studied before completion of study: 200

Serious/unexpected side effects in subjects participating in project: NA

Conclusions: It is feasible to follow patients by mail questionnaire. More specific information concerning outcome will be available when the questionnaires are systematically assessed.

Publications or Abstracts, FY-80: None.

Protocol No.: 7214 "Pre- and Post-Discharge Assessment of Psychiatric Patients"

Progress during FY-80: The return rate for the questionnaire has been approximately 85%. Three patients have committed suicide. A wide range of outcomes are thus far apparent with about one-third of the group experiencing rehospitalization thus far. We have completed the operational phse and the periodic mailing of questionnaires. Examination of the information obtained is approximately one-third completed. Preparation of final report is planned in the next 12 months.

| Date: 6 Oct 80 | Protocol No: 7217 | Status: [illegible] Final |
|---|---|---|

Title of Project: Management of Impairment of Accommodation Secondary to Psychotropic Medication

| Starting Date: 15 Apr 78 | Estimated Completion Date: 30 Sep 80 |
|---|---|

Principal Investigator: R. Harlan Bridenbaugh, COL, MC

| Associate Investigators:<br>Richard J. Sapolis, MAJ, MC<br>Daniel L. LaDuke, CPT, MC<br>Mary Barbara Papineau, CPT, MC | Facility: Walter Reed Army Medical Center<br>Dept/Svc Psychiatry |
|---|---|

Key Words: Blurred Vision; Anticholinergic/Psychotropic Medication

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: |
|---|---|---|
| FY-80 MEDCASE Cost: | Periodic Review Results: (to be filled in by DCI) | |

Study Objective: (1) To determine the incidence of impairment of accommodation secondary to the anticholinergic action of neuroleptics, tricyclic antidepressants, and anti-Parkinson agents; (2) to evaluate the effectiveness of optical management of such impairment secondary to the above psychotropic agents; and (3) to examine the relationship between dosage of medication and degree of impairment of accommodation.

Technical Approach: Patients who were receiving psychotropic agents that have anticholinergic action were evaluated by means of a near vision reading card. If blurring of vision was noted at a normal reading distance (16" to 20"), then patient was tried on + diopter eyeglasses in increasing increments of +0.5 dipoter. Final strength of glasses dispensed was determined by patient choice alone. Level of medication was recorded and monitored and patients were re-evaluated at weekly intervals.

Progress during FY-80: See attached continuation sheet.

Number of subjects to be studied before completion of study: See attached continuation sheet

Serious/unexpected side effects in subjects participating in project: NA

Conclusions: Blurring of vision from the anticholinergic action of certain psychotropic agents is very prevalent on an acute treatment psychiatric ward. The immediate management is the same as for presbyopia, i.e., the application of +dipoter reading glasses.

Publications or Abstracts, FY-80:

None.

Protocol No: 7217 "Management of Impairment of Accommodation Secondary to Psychotropic Medication"

Progress during FY-80: Nineteen (19) patients were formally entered into the project in 1978 and a large number of patients, over 30, were issued eyeglasses but not entered into the study. Screening was completed in June 1978 on Ward 108 on all patients receiving psychotropics with anticholinergic effect. Two-thirds of this sample showed evidence of impairment of accommodation. The results of this study were presented to the annual Department of Psychiatry Research Symposium in June 1978. Also, the results of this study have been used by the Principal Investigator in the teaching of psychopharmacology. A final report is being prepared at the present time and will be submitted through appropriate channels upon completion of same.

Number of subjects to be studied before completion of study: Nineteen (19) patients were studied in 1978. No further study is planned.

| Date: 6 Oct 80 | Protocol No: 7213 | Status: Interim / Final |
|---|---|---|

Title of Project: Physostigmine Infusion and Lithium Responsivity

| Starting Date: 25 Feb 80 | Estimated Completion Date: Jun 81 |
|---|---|

Principal Investigator: Paul Newhouse, CPT, MC

| Associate Investigators:<br>R. Harlan Bridenbaugh, COL, MC<br>Robert Watson, COL, MC | Facility:<br>Walter Reed Army Medical Center<br><br>Dept/Svc Psychiatry |
|---|---|

Key Words: Physostigmine-lithium responsivity

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: |
|---|---|---|

| FY-80 MEDCASE Cost: | Periodic Review Results:<br>(to be filled in by DCI) |
|---|---|

*Study Objective: To examine the mental status changes induced by physostigmine infusion and to determine if lithium responsivity is related to such mental status changes.

*Technical Approach: Patients who are going to begin lithium therapy are observed for 48 hours with no neuroleptic medication. Patient then receives two infusions (one placebo, one physostigmine - 4 mg.) on two separate days utilizing a randomized, double-blind, crossover design. Systematized ratings of mental status are made while undergoing the infusions and while on lithium therapy.

*Progress during FY-80: See attached continuation sheet.

Number of subjects to be studied before completion of study: Ten (10)

Serious/unexpected side effects in subjects participating in project: None

Conclusions: None.

Publications or Abstracts, FY-80: None.

Protocol No.: 7213 "Physostigmine Infusion and Lithium Responsivity"

Progress during FY-89: One patient has been entered into the study. Two patients have declined participation. Multiple factors, including recent reassignment of an Associate Investigator (RHB), have impeded progress on this protocol, and as of this date it is doubtful that further work is feasible. However, the Principal Investigator desires to keep protocol extant in the event other associate investigators can be obtained.

| Date: 6 Oct 80 | Protocol No: 7219 | Status: [illegible] Final |
|---|---|---|

Title of Project: Reliability of Serum Tricyclic Antidepressant Levels

| Starting Date: 6 Oct 79 | Estimated Completion Date: Nov 79 |
|---|---|

Principal Investigator: Robert L. Bank, MAJ, MC

| Associate Investigators: R. Harlan Bridenbaugh, COL, MC | Facility: Walter Reed Army Medical Center |
|---|---|
| | Dept/Svc Psychiatry |

Key Words: Antidepressant, tricyclic; blood levels; reliability

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: |
|---|---|---|

| FY-80 MEDCASE Cost: | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective: To examine the reliability and validity of laboratory reporting of serum tricyclic antidepressant levels.

Technical Approach: 20 cc. blood samples were drawn from patients taking amitriptyline. 4-5 ml. serum samples were mailed simultaneously to two different commercial laboratories offering analysis for antidepressants.

Progress during FY-80: See attached continuation sheet.

Number of subjects to be studied before completion of study: Seven

Serious/unexpected side effects in subjects participating in project: None

Conclusions: Until further data is gathered from or provided by laboratories offering tricyclic antidepressant blood levels, such blood levels should be interpreted with caution.

Publications or Abstracts, FY-80: None.

Protocol No: 7219 "Reliability of Serum Tricyclic Antidepressant Levels"

Progress during FY-80: Seven (7) patients were entered into the study. Levels determined by each of the two labs were in fair agreement in the lower range (50 to 150 ng/ml). However, one patient's levels were returned as 553 ng/ml vs. 191 ng/ml (both these are in the higher therapeutic range). The second part of the study (i.e., to send sequential, identical serum samples to the same lab) was not undertaken because of the relatively poor correlation of results noted between the two labs.

| Date: 6 Oct 80 | Protocol No: 7220 | Status: XXXXXXX Final |
|---|---|---|

Title of Project: The Developmental Significance of Transitional Objects

| Starting Date: 3 Mar 80 | Estimated Completion Date: 30 Jun 80 |
|---|---|

Principal Investigator: James G. Hunter, MAJ, MC

| Associate Investigators: R. Harlan Bridenbaugh, COL, MC | Facility: Walter Reed Army Medical Center<br>Dept/Svc Psychiatry |
|---|---|

Key Words: Transitional objects/pediatric clinic/child psychiatry clinic

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: |
|---|---|---|
| FY-80 MEDCASE Cost: | Periodic Review Results: (to be filled in by DCI) | |

Study Objective: (a) to compare the incidence of the history of transitional objects in a general pediatric population, ages 6-10, with the incidence of transitional objects in the same age group in an outpatient child psychiatric population; and (b) to correlate the presence or absence of transitional objects with maternal assessment of problem behaviors in their children as measured by the Conners' Behavioral Rating Scale.

Technical Approach: Mothers accompanying children between the ages of 6-10 to either the pediatric or child psychiatry clinic were asked to complete questionnaires that polled demographic and behavioral information.

Progress during FY-80: Questionnaires were completed by 50 mothers in the pediatric clinic and by 25 mothers in the child psychiatry clinic. Results were placed on flow sheets and statistical evaluation was completed. The Wilcoxon Rank Sum Test was used to compare the two clinic samples. The Principal Investigator presented results of the study to the Annual Department of Psychiatry Research Symposium on 13 June 1980.

Number of subjects to be studied before completion of study: See "Progress during FY-80"

Serious/unexpected side effects in subjects participating in project: None

Conclusions: The presence or absence of a transitional object, as reported by maternal polling, has no relationship to the presence of psychopathology as measured by the behavior symptom checklist employed in this study.

Publications or Abstracts, FY-80:

Paper presented to Annual Department of Psychiatry Research Symposium

| Date: 12/1/80 | Protocol No: 7221 | Status: Interim X<br>Final |
|---|---|---|

Title of Project:

"The Effect of Hypnotic Intervention on the Electroencephalogram of Low, Medium and High Hypnotic Patients"

| Starting Date: June 1980 | Estimated Completion Date: February 1981 |
|---|---|

Principal Investigator: Harold J. Wain, PhD

| Associate Investigators:<br>Glenn Harper, MD<br>Bahaman Jabbari, MD | Facility: WRAMC |
|---|---|
| | Dept/Svc: Department of Psychiatry<br>Neurology Service |

Key Words:

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: |
|---|---|---|

| FY-80 MEDCASE Cost: | Periodic Review Results:<br>(to be filled in by DCI) |
|---|---|

Study Objective:

To explore the effects of hypnotic intervention on the encephalographic tracings of low, medium and high hypnotic capacity patients before, during and after the induction of a hypnotic trance.

Technical Approach:

Each subject is to be evaluated for their hypnotic capacity. The subjects are then placed in low, medium and high hypnotic groupings. EEG recordings are then taken on one occasion before, during and after the induction of a hypnotic state.

Progress during FY-80:

Six subjects have been evaluated as of this date.

Number of subjects to be studied before completion of study: 9

Serious/unexpected side effects in subjects participating in project: None.

Conclusions:

Cannot draw conclusions at this time.

Publications or Abstracts, FY-80:

| Date: 10 OCT 1980 | Protocol No: 7300 | Status: Interim X / Final |
|---|---|---|

Title of Project: LSD Follow-Up Study (Establishment of Normal Controls for Neurophyschological Examination)

| Starting Date: October 1978 | Estimated Completion Date: October 1983 |
|---|---|

Principal Investigator: Francis J. Fishburne, Jr., LTC, MS

| Associate Investigators: | Facility: Walter Reed Army Medical Center |
|---|---|
| | Dept/Svc Psychology Service |

Key Words: Neuropsychological Examination, Normal Controls

| Accumulative MEDCASE Cost: $0 | Accumulative Contract Cost: $0 | Accumulative Supply Cost: $0 |
|---|---|---|

| FY-80 MEDCASE Cost: $0 | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective: To obtain approximately seventy-five (75) volunteer subjects for neurophysological evaluation to compare with LSD follow-up study subject population.

Technical Approach: Subjects were to be screened with preliminary neurological examination, electroencephalography, and computerized axial tomography (CATSCAN). Computerized axial tomography support provided by NIH has been terminated and this portion of the screening has been dropped.

Progress during FY-80: Ten volunteer subjects have been evaluated providing a current total of 37 normal control subjects evaluated.

Number of subjects to be studied before completion of study: 75

Serious/unexpected side effects in subjects participating in project: NONE

Conclusions: N/A

Publications or Abstracts, FY-80: NONE

Work Unit No.: 7300

Title of Project: LSD Follow-Up Study (Establishment of Normal Controls for Neuropsychological Examination)

Investigators: Francis J. Fishburne, LTC, MSC

Objectives: To obtain base rate values of a neurologically screened normal adult population with respect to the Halstead-Reitan neuropsychological battery.

Technical: Volunteer subjects are first screened using a clinical neurological examination, electroencephalography, and computerized axial tomography (CAT scan). Subjects who are normal on all screening procedures are then administered the Halstead-Reitan neuropsychological battery.

Progress and Results: Thirty-seven (37) subjects have been evaluated to date.

Conclusions: Deferred.

Funds Utilized: None

Funding Requirements, FY-81: None.

Publications: None.

Type of Report: Interim.

| Date: 9 October 1980 | Protocol No: 7301 | Status: Interim |
|---|---|---|

Title of Project: Baseline MMPI Profile for an Active Duty Military Population

| Starting Date: 3 January 1980 | Estimated Completion Date: October 1981 |
|---|---|

Principal Investigator: Francis J. Fishburne, Ph.D., Chief, Psychology Service

| Associate Investigators: Bruce R. Lockwood, Ph.D. Thomas W. Waddell, Ph.D. | Facility: Walter Reed Army Medical Center |
|---|---|
| | Dept/Svc: Psychology Service, Department of Psychiatry |

Key Words: MMPI, Military Norms

| Accumulative MEDCASE Cost: NONE | Accumulative Contract Cost: $1,550 | Accumulative Supply Cost: $1,574 |
|---|---|---|

| FY-80 MEDCASE Cost: NONE | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective: To obtain normative data for an active duty military population on the various scales comprising the Minnesota Multiphasic Personality Inventory, an objective personality assessment device frequently used by mental health professionals. It is expected that the normative data will be collected from approximately 5,000 active duty military personnel.

Technical Approach: The technical approach remains unchanged in terms of the experimental instruments being utilized; however, some modification has been made in the order in which the instruments will be administered. Following the explanation of the research project and the subjects' signing of the volunteer agreement form, each subject will be administered the MMPI, the Shipley Institute of Living Scale, and a background information questionnaire, in that order. The experimental data will be collected in one session of approximately two hours in length.

Progress during FY-80: Experimental procedures have been devised in detail and the testing materials necessary for the project have been acquired. Two pilot projects, totaling 50 subjects, have been conducted to test the feasibility and practicality of the research design, with the experimental procedures being (see next page)

Number of subjects to be studied before completion of study: 5,000

Serious/unexpected side effects in subjects participating in project: NONE

Conclusions: Undetermined

Publications or Abstracts, FY-80: NONE

Progress during FY-80: (Continued)

determined to be effective, with minor alterations in the details of the administration of the materials. A contract with a civilian service provider has been made for the scoring of the MMPI data to be collected during the study. It is anticipated that actual data collection will be begun in approximately one month.

## CLINICAL INVESTIGATION PROGRAM

Work Unit No.: 7301

Funds Utilized, FY-80: $3,124

Funding Requirements, FY-81:

Personnel: NONE

Equipment: NONE

Supplies: Xerox paper, pencils, and other miscellaneous costs: $1,000

Travel: Presentation of paper at American Psychological Association convention in Los Angeles, California: $1,000 approximately

Other: Contracts for service (MMPI scoring by computer): $1,550
Publication and reprints: $500

| Date: 10 Oct '80 | Protocol No: 9010 | Status: Interim X<br>Final |
|---|---|---|

Title of Project: Vitamin $B_6$ metabolism in patients receiving INH and patients with sideroblastic anemia.

| Starting Date: Sep 78 | Estimated Completion Date: Dec'81 |
|---|---|

Principal Investigator: John A. Kark, LTC, MC

| Associate Investigators:<br>MJ Haut, LTC, MC retired.<br>GS Schechter, MD, Chief, Hem-Onc. Washington V.A. Hosp. | Facility: Hematology, Internal Medicine: WRAIR, WRAMC |
|---|---|
| | Dept/Svc 1. Hem/Med WRAIR, C.I.S., WRAMC |

Key Words: Vitamin $B_6$, Red Cells, Isoniazid, Sideroblastic Anemia

| Accumulative MEDCASE Cost: none | Accumulative Contract Cost: none | Accumulative Supply Cost: none |
|---|---|---|
| FY-80 MEDCASE Cost: None | Periodic Review Results: (to be filled in by DCI) | |

*Study Objective:

1. To improve the management of isoniazid therapy.
2. To identify biochemical indicators for $B_6$-responsive sideroblastic anemia.

Technical Approach: 1. Pyridoxal kinase was separated from hemoglobin by chromatography and the effects of hemoglobin binding on kinetics were defined. 2. Previous data was collated, analyzed, illustrated, and manuscripts were drafted. 3. Plans were made to pursue measurements of INH metabolites in patients. 4. Plans were made to pursue correlations with heme-enzymes in sideroblastic anemias.

Progress during FY-80:

1. The effect of pyridoxal binding to hemoglobin on pyridoxal kinase kinetics was defined. 2. Three major papers were developed in draft.

Number of subjects to be studied before completion of study:

Serious/unexpected side effects in subjects participating in project:
Patient involvement is only to donate small venous blood samples. None.

Conclusions:

1. A rapid method of analysis of erythrocyte pyridoxal kinase activity was developed. 2. Dissociation of biochemical and hematologic responses to $B_6$ were found in the sideroblastic anemias.

Publications or Abstracts, FY-80:
see next page.

# 9010 John A. Kark, LTC, MC

Publications: none completed in FY '80.

The following manuscript has been completed and will be submitted in the next month: Kark, J.A., Haut, M.J., et. al. A rapid flurometric assay for erythrocyte pyridoxal kinase activity.

The following manuscripts are written in draft:

1. Dissociation of erythrocyte pyridoxal phosphate levels and hematologic response to vitamin $B_6$ in the sideroblastic anemias.
2. Erythrocyte metabolism of vitamin $B_6$ in the sideroblastic anemias.

(Authors: Kark, J.A., Haut, M.J., and Schechter, GS.).

Funding:

Funds utilized, FY-80: none

Funding requirements, FY-81:

| | |
|---|---|
| Personnel: | GS-09 10 hours |
| Supplies: | $1,000 |

Work Unit #9012

DATE: 30 September 1980 (Updated 30)
TITLE OF PROJECT: The Effect of Infectious Hepatitis on Erythroid Colony Formation in the Plasma Clot Culture System

Status: Interim X Final

STARTING DATE:
ESTIMATED COMPLETION DATE:
PRINCIPAL INVESTIGATOR: MAJ August J. Salvado, M.D. MC
ASSOCIATE INVESTIGATORS:
MAJ William M. Butler, M.D. MC
LTC Jeffrey L. Berenberg, M.D. MC
Nancy Josza
FACILITY: Walter Reed Army Medical Center
SERVICE: Hematology-Oncology
Department of Medicine
KEY WORDS: Infectious Hepatitis, Plasma Clot Culture System

| ACCUMULATIVE MEDCASE COST: | ACCUMULATIVE CONTRACT COST: | ACCUMULATIVE SUPPLY COST: |
|---|---|---|
| | | |

FY-80 MEDCASE COST:
PERIODIC REVIEW RESULTS:

STUDY OBJECTIVE: To determine whether the hepatitis virus injures erythroid progenitors (CFU-E and BFU-E) in the bone marrow and to clarify the mechanisms of this injury.

TECHNICAL APPROACH: The plasma clot culture technique for erythroid progenitors is used to determine colony growth of CFU-E and BFU-E from marrow of patients with acute hepatitis. Normal control marrow is obtained as an extra aspirate from patients having marrows done as part of a staging work-up for malignancy.

PROGRESS DURING FY-80: This project has been abandoned due to lack of evaluable patients, problems with erythropoietin supply and loss of our technician. One patient with hepatitis had been studied, this patient showed normal BC progenitor growth in culture with no evidence of a serum suppressor. He had no problems with the marrow aspiration and continues to be followed in the WRAMC Hematology Clinic.

NUMBER OF SUBJECTS TO BE STUDIED BEFORE COMPLETION OF STUDY: Closed
SERIOUS/UNEXPECTED SIDE EFFECTS IN SUBJECTS PARTICIPATING IN PROJECT:

CONCLUSIONS:

None

PUBLICATIONS/ABSTRACTS, FY-80:

None

| Date: 10 Oct '80 | Protocol No: 9016 | Status: Interim X<br>Final |
|---|---|---|

Title of Project: Pyridoxine as a treatment for sickle hemoglobinopathies

| Starting Date: June '77 | Estimated Completion Date: Aug 81 |
|---|---|

Principal Investigator: John A. Kark, LTC, MC

| Associate Investigators:<br>L.S. Lessin, MD, Prof Med, GWUSM<br>R. Bongiovanni, CPT, MSC | Facility: 1. Hematol lab, WRAIR<br>2. Biochem. lab, WRAMC<br>Dept/Svc 1. Hem/Med WRAIR, C.I.S., WRAMC |
|---|---|

Key Words: Sickle Cell Disease, Pyridoxine, Red Blood Cells

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: $6,194.25 |
|---|---|---|

| FY-80 MEDCASE Cost: | Periodic Review Recommendation:<br>(to be filled in by DCI) |
|---|---|

Study Objective:

1. To define the effect of pyridoxine on erythrocyte sickling in vitro.

Technical Approach:

1. Antisickling effects of pyridoxal were contrasted with pyridoxine.
2. Most of the active work on this project, in vitro, was transferred to protocol #9019.
3. LS Lessin studied the effect of pyridoxine on red cell filterability.

Progress during FY-80:

1. Increased filterability was demonstrated for pyridoxine-treated sickle cells.

Number of subjects to be studied before completion of study:

Serious/unexpected side effects in subjects participating in project:

None: at present, only participation is donation of small venous blood samples.

Conclusions:

1. Pyridoxine has some antisickling activity by an unkown mechanism.

Publications or Abstracts, FY-80:

1. Abstract. 2. One publication 3. Patent application award.

# 9016 JOHN A. KARK, LTC, MC

Abstract: Kark, JA, Hannah, JS, Hicks, CU, Bongiovanni, R., Lessin, LS, and K. Hayes. Vitamin B6 aldehydes as potential antisickling agents. Fifth International Red Cell Conference, Ann Arbor, Michigan, Sep '80. not published.

Publications: Some of our data was included in a review:
Kark, J.A. and Lessin, L.S. Sickle Cell Disease and Variants in Hematology and Oncology, M. Lichtman, editor. Grune & Stratton, Inc., New York, N.Y., pp 89-97, 1980.

Patent application. A US Gov. patent was submitted by the Military patent office. An award for a supported patent application was received by John A. Kark. The patent application has not yet been acted upon.

Funding:

Funds utilized, FY-80: $6,194.25

Funding requirements, FY-81: CU 00 [illegible]

Supplies: $1,000

Travel: 500

| Date: 10 Oct 80 | Protocol No: 9019 | Status: Interim X<br>Final |
|---|---|---|

Title of Project: Antisickling agents:alteration of hemoglobin oxygen affinity

| Starting Date: Aug 1979 | Estimated Completion Date: Aug 82 |
|---|---|

Principal Investigator: JOhn A. Kark, LTC, MC

| Associate Investigators: | Facility: 1. Hematol. lab, WRAIR<br>Biochem. lab, WRAMC |
|---|---|
| R. Bongiovanni, CPT, MSC<br>L.S. Lessin, MD, Prof. Med., GWUSM | Dept/Svc 1. Hem/Med WRAIR, C.I.S., WRAMC |

Key Words: Antisickling agents, red cells, hemoglobin, oxygen affinity, Sickle Cell

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: None | Accumulative Supply Cost: |
|---|---|---|

| FY-80 MEDCASE Cost: None | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective:

1. To compare and contrast the antisickling activity of pyridoxal and pyridox phosphate. 2. To develope safe prophylaxis for sickle trait soldiers.

Technical Approach: 1. Loading of sickle cells with PLP was followed by HPLC.
2. Percent sickling was determined as a function of $PO_2$ and PLP load by tonometry under varied gas tensions and examination of fixed sickle cells with or without PLP loading.

Progress during FY-80:

The antisickling activity of PLP was defined for varied $PO_2$ by the above assay, and correlations were made with oxygen affinity.

Number of subjects to be studied before completion of study: 10

Serious/unexpected side effects in subjects participating in project:
None: patient participation involves donation of venous blood or saving blood drawn for therapeutic reasons and otherwise discarded.

Conclusions:

1. PLP has definite antisickling activity, unrelated to changes in oxygen affinity.

Publications or Abstracts, FY-80:

1 abstract, 1 manuscript in preparation:next sheet

Protocol #9019 JOHN A. KARK, WRC, MC

Publications FY '80:

1. Abstract: Inhibition of erythrocyte sickling by pyridoxal phosphate. Kark, JA, Hicks, CU, and Bongiovanni, R. Clin Res 28: 315A, 1980.

2. Manuscript in preparation:
Kark, Bongiovanni, and Hicks. Inhibition of erythrocyte sickling by pyridoxal phosphate.
Data collection for this paper is complete, and data analysis is 85% complete.

Funding:

Funding requirements:

| | | |
|---|---|---|
| Personnel: | GS-09 | 20 hrs |
| Supplies: | $6,000 | |
| Travel: | 500 | |
| Other: | 500 | |

# DISPOSITION FORM

For use of this form, see AR 340-15, the proponent agency is TAGCEN.

| REFERENCE OR OFFICE SYMBOL | SUBJECT |
|---|---|
| SGRD-UWH-B | Report on Annual Progress Reports for FY80 |

79THRU: Ch, Dept of Hematology FROM Dept of Hematology DATE 5 Jan 8 CMT 1
Dir, Div of Medicine LTC Kark/jp/6-3040

TO: Ch, Clinical Investigation Service
WRAMC

1. Work Unit #9019

a. As you probably know, the first phase of this work is completed and is being written up. We have demonstrated that PLP inhibits sickling effectively in vitro, have defined the conditions required for loading of sickle cells and normal red cells with PLP, and have determined the mechanism of action of PLP in contrast to pyridoxal as antisickling agents in the intact red cell. This data is well summarized in the abstracts written prior to this report and the most recent abstract.

b. However, it should be clear to you that the next phase of this work will begin when the two papers are completed and submitted to J Lab Clin Med and J Clin Invest. Our scheduled deadline is to submit these papers by the end of January, 1981.

c. The next phase of this work, which has been outlined in the protocol is to analyze the exact site of modification on the hemoglobin molecule and to correlate the site of modification with changes in oxygen affinity and antisickling effect. We have reason to believe there is an important, interesting correlation between these two parameters. Since this work is active and substantial, I don't understand why you feel this work unit is nearly completed. However, if you would prefer, I could write up the second phase of the work as a new protocol and terminate this work unit. At the present, I can't see any advantage to doing this: but only additional paperwork for the same end result.

2. Work Unit #9020

a. The data collected, and referred to in the abstracts, includes data on changes in oxygen affinity. This data collection is largely complete. We have been working this month, nearly full time, on a complete definition of changes in oxygen affinity for red cells loaded with PLP. Definitive experiments for the first phase of the work will probably be completed by 15 January 1980, and will be written up and submitted for publication within the first quarter of 1981.

b. However, as indicated for Protocol #9010, the next phase of this work will be to correlate changes in oxygen affinity with the exact site of modification on the hemoglobin molecule. This will involve preparation of borohydride-

DA FORM 2496 REPLACES DD FORM 96, WHICH IS OBSOLETE.

reduced modified globin, separation of alpha from beta globin, digestion of globin chains to peptides, and analysis of modified peptides and amino acids. This is a substantial piece of work, which will be dealt with in a separate series of papers. It is covered by this protocol. However, if you prefer that we submit new protocols, we certainly could do this.

3. Summary. The first phase of work outlined on both protocols is nearly completed, and 75% of it is written in rough draft. We are preparing about five papers which will cover this data. The second phase of the work, to be done during fiscal year 81, is covered in these protocols. I don't see any advantage to submitting new protocols to cover this work. However, you understand the administration of funds and personnel better than I, and it may be preferable to submit new, updated applications. If so, please request this, and I will comply in February.

John A. Kark

JOHN A. KARK, M.D.
LTC, MC
Dept of Hematology



576

| Date: 10 Oct 80 | Protocol No: 9020 | Status: Interim X<br>Final |
|---|---|---|

Title of Project: The effects of $B_6$ aldehydes on red cell oxygen affinity

| Starting Date: Aug 1979 | Estimated Completion Date: Aug 1981 |
|---|---|

Principal Investigator: John A. Kark, LTC, MC

| Associate Investigators: | Facility: 1. Biochem. Lab, WRAMC<br>2. Hematol. Lab, WRAIR |
|---|---|
| R. Bongiovanni, CPT, MSC<br>L.S. Lessin, M.D., Prof Med. GWUSM | Dept/Svc 1. C.I.S. 2. Hematol., WRAIR, WRAMC |

Key Words: Vitamin $B_6$, Red Blood Cells, Oxygen Affinity, Hemoglobin

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: $1,886.00 |
|---|---|---|
| FY-80 MEDCASE Cost: | Periodic Review Results: (to be filled in by DCI) | |

Study Objective:

1. To compare and contrast the site of binding with hemoglobin and the effect on oxygen affinity for pyridoxal and pyridoxal phosphate.

2. To develope a procedure for correction of the red cell storage defect in oxygen affinity of hemoglobin.

Technical Approach:

1. $^{14}$-C-pyridoxal was prepared and cleaned up by HPLC.
2. $^{14}$-C-pyridoxal was used to validate a simple Bio-Rex HPLC assay for modified hemoglobin.
3. Rate of modification of intracellular hemoglobin and stability of the adduct in the red cell was tested using these methods.
4. An improved HPLC method for separation and analysis of vitamin $B_6$ compounds was devised.

Progress during FY-80:

1. An improved method for synthesis of $^{14}$-C-pyridoxal was devised. 2. The rate and extent of modification of hemoglobin with pyridoxal was measured, and stability was tested.

Number of subjects to be studied before completion of study: unknown;now involves only

Serious/unexpected side effects in subjects participating in project: small venous blood donati
None possible: protocol involves small venous blood donations.

Conclusions:
1. Pyridoxal reacts with red cells with a t1/2 of 20 min. Adducts are stable in the cell for several days.
2. Improved techniques for analysis of B6 in blood and for identificatic of hemoglobin binding sites are operational.

Publications or Abstracts, FY-80:

Protocol # 9020 John A. Kark, LTC, MC

Publications and abstracts, FY'80.

Abstract: Kark, J.A.Hicks, C.U., and Bongiovanni, R. Modification of intracellular hemoglobin by vitamin $B_6$. Blood 54: (Suppl 1): 55a, November '79.

Manuscripts in preparation:

1. Kark and Bongiovanni. Preparation of 14-C-pyridoxal.
2. Bongiovanni and Kark. An improved HPLC assay for the $B_6$ compounds.
3. Modification of intracellular hemoglobin with pyridoxal.
   Kark and Bongiovanni.

Data collection is complete for these 3 papers.

Funding:

Funding utilized, FY-80: $1,886.00

Funding requirements, FY-81:

| | | |
|---|---|---|
| Personnel: | GS-09 | 20 hours |
| Supplies: | $6,000 | |
| Other: | 500 | |
| Travel: | 500 | |

Work Unit No.: 9021

Title of Project: Human Marrow in Mouse Chimera

Investigator: COL William H. Crosby, M.D.

Starting Date: Use of human tissue has not yet begun. Preliminary animal studies are in progress. Estimated start up for use of human tissue is 1 January 1981.

Estimated Date of Completion: 1 July 1981

Objective: To establish proliferating human marrow tissue in mice after ablative total body radiation.

Key Words: Marrow Transplantation
Heterologous Transplantation

Technical Approach: A core of donor marrow is placed in a pouch beneath the abdominal stem of a mouse. Ten days is allowed for vascularization of the graft. The mouse is subjected to irradition: 900 r from a Cs source. Immediately thereafter a transfusion of $10^8$ donor marrow is given intravenously intending to populate the grafted marrow tissue.

Progress and Results: We have succeeded in transplanting rat marrow into mice, but the marrow tissue has not survived, apparently because of local infection.

Conclusion: Rat-in-mouse chimera has been accomplished previously. Survival of implanted marrow tissue has not been previously attempted. Until we accomplish this in the rat-mouse model, we shall not attempt to work with human tissue.

Publications: None.

Work Unit No.: 9022

Title of Project: Iron Tolerance Test

Investigators:

Principal: COL William H. Crosby, M.D.

Associate: SSG Darrell D. Ford

Starting Date: 9 April 1980

Estimated Date of Completion: 1 July 1981

Objectives: To determine if a small dose of oral iron (20 mg) can cause a change in the plasma iron concentration; effect upon such change of food and ascorbic acid.

Key Words: Iron absorption
Iron nutrition
Plasma (serum) Iron

Technical Approach: To a normal fasting subject, we give by mouth 100 mg of ferrous sulfate (20 mg of elemental iron). Plasma iron concentration is measured at intervals for eight hours to see if absorption of the iron causes an increase of the concentration. Some subjects are fed at the same time; some are given ascorbic acid; some receive both. We plan to substitute ferrous fumarate for ferrous sulfate. Furmarate is less soluble.

Progress and Results: Eighty-three iron tolerance tests have been completed using 11 healthy male volunteers. Those who are mildly iron deficient (having served as blood donors) have a definitely increased plasma iron concentration after dosing. Ascorbic acid does not increase absorption of iron-replete subjects.

Conclusion: The ITT using a small (20 mg) dose of inorganic iron provokes a significant rise in plasma iron concentration. This phenomenon may permit the study of absorption of food iron without using radioisotopes.

Publications: None.

| Date: October 1980 | Protocol No: 9024 | Status: Interim |
|---|---|---|
| | | Final XXX |

Title of Project:

The Effect of Microwave Exposure on Immune Regulatory Function.

| Starting Date: 17 Mar 80 | Estimated Completion Date: |
|---|---|

Principal Investigator: Ben H. Boedeker, CPT DVM

| Associate Investigators: | Facility: Bldg 40, WRAIR |
|---|---|
| LT Cindy Ewel, Dept of Clin Invest | |
| COL Robert Reid, GI Svc, WRAIR | Dept/Svc Department of Clinical Investigation |

Key Words:

| Accumulative MEDCASE Cost: 0 | Accumulative Contract Cost: 0 | Accumulative Supply Cost: 0 |
|---|---|---|

| FY-80 MEDCASE Cost: 0 | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective: Due to a breakdown of the microwave irradiation equipment at Forest Glen, this project has been discontinued. The equipment is indefinitely out of service.

Technical Approach:

Progress during FY-80:

Number of subjects to be studied before completion of study:

Serious/unexpected side effects in subjects participating in project:

Conclusions:

Publications or Abstracts, FY-80:

DATE: 22 September 80 PROTOCOL # 9030 STATUS: Interim

TITLE: Circulating Serum Isoenzymes in Mesenteric Infarction

STARTING DATE: 15 June 1979 COMPLETION DATE: December 1981

PRINCIPAL INVESTIGATOR: Geoffrey M. Graeber, MD, MAJ, MC

Associate Investigators: John W. Harmon, MD, LTC, MC, FACS
Patrick J. Cafferty, Sp4, USA
Michael J. Reardon, DVM, PhD, MAJ, VC

FACILITIES: Dept of Experimental Surgery, Division of Surgery, WRAIR
Dept of Clinical Pathology, Division of Pathology, WRAIR

KEY WORDS: MAI, CPK, LDH, ISOENZYMES

STUDY OBJECTIVE:
1. Evaluate the anticipated elevations of total serum CPK and LDH and the anticipated isoenzyme pattern changes in patients suffering from abdominal catastrophes.
2. Evaluate the anticipated elevations of total serum CPK and LDH and the isoenzyme patterns in patients after cardiac surgery.
3. Determine the diagnostic value of these tests in distinguishing mesenteric infarction from other abdominal catastrophes and the value in evaluating patients having postoperative MIs.

TECHNICAL APPROACH: Patients who are seen by the General Surgery Service for acute abdominal emergencies have been entered into the protocol as soon as their consent has been obtained. Blood samples have been drawn before surgery, in the recovery room, and for up to seven days after surgery. The samples are analyzed for total and respective isoenzyme concentrations of creatine phosphokinase (CPK) and lactic dehydrogenase (LDH). Two distinct groups of patients can be delineated: those who had mesenteric infarctions and those who suffered other acute conditions.

Patients that are seen by the Thoracic Surgery Service for cardiac surgery have been entered into the protocol as soon as their consent has been obtained. Specimens are drawn preop, q 8 hr for the first 2 PO days and daily until the 7th postop day. Samples are analyzed for their total and isoenzyme concentration.

Patients who are undergoing routine intraabdominal procedures have served as control groups. Their serum CPK and LDH values have been determined on a similar basis to provide a control group.

Patients admitted to the CCU have served as the control groups. Their serum CPK and LDH have been analyzed by the same methods.

PROGRESS AND RESULTS: As noted in the original protocol, the study will need to be run over 18 months to gain adequate numbers. A total of 431 patients have been entered into the study. No changes or modifications in the protocol have been made.

Initial results show that patients who have suffered mesenteric infarctions will exhibit CPK-MB bands in their sera. We have also seen minimal rises in the serum of the CPK-BB isoenzyme which was, theoretically, the most promising indicator.

The results from the study of the LDH isoenzyme system show that any elevations after routine surgery are due to $LDH_5$, the predominant isoenzyme in liver and skeletal muscle. When patients have suffered a mesenteric infarction, the LDH isoenzyme patterns show definite increases in $LDH_3$ and $LDH_4$. These findings are different from the changes seen in myocardial infarction when $LDH_1$, becomes the predominant serum isoenzyme.

Review of the patient values after cardiac surgery shows a small elevation of CPK-MB, though not as high as those seen with patients suffering a MI.

Review of the control group values shows that CPK-MB and CPK-BB do not elevate after routine surgery. LDH elevations are only those compatible with skeletal muscle injury.

CONCLUSIONS: There have been no serious or unexpected side effects of complciations in subjects participating in the project.

The CPK and LDH isoenzymes systems appear to be valid markers for mesenteric necrosis.

The serum changes in the CPK and LDH isoenzyme systems seen after surgery are compatible with skeletal muscle injury.

The elevations seen in CPK-MB after cardiac surgery are smaller than those seen with MI after cardiac surgery. CPK and LDH isoenzymes appear to be valid markers of myocardial damage.

| | | |
|---|---|---|
| USDS FY 80: | Personnel | None |
| | Equipment | None |
| | Supplies | $10,000 |
| | Reprints | None |
| Funds requested for FY 81 | | See inclosure #1 |

Work Unit #9030 Circulating Serum Isoenzymes in Mesenteric Infarction

To obtain and process each patient sample as noted in the approved protocol and addenda, the following are the anticipated costs to be incurred:

1. The following items are needed to draw a sample:

| | | |
|---|---|---|
| a. | syringe (10 cc) | $ . 628 |
| b. | needle (20 g) | . 06 |
| c. | serum separation tube ( 6 ml) | . 23 |
| d. | sample vials (3) | . 33 |
| e. | alcohol prep | . 006 |
| f. | 4 x 4 gauze | . 014 |
| | | $1.268 = $ 1.27 |

2. Analysis of the sample requires the following:
   a. CPK determinations:

| | | | | |
|---|---|---|---|---|
| 1. | antibody inhibition (total enzyme) | | | $ 1.63 |
| 2. | antibody inhibition (CPK-MB isoenzyme) | | | 3.93 |
| 3. | control reagents | | | .48 |
| 4. | centrifichem reagents | | | .24 |
| 5. | electrophoresis | | | |
| | a. sample tips (2) | x .085 ea = | . 17 | |
| | b. data card (1) | x .053 ea = | .053 | |
| | c. agarose film (1) | x .568 ea = | .568 | |
| | d. CK substrate (1) | x .612 ea = | .612 | |
| | e. MOPSO buffer (1) | x . 14 ea = | . 14 | |
| | | | 1.543 = | 1.54 |
| | Total cost of CPK analysis = | | | $7.82 ea |

   b. LDH determinations

| | | | | |
|---|---|---|---|---|
| 1. | centrifichem reagents | | | .13 |
| 2. | electrophoresis | | | |
| | a. sample tip (1) | x .085 ea = | .085 | |
| | b. data card (1) | x .053 ea = | .053 | |
| | c. agarose film (1) | x .583 ea = | .583 | |
| | d. LDH substrate (1) | x .586 ea = | .586 | |
| | e. universal buffer (1) | x .075 = | .075 | |
| | | | 1.382 | 1.38 |
| | Total cost of LDH analysis | | | $1.51 |

3. The total estimated cost to obtain process and analyze each specimen is:

   1. 1.27
   2a 7.82
   2b 1.51
   $10.60 each specimen

4. The anticipated numbers of patients entered into the protocol per week are –

| | |
|---|---|
| abdominal patients | 4 |
| coronary care unit | 7 |
| thoracic patients | 5 |
| emergency patients | 2 |
| Average patient load/week | 18 |

The number of patients times the number of samples per week 18x7 = 126 or approximatley 504 patient samples per month. Hence, the total number of patient samples for FY 81 is 504x12 = 6048.

The total anticipated cost of obtaining processing and analyzing these samples is

6048
$10.60
$64,108.80

5. Request funding also be available for service and parts for the following equipment:

| | |
|---|---|
| Gilford System 102 Spectrophotometer | 835.00 |
| Corning 702 and 722 Electrophoresis System | 2100.00 |
| | $2935.00 |

6. Total anticipated costs for WU #9030 for FY 81 is:

| | |
|---|---|
| Sample analysis | $64.108.80 |
| Contractual Svcs | 2,935.00 |
| | $67,043.80 |

| Date: 27 October 1980 | Protocol No: 9031 | Status: Interim x<br>Final |
|---|---|---|

Title of Project:

Study of Control Mechanisms for Human Gastric Parietal Cells

| Starting Date: 1980 | Estimated Completion Date: 1983 |
|---|---|

Principal Investigator: John Harmon

| Associate Investigators:<br>Schmmel Batzri<br>Richard Hirata | Facility: WRAIR -- Div Surgery and Gen Surgery<br>WRAMC, Dept Surgery<br>USUHS Dept Surgery |
|---|---|
| | Dept/Svc |

Key Words:

Stomach, Peptic Ulcer

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: |
|---|---|---|

| FY-80 MEDCASE Cost: | Periodic Review Results:<br>(to be filled in by DCI) |
|---|---|

Study Objective:

To identify control mechanisms for human parietal cells

Technical Approach:

To apply the methods developed for studying dispersed parietal cells developed in animals, to man.

Progress during FY-80: The protocol was approved late in FY 80. To date the methodology for studying parietal cells in animals has been set up a USUHS, but no human studies have been performed because no appropriate patients have been admitted to WRAMC

Number of subjects to be studied before completion of study: 20

Serious/unexpected side effects in subjects participating in project:

None

Conclusions:

Date: 27 October 1980 | Protocol No: 9032 | Status: Interim X / Final

Title of Project:

In Vitro Analysis of Human Colon Ion Transport Mechanisms

Starting Date: | Estimated Completion Date:

Principal Investigator: John W. Harmon, Roy Wong

Associate Investigators:
Yuan Hneg Tai PhD A. Olywole
Ed Boedeker
Richard Hirata
Lawrence Johnson

Facility: WRAIR, WRAMC

Dept/Svc: WRAMC - Surgery, Medicine
WRAIR - Surgery - Medicine

Key Words:
Colon Surgery

Accumulative MEDCASE Cost:

Accumulative Contract Cost:

Accumulative Supply Cost:

FY-80 MEDCASE Cost:

Periodic Review Results:
(to be filled in by DCI)

Study Objective:
To assess the effect of bile acids on ion transport in the colon of man

Technical Approach:

Colonic mucosa from human surgical specimens are obtained fresh in the WRAMC OR suite taken to WRAIR and studied in Ussing chambers.

Progress during FY-80:

The colonic mucosa from 12 surgical specimens has been studied.

Number of subjects to be studied before completion of study: 20

Serious/unexpected side effects in subjects participating in project:

None

Conclusions:
The study is progressing satisfactorily. It is essential to maintain good communication between the pathology service and the investigators to assure that the surgical specimens are properly studied for pathologic diagnosis, prior to their entry into the protocol.

Funding requirements, FY-81:

Travel, Conference: $1,200
Printing & Reproduction: $600

| Date: 15 Sep 80 | Protocol No: 9035 | Status: Interim X<br>Final |
|---|---|---|

Title of Project: Effects of Altitude, Mood, and Dietary Habits on Performance of a Choice-Reaction Time Task

| Starting Date: Jun 77 | Estimated Completion Date: Jun 81 |
|---|---|

Principal Investigator: Capt James P. Dixon, USAF, BSC

| Associate Investigators:<br>Col R.R. McMeekin, USA, MC | Facility:<br>AFIP |
|---|---|
| | Dept/Svc Aerospace Pathology |

Key Words:

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: |
|---|---|---|

| FY-80 MEDCASE Cost: | Periodic Review Results:<br>(to be filled in by DCI) |
|---|---|

Study Objective: To evaluate the subtle influence of mood, altitude, dietary habits and other stresses on performance and to relate these decrements to the jog performance of service personnel.

Technical Approach: By means of a choice-reaction time task, efficiency (number of correct divided by total time) will guage performance. This will be related to the physiological parameters of arterial oxygen saturation, respiration and heart rates at various altitudes.

Progress during FY-80: Eight subjects have been completed. Data has not been completely analyzed.

Number of subjects to be studied before completion of study: 5

Serious/unexpected side effects in subjects participating in project: None

Conclusions: None

Publications or Abstracts, FY-80: None

| Date: Sept. 19, 1980 | Protocol No: 9036 | Status: Interim x<br>Final |
|---|---|---|

Title of Project: Urease & Deaminases in Chemistry & Medicine

| Starting Date: June 28, 1977 | Estimated Completion Date: Ongoing |
|---|---|

Principal Investigator: William N. Fishbein, MD, PhD

| Associate Investigators: | Facility: AFIP |
|---|---|
| | Dept/Svc Biochemistry Division |

Key Words: myo-adenylate deaminase deficiency; lactate/ammonia exercise ratio

| Accumulative MEDCASE | Accumulative Contract | Accumulative Supply |
|---|---|---|
| Costs: 0 | Costs: 0 | Costs: 0 |

| FY-80 MEDCASE Cost: | Periodic Review Results:<br>(to be filled in by DCI) |
|---|---|

Study Objective: Development of a diagnostic clinical blood test for mMDD

Technical Approach: Measurement of lactate and ammonia in antecubital vein blood drawn and after sponge-squeezing with partial venous obstruction.

Progress during FY-80: Seven patients and five controls have now been tested without side-effects. No drugs or WRAMC funds have been used. The seven patients show no increase in NH3 despite normal increase in lactate, like the first three reported.

Number of subjects to be studied before completion of study: 30

Serious/unexpected side effects in subjects participating in project: None

Conclusions:

| Date: 17 Oct 80 | Protocol No: 9036A | Status: Interim X<br>Final |
|---|---|---|

Title of Project:

The Educational and Psychological Needs Specific to Human Sexuality of Middle-Aged Males Post Uncomplicated Myocardial Infarction.

| Starting Date: 24 April 1979 | Estimated Completion Date: 1980, Dec |
|---|---|

Principal Investigator: P.J. Baldwin, R.N., D.N.Sc., George Mason University

| Associate Investigators:<br>Liasion Officer:<br>MAJ(P) Janet R. Southby, ANC | Facility:<br>WRAMC, Unit 41<br>Dept/Svc Nursing Research Service |
|---|---|

Key Words:
Sexuality, Males, Myocardial Infarction

| Accumulative MEDCASE Cost: 0 | Accumulative Contract Cost: 0 | Accumulative Supply Cost: 0 |
|---|---|---|

| FY-80 MEDCASE Cost: 0 | Periodic Review Results:<br>(to be filled in by DCI) |
|---|---|

Study Objective:

To describe the educational and psychological needs specific to human sexuality of middle-aged males post uncomplicated myocardial infarction.

Technical Approach:

Unchanged since last Annual Progress Report

Progress during FY-80:

Ten subjects were obtained for the study this year.

Number of subjects to be studied before completion of study: 20 were desired

Serious/unexpected side effects in subjects participating in project:
None

Conclusions:

None to date. Data analysis is in progress.

Publications or Abstracts, FY-80:

CLINICAL INVESTIGATION PROGRAM

Work Unit No.: 9036A

Funds Utilized, FY-60: None

Funding Requirements, FY-61: $50.00

Personnel: (name and grade) MAJ Janet R. Southby, MSC

Equipment: (describe in detail including cost)

Supplies: (consumable, animal purchase) $50.00

Travel: (mission oriented, training and presentation)

Other: (equipment rentals, contracts for services, animal care and reprints)

# DISPOSITION FORM

For use of this form, see AR 340-15, the proponent agency is TAGCEN.

| REFERENCE OR OFFICE SYMBOL | SUBJECT |
|---|---|
| AFIP-CPQ-C | Annual Progress Report, #9037, Localization of Lymphocyte Antigen Markers in Fixed, Paraffin-Embedded Tissues |

TO: Timothy M. Boehm, LTC,MC
Department of Clinical
Investigation Service

FROM: Major John M. Langloss
Chief, Division of
Immunopathology

DATE: 14 October 1980

CMT 1 JML/rm/62816

Since submitting our request for surgical specimens from WRAMC, we have found an alternative substrate obtained from other sources for our investigation of intracytoplasmic lymphocyte markers. No material has been obtained from WRAMC. Please consider our project terminated. Thank you for your cooperation in this matter.

MAJOR JOHN M. LANGLOSS, USAF
Chief, Division of Immunopathology

DA FORM 1 FEB 67 2496 REPLACES DD FORM 96, WHICH IS OBSOLETE.

☆ GPO - 1975 - 665-429/1067

| Date: 17 Oct 80 | Protocol No: 90398 | Status: Interim X / Final |
|---|---|---|

Title of Project:

Nurse Controlled Factors That Influence the Development of Diarrhea in Tube-fed Patients

| Starting Date: 20 July 1979 | Estimated Completion Date: Dec 1980 |
|---|---|

Principal Investigator: LTC Reuben B. Bowie, ANC

| Associate Investigators: | Facility: WRAMC |
|---|---|
| | Dept/Svc Nursing Research Service |

Key Words:
Diarrhea, Tube Feeding

| Accumulative MEDCASE Cost: 0 | Accumulative Contract Cost: 0 | Accumulative Supply Cost: $43.50 |
|---|---|---|

| FY-80 MEDCASE Cost: 0 | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective: Primear - To ascertain whether a regime which increases the frequency of changing the nasogastric tube and/or the feeding bag leads to decreased incidence of diarrhea in tube-fed patients as compared to current standard procedure. Secondary - To describe gross changes of the nose and throat mucosa in response to increased increased frequency of changing the nasogastric tube.

Technical Approach:
No changes since last Annual Progress Report

Progress during FY-80: To date, a total of four (4) patients have completed the study.

Number of subjects to be studied before completion of study: 10 were desired

Serious/unexpected side effects in subjects participating in project:
None

Conclusions:
Availability of patients who meet the study criteria were a problem. Study will be terminated. Final report will be submitted by 31 Dec 80

Work Unit No.: 90393

Funds Utilized, FY-80: None

Funding Requirements, FY-81: See attached Funding Requirements Sheet

Personnel: (name and grade) LTC Reuben B. Bowie, ANC

Equipment: (describe in detail including cost)

Supplies: (consumable, animal purchase) Consumable: $50.00

Travel: (mission oriented, training and presentation)

Other: (equipment rentals, contracts for service, animal care and reprints) Printing and reproduction: $150.00

| Date: 12 October 1980 | Protocol No: 90408 | Status: Interim X<br>Final |
|---|---|---|

Title of Project: Reducing Discomfort from Intramuscular Injections in the Dorsogluteal Site by Proper Body Positions.

| Starting Date: 1 June 1979 | Estimated Completion Date: 31 Dec 1980 |
|---|---|

Principal Investigator: Fannie M. Rettig, MAJ-ANC

| Associate Investigators: NONE | Facility: WRAMC, Wards 57,67 and 68 |
|---|---|
| | Dept/Svc Nursing Research Service |

Key Words:
Intramuscular Injections, Proper Body Positions

| Accumulative MEDCASE Cost: NONE | Accumulative Contract Cost: NONE | Accumulative Supply Cost: NONE |
|---|---|---|

| FY-80 MEDCASE Cost: NONE | Periodic Review Results:<br>(to be filled in by DCI) |
|---|---|

Study Objective: (1) To ascertain whether patients would report less discomfort from dorsogluteal injection when they assume a prone position with femurs internally rotated than when femurs are externally rotated. (2) To ascertain whether the side-lying position with femurs internally rotated or externally rotated in an effective position for reducing discomfort from a dorsogluteal injection.

Technical Approach: The study will be comprised of approximately 60 adult patients on the general surgical and gynecology services. For the patients to be a part of the study, they must meet the following pre-operative criteria:

a. Oriented to time, place and person
b. Easily assume a prone or side-lying position.
c. Physician has ordered preoperative medications of Meperidine, Promethazine and Glycopyrrolate. (SEE THE ATTACHED)

Progress during FY-80:
Completed data collection in September, 1980 and started data analysis.

Number of subjects to be studied before completion of study: 60

Serious/unexpected side effects in subjects participating in project: NONE

Conclusions: Will be submitted by 31 December 1980.

Publications or Abstracts, FY-80: NONE

Continuation of Technical Approach: d. Could safely receive injections in the dorsogluteal site. Patients will have to be excluded from the study if only one injection is given or if there was a change in the type of medications after being randomly assigned to the study groups.

Each patient will receive two injections of Meperidine, promethazine and glycopyrrolate. All injections are given with a 22-gauge needle. The length of the needle will vary from 1-1 1/2 inches depending upon the size and weight of the patient. The number of patients comprising each group will remain even by assigning patients to one of the four conditions in a fixed order. Table 1 shows the four conditions which are the possible combinations of the three factors of concern.

The patient will be located by reviewing the operating room schedule the day prior to surgery. The patient will be randomly assigned to one of the four conditions (see table 1). Afterward the investigator will contact the patient and obtain the patient's written consent to participate in the study. At the time the preoperative medications will be ordered, the research nurse will give the appropriate medications at the bedside. The patient will be placed in the pre-defined position (hips either internally or externally rotated). The injection will be administered using the following technique. The nurse will locate the upper outer quadrant of the gluteus maximum muscle and palpate for underlying abnormally sensitive tissue. She will prepare the skin by swabbing with an alcohol sponge and then administer the designated medication taking no less than five seconds to complete the injection to reduce possible pain induced by rapid injection of medication. The area will be massaged using an alcohol sponge for approximately five seconds. The patient will be asked to rate his discomfort from the injection on a discomfort scale. The patient will be positioned in the second designated position and the second injection will be given in the opposite dorsogluteal site. The subject will then rate the discomfort from that injection.

TABLE 1

Assignment of Patients to Conditions

| Condition | Position | First Injection | Second Injection |
|---|---|---|---|
| A | Prone | Internal rotation | External rotation |
| | | Meperidine<br>Promethazine<br>Glycopyrrolate | Meperidine<br>Promethazine<br>Glycopyrrolate |
| B | Prone | External rotation | Internal rotation |
| | | Meperidine<br>Promethazine<br>Glycopyrrolate | Meperidine<br>Promethazine<br>Glycopyrrolate |
| C | Side-lying | Internal rotation | External rotation |
| | | Meperidine<br>Promethazine<br>Glycopyrrolate | Meperidine<br>Promethazine<br>Glycopyrrolate |
| D | Side lying | External rotation | Internal rotation |
| | | Meperidine<br>Promethazine<br>Glycopyrrolate | Meperidine<br>Promethazine<br>Glycopyrrolate |

CLINICAL INVESTIGATION PROGRAM

Work Unit No.: 9040B

Funds Utilized, FY-80: None

Funding Requirements, FY-81:

Personnel: (name and grade) MAJ Fannie M. Rettig

Equipment: (describe in detail including cost)

Supplies: (consumable, animal purchase) $100.00

Travel: (mission oriented, training and presentation) Conference Travel $570.00

Other: (equipment rentals, contracts for service, animal care and reprints) Printing & Reproduction. $150.00
Data Analysis $200.00

| Date: 10/6/80 | Protocol No: 90418 | Status: Interim X<br>Final |
|---|---|---|

Title of Project: Attitudes of Health Care Workers toward the Occurrence of Violence in close Relationships.

| Starting Date: 1 June 1979 | Estimated Completion Date: 1 Dec 80 |
|---|---|

Principal Investigator: Susan B. Shipley, MAJ/ANC

| Associate Investigators: | Facility: |
|---|---|
| Donna C. Sylvester, MAJ/ANC | Walter Reed Army Medical Center |
| | Dept/Svc Nursing Research Service |

Key Words: Violence, Abuse, Marriage, Family

| Accumulative MEDCASE Cost: 0 | Accumulative Contract Cost: 0 | Accumulative Supply Cost: $250.00 |
|---|---|---|

| FY-80 MEDCASE Cost: 0 | Periodic Review Results: (to be filled in by DCI) |
|---|---|

Study Objective: The purpose of this project was to a. gather baseline data on the present attitudes of various groups of health care workers toward the victims and users in the ocurence of violence in close relationships; b. determine the extent of experience health care workers with victims of purposeful injury who come in contact with the lth care system: and c. determine entry points to the health care system for the tim of purposeful injury in order to gain access to and characterize the victim and e of violence in further studies.

Technical Approach:

Survey questionnaire of a random sample of physicians and nurses at WRAMC. No Changes.

Progress during FY-80: Data Collection is completed.

Number of subjects to be studied before completion of study: 200 -done

Serious/unexpected side effects in subjects participating in project: NONE

Conclusions: Data analysis is underway. Final report to be written and submitted prior to 15 December 1980.

CLINICAL INVESTIGATION PROGRAM

Work Unit No.: 9041 8

Funds Utilized, FY-80: $250.00

Funding Requirements, FY-81:

Personnel: (name and grade) MAJ(P) Susan B. Shipley
MAJ Donna C. Sylvester

Equipment: (describe in detail including cost)

Supplies: (consumable, animal purchase)

Travel: (mission oriented, training and presentation) conference (2 persons) $1,000.00

Other: (equipment rentals, contracts for service, animal care and reprints)

Inking and reproduction $150.00

| Date: October 15, 1980 | Protocol No: work unit #9080 | Status: Interim X / Final |
|---|---|---|

Title of Project:

Coronary Artery Disease & Coronary-Prone Behavior

| Starting Date: September 26, 1978 | Estimated Completion Date: October 1, 1981 |
|---|---|

Principal Investigator: David Krantz, Ph.D., Assistant Professor, USUHS Department Med. Psych.

| Associate Investigators: | Facility: USUHS, WRAMC |
|---|---|
| James E. Davia, M. D.<br>Chief, Cardiology, WRAMC | Dept/Svc Cardiology, WRAMC, USUHS Medical Psychology |

Key Words: Coronary Artery Disease, Psychophysiology, Psychological Correlates

| Accumulative MEDCASE Cost: none | Accumulative Contract Cost: none | Accumulative Supply Cost: none |
|---|---|---|

| FY-80 MEDCASE Cost: none | Periodic Review Results: (to be filled in by DOI) |
|---|---|

Study Objective:

SEE CONTINUATION SHEET

Technical Approach:

Progress during FY-80:

SEE CONTINUATION SHEETS

Number of subjects to be studied before completion of study: 200

Serious/unexpected side effects in subjects participating in project: none

Conclusions:

SEE CONTINUATION SHEET

Publications or Abstracts, FY-80: SEE CONTINUATION SHEET

Objectives, Methods, and Progress:

1. One area of this research project concerns associations between aspects of behavior and presence of coronary artery disease. Approximately 115 consecutive patients of WRAMC who were awaiting cardiac catheterization completed the Jenkins Activity Survey and were given the Rosenman diagnostic interview to measure Type A behavior. We have been investigating the possible relationship to various components of Type A (e.g., hostility, competitiveness, time urgency, speech patterns, etc.) to presence of coronary artery disease. It remains unclear from previous research whether the intensity of various components of Type A behavior is associated with greater risk of disease. While, strictly speaking, this question can only be answered by prospective study, tape recorded interviews of cardiac catheterized patients are being broken down and analyzed item-by-item. We will examine the relationship of Type A components to angiographic results of cardiac catheterization and other standard risk factors obtained from WRAMC medical records. Angiographic data have been obtained for each patient. This analysis is nearing completion and should be concluded within six to eight months.

2. The second line of research being investigated in this project concerns possible physiologic mechanisms linking behavior processes with coronary artery disease. Research by Dembroski, Manuck and others has demonstrated that Type A subjects display elevated cardiovascular reactivity when presented with challenging tasks and situations. Dembroski and McDougall have recently presented some suggestive evidence that patients with a history of ischemic heart disease show a trend toward similar enhanced cardiovascular responsiveness. Since January 1979, we have been measuring cardiovascular reactivity (blood pressure and heart rate) in conse[illegible]

ested in determining how heart rate and blood pressure responsiveness vary in these patients as a function of a) magnitude of coronary artery disease and b) magnitude of Type A behavior. An association between cardiovascular responsiveness and coronary artery disease would lend credence to the notion that this responsiveness (or other physiologic correlates of this responsiveness) play a role in the pathogenesis of coronary disease. It is also not known how various processes which have been shown to be related to elevated pressor response (e.g., Type A; family history of disease) are themselves related to each other. Eighty-three patients have been tested so far in this study, and data have been analyzed and written up for presentation at scientific meeting (see enclosed paper).

Research Goals for the Upcoming Year

We plan to complete data analysis for Study I and to collect data for reaction-time study outlined in original proposal.

Conclusions: Coronary artery disease, angiographically measured does not seem to be related systematically to cardiovascular response. We plan to repeat this study using a psychomotor reaction-time task which may reduce variability between conditions. There have been no side effects/complications associated with this research project.

Funds Utilized: The study is funded by grants from NIH and USUHS. No additional funding is required from WRAMC.

Publications:

1. Krantz, D. S., Sanmarco, M. E., Selvester, R. & Matthews, K. A. Psychological correlates of progression of atherosclerosis in men. Psychosomatic Medicine, 1979, 41, 467-475.

2. Krantz, D. S. Cognitive processes and recovery from heart attack: A review and theoretical analysis. Journal of Human Stress, 1980, 6 (2), 27-38.

3. Krantz, D. S., Glass, D. C., Schaeffer, M. & Davia, J. E. Behavior patterns and coronary disease: A critical evaluation. In J. T. Cacioppo & R. E. Petty (Eds.) Focus on cardiovascular psychophysiology. New York: Guilford, in press.

4. Krantz, D. S., Schaeffer, M., Davia, J. E., Dembroski, T. M., MacDougall, J. M. & Shaffer, R. T. Investigation of extent of coronary atherosclerosis, Type A behavior and cardiovascular response to social interaction. Paper presented at Society for Psychophysiological Research, Vancouver, B. C., October, 1980.

Type of Report: Interim: Approval for continuation of project requested for FY-81.

Work Unit No.: 0082

Title of Project: Treatment and Rehabilitation of Knee Injuries at the United States Military Academy, West Point, NY 10996

Investigators:

Principal: LTC Walton W. Curl

Associate: LTC Keith L. Markey

Objectives: To develop predictive parameters and programs to lower the knee injury rate of cadets at the United States Military Academy. It is also the objective to analyze and develop better treatment modalities for those injuries which do occur.

Technical Approach: Cadets who are participating in the intramural and intercollegiate football, wrestling, and lacrosse programs are being screened as part of the pre-season physical examination for multiple parameters which might effect knee injury rate. These parameters include: joint laxity, height, weight, body type, etc. This data and following the individuals through the sport season, determine what types of injuries they incur and it is hoped that a statistical correlation can be performed to relate these various parameters to knee injuries.

The treatment phase deals with the diagnosis and treatment of essentially isolated tears of the anterior cruciate ligament. Those who have a proven torn anterior cruciate ligament then undergo an acute repair and reconstruction of the torn anterior cruciate ligament utilizing the medial third of the patellar tendon. They are then casted with a long-leg cast with the bent knee at $60^{\circ}$ for six weeks and then a cast-brace at $30\text{-}60^{\circ}$ for six weeks. They are then started on a knee rehabilitation program. These patients are then followed at a 3 and 6 months, 1 year, 2 year, and 5 year, and 10 year intervals for long term sequelae.

Progress and Results: Preventive phase: The 200 intramural football players which were examined and evaluated utilizing Cybex, physical exam, and questionaire at the start of the intramural season are currently being analysed. No results have been concluded from this aspect of the study as yet. We are currently trying to correlate ligament laxity with injuries in a second on-going study and will try to incorporate these results with this aspect of the study.

Treatment phase: 132 anterior cruciate ligament injuries have been identified utilizing arthroscopy. Of these 43 have been treated using the medial one-third of the patella tendon to augment the repair of the anterior cruciate ligament and are undergoing treatment at the present time. There have been anterior cruciate ligaments that have not been operated on, however,none of these have been casted for a twelve week period, as the operated cruciate ligaments have been, since the cadets did not desire the twelve week casting. We have been in contact with the United States Naval Academy to discuss the combined study with their facility. The USNA is currently following their anterior cruciate ligament injuries non-operatively on a prospective basis and their data will, hopefully, be correlated with our results in the end.

Conclusions: The study continues to be on-going. There have been no unexpected side effects or complications in the individuals participating in this project. Again no conclusions can be made as to the efficacy of the treatment phase nor can conclusions be drawn as to specific parameters which may lead to knee injuries. We feel that this is a reasonable alternative to not operating on the anterior cruciate ligament and also seems to be doing better than repairing the cruciate ligament alone. The answers to these questions will not be able to be answered however, until the end of a five year course has past.

Funds Utilized, FY-80: The research secretary is funded for a part-time basis for FY-80. No other funds were utilized out of the clinical research investigation project.

Funding Requirements, FY-81:

Personnel: 683 - [illegible] for FY-81.

Equipment: Lenox Hill Braces for bracing anterior cruciate ligaments - $285.00 ea, estimated number required - 60.

Travel: $1,000.00 for TDY for the purpose of presenting results as well as visiting other medical centers to discuss the role of the anterior cruciate ligament.

Supplies: None

Other: None

Publications & Abstracts FY80: None as of yet.

| Date: 12 October | Protocol No: 9026 | Status: Interim / Final X |
|---|---|---|

Title of Project: The Physical Fitness of Military Women Employed in Health Care Occupations

| Starting Date: None | Estimated Completion Date: None |
|---|---|

Principal Investigator: LTC Eileen L. Fox, LTC Caroline G. Brodkey and MAJ Fannie M. Rettig ANC

| Associate Investigators: | Facility: WRAMC, Ft. Meade, MD and Ft. Belvoir, VA |
|---|---|
| | Dept/Svc Nursing Research Service, WRAMC |

Key Words: Physical Fitness

| Accumulative MEDCASE Cost: $1,500 (Not Expended) | Accumulative Contract Cost: None | Accumulative Supply Cost: None |
|---|---|---|
| FY-80 MEDCASE Cost: NONE | Periodic Review Results: (to be filled in by DCI) | |

Study Objective: To evaluate the physical fitness of military women in the health care occupations. To determine if physical fitness of military women in health care occupations is commensurate with military expectations. To implement a three-month physical conditioning program with the goal of effecting an improvement of physical fitness in a group of military women health care providers. To observe for changes and/or correlations between variables such as weight, anthrometric measures, pulse rate, blood pressure, vital respiratory capacity, smoking, sleep

Technical Approach: (SEE THE ATTACHED)

It was planned to selected a control and experiment group from female volunteers who fail the physical training test and step test. Both would have receive a demographic data questionnaire, self-image questionnaire and cardiorespiratory test at the beginning and ending of the study period. After each group completed a physical fitness test, the experiment group would have followed an exercise program for three months. Follow-up evaluation would have been planned.

Progress during FY-80: The protocol was cancelled because of inadequate funding for three Ohio halioscale respirometers. While awaiting purchase of this equipment, the senior investigator retired and the other two officers have been reassigned.

Number of subjects to be studied before completion of study: NA

Serious/unexpected side effects in subjects participating in project: NA

Conclusions: A film was made of the staff and specialist physical test for women and WRAMC, PO & T Section decided to adopt this P.T. Test for their program for FY 80. A Program about Physical Fitness will be presented to WRAMC, Dept. of NSG, 6 Nov 80 as approved program for continuied education.

Publications or Abstracts, FY-80: N/A

Continuation of Study Objective: patterns, work patterns, self image, nutritional patterns, and improved physical fitness.

CLINICAL INVESTIGATION PROGRAM

Work Unit No.: 9086

Funds Utilized, FY-80: NONE

Funding Requirements, FY-81: NONE

Personnel: (name and grade) LTC Eileen L. Fox, LTC Caroline G. Brodkey, MAJ FANNIE M. RETTIG

Equipment: (describe in detail including cost) NONE

Supplies: (consumable, animal purchase) NONE

Travel: (mission oriented, training and presentation) NONE

Other: (equipment rentals, contracts for service, animal care and reprints) NONE

| Date: 6 October 1980 | Protocol No: 9088 | Status: Interim X<br>Final |
|---|---|---|

Title of Project: A comparison of the Use of Cognitive Therapy and Hypnosis in a Group Setting for Treating Obesity.

| Starting Date: 29 April 1980 | Estimated Completion Date: 30 June 1980 |
|---|---|

Principal Investigator: Edmund G. Howe, M.D.

| Associate Investigators: | Facility: WRAMC, USUHS, NNMC |
|---|---|
| Charles B. Slater, CDR, MC, USN<br>Angela LePage, Ens, USNR<br>(3rd year medical student) | Dept/Svc Psychiatry, USUHS |

Key Words: Obesity, cognitive therapy, hypnosis, group

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: |
|---|---|---|
| FY-80 MEDCASE Cost: | Periodic Review Results: (to be filled in by DCI) | |

Study Objective: To determine whether the proposed treatment for obesity will be effective as a means of persons with obesity losing weight and maintaining weight loss. To compare treatments and to generate hypotheses for further studies.

Technical Approach: Original study is being extended and modified to include a third group which combines hypnosis and cognitive therapy, to take place once a week over 10 weeks instead of twice a week over 5 weeks, and to be carried on by only the principal investigator.

Progress during FY-80: Of 22 persons beginning in hypnosis groups, 16 finished program and 11 lost weight at 3 month follow-up. Of 26 persons beginning cognitive therapy groups, 19 finished program, 18 lost weight at 3 month follow-up.

Number of subjects to be studied before completion of study: approximately 70

Serious/unexpected side effects in subjects participating in project: none

Conclusions: Though initial results are encouraging, they are not of significance unless weight losses are maintained at 6 month and 1 year follow-ups. Thus, conclusions cannot be made at this time.

Publications or Abstracts, FY-80:

| Date: 30 September 1980 | Protocol No: 9100 | Status: Interim XXX XXXXX |
|---|---|---|

Title of Project: Evaluation of Computer Assisted Drug -- Drug Interaction Monitoring.

| Starting Date: 1 September 1980 | Estimated Completion Date: 30 September 1981 |
|---|---|

Principal Investigator: Carl C. Peck, LTC MC

| Associate Investigators: | Facility: WRAMC/USUHS |
|---|---|
| Lawrence Fleckenstein, Pharm D.<br>Brian G. Schuster, MAJ MC<br>James Wilson, Pharm D. | Dept/Svc: Clinical Pharmacology<br>Department of Clinical Investigation |

Key Words: Drug Interactions, Physician Education, Pharmacology

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: |
|---|---|---|
| FY-80 MEDCASE Cost: | Periodic Review Results: (to be filled in by DCI) | |

Study Objective: To evaluate the impact of a computer-based drug-drug interaction surveillance program on adverse drug interactions. We intend to evaluate the computer program MEDIPHOR for its clinical utility in detecting drug interactions and reducing the frequency of adverse drug reactions, and its impact on physicians prescribing of multiple drug regimens.

Technical Approach: Select high risk patients (receiving 2 or more simultaneously) at WRAMC will be screened for potential drug interactions utilizing the MEDIPHOR computerized drug monitoring program developed at Stanford University. Information obtained will be provided primary physicians to assist them in their patient care and to educate them in the potential problems of multiple drug regimens.

Progress during FY-80: Study just began and results of pilot show, 3 out of 4 patients screened to date had potential interactions.

Number of subjects to be studied before completion of study: 50

Serious/unexpected side effects in subjects participating in project: None

Conclusions: Would predict computer assisted search will impact on patient care as well as physician awareness of drug interaction.

Publications:

CLINICAL INVESTIGATION PROGRAM

Work Unit no.: 9100

Funds Utilized, FY-80: None

Funding Requirements, FY-81: $3,000

Personnel: (name and grade)

Equipment: (describe in detail including cost)

Supplies: (consumable, animal purchase)

Travel: (mission oriented, training and presentation) $500

Other: (equipment rentals, contracts for service, animal care and reprints) $2,500 - Stanford Univ for access to MEDIPHOR

*WR 70-1

DEPARTMENT OF THE ARMY
HEADQUARTERS WALTER REED ARMY MEDICAL CENTER
Washington, D.C. 20012

WRAMC Regulation
70-1

8 January 1979

# Clinical Investigation Program

## WRAMC RESEARCH ACTIVITIES


| | Paragraph |
|---|---|
| Purpose | 1 |
| Criteria | 2 |
| Definitions | 3 |
| Committees | 4 |
| Clinical Investigation Committee | 5 |
| Human Use Committee | 6 |
| Chief, Clinical Investigation Service | 7 |
| Records and Reports | 8 |
| Reports to Pharmaceutical Companies | 9 |
| Request for Funds | 10 |
| Informed Consent | 11 |
| Research Involving Children | 12 |
| Low Risk Protocols in Adults | 13 |
| Research in Pregnant Women Fetuses | 14 |
| Research Terminally Infirmed | 15 |


1. PURPOSE. This regulation prescribes the policies and procedures applicable to the Clinical Investigation Program within the patient care facility at Walter Reed Army Medical Center.

2. CRITERIA. Clinical investigation activities will meet the following criteria:

a. The objectives have scientific merit and are reasonably attainable.

b. The investigators are competent to perform the studies proposed.

c. Resources required for the proposed studies are either available, or can be obtained, and are proportionate to the merit of the proposal.

d. The studies will not have a deleterious effect upon the care of the sick and wounded.

---

*This Regulation supersedes WR 70-1, dated 1 Jan 73.

e. The studies are performed in a considered, coordinated, and professional manner.

f. Whenever feasible, studies should be initially performed in animal models.

g. The rights, well-being, and dignity of human subjects are maintained in accordance with the principles of the Declaration of Helsinki of the World Medical Association, and that written consent is obtained when indicated.

h. Any research involving animals will conform with AR 70-18 and the Laboratory Animal Welfare Act (Public Law 89-544; 7 USC 2131 et seq).

i. Assure compliance with existent military regulations to include AR 40-7, Use of Investigational Drugs in Humans; AR 40-37, Radioisotope License Program (Human Use); AR 70-25, Use of Volunteers as Subjects of Research; and WRAMC Reg 40-10, Health Physics Regulation; AR 40-38, Medical Services Clinical Investigation Program.

j. The voluntary consent of each adult human subject is essential. Each individual who initiates or directs the clinical investigation has a personal duty and responsibility for ascertaining the quality of the subject's consent. Before the acceptance of the subject, he must be given adequate explanation. He must be informed of the nature, duration and purpose of the study; the methods and means by which it is to be conducted; all inconveniences and means by which it is to be conducted; all inconveniences and hazards reasonably to be expected; and the effects upon his health or person which may possibly come from his participation in the study. He should be informed of any benefits he may acquire from participation in the study, and if there should be no benefits, the participant should be so informed. The process of obtaining voluntary consent must be witnessed by an observer who is not a coinvestigator on the research protocol. Written consent will be obtained in accordance with the format outlined in the appendix and will be in nonmedical language that is easily understood by the subject. The investigator will be required to maintain copies of the written voluntary consent for five years following completion of the study. Copies of the consent forms for all protocols must be forwarded to Chief, Clinical Investigation Service, within one month of entry of the patient onto study. The consent form must include the patient's printed or typed name, address, and social security number.

k) Children older than age seven, unless incapacitated, must assent (See definition section for definiton of assent.) to participation in studies. Additionally, the written consent of the parent or

guardian must be secured and properly witnessed. An effort should be made to secure the written consent of the child utilizing a consent form written at his age level. In addition, "instructions to guardian" may need to be prepared that is written at an adult level. Both the processes of assent and securing written consent should be directed toward providing the patient and parent (guardian) the information given to adult volunteers, i.e., the nature, duration and purpose of the study, the methods and means by which it is to be conducted, etc.

3. DEFINITIONS.

a. Clinical investigation under this program consists of the organized scientific inquiry, both in humans and by directly related laboratory work, into clinical problems of significant concern in the necessary health care of members of the military community, including active duty personnel, dependents, and retirees. Clinical investigation at WRAMC shall include projects involving WRAMC patients, investigators, or facilities.

b. Subjects are any persons who may be at risk because of participation as an object of clinical investigation by members of the AMEDD or their appointed representatives. These may include in-patients, outpatients, organ donors, informants, or normal individuals who participate in studies of medical, physiological, sociological, or psychological orientation. Selection of subjects must be equitable.

c. At risk: A person is "at risk" if he/she may be exposed to the possibility of harm (physical, psychological, or sociological) as a consequence of activity which extends beyond use of established and accepted methods necessary to meet his/her needs. Determination of nature and extent of "at risk" is a matter of common sense and professional judgment. In most cases, utilization of someone's time (inconvenience) will constitute "risk" since the activity is not an accepted method to meet the person's needs. Responsibility for this determination resides at all levels of institutional and departmental review.

d. Children: Persons who have not attained the legal age of consent to general medical care as determined under the law of the jurisdiction in which the research is to be conducted (DC - age 18)

e. Research: A formal investigation designed to develop or contribute to generalizable knowledge. This may involve dietary manipulations, alteration of daily routine or environment, questionnaires, record review,

f. Minimal Risk in Children: The probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical or psychological examination of healthy children. Examples include immunization, modest changes in diet or schedule, obtaining blood and urine specimens, and most behavioral research.

g. Assent: A child's affirmative agreement to participate in research which can only be given following an explanation appropriate to the level of understanding of the child. It is recognized that "assent" may have no legal status and may be difficult to obtain in young children; nevertheless, some sort of opportunity should be offered the child to agree to participate. (Ref Federal Register 43:2084-2114, Jan 13, 1978, and 43:31786-31794, Jul 21, 1978.)

4. COMMITTEES: The following committees will be appointed. At the option of the Chairman, the Clinical Investigation Committee and the Human Use Committee will meet either separately or simultaneously.

a. Clinical Investigation Committee: To review all clinical investigation proposals for scientific adequacy and to establish priorities for support. For the purpose of recommending new drugs which have not been released by the Food and Drug Administration, the Committee will serve also as the Therapeutic Agents Board (para 126, AR 40-2). This committee will be composed of a representative from each of the following:

Director, Medical Education (Chairman)
Chief, Clinical Investigation Service (Secretary)
Chief, Department of Medicine
Rotating Service Chief from Department of Medicine
Chief, Department of Surgery
Rotating Service Chief from Department of Surgery
Chief, Department of Pathology
Chief, Department of Radiology
Chief, Department of Pediatrics
Chief, Department of Psychiatry
Chief, Department of Obstetrics and Gynecology
Commander, USA Dental Activities (DENTAC)
Director, WRAIR
Chief, Nuclear Medicine Service
Chief, Health Physics
Chief, Pharmacy Service
Director, Patient Administration Directorate
Chief, Nursing Research Service
Assistant Chief, Clinical Investigation Service
A rotating senior clinical investigator (list to be established by Chief, Clinical Investigation Service)
Representative (USUHS)

The attendance of each member will be recorded in the minutes.

b. Human Use Committee: To review for medical safety and suitability all clinical investigation protocols involving the use of human subjects. This committee will be composed of a representative from each of the following:

Director, Medical Education (Chairman)
Chief, Clinical Investigation Service (Secretary)
Chief, Department of Clinical Pastoral Service
A Legal Counsel
Chief, Department of Nursing
Chief, Department of Psychiatry
Chief, Department of Obstetrics and Gynecology
Chief, Nuclear Medicine Service
Command Sergeant Major
Director, Human Resources Directorate
CDR, USA Dental Activities (DENTAC)
Clinical Pharmacist, Hematology-Oncology Service
Assistant Chief, Clinical Investigation Service
Patients' rights representative
Representative (WRAIR)
Director, Patient Administration Directorate
A rotating senior clinical investigator (list to be established by Chief, Clinical Investigation Service)

The Attendance of each member will be recorded in the minutes.

c. Radioactive Drug Research Committee (RDRC): To review all research protocols using radioactive drugs in human subjects, and to insure that such protocols are in compliance with the Code of Federal Regulations, Title 21, Chp I, Part 361. All protocols utilizing radioactive drugs will include radiologic assessment data, as an appendix to the protocol, including name of the radionuclide, presence of any contaminants, maximum dose to be administered, radiation absorbed doses to whole body and other organs accumulating the isotope, dosage from any X-ray procedures that are part of the research study, and any limitation regarding patient population due to sex and age. A report will be made by the RDRC to the Clinical Investigation Committee regarding each radioactive drug protocol in humans. In addition, the Committee will be responsible for preparing the annual report on research use of a radioactive drug to the FDA. This Committee will be composed of at least five individuals, including Chief, Nuclear Medicine Service; Chief, Health Physics; Chief, Clinical Investigation Service; Nuclear Medicine Service Pharmacist; and Chief, Radiation Therapy Service.

The RDRC will select a chairman, who will sign all applications, minutes, and reports of the Committee as well as a secretary. The RDRC will meet at least quarterly. A quorum consisting of a majority of the membership must be present, with attendance of at least individuals who are specialists in nuclear medicine, radioactive drug formulation, and radiation safety and dosimetry. Minutes will be kept, including numerical results on voting. No member shall vote on a protocol in which he is an investigator. The RDRC will submit an annual report to the FDA prior to 31 January of each year.

The investigator must submit a report (Appendix C) and a copy of the signed consent form to the RDRC within 15 days from the date of administration of the isotope.

d. Functions of the Committees: Either the Clinical Investigation Committee or Human Use Committee can terminate any investigation or place restrictions on a study at any time the Committees become concerned about the scientific merit of the study or adequacy of protection of human subjects. The Chief, Clinical Investigation Service can order a cessation of activity in any study pending an evaluation of the circumstances.

5. CLINICAL INVESTIGATION COMMITTEE: The Clinical Investigation Committee will meet once monthly, usually on the fourth Tuesday at 1400 hours. Special meetings can be called at any time, either upon request of the Commander, Chief, Clinical Investigation Service, or by written request of three Committee members. The Committee will review all new research proposals, either involving WRAMC patients, investigators, or facilities. Their review of proposals will address in particular scientific design, merit and funding. Departmental chairman will not vote on protocols from their own department, nor will any member vote on any protocol in which he is a coinvestigator. Periodically, the Committee will review approved and ongoing research. Each project will be reviewed at least once yearly, at the termination of the research and whenever there is a change either in the goals or the procedures or drugs used in human subjects, or deviation from the approved protocol. Adverse reactions to investigational drugs or procedures will be promptly reported to the Committee. The Committee will make recommendations to the Commander. Two-thirds of the membership in attendance will constitute a majority. A majority is necessary for protocol approval. A majority of the Committee will constitute a quorum and will include at least three physicians and three nonphysicians. There will be no proxy voting. Investigators will be informed within one week of the meeting in writing of the approval/disapproval of the project and reasons for so doing. A disapproved protocol must be resubmitted for approval. The Committee

may elect to approve a study with the addition of certain minor restraints/modifications. The Commander will have the right to disapprove any protocol on the grounds of being unsuitable for implementation at WRAHC but cannot overrule the disapproval of the Committee. Appendix D outlines the administrative methods by which primary and secondary review of protocols and review of annual progress reports will be achieved.

6. HUMAN USE COMMITTEE: The Human Use Committee will meet once monthly, usually on the fourth Tuesday either concurrently or with the Clinical Investigation Committee following the Clinical Investigation Committee meeting. Special meetings can be called at any time, either upon request of the Commander, Chief, Clinical Investigation Service, or by written request of three Committee members. The Committee will review all new research proposals in which human subjects are used. Their review of proposals will address in particular, the protection of human research subjects. Periodically, at least once yearly, the Committee will review approved and ongoing investigational studies in which humans are used. Each project will be reviewed at least once yearly and whenever there is a change in the goals or the procedures or drugs used in human subjects. The Committee will make recommendations to the Commander. Two thirds of the membership in attendance will constitute a majority. A majority is necessary for protocol approval. A majority of the Committee will constitute a quorum and will include at least three physicians and three nonphysicians. The Commander will have the right to disapprove any protocol on the grounds of being unsuitable for implementation at WRAHC but cannot overrule the disapproval of the Committee. There will be no proxy voting.

7. CHIEF, CLINICAL INVESTIGATION SERVICE.

a. Shall function as secretary/recorder at meetings; he will summarize the discussion on issues. Records of institutional review board's activities will be retained indefinitely.

b. Can terminate any project at any time pending Clinical Investigation Committee and Human Use Committee review.

c. Will be the contact with the Commander to assesss availability of resources to support projects and will manage those resources with guidance from Committees and Commander.

d. Will keep the Commander and Committees informed of the continuing changes in FDA/DOD requirements.

e. Will supervise under the guidance of the Clinical Investigation Committee and Human Use Committee, the secretarial, administrative support staff [illegible] regulations.

f. Will advise the Clinical Investigation Committee regarding alternatives if priorities for support need to be established.

8. RECORDS AND REPORTS.

a. Initial Protocol. Requests for initiating research projects will be submitted in one copy to the Commander, Walter Reed Army Medical Center, ATTN: Chief, Clinical Investigation Service. This will be submitted by the principal investigator through the chief of the respective service and department, and prepared as described in Appendix A. Protocols which do not conform to Appendix A will not be accepted by the Chief, Clinical Investigation Service. Frequent deficiencies in protocols include omission of an impact statement, failure to state the time required to complete the project, failure to include budget information, and failure to include signatures of the respective chief of service and department. When radiological, laboratory, or nursing support is required, the principal investigator should have obtained the concurrence of the appropriate chief of service prior to submission to the Clinical Investigation Committee. The chief of the department proposing the study will provide an indorsement that the proposal conforms to the criteria described in paragraph 2 above. To be placed on the agenda for the monthly committee meeting, the research protocol must be received by the 25th of the month preceding the meeting. Protocols will be distributed to the Committee members at least one week prior to the meeting, with appropriate agenda. Under no circumstances will a project require greater than three years to complete. If more than three years are needed, submission of a new protocol will be required.

b. Addenda to Initial Protocols. Whenever there is a change either in the goals or the procedures or drugs used in human subjects, the investigator will submit an addendum to the Commander thru the chief of the respective service and department, and Chief, Clinical Investigation Service. If necessary, the Committee will review this addendum as a new research proposal.

c. Annual Progress Reports: Annual progress reports will be prepared for each approved project as prescribed by AR 40-38, Clinical Investigation Program and will be submitted to Clinical Investigation Service prior to 15 August of each year until the investigation is completed. See Appendix B. Accurate preparation of budgetary data and/or documentation of abstracts or publications is essential. Failure to submit an annual progress report will result in termination of the project and withdrawal of the principal investigator's privilege to function as a principal investigator in any project.

d. Interim Reports. Interim reports must be submitted at any time when important development, adversities or other circumstances occur which should be brought to the attention of higher headquarters. In particular, interim reports must be submitted when unexpected deaths or [illegible] during the [illegible] investigation. Interim reports are required within three working days of the

development. They will be considered by the Chief, Clinical Investigation Service, who may elect to suspend work on the investigation until the Committee has an opportunity to meet.

e. Final Reports. Final reports are required upon completion or termination of a specific research effort. The report will include a summary of all work performed, results obtained, together with copies of all publications, whether printed, in press or submitted for publication. Inclusion of references to previous progress reports is optional. If the project is terminated prior to completion, the reasons for termination should be reported. Report is due within 30 days following completion or termination of effort.

f. Special Therapeutic or Diagnostic Procedures. Any special therapeutic or diagnostic procedures or any new, hazardous, or otherwise noteworthy therapeutic or diagnostic measures will be recorded in Space 24 of DA Form 8-274, Clinical Record Cover Sheet for Inpatients.

g. All reports will be forwarded to the Clinical Investigation Service following review by the appropriate chief of service and department. The Clinical Investigation Service will schedule presentations to the appropriate hospital review committees. Following review by the Commander of committee reports the Clinical Investigation Service will insure that reports are forwarded to the Surgeon General as required by AR 40-38.

h. Radioactive Drug Protocols Involving Administration of Radioactive Drugs to Humans. The investigator must submit a report (Appendix C) and a copy of the signed consent form to the Radioactive Drug Research Committee (RDRC) within 15 days from administration of the isotope.

i. Volunteer Agreements. Copies of volunteer agreements for all protocols must be forwarded to Chief, Clinical Investigation Service, within one month of entry of the patient onto study. The consent form must include the patient's printed or typed name, address, and social security number (see Appendix A).

8. REPORTS TO PHARMACEUTICAL COMPANIES. For procurement of investigational drugs which have not yet been released by the Food and Drug Administration, detailed reports to the drug company are required by FDA (Form FD 1573). The reports are the responsibility of the principal investigator, and are a matter of direct communication between him and the drug company

9. REQUEST FOR FUNDS. Requests for funds to support the clinical investigation program are presented to the Center Command annually during the month of March.

a. Projects requiring refunding in the amount of $1,000 or more are submitted each year prior to 1 March in the format of Appendix A for consideration. Projects requiring substantial increases (> 20% increase) in funding must undergo review by the Committee before funding will be approved.

b. New proposals which require funds may be submitted at any time. Approval of funding is dependent upon availability of local, Health Services Command or Surgeon General resources. Format Appendix A.

10. INFORMED CONSENT.

a. Patient Consent. The utilization of drugs or procedures which have not yet been accepted or established by common use require the patient's consent. The patient must be informed, i.e., his/her consent must be based upon his/her having knowledge of the experimental nature, purpose, and possible hazards. The consent should be in writing, except as provided in paragraph 7b, AR 40-7, or if the patient is a child (see 11). The consent form must be witnessed by someone other than an investigator on the project. Copies of the written voluntary consent will be maintained by the principal investigator for five years after termination of the study and will be forwarded to the Chief, Clinical Investigation Service, within 30 days of entry of the patient onto study.

b. Human Volunteer. Investigative studies in which drugs are employed are subject to, and must comply with AR 40-7, Use of Investigational Drugs and/or AR 70-25, Use of Volunteers as Subjects of Research in addition to AR 40-38.

11. RESEARCH INVOLVING CHILDREN.

a. In general, research in children will not be undertaken unless appropriate studies have first been undertaken in animals, adults, or older children. If the project is minimal risk, it may be undertaken if the Clinical Investigation Committee and Human Use Committee have approved the protocol, the assent of the child capable of understanding is obtained (possibly in writing), and written permission of the parent or guardian is secured

b. If the project is more than minimal risk, research that has potential direct benefit to the child, may be undertaken if the Clinical Investigation Committee, Human Use Committee, and the Office of the Surgeon General have approved the protocol, considering that the risk is justified by the anticipated benefit, that the risk benefit ratio is at least as favorable as that presented by alternative approaches, the assent of the child capable of understanding is obtained (possibly in writing), and written permission of the parent or guardian is secured.

c. If the project is more than minimal risk and of no direct benefit for subjects, the research may be undertaken if the Clinical Investigation Committee, Human Use Committee, and the Office of the Surgeon General have approved the protocol, that the procedure presents experiences commensurate with those inherent in their actual medical situation and is likely to yield generalizable knowledge about the subject's condition, the knowledge is of vital importance, the assent of the child capable of understanding (possibly in writing) is obtained, and written permission of the parent or guardian is secured.

d. Appendix A includes the appropriate volunteer agreement for protocols involving research in children. On the opposite side must be "instructions to guardian" and if the project is directed at children capable of understanding written instructions, there must be "instructions to patient" written at a level comprehensible by the average aged participant in the project.

e. The Human Use Committee will periodically monitor the process of assent and permission in research involving children.

12. LOW RISK PROTOCOLS IN ADULTS. A protocol in which there is a minimum possibility [illegible] to be subjected [illegible] as a result of the study. The study may not involve an investigational drug or device and may involve only human subjects who [illegible] given fully informed consent. That is, the study may not involve subjects who are minors, prisoners, institutionalized mental [illegible] or mentally disabled. The study also may not include subjects temporarily mentally disturbed by reasons of unconsciousness or coma. Low risk protocols may be undertaken after local approval by the Clinical Investigation Committee and Human Use Committee. These protocols will continue to be forwarded to the Human Use Review Office, who will notify the Chief, Clinical Investigation Service, immediately if there is any difficulty with either the protocol or the assessment of level of risk. The following types of [illegible] examples of low risk studies

a) Collection and analysis of additional small amounts of cerebrospinal fluid, amniotic fluid and venous or arterial blood when taken in conjunction with specimens of these fluids which are to be drawn for accepted clinical indications and do not require another puncture to obtain the additional amounts of these fluids for investigational purposes.

b) Analysis of hair and nail clippings collected in a nondisfiguring manner and the analysis of deciduous teeth.

c) Collection for analysis of excreta and external secretions including feces, urine, sweat, saliva, cerumen and tears or swab culture specimens of body orifices, placenta expelled at delivery, umbilical cord blood after the cord is clamped at delivery, and amniotic fluid at the time of artificial rupture of the membranes prior to or during delivery.

d) Recording of data by physical sensors applied either superficially or at a distance and which do not involve significant input of energy into the subject. Such procedures include, but are not necessarily limited to weighing, electrocardiography, electromyography and detection of naturally occurring radioactivity, electroencephalogram, thermography, diagnostic echography and electroretinography, caliper measure of anthropomorphic characteristics and detection of naturally occurring radioactivity.

e) Blood drawing of quantities of blood less than 20 cc/6 weeks from adult subjects in whom their underlying medical condition is not known to be associated with anemia. These patients need not have a hematocrit done before obtaining the blood specimens.

f) Blood drawing of quantities of blood less than 450 cc/8 weeks or 12% of the estimated blood volume, 7% of the body weight, whichever is lesser, from subjects who are not anemic. (Anemia is defined as a hematocrit < 40 for males, < 35 for female and a reticulocyte count > 1.5%). If quantities of blood > 20 cc/6 weeks are to be obtained, the protocol must state that a hematocrit and reticulocyte count be obtained in patients prior to entry onto study and be not anemic.

g) Studies involving generally accepted, medically indicated diagnostic or therapeutic procedures or comparisons of two or more generally accepted alternative procedures.

h) Noncontinuous or additional analysis of anatomic or biopsy specimens removed as the sole consequence of a medically indicated surgical indication.

i) Collection of both supra- and subgingival plaque, provided the procedure is no more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques.

j) Voice recordings made for research purposes such as investigations or speech deficits.

k) Moderate exercise by healthy volunteers.

l) The use of survey research instruments (interviews or questionnaires) and psychological tests, interviews and procedures that are part of the standard battery of assessments used by psychologists in diagnostic studies and in the evaluation of judgmental, perceptual, learning and psychomotor processes, provided that the subjects are normal volunteers and that the data will be gathered anonymously or that confidentiality will be protected by procedures appropriate to the sensitivity of the data.

m) Program evaluation projects that make no extra requirements of the subjects participating in the program and that will not benefit the subjects in the program.

n) Noninvasive pulmonary function testing such as (but not limited to) spirometry and plethysmography.

o) Collection and analysis of small amounts of internal secretions such as gastric contents and pulmonary aspirates when collection of these secretions does not involve the placement of either a nasogastric tube or endotracheal suction tube solely for obtaining specimens for research purposes.

p) Diary recordings of dietary intake, symptoms, activities and the like, whether the diarist remains anonymous or not.

13. Research in Pregnant Women Fetuses -- shall conform to the requirements of DHR 46.205 - 46.208.

A. General limitations.

1. No activity to which this subpart is applicable may be undertaken unless:

a) Appropriate studies on animals and nonpregnant individuals have been completed;

b) Except where the purpose of the activity is to meet the health needs of the mother or the fetus [illegible] the fetus is viable and, in all cases [illegible] achieved.

c) Individuals engaged in the activity will have no part in: (i) Any decisions as to the timing, method, and procedures used to terminate the pregnancy, and (ii) determining the viability of the fetus at the termination of the pregnancy; and

d) No procedural changes which may cause greater than minimal risk to the fetus or the pregnant woman will be introduced into the procedure for terminating the pregnancy solely in the interest of the activity.

2. No inducements, monetary or otherwise, may be offered to terminate pregnancy for purposes of the activity.

B. Activities directed toward pregnant women as subjects.

a) No pregnant women may be involved as a subject in an activity covered by this subpart unless: (1) The purpose of the activity is to meet the health needs of the mother and the fetus will be placed at risk only to the minimum extent necessary to meet such needs, or (2) the risk to the fetus is minimal.

b) An activity permitted under paragraph (a) of this section may be conducted only if the mother and father are legally competent and have given their informed consent after having been fully informed regarding possible impact on the fetus, except that the father's informed consent need not be secured if:

1) The purpose of the activity is to meet the health needs of the mother;

2) His identity or whereabouts cannot reasonably be ascertained;

3) He is not reasonably available;

4) The pregnancy resulted from rape.

C. Activities directed toward fetuses in utero as subjects.

1. No fetus in utero may be involved as a subject in any activity covered by this subpart unless:

a) The purpose of the activity is to meet the health needs of the particular fetus and the fetus will be placed at risk only to the minimum extent necessary to meet such needs, or

b) The risk to the fetus imposed by the research is minimal and the purpose of the activity is the development of important biomedical knowledge which cannot be obtained by other means.

2. An activity permitted under paragraph (1) of this section may be conducted only if the mother and father are legally competent and have given their informed consent, except that the father's consent need not be secured if:

a) His identity or whereabouts cannot reasonably be ascertained,

b) He is not reasonably available, or

c) The pregnancy resulted from rape.

D. Activities directed toward fetuses ex utero, including nonviable fetuses, as subjects.

1. Until it has been ascertained whether or not a fetus ex utero is viable, a fetus ex utero may not be involved as a subject in an activity covered by this subpart unless:

a) There will be no added risk to the fetus resulting from the activity, and the purpose of the activity is the development of important biomedical knowledge which cannot be obtained by other means, or

b) The purpose of the activity is to enhance the possibility of survival of the particular fetus to the point of viability.

(c) No nonviable fetus may be involved as a subject in an activity covered by this subpart unless:

(1) Vital functions of the fetus will not be artificially maintained,

(2) Experimental activities which of themselves would terminate the heartbeat or respiration of the fetus will not be employed, and

(3) The purpose of the activity is the development of important biomedical knowledge which cannot be obtained by other means.

a) In the event the fetus ex utero is found to be viable, it may be included as a subject in the activity only to the extent permitted by and in accordance with the requirements of other subparts of this part.

b) An activity permitted under paragraph (1) or (2) of this section may be conducted only if the mother and father are legally competent and have given their informed consent, except that the father's informed consent need not be secured if: (1) his identity or whereabouts cannot reasonably be ascertained, (2) he is not reasonably available, or (3) the pregnancy resulted from rape.

14. RESEARCH, MENTALLY INFIRMED. An appropriate addendum to these regulations will be published when the federal regulations regarding research in the mentally infirmed are promulgated.

HSHP-QCR

FOR THE COMMANDER:

FRANCIS J. GORZO
MAJ, MSC
ADJUTANT

DISTRIBUTION:

I plus 100 copies to
Clinical Investigation

APPENDIX A

APPLICATION FOR CLINICAL INVESTIGATION PROJECT
(New protocols must conform to this format and be complete.)

1. PRINCIPAL INVESTIGATOR:

2. PROJECT TITLE: (Enter short project title.)

3. OBJECTIVE: (Brief but specific statement of the objective of the project.)

4. MEDICAL APPLICATION: (Explain briefly the medical importance and possible usefulness of the project.)

5. STATUS: (What has been accomplished or published in the proposed area of study and in what manner will the project relate to or differ from that which has been accomplished. If references or personal communication with other Army medical facilities are involved, so indicate.)

6. PLAN: (Outline exactly what is proposed to be accomplished in sufficient detail to indicate a clear course of action. Technological validity of procedures and chronological steps should be shown.) (NOTE: The Surgeon General and the local Commander must have a very clear picture of how the investigation will proceed to meet the objective of the project. This paragraph frequently furnishes the basis for approval or disapproval of the project.)

7. BIBLIOGRAPHY: (List source of information.) (Include pertinent references and attach.)

8. FACILITIES TO BE USED: (Such as laboratory, ward or clinic.)

9. TIME REQUIRED TO COMPLETE: (Give month and year of expected start and anticipated completion. Under no circumstances will projects be funded for longer than three years without submission of a new protocol).

10. PERSONNEL TO CONDUCT PROJECT: (List names and positions of persons to be directly involved in project work. Attach short biographical sketch, including resume of education, research training, and list of publications, for each person named.)

11. FUNDING IMPLICATIONS: (List total budget for the protocol, as well as the budget for the FY in which the protocol is approved.)

| | FY-78 | Total for the Protocol |
|---|---|---|
| a. Personnel: (itemize and explain need) | $____ | $____ |
| b. Equipment: (itemize and explain need) | ____ | ____ |
| c. Consumable Supplies: (itemize) | ____ | ____ |
| d. Travel: (itemize and explain need) | ____ | ____ |
| e. Modification of Facilities: (explain) | ____ | ____ |
| f. Other (explain) | ____ | ____ |
| TOTAL | ____ | ____ |

12. DATE PREPARED: (give day, month and year of preparation)

_____
(Signature of Principal Investigator)

_____
(Signature of Department Chief)

_____
(Enter title and mailing address of Principal Investigator)

APPENDIX A

IMPACT STATEMENT

(Must be attached to each protocol enumerating impact considered to be beyond good patient care.)

Patients:

Bed Occupancy:

Laboratory:

Radiology:

Pharmacy:

Nursing Service:

Registrar:

Other:

| Approvals | Chief of Service | Chief of Dept | for Ethics Comm |
|---|---|---|---|
| Date: | | | |
| Signature: | | | |
| Name: | | | |
| Grade: | | | |
| Position: | | | |

APPENDIX A

VOLUNTEER AGREEMENT

Work Unit #_____

I,_____, having attained my eighteenth (18th) birthday, and otherwise having full capacity to consent, do hereby volunteer to participate in an investigational study entitled:

_____ under the direction of_____ of the Department/Service/Institute of _____, Walter Reed Army Medical Center, Washington, D.C.

The implications of my voluntary participation; the nature, duration and purpose of the study; the methods and means by which the study is to be conducted; and the known inconveniences and hazards have been thoroughly explained to me by the principal investigator or by one of the coinvestigators and such inconveniences and hazards are set forth in detail on the attached page of this Agreement, along with my initials or signature. I have been given an opportunity to ask questions concerning this investigational study and my participation in the study, and any such questions have been answered to my full and complete satisfaction.

During the course of my treatment as a patient at Walter Reed Army Medical Center, I have been provided with a copy of a Privacy Act statement (DD Form 2005) which has made me aware of the safeguards available to me because of the Privacy Act of 1974. I have been given the opportunity to review the DD Form 2005, ask questions and to retain a personal copy. I have been made aware that the information gained about me, because of my participation in this investigational study, may be publicized in medical literature, discussed as an educational model, and used generally in the furtherance of medical science. I freely consent to provide such personal information as is requested of me for this investigational study and freely consent to the disclosure of pertinent personal information derived from my participation in this investigational study for reasons of publication in medical literature, discussion as an educational model and for those additional reasons which specifically relate to the furtherance of medical science.

I understand that in the event of physical injury resulting from the research procedures, medical treatment for injuries or illness is available and that compensation may be available through judicial avenues. Information regarding judicial avenues of compensation is available from the Center Judge Advocate General.

WR 70-1 8 January 1979

I am aware that at any time during the course of this investigational study I may revoke my consent and withdraw from this study, without prejudice; however, I may be requested for medical reasons to undergo further examinations if in the opinion of my attending physician such examinations are necessary for my health or well being.

If there is any portion of this explanation that you don't understand, ask your doctor before signing.

| | |
|---|---|
| Signature | Date |
| Printed Name | Social Security Number |
| Address (permanent) | |

I was present during the explanation referred to above, as well as during the Volunteer's opportunity to ask questions. I hereby witness the Volunteer's signature.

| | |
|---|---|
| Signature | Date |
| Principal Investigator's Signature | Date |

this page of the Volunteer Agreement, the principal investigator should set forth full details concerning the investigational study, insofar as such would affect or influence the tentative subject in any way. This explanation should be worded so that it can be clearly understood by the subject. The subject should place his initials at the end of the last line of explanation.

A proper explanation should, at a minimum, provide the answers to the following questions in lay language:

1. What will be administered or done to the subject?
2. How long will the subject's participation last?
3. To what tests or examinations will the subjects be required to submit?
4. Why is the investigation being conducted?
5. Has this particular study been done previously, and, if so, with what results?
6. What inconveniences or discomforts is the subject likely to experience?
7. What risks or hazards can be reasonably anticipated?
8. What steps will be taken to prevent or minimize these risks or hazards?
9. If blood is being drawn in the study, the total amount of blood should be accurately quantitated in both cc's and ounces.
10. The volunteer should be offered the opportunity to ask questions.
11. Alternatives to participation in the study should be identified. It Should be emphasized that participation in the study is entirely optional
12. An instruction that the subject is free to decline participation or terminate participation at any time without prejudice.
13. Can the patient expect to accrue any benefit from participation in the study; if none, so state.
14. A statement informing the volunteer of available opportunities for compensation for any injury incurred during the study.
15. Exculpatory language should not be used.
16. For Onc[illegible], there should be a statement that "there is no guarantee that the proposed treatment will [illegible]

635

VOLUNTEER AGREEMENT

(Children Under Legal Age of Consent)

I/We _____, having full capacity to consent, do hereby consent for my/our _____, _____, (relationship) (name of participant) to participate in an investigational study entitled: _____

_____

_____

under the direction of _____ of the Department/Service/Institute of _____ Walter Reed Army Medical Center, Washington, D.C.

The implications of his/her participation; the nature, duration, and purpose of the investigational study; the methods and means by which it is to be conducted; and the inconveniences and hazards which may reasonably be expected have been explained to me/us by _____, and are set forth on the attached page(s) of this Agreement which I/we have initialed or signed. I/We have been given an opportunity to ask questions concerning this investigational study, and any such questions have been answered to my/our full and complete satisfaction.

I/We certify that my/our child has received an explanation of this investigational study in terms that he/she can understand, that he/she has had an opportunity to ask and has had answered any questions concerning this study, and that he/she assents to participating in this study.

I/We have been provided with a copy of the Privacy Act statement (DD Form 2005) which has made me/us aware of the safeguards available to me/us as a result of the Privacy Act of 1974. I/We have been given a chance to review the DD Form 2005, to ask questions, and to retain a personal copy. I/We Have been made aware that the information gained about my/our child, because of his/her participation in this investigational study, may be published in medical literature, discussed as an educational model, and used personally in the furtherance of medical science. My/Our child along with myself/ourselves consent to provide such personal information as is requested of us for this investigational study and freely consent to the disclosure of personal information derived from his/her participation in this study for reasons of publication in medical literature, discussion as an educational model, and for those additional reasons which specifically relate to the furtherance of medical science.

I/We understand that I/we may at any time during the course of this investigational study revoke my/our consent and withdraw my/our child from this study without prejudice; however, he/she may be requested to undergo further examinations, if, in the opinion of the attending physician, such examinations are necessary for his/her well being.

I/we understand that in the event of physical injury resulting from the research procedures, medical treatment for the injuries or illness is available and that compensation may be available through judicial avenues.

| signature | relationship | date |
|---|---|---|
| signature | relationship | date |

I was present during the explanation referred to above, as well as during the parents'/guardians' and the child's opportunity for questions and hereby witness their signatures.

| witness's signature | date |
|---|---|
| physician's signature | date |

ASSENT STATEMENT (Children Under Legal Age of Consent)

I certify that I have received an explanation of this investigational study in terms that I can understand, that I have had an opportunity to ask and have received answers to any questions I had concerning this study, and that I agree to participate in this study.

| patient's signature | date |
|---|---|

APPENDIX B

Annual Progress Report FY

Work Unit No.:

Title of Project:

Investigators:

Principal: (senior investigator responsible for project)

Associate: (coinvestigators)

Objectives: (goal of research)

Technical Approach: (method of attaining objectives)

Progress and Results: (formalized description of the research effort in relation to this work unit which was performed during the period of this report. If investigational drugs were used the information required by AR 40-7 must be included. The number of patients studied must be precisely delineated.)

Conclusions: (A precise statement of goals achieved by current studies) Have there been serious or unexpected side effects/ complications occurring in subjects participating?

Funding Requirements: (present and next FY)

Personnel: (name and grade)
Equipment:
Supplies:
Travel:
Other:

Publications: (list only those published during present FY or abstracts from your service which are related to the research described in this report. Failure to enumerate publications or abstracts may compromise funding of the protocol.)

Type of Report (new, revised, terminal, interim)

(Report should be typed on 8 x 10 1/2" white paper with 1" margins on all four sides. Do not number pages. Double space between sections of the report, single space type within each section. Do not use a staple to bind the report.)

# DISPOSITION FORM

For use of this form, see AR 340-15; the proponent agency is TAGCEN.

| REFERENCE OR OFFICE SYMBOL | SUBJECT |
|---|---|
| HSWP-QCR | Radioactive Drug Research Report |

TO Secretary, RDRC
Room 3E05, CIS
WRAMC

FROM

DATE

CMT 1

1. Work Unit #: _____

2. Work Unit Title: _____

_____

_____

3. Patient Information:

a. Identification Code: _____ (This number must allow for referencing back to a specific patient)

b. Age: _____

c. Sex: _____

d. Weight: _____

4. Pharmacological Dose Information:

a. Active Ingredients: _____

b. Maximum Amount Administered per Subject: _____

5. Radionuclide Information:

a. Radionuclide Used (Include any significant contaminants): _____

b. Activity of Radionuclide Used: _____

c. Date Radionuclide Administered: _____

Were X-ray procedures utilized in conjunction with this research protocol? YES _____ NO _____

Has any subject used in this study participated in other radioactive drug research studies? YES _____ NO _____

839

DA FORM 2496 REPLACES DD FORM 11, WHICH IS OBSOLETE.

Administrative Checklist for Evaluation of Protocols
(available for distribution to principal investigators)

| | YES | NO |
|---|---|---|
| 1. Administrative inadequacies: | | |
| Is the format inappropriate? | | |
| Has the protocol been signed off by the Chief of Service and Chief of Department? | | |
| Is there an impact statement? | | |
| Is the impact statement signed off by the involved Services? | | |
| Is the budgetary information sufficiently explicit? The exact type of supplies should be enumerated. | | |
| Is there a justification for major equipment purchases? | | |
| 2. Adequacies of consent forms: | | |
| A. Does the consent form contain: | | |
| 1) An explanation of the purpose of the study | | |
| 2) The duration of the study | | |
| 3) A full explanation of what is going to happen to the patient | | |
| 4) A description of all discomforts and risks reasonably related to the research | | |
| 5) A disclosure of an alternative to participation in the study. It should be emphasized that participation in the study is entirely optional. | | |
| 6) A description of any benefits to be expected from participation in the study | | |
| 7) An offer to answer any questions concerning the study | | |
| 8) An instruction that the subject is free to decline participation or terminate participation at any time without prejudice | | |

| | YES | NO |
|---|---|---|
| 9) A statement informing the volunteer of available opportunities for compensation for any injury incurred during the study. | | |
| 10) For Oncology protocols, a statement that "there is no guarantee that the proposed chemotherapy program is better than a standard program" | | |
| B. Is the language used in the consent form comprehensible by lay patients? | | |
| C. Is there exculpatory language in the protocol? | | |

Signature _____

Date _____



C-1

Form for Primary and Secondary Review of Protocols

Protocol Title: _____

_____

Reviewer: _____

Recommendations to the Committee:

☐ approval ☐ disapproval ☐ provisional approval with stipulation

Narrative justification for recommendations:

Prioritization (Assign a number between 1 and 5 with 1.0 being outstanding, 3.0 average, and 5.0 disapproval.)

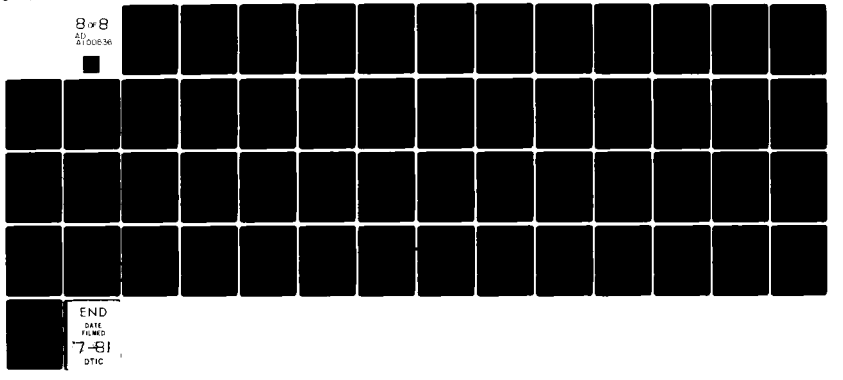
Scientific merit _____ (Assign a number)

Priority for funding _____

Is the budget realistic and adequately justified?

AD-A100 636 WALTER REED ARMY MEDICAL CENTER WASHINGTON DC F/G 6/5
ANNUAL PROGRESS REPORT (FY-80) DEPARTMENT OF CLINICAL INVESTIGA--ETC(U)
SEP 80 T M BOEHM

UNCLASSIFIED NL



8 of 8
AD
A100636

END
DATE FILMED
7-81
DTIC

Form for Primary and Secondary Review of Protocols

Protocol Title: _____

_____

Reviewer: _____

Recommendations to the Committee:

☐ approval ☐ disapproval ☐ provisional approval with stipulation

Narrative justification for recommendations:

Prioritization (Assign a number between 1 and 5 with 1.0 being outstanding, 3.0 average, and 5.0 disapproval.)

Scientific merit _____ (Assign a number)

Priority for funding _____

Is the budget realistic and adequately justified?

Dear Professional Committee Member of Clinical Investigation Committee:

Enclosed is the FY-1978 Annual Progress Report (APR) for Work Unit 6

It is requested that you represent the Clinical Investigation Committee by reviewing the APR for the enclosed protocol. Upon request, we will provide you with the original protocol, or you may come to the Clinical Investigation Service office during duty hours. The following questions are offered to you as guidelines to assist you in your review.

1) Is progress being made on the protocol?

2) Does the progress report indicate substantial deviation from the original protocol?

3) Is there any evidence of either unexpected side effects or an increased incidence of expected untoward side effects?

4) Is the request for funding appropriate? (One should consider here the merit of the project, previous budget, previous progress as documented by abstracts or publications, and justification for funding in the APR.)

Comments:

Recommendations: (please check in box)

☐ 1) That the APR and request for funding be approved by the Committee.

☐ 2) That the following additional information/clarification be furnished by the principal investigator.

☐ 3) That the entire Committee closely scrutinize this APR and examine the following specific aspects of the APR.

_____

Date

APPENDIX D

I. Implementation of the System of Protocol Review (including the System of Primary and Secondary Reviewers).

A. Protocols must be received by the 25th of the preceding month (or next working day if the 25th is a weekend day or holiday) in order to be considered at the next meeting, usually the fourth Tuesday of each month. Protocols not approved by the Department and Service Chief would not be accepted. The investigator would be expected to provide Clinical Investigation Service with several key references from the bibliography of the protocol.

B. Upon receipt of the protocol by Clinical Investigation Service, an administrative review and evaluation of the consent form would be undertaken. (See Incl #1 explanation and review sheet.) Any protocol with deficiencies would not proceed further in the review process until the deficiencies were resolved. Minor deficiencies in the consent form would be corrected by the editorial staff in the Clinical Investigation Service office. The investigator would receive a revised consent form and an explanation for revisions.

C. Protocols would then be read and reviewed by Chief and Asst Chief, Clinical Investigation Service, who would evaluate them primarily for adequacy of experimental design. The Chief and Asst Chief might elect to have an outside consultant review some protocols.

D. These protocols judged to be of reasonably sound design would be forwarded on about the first of the month to two (2) primary reviewers and two (2) secondary reviewers. The primary and secondary reviewers would be members of the Committee. Any of the primary and secondary reviewers could utilize additional consultation. An attempt would be made to select primary reviewers from the Committee on the basis of knowledge/expertise allied with the area under investigation in the project. An exception would be Oncology protocols, which would be distributed to the Committee on a rotational basis. Primary reviewers would attempt to assess scientific merit, experimental design, and give some priority for funding. They would be provided the key references submitted by the principal investigator. Each primary reviewer would submit a written report to Clinical Investigation Service of his assessment of the protocol by the 15th of the month (see Incl #2). At his discretion, he could consult with the investigator, and/or another consultant reviewer and suggest modifications or simply submit a written report to Clinical Investigation Service.

The secondary reviewers would also be selected from the Committee, except that they would not have expertise or knowledge allied with the area under investigation. They would be selected on a rotational basis, would submit the same written reports as first reviewers, and would be especially expected to provide some degree of more remote perspective regarding the merit of a project.

E. The entire Committee would be provided copies of the protocol, primary review and secondary review. Attendance of the investigator at the meeting would be optional but he would be provided with a copy of the minutes which would contain the reasons for approval/disapproval. The written protocol would be expected to be sufficiently explanatory that only adjunctive information would be the only input requested of the investigator at the meeting. The entire Committee would consider the protocol and reviewer's comments and vote for approval/disapproval. The numerical estimation of scientific merit and priority for funding from the reviewers would be recorded in the minutes. The entire Committee would have an opportunity to revise the numerical estimate of scientific merit and priority for funding.

F. A list of volunteer consultants and their areas of expertise would be compiled from USUHS, AFIP, WRAIR and NNMC.

II. Annual Review of Protocols

A. Henceforth, the Service will issue investigators lab notebooks, which will be available for inspection upon 24 hour notice and will be returned to Clinical Investigation Service upon completion of the project or the investigator's departure from WRAMC, at the discretion of the Chief, Clinical Investigation Service. For certain types of projects, a study record could suffice in lieu of a lab notebook.

B. Funded protocols which have been approved more than three years before must be resubmitted to the Committee for approval. Cooperative group protocols not requiring funding will be exempted from the three year limit. After three years, they are automatically considered terminated. Notice will be given to the principal investigator of these protocols three months prior to termination.

C. On a random basis, periodic inspections will be made of the data books, consent forms, and general status of individual work units. Written recommendations will be made to the Committee based on the basis of these inspections. At least one week notice will be afforded investigators. The Committee may elect to terminate a project or give the investigator time to correct deficiencies prior to a reinspection.

b. This year's Annual Progress Report will be divided into equal packages for each member of the Committee (see Incl #3) who can:

1) Certify that the Annual Progress Report is adequate and the project merits continuation.

2) Request additional data from the principal investigator.

3) Recommend the entire Committee closely scrutinize the project and decide whether or not continuation is warranted.

# HOW TO WRITE A PROTOCOL

A. The research process, a stepwise development

1. Prior knowledge or opinion
2. Inductive reasoning
3. Formulation of hypotheses
4. Deductive reasoning leading to experimental design, to test hypothesis
5. Experimentation
6. Evaluation and interpretation of data
7. Conclusion

B. Protocol writing is a specific exercise in the scientific method. Its central feature is the statement of a hypothesis which is verifiable by experimentation. In addition, the protocol specifies planned procedures by which evidence may be obtained either to verify or to reject the hypothesis. Thus the protocol is a brief, orderly statement of the information and directions pertinent to carrying out the research process in a specific instance. The discipline it imposes is that of exact thinking and expression.

C. A suggested form:

1. Title
2. Background: Prior knowledge or opinion; inductive and deductive reasoning leading to the statement of the hypothesis
3. Hypothesis: Statement to be verified or rejected
4. Objectives: Information to be gained

5. Materials and methods:

a. Experimental subjects; materials

b. Technical methods (quantitative determinations)

c. Experimental design and procedures (the formal plan and directions for experimentation)

d. Analysis and interpretation of data, to include:

(1) Data tables in outline

(2) Outline of proposed calculations and statistical procedures as determined by the experimental design. These calculations should include prescriptions for:

(a) The reduction of data

(b) The determination of their characteristics, descriptive values

(c) Estimates regarding the population parameters as indicated by the sample statistics, with an assessment of the uncertainty of such estimates

(d) Comparison between groups and the measure of uncertainty of such comparisons

(e) Provision for the discovery of interdependency of variables and the effect of such interdependency on interpretation of the results

6. Bibliography

## TIPS FOR WRITING AND PROCESSING PROTOCOLS

1. Make certain that approval of department chiefs is obtained before submission to Clinical Investigation Service.

2. Curriculum Vitae's are required of each investigator.

3. An appropriately signed off impact statement must be included.

4. Experimental design must be clearly specified.

5. Too frequently, the planned method of data analysis is inadequately outlined. This can lead to local disapproval, inordinate delay, or questions from the Office of the Surgeon General.

6. The exact population of patients to be studied is often inadequately identified. The age groups and excluding conditions from study must be precisely identified.

7. If the patients are at risk, there need be a description of how the risk will be minimized, i.e.; constant attendance by a physician.

8. Any requests for funding should be substantiated in detail. You should be prepared for your requests to be critically analysed at the Clinical Investigation Committee meeting.

9. The major problem with protocols that are not approved is clarity in the writing of the protocols. All parts of the protocol should be comprehensible by lay personnel, as well as physicians and other professionals not in the particular area of investigation.

0. Leave one inch margins on all four sides of the page.

# IMPACT STATEMENT

Patients:

Bed Occupancy:

Laboratory:

Radiology:

Pharmacy:

Nursing Service:

Registrar:

Other:

Approved: Chief of Service Chief of Dept

Date:

Sig:

Name:

Grade:

Position:

Adler RA: 39
Alford JP: 68
Anderson JH: 493
Annable CR: 368
Armbrustmacher V: 146

Baker J: 415
Baldwin PJ: 591
Bank RL: 552, 560
Barnes S: 168, 174
Bass JW: 509
Berenberg JL: 7, 139, 140, 204, 205, 208, 209, 211, 212, 215, 216, 217, 219, 221, 223, 226, 227, 228, 229, 230, 231, 232, 236, 237, 238, 239, 240, 241, 245, 246, 247, 248, 249, 250, 251, 252, 253, 255, 257, 258, 259, 262, 264, 267, 270, 272, 274, 275, 276, 496, 570
Bergman SM: 22, 28, 30
Bergquist RJ: 336
Berne BH: 10, 401, 418, 430
Berry WR: 6, 200, 324
Blom J: 206, 214, 224. 233, 235, 254, 260, 261, 273
Bloomfield CJ: 233
Boedeker BH: 188, 203, 581, 588
Boehm TM: 7, 8, 10, 37, 40, 58, 62, 97, 156, 400
Bond-Liebertz MD: 360
Bongiovanni B: 396
Bongiovanni R: 8, 11, 135, 136, 318, 395, 515, 571, 572, 573, 574, 578
Boslego JW: 6, 296, 297, 308
Boswell B: 438
Bowie RB: 480, 594
Braham SL: 498, 501
Brewer TG: 6
Bridenbaugh RH: 554, 556, 558, 560, 562
Brinton CC: 6, 296, 297, 308
Brodkey CG: 609, 611
Bruton J: 5, 40, 41, 77, 125, 130, 155, 158, 167
Bryan J: 6, 297
Burgess DP: 11, 81, 502, 506, 507, 508, 510, 513, 516, 517, 518, 519
Burkhalter EL: 191, 193
Burman KD: 5, 6, 8, 36, 37, 38, 39, 40, 41, 43, 45, 48, 49, 50, 52, 54, 58, 59, 60, 62, 63, 68, 74, 82, 104, 106, 108, 109, 111, 112, 113, 114, 115, 117, 118, 123, 124, 133, 134, 135, 137, 138, 140, 144, 154, 159, 163, 164, 167, 168, 169, 170, 171, 173, 175, 176, 177, 178
Burton CL: 333
Butkus DE: 22
Butler P: 500
Butler VM: 78, 92, 122, 132, 168
Butler WM: 570



PRECEDING PAGE BLANK-NOT FILMED

Cabellon S: 328
Cafferty PJ: 582
Callahan M: 380
Canfield CJ: 312
Cannmann D: 50
Cassimatis EG: 554
Castell D: 0, 8, 180, 188, 196, 199
Cavalli F: 235
Chadwick SG: 353
Chapman R: 139, 140, 288
Charya RV: 415
Cheatham WW: 91
Chernow B: 8, 196
Chi G: 360
Chulay JD: 312, 314
Chun PKC: 35
Chow JA: 380
Ciak J: 6, 296, 297, 308
Clagett GP: 326, 328, 330
Collins GJ: 326, 328, 329
Copley B: 33
Corcoran R: 49
Corley J: 485
Corrigan DF: 40
Crosby WH: 579, 580
Cross AL: 320, 321
Crowley JM: 357
Cultner J: 208
Cupples HP: 334
Curl WW: 907
Curtis DJ: 187, 408, 501

Dahms WT: 67
Davia JE: 11, 35, 603, 606
Davis C: 377
Davis P: 10, 385
Davis RW: 10, 383
Dawson E: 78, 120
Dembroski TM: 606
DeMeester TR: 196
DeShazo RD: 10, 382, 383, 400
Detrick-Hooks B: 530, 540, 543, 551
Deutsch AJ: 396, 398, 435
Dickson E: 6, 317
Dimond RC: 7, 8, 39, 40, 41, 119, 121, 154, 157
Dixon JP: 589
Djuh Y-Y: 40, 118, 137, 138, 160
Dobek A: 6, 316, 317, 320, 321
Dubois A: 180
Duff P: 466, 467, 477, 478

Dugar M: 24
Dunn MA: 200
Dunne MJ: 353
Durakovic A: 490
Dvorak HM: 10, 382, 383

Earll JM: 39, 40, 41, 95
Eddleman WL: 328
Edwards MS: 387
Eil E: 5, 125
Evans R III: 10, 37, 384, 387, 389, 390, 391, 392, 395, 415, 435, 436, 437
Ewel CH: 396, 398, 581

Fair C: 360
Fischer GW: 11, 502, 506, 507, 509
Fishbein WN: 590
Fishburne, FJ: 564, 565, 566
Fitz JD: 22
Fleckenstein L: 612
Floyd M: 10
Ford DD: 580
Fowler JE: 371, 376, 378
Fox EL: 609, 610
Frank T: 442, 443, 458, 459, 460
Frantz AG: 39, 40
Friedman M: 207

Galloway JA: 10, 400
Gemayal N: 75
George E: 522, 528, 531, 545
Gilbreath M: 297
Ginsburg SJ: 233
Glaines LT: 436
Glass AR: 5, 6, 7, 8, 11, 65, 70, 72, 75, 83, 85, 87, 89, 98, 100, 102, 104, 148
Glass DC: 606
Glickman A: 217
Golden R: 499, 500
Goldner FH: 179
Gotliet AJ: 211, 233
Graeber GM: 360, 582
Green BJ: 63
Gurevich Uvena J: 360

Haddock JB: 441, 442, 443, 458, 510, 511
Hannah JS: 11, 572
Harmon JS: 6, 9, 200, 322, 323, 324, 325, 588, 589
Harper G: 563
Harrison SM: 293, 294

Harton J: 119
Hasbargen J: 31, 32, 33
Haut MJ: 568, 569
Hayes K: 11
Heller PB: 440, 444, 445, 446, 447, 448, 449, 450, 451, 452, 453, 454, 455, 456, 457, 461, 462, 463, 464, 465, 468, 469, 470, 471, 472, 473, 474, 475, 483, 484
Henderson RL: 351, 355
Hendricks LD: 312
Henry A: 31, 32, 33
Herald WJ: 293, 294
Hicks CU: 11, 572, 574, 578
Hirata RM: 189, 190
Hodges W: 297
Howe EG: 611
Hubbard V: 10, 385
Hunter JG: 11, 502, 562
Hunter KW: 11, 507
Hutchison GB: 496, 497

Jabbari B: 563
Jahrling PB: 493
Janowitz WR: 8, 196
Jewell JS: 353
Johnson C: 35
Johnson JP: 5, 18, 19
Johnson LF: 8, 13, 144, 180, 182, 187, 188, 189, 190, 191, 193, 194, 195, 196, 197, 199, 200, 203, 322, 588
Jones L: 74

Kaliner M: 10, 385
Kaminski RJ: 195, 493
Karcher D: 520, 530, 535, 536, 540, 541, 543
Kark JA: 11, 568, 569, 571, 572, 573, 574, 575, 576, 577, 578
Keegan MT: 13
Keiser JF: 320, 467
Kern S: 377
Kesler P: 40
Kessler P: 8, 168, 175
Kidd GS: 7
Kikendall WJ: 187, 203
Killian PJ: 432, 433
Kimball DB: 14, 16, 256, 265
Klapholz H: 441, 443
Klayman D: 6
Klein T: 148
Kopecko D: 320
Kramer KK: 9, 331, 332
Krantz DS: 11, 603, 605, 606
Kumar DD: 10, 400

LaDuke DL: 556
Landes D: 510, 511, 513
Langloss JM: 593
Latham KR: 8, 54, 108, 109, 117, 118
Layland DH: 344
Lawless OJ: 10, 412, 414, 417, 418, 430
Leapley P: 97
LePage A: 611
Lessin LS: 11, 571, 572, 573, 577
Levine M: 536, 549
Levinson HI: 10, 383, 392
Lewis GE: 493
Light JA: 9, 363, 364, 366, 367, 369, 370, 371, 373, 495
Lillemoe K: 324
Lindsey SM: 430
Lockwood BR: 566
Lohsen BW: 360
Lolik A: 6, 297
Londono S: 396
Lowell G: 509
Lukes Y: 104, 108, 112, 114, 116, 174, 176, 177, 178

MacDougall JM: 11, 606
McChesney D: 6, 296, 308
McLeod DG: 379, 544
McMeekin RR: 589
Mansfield LE: 10, 383
Markey KL: 607, 907
Matthews KA: 605
Mayer MH: 357
Mehlman T: 6, 7, 77, 146, 152, 165
Mellitt R: 7
Merriken RA: 353
Messe AD: 11, 502, 507, 517
Metcalfe DD: 10, 385
Metzger JF: 493
Michel TJ: 440, 444, 445, 446, 447, 448, 449, 450, 451, 452, 453, 454, 455, 456, 457, 461, 462, 463, 464, 468, 469, 470, 471, 472, 473, 474, 475, 483, 484
Montgomery AA: 342, 344, 345, 346, 351
Moore JJ: 18, 19, 30, 31, 32
Morgan DW: 554
Mozingo D: 5, 125
Mutter MM: 28, 129

Nash DA: 20, 22, 24, 26, 31, 32, 33
Neglia W: 440, 444, 447, 457, 496, 520, 522, 536, 537, 538, 540, 543, 544, 545, 546, 547, 548
Nelson HS: 10, 383, 438
Newhouse P: 558

Nickson JJ: 497
Nisce L: 207
Noel G: 39, 40
Nosler HJ: 353

O'Brian JT: 74
Oetgen W: 129
Ortiz A: 435
Osburne R: 8, 40
Oster CN: 293, 294, 310, 312, 314, 318, 320, 321
Oyewole MA: 189, 190, 588

Pamplin C: 312
Pangaro L: 5, 50, 52, 81
Papineau MB: 556
Park RC: 440, 444, 445, 446, 447, 448, 449, 450, 451, 452, 453, 454, 455, 456, 457, 461, 462, 463, 464, 465, 468, 469, 470, 471, 472, 473, 474, 475
Peck CC: 612
Perone P: 146
Peters CJ: 493
Peterson HD: 380
Peura DA: 189, 190, 191, 193, 201, 202
Porpatich RK: 320
Potter MW: 142
Presbylick A: 442, 443, 458, 459, 460
Pulaski ET: 500, 501
Punch JL: 9, 345
Purohit V: 5, 125

Rajagopal KR: 291
Ramirez DA: 10, 390, 391
Raum WJ: 7
Raveche E: 6, 161
Reardon MJ: 582
Reid R: 581
Reltig FM: 596, 600, 609, 610
Rice MK: 162
Rich NM: 326
Rogers JE: 40
Roggers JE: 493
Ruymann FB: 11, 214, 502, 506, 507, 509, 514, 516, 518, 520, 522, 523 524, 525, 526, 527, 528, 529, 530, 531, 532, 533, 534, 535, 536, 537, 538, 539, 540, 541, 542, 543, 544, 545, 546, 547, 548, 549, 550, 551

Sadoff J: 6, 296, 297, 308
Salander JM: 326, 328
Salvado AJ: 570
Sanmarco ME: 605

Schaaf M: 7, 8, 39, 40, 119, 121, 146
Schaeffer M: 11, 606
Schctz M: 438
Schechter GS: 568, 569
Schuster BG: 612
Schuster DL: 392
Schwartz DM: 9, 337, 338, 339, 341, 342, 344, 346, 351, 355, 357
Scovill J: 6, 317
Sedge RK: 348, 355
Selvester R: 605
Shaffer RT: 11
Shaw F: 35
Shay SS: 195
Sheldon GM: 92, 120
Shelhamer J: 10, 385
Shipley SB: 601
Silverwood P: 360
Simon CMB: 480, 482
Sjogren RW: 184
Skiba-Powell H: 440, 441, 443, 458, 459, 460
Slater CB: 611
Smallridge RC: 5, 6, 7, 8, 40, 45, 50, 54, 59, 63, 74, 81, 104, 119, 121, 123, 129, 131, 133, 144, 146, 154, 157
Smith B: 28
Smith CE: 6, 7, 63, 153, 165
Smith JA: 10, 383
Smith LJ: 10, 384, 385
Smith PN: 467
Snyder KL: 430
Sonies BC: 362
Sopolis RJ: 556
Southby JR: 481, 591, 592
Spebar MJ: 326, 328
Speilman DE: 348
Stanbaugh KF: 346
Stein MR: 195
Steinberg A: 6, 161
Stotler R: 485
Strong D: 433
Strong S: 467
Stutzman L: 207
Stutzman RE: 378, 379
Summers RJ: 384, 387, 388, 435, 438, 439
Surr RK: 9, 337, 338, 339, 341
Swerdloff RS: 6, 7

Tai YH: 588
Takafuji E: 312
Taylor H Grant: 278, 280
Taylor I: 322

Tesar JT: 10, 412, 414, 432, 433
Thomas PJ: 11, 502, 506, 507, 509, 511, 516, 517, 518, 520, 522, 523, 524, 525, 526, 527, 528, 529, 530, 531, 532, 533, 534, 535, 536, 537, 538, 539, 540, 541, 542, 543, 544, 545, 546, 547
Thompson PF: 142, 144, 360
Thrall J: 49
Tiwary CM: 504, 505, 510, 511, 513, 515
Tjio JH: 6, 161
Tramont EC: 6, 293, 294, 295, 296, 297, 298, 308, 309, 312, 314, 317, 318, 320
Tseng YL: 8

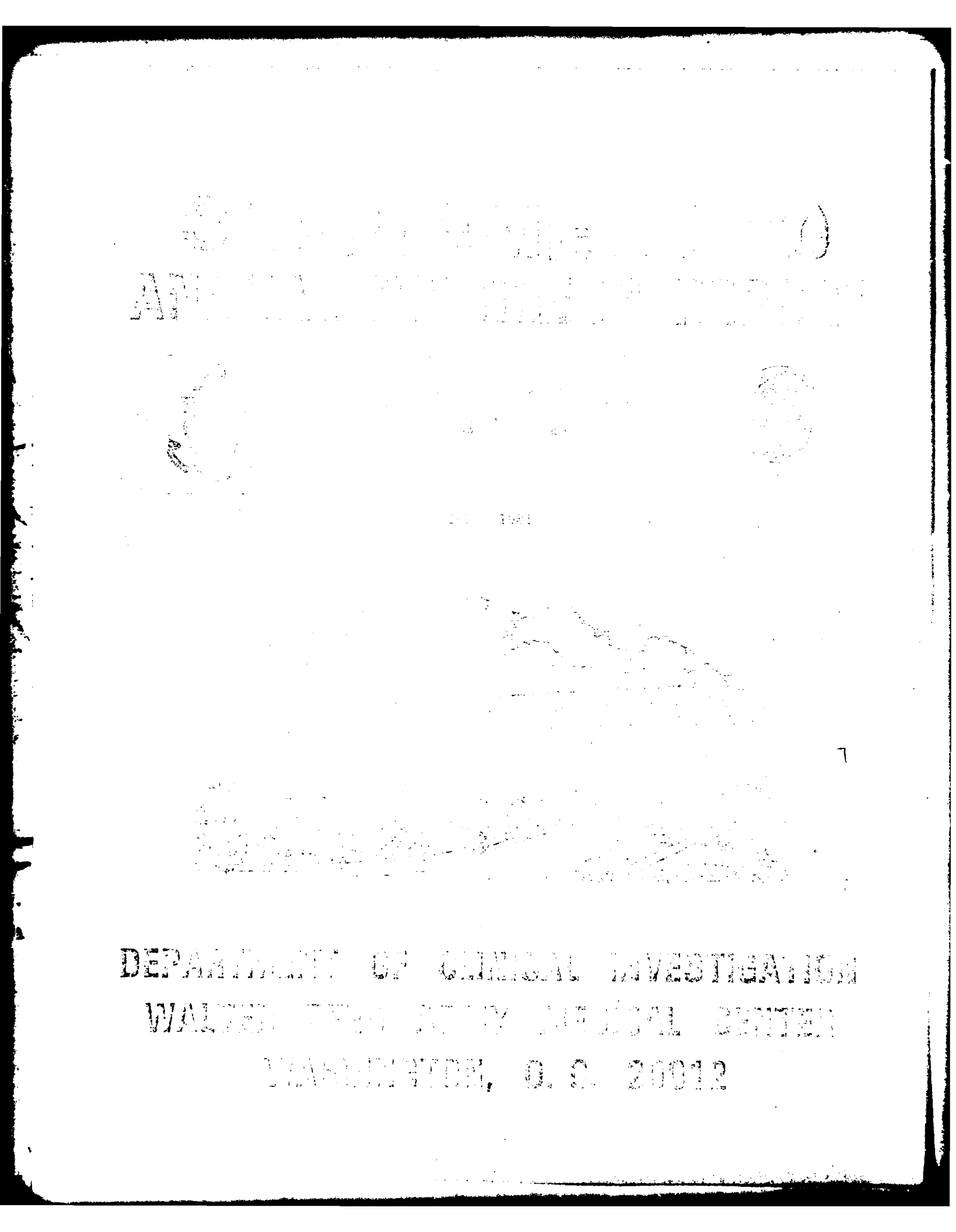
Van Nostrand D: 48, 129, 180, 182, 485, 487, 489, 490, 491, 492, 495
Vigersky RA: 5, 6, 7, 8, 56, 66, 79, 93, 95, 100, 110, 125, 127, 139, 140, 150, 152, 161, 165, 167, 168
Virtue C: 438

Waddell TW: 566
Wain AJ: 563
Walden BE: 9, 342, 344, 345, 346, 348, 351, 357
Walker PF: 395
Wang MD: 348
Ward KE: 8
Wartofsky L: 5, 8, 38, 39. 40. 41, 42, 43, 47, 48, 49, 50, 52, 54, 58, 59, 60, 62, 63, 68, 74, 81, 104, 108, 117, 123, 133, 137, 138, 142, 144, 154
Washburn TB: 40
Watkins B: 24
Watson R: 558
Weber R: 438
Weisbaun G: 440, 452, 453, 454, 455, 456, 457
Weltz MD: 189, 190, 268, 271, 277, 278, 289
Wergeland FL: 335, 432, 433
Wertz FD: 333
Wheeler L: 148
Whitmore P: 539, 546
Whitmore PV: 333, 334
Whorton NE: 8, 40, 154, 157
Wilkinson EV: 342, 353
Williams DL: 357
Williams H: 146
Wilson J: 612
Wong HYC: 375
Wong RKH: 180, 182, 188, 194, 197, 199
Wray HL: 5, 6, 59, 68, 77, 91, 106, 119, 121, 167, 168, 177

Zajtchuk JT: 353
Zollinger W: 6, 296, 297, 308

DISTRIBUTION

| Number of Copies | Agency |
|---|---|
| 2 | Commander<br>US Army Medical Research Command<br>ATTN: SGRD-AJ<br>Fort Detrick, MD 21701 |
| 2 | Commander<br>US Army Medical Research Command<br>ATTN: SGRD-HR<br>Fort Detrick, MD 21701 |
| 1 | Defense Documentation Center<br>ATTN: DDC-TCA, Cameron Station<br>Alexandria, VA 22314 |
| 2 | Commander<br>HQ, US Army Health Services Command<br>ATTN: HSPA-CI<br>Fort Sam Houston, TX 78234 |
| 1 | Superintendent<br>Academy of Health Sciences, US Army<br>ATTN: AHS-COM<br>Fort Sam Houston, TX 78234 |
| 1 | Each US Army Medical Center |



DEPARTMENT OF CLINICAL INVESTIGATION
WALTER REED ARMY MEDICAL CENTER
WASHINGTON, D. C. 20012

SUPPLEMENT TO ANNUAL PROGRESS REPORT

FY-80

DEPARTMENT OF CLINICAL INVESTIGATION

Table of Contents

These reports were not submitted on time, so consequently this supplement had to be undertaken for all of the late investigators


| | | PAGE |
|---|---|---|
| *1004 | Stress Ulceration in a Medical ICU: Incidence and Possible Prevention with Cimetidine. (FY-77 F) | 1 |
| 1388 | The Development of a Radioimmunoassay for Thyronine and 3,5-T2. (FY-78 F) | 2 |
| 1306-79 | Thyroid Status in Ob/Ob Mice. (FY-79 F) | 3 |
| 1516 | CALGB #7291, Postop Radiotherapy and Combinations of VCR, Cytoxan, Adriamycin, Actinomycin D in Rhabdomyosarcoma. (FY-73 F) | 5 |
| 1528 | CALGB #7391, Clinical Trial of Radiotherapy + Chemotherapy (Cytoxan, VCR, Actinomycin D) in Managing Non-Metastatic Ewing's Sarcoma. (FY-73 F) | 6 |
| 1542 | CALGB #7583, Adjuvant Chemotherapy in Osteogenic Sarcoma: Adriamycin Vs SEq Adriamycin, HD MTX - Leukoveric Rescues Vs SEq Adriamycin - Cytoxan. (FY-76 F) | 7 |
| 1548 | CALGB #7681, Effects of Adriamycin with and without Added MER in Soft Tissue Sarcomas (A Phase III Study) (FY-77 F) | 8 |
| 1566 | CALGB #7811, Remission Induction of Recurrent Childhood ALL. (FY-79 F) | 9 |
| 1568 | CALGB #7892, Multimodel Therapy for Management of Primary Non Metastic Ewing's Sarcoma of Pelvic and Sacral Bones. (FY-79 F) | 10 |
| 1569 | CALGB #7893, Multimodal Therapy for the Management of Primary, Non-Metastatic Ewing's Sarcoma of Bone, Pelvic/Sacral Areas Excluded. (FY-79 F) | 11 |
| 1571 | CALGB #7891, Intergroup Rhabdomyosarcoma Study III: Alveolar Rhabdomyosarcoma of the Extremity in Clinical Groups I and II Patients. (FY-79 F) | 12 |


*This Annual Progress Report was not late, but terminated, so it is included in this Supplement.

Ovarian Carcinoma, Breast Carcinoma, Lymphoma, and Hepatoma. (FY-80 I)

1573 CALGB #7911, Treatment of Primary Untreated Acute Lymphocytic Leukemia. (FY-79 F) 14

1574 CALGB #7981, Comparison of FAM Vs MA in Locally Advanced or Metastatic Gastric Cancer. A Phase III Study. (FY-80 I) 15

1577 CALGB #7921, Comparative Study of Three Remission Induction Regimens and Two Maintenance Regimens in Acute Myelogenous Leukemia. (FY-80 I) 16

1579 CALGB 7983, Surgical Adjuvant Systemic Chemotherapy with 5-FU, Adriamycin, and Mitomycin-C Vs Observation only in Gastric Adenocarcinoma. (FY-80 I) 17

1604 WRAMC 7205, Chemotherapy with DTIC and Adriamycin in Soft Tissue and Bone Sarcomas. (FY-73 F) 18

1626 WRAMC 7405, Treatment of Advanced Renal Cell Carcinoma with a Combination of CCNU and Bleomycin. (FY-77 P F) 19

1644 WRAMC 7501, Evaluation of Adriamycin and Cis-Platinum Combination Chemotherapy in Treatment of Malignant Disease. (FY-75 F). 20

1649 WRAMC 7602, Chemoimmunotherapy of Prostatic Carcinoma. (FY-76 I). 21

1658 WRAMC 7702, Adjuvant Chemotherapy of Prostatic Carcinoma with Adriamycin and Cis-Diamminedichloroplatinum II. (FY-78 I) 22

1666 WRAMC 7801, Immunological Evaluation and Phase One Immunotherapy of Patients with Various Carcinomas. (FY-78 I) 23

1672 Tumor Tissue for Extract Preparation. (FY-79 I) 24

1680 WRAMC 7908, Use of Streptozotocin in the Treatment of Metastatic Islet Cell Carcinoma of the Pancreas and Metastatic Carcinoid. (FY-80 I) 25

1683 WRAMC 7911, Use of L-Asparaginase in the Treatment of Acute Lymphoblastic Leukemia in Adults and Children. (FY-80 I) 26

2104 Evaluation of Efficacy of Suppressing Platelet Activity in Patients with Intermittent Claudication. (FY-77 F) 27

2105 Rapid Screening for Coagulation Abnormalities. (FY-78 F) 29

2810 Comparative Study of High Dose Versus Low Dose Pre-Operative Radiation to Radical Cystectomy for Control of Transitional Cell Carcinoma of the Bladder. (FY-78 I) 30

4501 Clinical Evaluation of Fluorescence Scanning of the Thyroid with an Americium Source. (FY-73 F) 31

Author Index 33

HSLP-SGF

24 February 1981

SUBJECT: Minutes of the Clinical Investigation and Human Use Committee Meeting

5. New Business:

a) The minutes of the last meeting were reviewed and approved with one modification. MAJ Wilson's TRC protocol will be classified as a "10 day" group oncology protocol and so reflected in the minutes. After review of the specifics of AR 40-23 regulations, this was indeed considered to be a cooperative group oncology protocol, since the drug is a NCI sponsored Group C drug.

The Committee refused to approve the request for amendment of the 30 Sep 80 minutes classifying MAJ Read's Sweat Inhibition protocol as "non significant risk." The manufacturer will have to submit justification that the iontophoresis device is a nonsignificant risk device.

b) The rotating Committee members were introduced: Daniel B. Nash, LTC MC, Chief, Nephrology Svc, (Rotating Svc Chief, Dept. of Medicine), Eugene D. George, COL MC, Chief, Neurosurgery Svc, (Rotating Svc Chief, Dept. of Surgery), and Robert A. Prosek, Ph.D., Staff Audiologist, Army Audiology and Speech Center, (Rotating Senior Investigator, Department of Clinical Investigation).

c) Dr. Boehm reviewed the new DHHS-FDA regulations, discussing expedited review, liability of Committee members, new ingredients for informed consent, no compensation clause for low risk research, categories of research exempt from institutional review, opportunity for subjects to review the consent form. Copies of the new regulations, as well as summary sheets, were distributed to the Committee.

d) The following annual progress reports were reviewed by the Committee: a) Work Unit 1905, Dr. Harrison's request for continuation of the T. Pallidum in N.S. protocol was approved. b) Work Unit 3159R, Dr. Berne's annual progress report was accepted as a final progress report. Dr. Berne was encouraged to write a new protocol identifying current directions of the research and justifying the request for funding. c) Work Units 1308, 1311, 1359 and 1360, Dr. Burman's annual progress reports were accepted by the Committee. d) Work Unit 1677, Dr. Bereuberg explained that mucositis is a known side effect of adriamycin but that the incidence seen was higher than they expected. The annual progress report was accepted. e) Work Units, 1334, 1346, 1347 and 1353, these annual progress reports of Dr. Burman's were accepted as final reports. New protocols will be submitted. No funding is authorized for FY 81. f) Work Unit 7218, because he was absent, Dr. Newhouse's annual progress report was tabled. g) Work Units 2610, 2615, 2618 and 2619, Dr. Wyatt's annual progress reports were accepted. Work Unit 2610 was accepted as a final progress report, while 2615, 2618, 2619 were accepted as annual progress reports.

6. The following addenda were presented to the Committee:

a) Amendment to SGRD-7[illegible]. Principal Investigator: Frederick B. Burman, [illegible], Pediatric Renal Oncology Svc, [illegible]. Dr. Burman explained that [illegible]

The following Annual Progress Reports were reviewed by the Clinical Investigation Committee on 24 Feb 81, and the following action was taken: (A copy of the minutes of that date involving the APR's is attached.)

1308 Inderal Kinetics in Hyperthyroidism. (FY-74 F)

1311 Treatment of Thyroid Storm with Anion-Exchange Resin. (FY-74 I)

1334 The Regulation of Extrathyroidal Conversion of Thyroxine (T4) to Triiodothyronine (T3). (FY-75 F)

1346 Thyroid Function Tests in Cord Blood, Maternal Sera and Aminotic Fluid. (FY-76 F)

1347 Investigations into the Physiology of L-Reverse T-3 (rT3) and -3-Diiothyronine (3-3 T2). (FY-76 F)

1353 The Regulation of T4 Conversion. A Grant Proposal. (FY-77 F)

1359 The Effect of Reverse T3 and 3, 3 T2 on Thyroid Gland Secretion, T4 Degradation, and Iodide Leak in Thyrotoxic Patients. (FY-77 F)

1360 Investigations Concerning T3 Production Rates. (FY-77 I)

1677 WRAMC #7905, Treatment of Acute Leukemia with Low Dose Adriamycin Infusion. (FY-79 I)

1903 Persistence of T Pallidum in Neurosyphillis. (FY-75 I)

2610 Antilymphocyte Globulin (ALG) and Kidney Transplantation. A Controlled Double Blind Study (FY-73 F)

2615 Immunological Monitoring of the Transplant Recipient. (FY-78 F)

2618 Inteitional Donor Specific Pretransplant Transfusion. (FY-80 I)

2619 Histocompatibility Antigens and Interstitial Cystitis. (FY-80 I)

3159R In Vivo Removal of Circulating Antibodies and Immune Complexes by Immunoadsorption. (FY-79 F)

7218 Physotigmine Infusion and Lithium Responsitivity. (FY-79 F)

| Date: 3 MARCH 81 | Protocol No: 1004 | Status: Interim / Final |
|---|---|---|

**Title of Project:** Stress Ulceration in a Medical ICU: Incidence and Possible Prevention with Cimetidine

| Starting Date: | Estimated Completion Date: Terminated 1 March 81 |
|---|---|

**Principal Investigator:** LAWRENCE F. JOHNSON

| Associate Investigators: Michael T. Keegan, David A. Peura | Facility: WRAMC |
|---|---|
| | Dept/Svc: DEPT OF MED/GI SVC |

**Key Words:**

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: |
|---|---|---|
| FY-80 MEDCASE Cost: | Periodic Review Results: (to be filled in by DCI) | |

**Study Objective:** See protocol

**Technical Approach:** See protocol

**Progress during FY-80:** Study terminated by Smith Kline & French 1 March 81 due to failure of efficacy

Number of subjects to be studied before completion of study:

Serious/unexpected side effects in subjects participating in project:

**Conclusions:** Cimetidine is no more effective than placebo in preventing stress related bleeding from UGI tract - Data analysis and publicaton of results pending.

| Date: | Protocol No: 1383 | Status: Interim / Final X |
|---|---|---|

Title of Project: The Development of a Radioimmunoassay for Thyronine and 3,5-T2.

| Starting Date: 5 Jan 1978 | Estimated Completion Date: 30 Sept 1980 |
|---|---|

Principal Investigator: Keith R. Latham, Ph.D.

| Associate Investigators: | Facility: WRAMC |
|---|---|
| Kenneth D. Burman, M.D.<br>Leonard Wartofsky, M.D.<br>Robert C.Smallridge, M.D. | Dept/Svc Endocrine, Ward 47 |

Key Words: Radioimmunoassay, Diiodothyronine

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: |
|---|---|---|
| FY-80 MEDCASE Cost: | Periodic Review Result: (to be filled in by DCS) | |

Study Objective:

Objective: to Develope a radioimmunoassay for T0 and 3,5-T2 and to utilize the assay to study the levels of these hormones under a variety of normal and pathophysiologic conditions.

Technical Approach:

1. Antibody to Tn was prepared in rabbits as previously described.
2. Purified antigen was radiolabelled and utilized in defining a standard curve.
3. Blood samples were collected and assayed by standard methods.

Progress during FY-80: Assay for 3,5 T2 completed: Pangaro, L., Burman, K.D., Wartofsky, L., Wright, F.J. and Latham, K.R. (1980) J.Clin.Endoc.Metab. 50:1075.

Number of subjects to be studied before completion of study: 30

Serious/unexpected side effects in subjects participating in project:
None: only blood was utilized. (Note : blood was obtained on other protocols and shared.

Conclusions:

An effective assay for 3,5 T2 has been established and utilized.

2

Publications or Abstracts, FY-80:

Date: | Protocol No: [illegible] | Check if Info for Final

Title of Project: Thyroid Status in Ob/Ob Mice.

Starting Date: 27 Feb 1979 | Estimated Completion Date: 30 September 1980

Principal Investigator: Keith R. Latham, Ph.D.

Associate Investigators:

Allen R. Glass, MD
Yueh-Chu L. Tseng, Ph.D.

Facility: WRAMC

Dept/Svc: Endocrine, Ward 47

Key Words: Thyroid, Obese, Mice, Receptor

Accumulative MEDCASE Cost:

Accumulative Contract Cost:

Accumulative Supply Cost:

FY-80 MEDCASE Cost:

Protocol Review Date: (to be filled in by DCS)

Study Objectives:

Objective: To determine if the genetically obese mouse (ob/ob) accumulates fat because of a thyroid hormone defect

Technical Approach:

1. Liver thyroid hormone receptors were measured in the obese and lean controls.
2. Pathways of thyroid hormone metabolism were investigated.

Progress during FY-80:

Abstract (enclosed) Tseng, Y.L., Glass, A.R. and Latham, K.R. (1980)Program 62nd Meeting National Endocrine Society, Washington, DC.

Number of subjects to be studied before completion of study: None

Serious/unexpected side effects in subjects participating in project:

Conclusions:

The obese condition in the ob/ob mouse is not due to an obvious peripheral receptor defect. However, thyroid hormone metabolism alterations were observed and reported.

*CLINICAL RESEARCH*

# Abstract Reproduction Form

[illegible] and telephone number of author to whom all correspondence is to be sent. Complete Boxes B, C and D.

Telephone (202) 576-3849 (301) 926-3254
(Area code) office (Area code) home

A
Name Keith R. Lathan, Ph.D.
Address Department of Medicine
Uniformed Services University of the Health Sciences
Bethesda, MD 20814

[illegible] 935-2701-1271
B (See Rule 1.0)
[illegible]
For [illegible] (Staff Use)
Control Number [illegible]
Paper accepted for [illegible]
Date [illegible] USUHS
(Name of Meeting)
A [illegible] abstract must [illegible]
[illegible]

**TYPE ABSTRACT HERE/BE SURE TO STAY *WITHIN* BORDER**

C
*CHECK ONE*
(for national meetings only)
Poster poster session presentation ☐
Consider for poster session if not selected for oral presentation ☒
Do not consider for poster session under any circumstances ☐

D
*CHECK SINGLE SUBSPECIALTY CLASSIFICATION*
code
Cardiovascular* (____)
Clinical Epidemiology
Clinical Nutrition
Clinical Pharmacology
Dermatology
Endocrinology (see Rule 5) X
Gastroenterology
Genetics
Health Care Research
Hematology
Hypertension
Immunology & Rheumatology
Infectious Disease
Metabolism (see Rule 5)
Oncology
Pulmonary
Renal & Electrolyte

*For abstracts submitted to Cardiovascular only, select single subcategory and enter code no. (1-6) in space above. (1) Clinical, (2) Basic Science, (3) Electrophysiology-Dysrhythmias, (4) Echocardiography, (5) Radiology-Radionuclides, (6) Other. Subclassification is designed to aid in reviewing process only and is independent of program selection.

NUCLEAR THYROID HORMONE RECEPTORS IN OB/OB MICE. K.R. Lathan, Y.L. Tseng* and A.R. Glass. Uniformed Services University of the Health Sciences, Bethesda, MD, and Walter Reed Army Medical Center, Washington DC.

Mice (C57BL/6J) homozygous for the recessive ob gene (ob/ob) develop obesity, hypometabolism, and hypothermia after cold stress, the latter two conditions being reversible with high dose thyroid hormone (TH) therapy. To evaluate the possibility of hypothyroidism in ob/ob, serum T4 and T3 (RIA, ng/ml) and levels of hepatic nuclear receptors for T4 and T3 were measured in 10 wk old female ob/ob and their thin littermates (ob/+, +/+). Solubilized nuclear receptors (NR) were obtained by sedimentation of nuclei through 2.1M sucrose, triton X-100 treatment, and extraction in high salt. Maximum binding capacity (MBC, fmol/mg DNA) and affinity ($K_d$, M x $10^{-10}$) of NR for both T4 and T3 were determined by saturation analysis (Scatchard). (* = $p < .05$ vs. ob/+ or +/+).

| | ob/ob | | ob/+ | | +/+ | |
|---|---|---|---|---|---|---|
| | T3 | T4 | T3 | T4 | T3 | T4 |
| Serum TH | 1.00 ± 0.05* | 18 ± 3* | 0.74 ± 0.07 | 71 ± 4 | 0.81 ± 0.01 | 60 ± 4 |
| MBC | 14 ± 5 | 22 ± 3 | 16 ± 6 | 21 ± 2 | 16 ± 5 | 22 ± 2 |
| $K_d$ | 10 ± 2 | 2* ± 1 | 9 ± 1 | 18 ± 1 | 6 ± 1 | 25 ± 1 |

MBC and $K_d$ of NR for T4 and T3 were not significantly different among groups; therefore, potential hypothyroidism in ob/ob is probably not related to defects in TH receptors. Low serum T4 and high serum T3 in ob/ob may represent "low T4 euthyroidism", perhaps a compensatory response to increased T4 to T3 conversion secondary to increased food intake.

**PLEASE CHECK ABSTRACT CAREFULLY FOR APPEARANCE BEFORE MAILING**

BOTH THIS FORM AND THE FORM LETTER OF TRANSMITTAL MUST BE SIGNED BY A MEMBER (RULE 2)

KEITH R. LATHAN, Ph.D.
(please type or print name)

MEMBER'S SIGNATURE [signature]

Revised May 1978

1

DATE: 03 September 1980 | PROTOCOL for: CALGB 7 41 | CANCER: Ewing's
TITLE OF PROTOCOL: Early Radiotherapy + Combinations of VCR, Cyclo, Adriamycin, Actinomycin D [illegible]osarcoma

STATUS DATE: 1-82 | ACCRUED CASES TO DATE: 1000
PRINCIPAL INVESTIGATOR: Dr. Johnson [illegible]
ASSOCIATE INVESTIGATORS:
Dr. Frederick Ruyman, M.D., [illegible] NC
FACILITY: Walter Reed Army Medical Center
SERVICE: Hematology-Oncology
Department of Medicine

FOR PCB'S:
ACCRUAL MEDIANS COST: NA | ACCRUAL RATE/MONTH: NA | ACTIVE/CLOSED: Active
FY-80 REQUEST (K$): NA | PERSONNEL REQUIRED:

STUDY OBJECTIVES: 1. To [illegible] control and survival rate. 2. To examine the adjuvant role of chemotherapy in prolonging disease free survival. 3. To [illegible] therapy and possible cure of patients with advanced disease.

TECHNICAL APPROACH: Group 1 pts (1-99) → 1. VCR 2 MG/M$^2$ qwk x12 + Dact 0.015 MG/KG IV daily 5 at wk 12, 24, 36, 48 + Cyt 25 MG/M2 postact d 42, vs 2. RT + 1.
Group 2 (intergroup resident) → 1. Above vs 3 RT + Dact 0.015 MG/KG 1-5 at 9,18,27,36 wks + VCR [illegible] + ACT D 1-3 mos 15,21,47,53 + cytoxan 1-7d at 1½ wk [illegible] vs 5. VCR + ACT D + cytoxan as above + RT + Adr. 50 MG/M2 IV at 5,13,27,39,51 wks

PROGRESS DURING FY-80: 11 pts from 9/1/80 have been entered. One was [illegible] on day 127. 5 have had PD at day 60 w/o death; 1 yr→ death; day 117 and 178; Day 32→ death; <2 yrs→death. 2 were [illegible] & then 127 & are NED at 3 yrs, 4 yrs, 3 yrs and 3 yrs [illegible]. 1 [illegible]

REASONS FOR [illegible] | TYPES OF [illegible]:
SERIOUS [illegible] OF GRADE III OR GREATER TOXICITY:
1 developed radiation necrosis of brain and 1 developed DIC also 2nd tumor (osteosarcoma)
CONCLUSIONS: This is a pediatric protocol and as CALGB has closed its pediatric section it is felt follow-up should be transferred to the pediatric department.

PUBLICATIONS/REPORTS, IF ANY:
Already published 1977 Ca 2915, 1977

DATE: 30 September 1980 | PROTOCOL NO: CALGB 7490 | LOCK UP: [illegible]
TITLE OF PROJECT: CLINICAL TRIAL OF RADIOTHERAPY + CHEMOTHERAPY (CYTOXAN, VCR, ACTINOMYCIN D) IN MANAGING NON-METASTATIC EWING'S SARCOMA | STATUS: Interim Final

STARTING DATE: 1973 | ESTIMATED COMPLETION DATE: 1980 - [illegible]
PRINCIPAL INVESTIGATOR: Dr. James Blom
ASSOCIATE INVESTIGATORS:
FACILITY: Walter Reed Army Medical Center
SERVICE: Hematology-Oncology Department of Medicine
KEY WORDS: Ewing's Sarcoma

| ACCUMULATIVE MEDCASE COST: NA | ACCUMULATIVE CONTRACT COST: NA | ACCUMULATIVE SUPPLY COST: NA |
|---|---|---|
| FY-80 MEDCASE COST: NA | PERIODIC REVIEW RESULTS: | |

STUDY OBJECTIVE: 1. To study interval & pattern of metastic and local recurrence of tumor treating with either 1. irradiation to 1° alone 2. irrad of 1° + systemic chemotherapy or 3. irrad of 1° + chemotherapy + bilateral pulmonary irradiation.
2. To study survival time.

TECHNICAL APPROACH: Regimen I - VCR 5 mg/M$^2$/wk x 6 + cytoxan 500 mg/M$^2$ IV x 6 + RT to lesion. vs Regimen II - VCR 1.5 mg/M$^2$/wk x 6 + cytoxan 500 mg/M$^2$ IV x 6 + RT to lesion + both lung fields then actin D 15 mg/KG qd 1-5 at 3 mos then VCR + pred 3rd - 7th wk then repeat q 3 wks x 6.

PROGRESS DURING FY-80: [illegible] has entered 8 pts. 2 pts are greater than 3 yrs p therapy and have no evidence of disease. 1 pt was 5 yrs p RT & was LFU. 1 pt went off study early & was LFU. 1 pt relapsed on day 584 & LFU. 1 pt expired on day 356. 2 pts were greater than 2 yrs p therapy with NED but lost to follow up.

NUMBER OF SUBJECTS TO BE STUDIED BEFORE COMPLETION OF STUDY: Completed
SERIOUS/UNEXPECTED SIDE EFFECTS IN SUBJECTS PARTICIPATING IN PROJECT: None
CONCLUSIONS: This study has been discontinued by CALGB and should be closed here. Remaining pts will be followed for long term toxicity.

PUBLICATIONS/ABSTRACTS, FY-80: ASCO ACA C-425 413, 1978.

Work Unit # 1542

DATE: 30 September 1980 | Prog Code No: [illegible] | Status: Ongoing / Project

TITLE OF PROJECT: Adjuvant Chemotherapy in Osteogenic Sarcoma: Adriamycin vs Seq Adriamycin, HD MTX - Leuko orin vs Seq Adriamycin - Cytoxan

STARTING DATE: 1975 | ESTIMATED DATE OF COMPLETION: 4/80

PRINCIPAL INVESTIGATOR:

ASSOCIATE INVESTIGATORS:

FACILITY: Walter Reed Army Medical Center

SERVICE: Hematology-Oncology Department of Medicine

KEY WORDS: Osteogenic Sarcoma

| ACCUMULATIVE MEDCASE COST: | ACCUMULATIVE CONTRACT COST: | ACCUMULATIVE SUPPLY COST: |
|---|---|---|
| FY-80 MEDCASE COST: | PERIODIC REVIEW RESULTS: | |

STUDY OBJECTIVE: To determine the DFIT survival of patients with surgery for 1° lesion or pulmonary mets of osteogenic and either 1. Adriamycin 2. Adriamycin - hi dose MTX or 3. Adriamycin - Cytoxan. To determine side effects.

TECHNICAL APPROACH: 1. Adriamycin 30 mg/M$^2$ qd x 3 q 4 weeks x 6 courses. 2. Adriamycin 30 mg/M$^2$ IV qd Days 1-3 & 28-30 and hi dose MTX 200 mg/KY x 6 hours with subsequent leukovovium 12 mg IM q 6 h x 12 doses Day 56 & 77. Repeat cycle Day 105 6 courses each day. 3. Adriamycin - Cytoxan - closed June 1977.

PROGRESS DURING [illegible] patients have been entered [illegible]. 3 patients [illegible] - 1 had progressive disease (PD) day 563, 1 PD day 134, and 1 PD day 448, 5 patients have no evidence of disease at 4 years, 4 years, day 493, 33 months, day 433. 1 patient was NED day 214 but subsequently LFU and 1 patient was LFU.

NUMBER OF SUBJECTS TO BE STUDIED BEFORE COMPLETION OF STUDY:

SERIOUS/UNEXPECTED SIDE EFFECTS IN SUBJECTS PARTICIPATING IN PROJECT:

None

CONCLUSIONS: 98 patients were accrued to this study. This was sufficient for closure. This study was closed 4/80 - Patients will be followed.

PUBLICATIONS/ABSTRACTS, FY-80: Manuscript for this study is pending.

WORK UNIT # 1548

DATE: 30 September 1980 | PROTOCOL NO: CALGB 7681 | STATUS: Interim ___ Final X

TITLE OF PROJECT: Effects of Adriamycin with & without Added MER in Soft Tissue Sarcomas (A phase III Study)

| | |
|---|---|
| STARTING DATE: 1976 | ESTIMATED COMPLETION DATE: 1980 |
| PRINCIPAL INVESTIGATOR: Dr. Hannes Blom | |
| ASSOCIATE INVESTIGATORS: | FACILITY: Walter Reed Army Medical Center |
| | SERVICE: Hematology-Oncology Department of Medicine |

KEY WORDS: Sarcoma

| ACCUMULATIVE MEDCASE COST: | ACCUMULATIVE CONTRACT COST: | ACCUMULATIVE SUPPLY COST: |
|---|---|---|
| NA | NA | NA |

| | |
|---|---|
| FY-80 MEDCASE COST: None | PERIODIC REVIEW RESULTS: NA |

STUDY OBJECTIVE: To compare Adriamycin alone & with MER in induction of remission in inoperable soft tissue sarcomas and to compare monthly single vs 3 consequentive daily doses.

TECHNICAL APPROACH:
1. Adriamycin 75 MG/$M^2$ IV q 4 weeks
vs 2. Adriamycin & MER 1 mg IC on days 1 & 8 q4 weeks
vs 3. Adriamycin 25 mg/$M^2$ days 1,2 & 3 q4 weeks
vs 4. Number 3 plus MER 1mg IC on days 1 & 8 q4 weeks

PROGRESS DURING FY-80: 5 WRAMC pts. have been entered. 3 died in 1978. 1 was LFU on day 16 in 1978 and one had progressive disease in Feb 79 (day 100) and lost to follow up. CALGB entered 75 patients. There was an overall 25% response rate which did not vary per arm.

NUMBER OF SUBJECTS TO BE STUDIED BEFORE COMPLETION OF STUDY:

SERIOUS/UNEXPECTED SIDE EFFECTS IN SUBJECTS PARTICIPATING IN PROJECT:
None

CONCLUSIONS: This study was closed to pt. accrual. There was no difference in the Adriamycin schedules. Only 25% response rate was seen. Study is terminated.

PUBLICATIONS/ABSTRACTS, FY-80: Manuscript in draft form.

WORK UNIT NO. 1566

DATE: 30 September 1980 | PROTOCOL NO: CALGB 7911 | STATUS: Interim / Final X

TITLE OF PROJECT:
Remission Induction of Recurrent Childhood ALL

STARTING DATE: 1978 | ESTIMATED COMPLETION DATE: Closed

PRINCIPAL INVESTIGATOR:

ASSOCIATE INVESTIGATORS:

FACILITY: Walter Reed Army Medical Center

SERVICE: Hematology-Oncology
Department of Medicine

KEY WORDS:

ACCUMULATIVE MEDCASE COST: None

ACCUMULATIVE CONTRACT COST: None

ACCUMULATIVE SUPPLY COST: None

FY-80 MEDCASE COST: None

PERIODIC REVIEW PERIODS:

STUDY OBJECTIVE: Effective therapy for relapsed childhood ALL.

TECHNICAL APPROACH: Comparison of L-NOPP and L-COP (see 1979 report)

PROGRESS DURING FY-80: Protocol closed because of lack of funding of CALGB Pediatric group.

ANSWER TO REVIEWER'S COMMENTS: No patients entered at WRAMC or CALGB. Study closed. This is a final report. There are no possible conclusions.

NUMBER OF SUBJECTS TO BE STUDIED BEFORE COMPLETION OF STUDY: None

SERIOUS/UNEXPECTED SIDE EFFECTS IN SUBJECTS PARTICIPATING IN PROJECT: Anaphylaxis not experienced.

CONCLUSIONS:
None

PUBLICATIONS/ABSTRACTS, FY-80: None

WORK UNIT # 1516

| | | |
|---|---|---|
| DATE: 30 September 1980 | PROTOCOL NO: CALGB 7892 | STATUS: Interim<br>Final X |

TITLE OF PROJECT: Multimodel Therapy In Management of Primary Non Metastic Ewing's Sarcoma of Pelvic And Sacral Bones.

| | |
|---|---|
| STARTING DATE: 1978 | ESTIMATED COMPLETION DATE: 1980 |
| PRINCIPAL INVESTIGATOR: Bruce Booth, M.D., MAJ MC | |
| ASSOCIATE INVESTIGATORS: | FACILITY: Walter Reed Army Medical Center |
| | SERVICE: Hematology-Oncology Department of Medicine |

KEY WORDS: Ewing's Sarcoma

| | | |
|---|---|---|
| ACCUMULATIVE MEDCASE COST: NA | ACCUMULATIVE CONTRACT COST: NA | ACCUMULATIVE SUPPLY COST: NA |
| FY-80 MEDCASE COST: NA | PERIODIC REVIEW RESULTS: NA | |

STUDY OBJECTIVE:

Not applicable.

TECHNICAL APPROACH: Not applicable.

PROGRESS DURING FY-80: No patients entered this study and CALGB no longer participates in intergroup studies.

NUMBER OF SUBJECTS TO BE STUDIED BEFORE COMPLETION OF STUDY: None

SERIOUS/UNEXPECTED SIDE EFFECTS IN SUBJECTS PARTICIPATING IN PROJECT: None

CONCLUSIONS: None. CALGB no longer participates in this study.

PUBLICATIONS/ABSTRACTS, FY-80:

WORK UNIT # 1569

DATE: 7 Sept 1980 PROTOCOL NO: CALGB 7893 [illegible]
TYPE OF PROJECT: X

MULTIMODAL THERAPY FOR THE MANAGEMENT OF PRIMARY, NON-METASTATIC EWING's SARCOMA OF BONE, PELVIC/SACRAL AREAS EXCLUDED

| | |
|---|---|
| STARTING DATE: 29 Aug 79 | ESTIMATED COMPLETION DATE: Closed |
| PRINCIPAL INVESTIGATOR: LTC JEFFREY L. BERENBERG, MC | |
| ASSOCIATE INVESTIGATORS: | FACILITY: Walter Reed Army Medical Center |
| | SERVICE: Hematology-Oncology Department of Medicine |

KEY WORDS:

| | | |
|---|---|---|
| ACCUMULATIVE MEDCASE COST: | ACCUMULATIVE OR [illegible] COST: | ACCUMULATIVE SUPPLY COST: |
| FY-80 MEDCASE COST: | PERIODIC [illegible] COSTS: | |

STUDY OBJECTIVE: Improve the survival of patients with localized Ewing's sarcoma of bone who have no evidence of metastases at diagnosis with an intensive multimodal therapeutic approach.

TECHNICAL APPROACH: Regimen I - High Intermittent Chemotherapy with vincristine, adriamycin, cyclophosphamide, and actinomycin-D
Regimen II- Moderate Dose Continuous Chemotherapy with vincristine, cyclophosphamide, adriamycin, and actinomycin-D

PROGRESS DURING FY-80: No WRAMC patients were entered on this study, from starting date to closing of study.

NUMBER OF SUBJECTS TO BE STUDIED BEFORE COMPLETION OF STUDY:
SERIOUS/UNEXPECTED SIDE EFFECTS IN SUBJECTS PARTICIPATING IN PROJECT:
None
CONCLUSIONS:
This study has been closed to patient entry.

11

WORK UNIT # 1571

DATE: 30 September 1980 | PROTOCOL NO: CALGB 7891 | STATUS: Interim / Final X

TITLE OF PROJECT: Intergroup Rhabdomyosarcoma Study III: Alveolar Rhabdomyosarcoma of the Extremity in Clinical Groups I & II Patients

STARTING DATE: 1979 | ESTIMATED COMPLETION DATE: N/A

PRINCIPAL INVESTIGATOR: Dr. Johannes Blom

ASSOCIATE INVESTIGATORS:

FACILITY: Walter Reed Army Medical Center

SERVICE: Hematology-Oncology Department of Medicine

KEY WORDS: Rhabdomyosarcoma

| ACCUMULATIVE MEDCASE COST: | ACCUMULATIVE CONTRACT COST: | ACCUMULATIVE SUPPLY COST: |
|---|---|---|
| NA | NA | NA |

FY-80 MEDCASE COST: NA

PERIODIC REVIEW RESULTS:

STUDY OBJECTIVE: To determine optimal therapy of rhabdomyosarcoma Cau 1. cytoxan be dropped from study VAC Rx 2. is VAC pulse better than sequential 3. will Adriamycin + VCR + Cytoxan result in increased CR 4. what pathology is prognostic 5. what significance is LW involvement.

TECHNICAL APPROACH: Multiple areas - very complex therapeutic schedules. Our pt received Regimen 25 - VCR 2mg/$M^2$ IV q wk x 12 doses + DACT 0015 mg/KG/d d1-5 + Cytoxan 10 mg/KG/day IV d1-3 then 20 mg/$M^2$ IV d o & 4 + DACT d1-5 + cytoxan d1-3 repeat this q 4 wks x 2 yrs.

PROGRESS DURING FY-80: One patient with extensive intrathoracic disease has been entered on this study. She received VCR, Actinomycin D, and Cytoxan per treatment arm #25 and obtained a CR when last seen on Day 116.

NUMBER OF SUBJECTS TO BE STUDIED BEFORE COMPLETION OF STUDY: See conclusions.

SERIOUS/UNEXPECTED SIDE EFFECTS IN SUBJECTS PARTICIPATING IN PROJECT: None

CONCLUSIONS: Too early. This study is now under the direction of SWOG and follow up should therefore be transferred to Dept. Pediatrics.

12

Work Unit No. 1572

Title of Project: Phase II Study of M-AMSA (NSC 249992) - Treatment for Melanoma, Ovarian Carcinoma, Breast Carcinoma, Hypernephroma, and Hepatoma.

START (FY): May 1979 | EST. COMPLETION (FY): 1983

PRINCIPAL INVESTIGATOR: LTC Jeffrey L. Berenberg, MC

ASSOCIATE INVESTIGATORS:

FACILITY:

COOP:

SERVICE:

KEY WORDS: M-AMSA, Melanoma, Ovarian Carcinoma, Breast Carcinoma, Hypernephroma, Hepatoma

| ACCUMULATED MANDAYS | CUMULATIVE CONTRACT | ACTIVE (Next FY) |
|---|---|---|
| COST: | COST: | COST: |

FY-80 MEDCASE COST:

PERIODIC REVIEW RESULTS:

STUDY OBJECTIVE: This Phase II study of M-AMSA (NSC 249992) is designed to: Determine the complete or partial response frequencies of the various selected tumors (Sec. 4.2) to treatment with M-AMS. Determine the duration of response in those patients responding to continued M-AMSA administration. Provide additional clinical and laboratory data regarding toxicity.

TECHNICAL APPROACH: The first treatment dose will be 120 mg/M$^2$. Patients previously heavily treated with chemotherapy (expecially nitrosourea) or radiotherapy or with hepatic dysfunction may start at 60 mg/M$^2$. Every three weeks the dose will be increased by 20 mg/M$^2$ over the previous dose until 160 mg/M$^2$ is reached, or until myelosuppression is encountered. Myelosuppression will require dose modification. Other severe toxicities such as extreme nausea and vomiting, mucositis, and hepatic toxicity may also be indications for dose modification.

PROGRESS DURING FY-80: Six patients are entered on this study. There have been no responses. Three patients have subsequently expired and three remain on study.

NUMBER OF SUBJECTS TO BE STUDIED BEFORE COMPLETION OF STUDY: 162

SERIOUS/UNEXPECTED SIDE EFFECTS IN SUBJECTS PARTICIPATING IN PROJECT:

none

CONCLUSIONS:

none

PUBLICATIONS/ABSTRACTS, FY-80:

none

WORK UNIT NO. 1573

DATE: 30 September 1980 | PROTOCOL NO: CALGB 7921 | STATUS: Interim / Final X

TITLE OF PROJECT:
Treatment of Primary Untreated Acute Lymphocytic Leukemia.

STARTING DATE: 25 Sept 79 | ESTIMATED COMPLETION DATE: Close 4/12/80

PRINCIPAL INVESTIGATOR: Dr. Jeffrey L. Berenberg

ASSOCIATE INVESTIGATORS:

FACILITY: Walter Reed Army Medical Center

SERVICE: Hematology-Oncology
Department of Medicine

KEY WORDS: Acute Lymphocytic Leukemia

| ACCUMULATIVE MEDCASE COST: | ACCUMULATIVE CONTRACT COST: | ACCUMULATIVE SUPPLY COST: |
|---|---|---|
| None | None | None |

| FY-80 MEDCASE COST: | PERIODIC REVIEW RESULTS: |
|---|---|
| None | |

STUDY OBJECTIVE: 1. To improve response rate and duration in acute lymphocytic leukemia by testing high dose vs low dose prednisone in induction.

TECHNICAL APPROACH: Three arm protocol comparing prednisone 40 mg/M$^2$ with 120 mg/M$^2$ and vs prednisone 40 mg/M$^2$ plus dexamethasone 12 mg/M$^2$. All patients receive vincristine 2 mg/M$^2$ IV q week x 4.

PROGRESS DURING FY-80: One patient entered, achieved complete remission. (used 1st arm of regime.) Protocol closed because of lack of funding of Pediatric group -- CALGB.

NUMBER OF SUBJECTS TO BE STUDIED BEFORE COMPLETION OF STUDY: N/A

SERIOUS/UNEXPECTED SIDE EFFECTS IN SUBJECTS PARTICIPATING IN PROJECT:

CONCLUSIONS: The only patient treated will be followed for long term toxicity and survival. No subsequent reports will be submitted.

PUBLICATIONS/ABSTRACTS, FY-80: None

14

WORK UNIT # 1574

DATE: [illegible] PROTOCOL #: CALGB 7981 STATUS: Interim X
TITLE OF PROTOCOL: Final
COMPARISON OF FAM VS MA IN LOCALLY ADVANCED OR METASTATIC GASTRIC CANCER. A PHASE III STUDY.

STARTING DATE: 12 Dec 79 ESTIMATED COMPLETION DATE: 1982
PRINCIPAL INVESTIGATOR: LTC JEFFREY L. BERENBERG, MC
ASSOCIATE INVESTIGATORS: FACILITY: Walter Reed Army Medical Center
SERVICE: Hem-Onc Dept of Medicine

KEY WORDS: Gastric cancer

ACCUPT [illegible] ACCESS: ACCUMULATIVE ACCESS: ACCESS LAST YEAR:
COST: COST: COST:
FY-80 [illegible] COST: PATIENT [illegible]:

STUDY [illegible]: 1. To determine whether intensified induction therapy with a two-drug combination, excluding 5-fluorouracil will prolong the time to disease progression when compared to therapy with FAM in the treatment of patients.

2. To determine partial and complete response frequency, and the duration of response and survival of patients with measurable, locally advanced, or with metastatic gastric cancer when the patients are treated with MA versus FAM and both regimens are followed by a common maintenance therapy employing mitomycin-C and 5-fluorouracil.

TECHNICAL APPROACH: Regimen A - 5-fluorouracil, mitomycin-C and adriamycin
Regimen B - Mitomycin-C and adriamycin

PROGRESS DURING FY-80: No WRAMC patients have been entered on study. CALGB has entered 50 patients, however it is to early for evaluation of this study.

NUMBER OF SUBJECTS TO BE STUDIED BEFORE COMPLETION OF STUDY:
SERIOUS/UNEXPECTED SIDE EFFECTS IN SUBJECTS PARTICIPATING IN PROJECT:

CONCLUSIONS: Too early for evaluation.

DATE: 30 September 1980 | PROTOCOL NO: [illegible] | LAST UPD: 1 1977 | STATUS: Interim X Final

TITLE OF PROJECT:
Comparative Study of Three Remission Induction Regimens and Two Maintenance Regimens in Acute Myelogenous Leukemia

| | |
|---|---|
| STARTING DATE: 20 Jan 80 | ESTIMATED COMPLETION DATE: 1982 |
| PRINCIPAL INVESTIGATOR: Dr. Jeffrey L. Berenberg | |
| ASSOCIATE INVESTIGATORS: | FACILITY: Walter Reed Army Medical Center |
| | SERVICE: Hematology-Oncology Department of Medicine |

KEY WORDS: Acute Myelogenous Leukemia

| ACCUMULATIVE MEDCASE COST: | ACCUMULATIVE CONTRACT COST: | ACCUMULATIVE SUPPLY COST: |
|---|---|---|
| None | None | None |

| | |
|---|---|
| FY-80 MEDCASE COST: None | PERIODIC REVIEW RESULTS: |

STUDY OBJECTIVES: 1. To determine if increasing intensity of induction therapy will increase remission rate. 2. To determine if clotrimazole will decrease infection rate during remission induction.

TECHNICAL APPROACH: Randomized: Regimen A with CO-Trimoxazole po bid during induction. Regimen B without CO-Trimoxazole. Randomize between Regimen 1) Daunomycin (DNR) 45 mg/M$^2$ IV days 1,2,3 + ARA-C 100 mg/M$^2$ IV by continuous infusion days 1-7. Regimen 2) DNR 45 mg/M$^2$ IV days 1, 2, 3 + ARA-C 100 mg/M$^2$ IV by continuous infusion 6-Thioguanine 100 mg/M$^2$ po days 1-7. Regimen 3) DNR 45 mg/M$^2$ IV + ARA-C 100mg/M$^2$ IV by continuous infusion days 1-10. ANSWER TO REVIEWER'S COMMENTS: Maintenance: All patients receive two cycles of four monthly courses of chemotherapy: (1) ARA C 100 mg/m$^2$ SC q 12 h x 10 + 6 100 mg/m$^2$ po q 12 h x 10; (2) ARA-C (as above) + Prednisone 40 mg/m$^2$ po day 1:5 + Vincristine (VCR) 2 mg/m$^2$ iv on day 1 (3) ARA-C (as above) + (continued on next paragraph)

PROGRESS DURING FY-80: Two WRAMC patients entered, both achieved a complete remission. CCLCS - received no reports

Continued from Technical Approach:

Daunomycin iv 45 mg/m$^2$ on day 1 and 2. (4) Same as course 2. After these cycles, patient are randomized to discontinuing therapy or continued therapy until relapse.

NUMBER OF SUBJECTS TO BE STUDIED BEFORE COMPLETION OF STUDY: 550

SERIOUS/UNEXPECTED SIDE EFFECTS IN SUBJECTS PARTICIPATING IN PROJECT:
None

CONCLUSIONS: Too early to evaluate.

PUBLICATIONS/ABSTRACTS, FY-80:

None

WORK UNIT NO. 1579

DATE: 30 September 1980 | PROTOCOL NO: CALGB 7923 | STATUS: Interim / Final

TITLE OF PROJECT: Surgical Adjuvant Systemic Chemotherapy with 5-FU, Adriamycin, and Mitomycin-C VS Observation only in Gastric Adenocarcinoma.

STARTING DATE: 1979 | ESTIMATED COMPLETION DATE: 1982

PRINCIPAL INVESTIGATOR: LTC Jeffrey L. Berenberg, MSC MC

ASSOCIATE INVESTIGATORS:

FACILITY: Walter Reed Army Medical Center

SERVICE: Hematology-Oncology / Department of Medicine

KEY WORDS: Gastric Adenocarcinoma

| ACCUMULATIVE MEDCASE COST: | ACCUMULATIVE CONTRACT COST: | ACCUMULATIVE SUPPLY COST: |
|---|---|---|
| FY-80 MEDCASE COST: | PERIODIC REVIEW DATES: | |

STUDY OBJECTIVE: The specific aim of this study is to ascertain if 6 two-monthly cycles of fluorouracil, adriamycin and mitomycin-C following potentially curative surgery for adenocarcinoma of the stomach produces a longer disease free survival in comparison to standard surgical resection alone.

TECHNICAL APPROACH: Regimen 1: Observation only. Regimen II: Adjuvant Chemotherapy, 5-Fluorouracil 600 mg/M$^2$ i.v. days 1, 8, 29 and 36 of each cycle, Mitomycin-C 10 mg/M$^2$ i.v. day 1 of each cycle, Adriamycin 30 mg/M$^2$ i.v. days 1 and 29 of each cycle.

PROGRESS DURING FY-80: Too early for accrual of patients.

ANSWER TO REVIEWER'S COMMENTS: No patients have been entered to date.

NUMBER OF SUBJECTS TO BE STUDIED BEFORE COMPLETION OF STUDY: 176

SERIOUS/UNEXPECTED SIDE EFFECTS IN SUBJECTS PARTICIPATING IN PROJECT:

CONCLUSIONS: None

WORK UNIT # 1694

DATE: 30 September 1980 | PROTOCOL NO: WRAMC 7265 | STATUS: Interim / Final X

TITLE OF PROJECT: Chemotherapy with DTIC & Adriamycin in Soft Tissue & Bone Sarcomas

STARTING DATE: 1972 | ESTIMATED COMPLETION DATE: Closed May 78

PRINCIPAL INVESTIGATOR: Dr. Johannes Blom

ASSOCIATE INVESTIGATORS:

FACILITY: Walter Reed Army Medical Center

SERVICE: Hematology-Oncology Department of Medicine

KEY WORDS: Sarcoma

| ACCUMULATIVE MEDCASE COST: | ACCUMULATIVE CONTRACT COST: | ACCUMULATIVE SUPPLY COST: |
|---|---|---|
| NA | NA | NA |

FY-80 MEDCASE COST: NA

PERIODIC REVIEW RESULTS: NA

STUDY OBJECTIVE:

To determine the efficacy of DTIC & Adriamycin with soft tissue and bone sarcomas.

TECHNICAL APPROACH: Good risk pts: Adriamycin 60 mg/M$^2$ day 1 and DTIC 250 mg/M$^2$ IV x 5 days. Poor risk - Adriamycin 45 mg/M$^2$ day 1 & DTIC 200 mg/M$^2$ IV x 5 days.

PROGRESS DURING FY-80: This study was closed in May 1978. In past year 5 patients were lost to follow up. Other conclusions are as per 1978-79 report.

NUMBER OF SUBJECTS TO BE STUDIED BEFORE COMPLETION OF STUDY:

SERIOUS/UNEXPECTED SIDE EFFECTS IN SUBJECTS PARTICIPATING IN PROJECT:

None

CONCLUSIONS: DTIC & Adriamycin - low response rate
Study should be terminated

PUBLICATIONS/ABSTRACTS, FY-80:

None

WRAIR UNIT # 1626

DATE: 30 September 1980 | PROTOCOL NO: WRAMC 7405 | STATUS: Interim / Final X

TITLE OF PROJECT: Treatment of Advanced Renal Cell Carcinoma with a Combination of CCNU and Bleomycin.

STARTING DATE: 1974 | ESTIMATED COMPLETION DATE: Closed 24 Aug 79

PRINCIPAL INVESTIGATOR: Dr. Johannes Blom

ASSOCIATE INVESTIGATORS: Dr. Charles Miller

FACILITY: Walter Reed Army Medical Center

SERVICE: Hematology-Oncology Department of Medicine

KEY WORDS: Renal Cell Carcinoma

| ACCUMULATIVE MEDCASE COST: | ACCUMULATIVE CONTRACT COST: | ACCUMULATIVE SUPPLY COST: |
|---|---|---|
| None | None | |

FY-80 MEDCASE COST: None

PERIODIC REVIEW RESULTS:

STUDY OBJECTIVE:
1. To examine efficacy of CCNU and Bleomycin in the treatment of advanced renal cell carcinoma.
2. To determine if this regimen would extend disease free survival in patients with locally advanced disease.

TECHNICAL APPROACH: CCNU 130 mg/$M^2$ p.o., every 6 weeks
Bleomycin 15 mg I.V. weekly

PROGRESS DURING FY-80: One patient relapsed, leaving 7 still disease free. This patient developed bleomycin pulmonary toxicity.

NUMBER OF SUBJECTS TO BE STUDIED BEFORE COMPLETION OF STUDY: None

SERIOUS/UNEXPECTED SIDE EFFECTS IN SUBJECTS PARTICIPATING IN PROJECT: Bleomycin lung toxicity producing death in two patients and morbidity in one.

CONCLUSIONS: This is a potentially toxic regimen with uncertain benefit. The remaining seven patients will be followed for long term toxicity.

PUBLICATIONS/ABSTRACTS, FY-80: Miller, C.F. et al: Adjuvant Chemotherapy of Renal Cell Carcinoma Using a Combination of Bleomycin and Lomussine, ASCO vol 28 page 362, March 1980.

WORK UNIT #1644

| | | |
|---|---|---|
| | WRAMC 7501 | STATUS: Continuing X |

EVALUATION OF ADRIAMYCIN AND CIS-PLATINUM COMBINATION CHEMOTHERAPY IN TREATMENT OF MALIGNANT DISEASE

| | |
|---|---|
| STARTING DATE: 1975 | ESTIMATED COMPLETION DATE: 1980 |
| PRINCIPAL INVESTIGATOR: JOHANNES BLOM, MD | |
| ASSOCIATE INVESTIGATORS: | FACILITY: Walter Reed Army Medical Center |
| | SERVICE: Hematology-Oncology Department of Medicine |

KEY WORDS: ADRIAMYCIN, CIS-PLATINUM, MALIGNANCY

| | | |
|---|---|---|
| ACCUMULATIVE MEDCASE COST: | ACCUMULATIVE CONTRACT COST: | ACCUMULATIVE SUPPLY COST: |
| FY-80 PROJECT COST: | PERIODIC REVIEW RESULTS: | |

STUDY OBJECTIVE: To evaluate the efficacy of cis-platinum and adriamycin in patients with malignancies.

TECHNICAL APPROACH: Adriamycin 60 mg/$m^2$/day IV every 21 days
Cis-platinum 60 mg/$m^2$/day IV every 21 days

PROGRESS DURING FY-80: No patients entered during 1980. Thirty-nine patients were entered prior to 1980.

REASONS FOR SIGNIFICANT DEVIATION OF STUDY: NONE

SPECIFIC PROBLEMS EXPERIENCED IN PERFORMANCE: Three patients with prior radiation experienced severe leukopenia.

OTHER: This combination has also been piloted by CALGB and appears to have possible activity in prostate carcinoma.

PLANNED ACTIVITIES: Consideration will be given to publication of the prostate subset.

WORK UNIT # 1649

DATE: [illegible] WRAMC 7602 X
TITLE OF PROJECT: Chemoimmunotherapy of Prostatic Carcinoma.

STARTING YEAR: 1975 1981
PRINCIPAL INVESTIGATOR: LTC Jeffrey L. Berenberg, MC
ASSOCIATE INVESTIGATORS:

KEY WORDS:
ACCUMULATIVE MANDAY COST:
FY-80 MANDAY COST:

STUDY OBJECTIVE: To study the efficacy of the combination of cyclophosphamide and 5-fluorouracil with and without BCG immunotherapy in the treatment of advanced Stage D carcinoma of the prostate.

TECHNICAL APPROACH: Regimen A - Cyclophosphamide 1000 mg/$m^2$ I.V. on day 1 5-fluorouracil 600 mg/$m^2$ I.V. on days 1 and 8 BCG $6 \times 10^8$ units on days 14 and 21. Regimen B - Cyclophosphamide 1000 mg/$m^2$ I.V. on day 1 5-fluorouracil 600 mg/$m^2$ I.V. on days 1 and 8. This cycle to be repeated every 28 days. Addendum #1 changed the BCG vaccine to the Pasteur strain, $2-\times10^8$ viable units.

PROGRESS DURING FY-80: Desired objective of 30 patients accumulated for evaluation. Protocol 7602 to be evaluated and findings published.

NUMBER OF SUBJECTS TO BE STUDIED BEYOND COMPLETION OF PHASE: 20
SERIOUS/UNEXPECTED SIDE EFFECTS IN PEOPLE PARTICIPATING IN PROJECT:

CONCLUSIONS: Pending evaluation of median survival values.

PUBLICATIONS/ABSTRACTS, FY-80: In progress.

WORK UNIT # 1658

DATE: [illegible] WRAIR 7782

TITLE OF PROJECT: Adjuvant Chemotherapy of Prostatic Carcinoma with Adriamycin and Cis-Diamminedichloroplatinum II.

STARTING DATE: 1977 | ESTIMATED COMPLETION DATE: 1984

PRINCIPAL INVESTIGATOR: LTC Jeffrey L. Berenberg, M.D. MC

ASSOCIATE INVESTIGATORS:

SERVICE:

KEY WORDS:

| ACCUMULATIVE INCREASE COST: | ACCUMULATIVE COST TO DATE: | ACTUAL COSTS DURING FY-79: |
|---|---|---|
| | COST: | COST: |
| FY-80 INCREASE COST: | PERIODIC MAJOR MILESTONES: | |

STUDY OBJECTIVE: To compare the efficacy of radiation therapy alone versus the combination of radiation therapy plus chemotherapy in the treatment of patients with operatively staged and histologically proven stage DI prostatic carcinoma.

TECHNICAL APPROACH: Regimen A Whole pelvic irradiation to a total dose of 4600 rads with an additional 2000 rads to the prostate bed. Regimen B - Radiation therapy as above Adriamycin 60 mg/m$^2$ I.V. day 1 every 28 days, Cis-Platinum 60 mg/m$^2$ I.V. day 1 every 28 days. Addendum #1 increased type of patients eligible for this protocol. Addendum #2 modified administration of cis-platinum to decrease toxic side effects.

PROGRESS DURING FY-80: Two patients have been entered on study. No additional patients entered in FY 1980.

NUMBER OF SUBJECTS TO BE STUDIED BEFORE COMPLETION OF PROJECT:

SERIOUS/UNEXPECTED SIDE EFFECTS IN SUBJECTS PARTICIPATING IN PROJECT:

CONCLUSIONS: Too early for evaluation. The fall-off in accrual is due in part to competition with National Prostate Cancer Project protocol #600 which also evaluates adjuvant therapy in patients with DI disease. The desired number of patients can probably be entered by 1984. As the NPCP protocols do not look at adjuvant therapy with cis-platinum, this study should remain open.

PUBLICATIONS/ABSTRACTS, FY-80:

NONE

WORK UNIT #1666

DATE: 30 September 1980 | PROTOCOL NO: WRAMC 7801 | NEW: Initial X
TITLE OF PROJECT: PROTOCOL FOR IMMUNOLOGICAL EVALUATION AND PHASE ONE IMMUNOTHERAPY OF PATIENTS WITH VARIOUS CARCINOMAS

| | |
|---|---|
| STARTING DATE: 1978 | ESTIMATED COMPLETION DATE: Accrual completed |
| PRINCIPAL INVESTIGATOR: JOHANNES BLOM, MD and MAJ LOUIS F. DIERL, MC | |
| ASSOCIATE INVESTIGATORS: DR. HERBERMAN - NIH | FACILITY: Walter Reed Army Medical Center |
| | SERVICE: Medical Oncology, Dept. Chief of Medicine |

KEY WORDS: IMMUNOTHERAPY, CARCINOMA

| | | |
|---|---|---|
| ACCUMULATIVE MEDCASE COST: | ACCUMULATIVE CONTRACT COST: | ACCUMULATIVE SUPPLY COST: |
| FY-80 MEDCASE COST: | PERIODIC REVIEW RESULTS: | |

STUDY OBJECTIVE: To perform detailed immune evaluation in patients with tumor present and tumor entirely resected, following immunization with C. Parvum in an attempt to ascertain changes in cytotoxicity induced by immune agents and to determine if immune depression in cancer patients can be reversed.

TECHNICAL APPROACH: As per outlined submitted for FY 80 and detailed in original protocol.

PROGRESS DURING FY-80: Three patients were added to the study

NUMBER OF SUBJECTS TO BE STUDIED BEFORE COMPLETION OF STUDY: Completed
SERIOUS/UNEXPECTED SIDE EFFECTS IN SUBJECTS PARTICIPATING IN PROJECT:
None
CONCLUSIONS: Too early - will require follow-up. Data is now being processed at NIH. The results of this data will be compared to the patients' clinical course.

PUBLICATIONS/ABSTRACTS, FY-80: None

WORK UNIT NO. 1672

DATE: [illegible] | PROTOCOL NO: | STATUS: [illegible] X

TITLE OF PROJECT: Tumor Tissue for Extract Preparation | [illegible]

START[illegible]: 1978 | EST[illegible] COMPLETION DATE: 1981

PRINCIPAL INVESTIGATOR: LTC Jeffrey L. Berenberg, MC

ASSOCIATE INVESTIGATORS:

FACILITY: Walter Reed Army Medical Center

SERVICE: Hematology-Oncology
Department of Medicine

KEY WORDS: Tumor tissue; extract preparation; colon cancer; antigen

| ACCUMULATED DOLLARS COST: | ASSOCIATED CONTRACT COST: | ACCUMULATED SUPPLY COST: |
|---|---|---|
| FY-80 [illegible] COST: | PERIODIC REVIEW PERIODS: | |

STUDY OBJECTIVE: Evaluation of immunotherapy in carcinoma of the colon using an antigen prepared from human colon tumor tissue.

TECHNICAL APPROACH: Obtain tumor tissue remaining after the Department of Pathology has obtained the necessary samples for diagnostic purposes. Tissue should not be deposited in formalin, should be kept sterile, and rinsed with normal saline. Tumor tissue should be trimmed of fat and other tissue as much as possible.

PROGRESS DURING FY-80: No tissue obtained to date.

NUMBER OF SUBJECTS TO BE STUDIED BEFORE COMPLETION OF STUDY:

SERIOUS/UNEXPECTED SIDE EFFECTS IN SUBJECTS AND PERSONNEL IN PROJECT:

CONCLUSIONS: No data for evaluation. Study will be closed if no tissue is obtained within next 6 months.

MACS UNIT NO. 1650

DATE: 30 September 1980 | PROTOCOL NO: WRAMC 7903 | STATUS: Interim X / Final

TITLE OF PROJECT: Use of Streptozotocin in the Treatment of Metastatic Islet Cell Carcinoma of the Pancreas and Metastatic Carcinoid

STARTING DATE: Oct 79 | ESTIMATED COMPLETION DATE:

PRINCIPAL INVESTIGATOR:

ASSOCIATE INVESTIGATORS:

FACILITY: Walter Reed Army Medical Center

SERVICE: Hematology-Oncology Department of Medicine

KEY WORDS:

| ACCUMULATIVE MEDCASE COST: | ACCUMULATIVE CONTRACT COST: | ACCUMULATIVE SUPPLY COST: |
|---|---|---|
| FY-80 MEDCASE COST: | PERIODIC REVIEW RESULTS: | |

STUDY OBJECTIVE: Streptozotocin has shown a great degree of effectiveness in metastatic islet cell carcinoma of the pancreas and metastatic carcinoid. Clinical responses have been reported in patients with malignant islet cell tumors. Streptozotocin yields an overall response rate of approximately 70%. Even if an objective response does not occur, amelioration of symptoms from hormonal producing tumors (insulinoma and carcinoid) may occur. Adequate clinical trials with this drug have not yet been performed in other tumor types.

TECHNICAL APPROACH: Streptozotocin is available for intravenous administration only. Both a five-day intensive course regimen and a weekly regimen have been widely employed using this drug, with current favor given to a schedule of 500 mg/$m^2$ IV bolus daily x 5 every 4-6 weeks. The weekly schedule has usually been 1 gm/$m^2$/week x 4 weeks.

PROGRESS DURING FY-80: These patients entered on study - all patients had clinical diagnosis of carcinoid tumors. There were no responses and all patients have expired. At post mortem, one patient was found to have metastatic melanoma instead of carcinoid. This is part of a cooperative effort with NCI to study response with toxicity of class "C" drugs.

ANSWER TO REVIEWER'S COMMENTS: This is a class C NCI Study for use of Streptozotocin. Patient data is reported for information only. It will remain open.

NUMBER OF SUBJECTS TO BE STUDIED BEFORE COMPLETION OF STUDY:

SERIOUS/UNEXPECTED SIDE EFFECTS IN SUBJECTS PARTICIPATING IN PROJECT: None.

CONCLUSIONS:

None.

PUBLICATIONS/ABSTRACTS, FY-80:

None.

WORK UNIT NO. 1683

DATE: 30 September 1980 | PROTOCOL NO: WRAMC 7911 | STATUS: Interim X Final

TITLE OF PROJECT: Use of L-Asparaginase in the Treatment of Acute Lymphoblastic Leukemia in Adults and Children.

STARTING DATE: October 1979 | ESTIMATED COMPLETION DATE:

PRINCIPAL INVESTIGATOR:

ASSOCIATE INVESTIGATORS:

FACILITY: Walter Reed Army Medical Center

SERVICE: Hematology-Oncology Department of Medicine

KEY WORDS:

| ACCUMULATIVE MEDCASE COST: | ACCUMULATIVE CONTRACT COST: | ACCUMULATIVE SUPPLY COST: |
|---|---|---|
| FY-80 MEDCASE COST: | PERIODIC REVIEW RESULTS: | |

STUDY OBJECTIVE: Erwina Cartovora asparaginase is an antigenically noncross-reactive asparaginase. It has activity comparable to that of the E. Coli preparation in both animal tumor systems and in human ALL. Compared with E. Coli asparaginase its toxicity is qualitatively and quantitatively the same. Therefore, this drug represents an alternative to E. Coli asparaginase in those situations where repeat coursed of asparaginase therapy are required or where allergic reactions force the discontinuance of the E. Coli preparation.

TECHNICAL APPROACH: Intravenously 1,000 IU/Kg 30,000 IU/$m^2$ per day x 10-20 days. Intramuscularly 6,000 IU/$m^2$ t.i.w. x 3 weeks (9 doses).

PROGRESS DURING FY-80: No patients entered.

NOTE ADDED FOR APPROVAL OF ANNUAL PROGRESS REPORT: This is a class "C" protocol for use in patients allergic to E. Coli L-ASE. It will remain open. Perhaps one or two patients per year will be entered.

NUMBER OF SUBJECTS TO BE STUDIED BEFORE COMPLETION OF STUDY:

SERIOUS/UNEXPECTED SIDE EFFECTS IN SUBJECTS PARTICIPATING IN PROJECT: None

CONCLUSIONS: None

26

| Date: 8 March 1981 | Protocol No: 2104 | Status: Interim / Final X |
|---|---|---|

**Title of Project:**
Evaluation of Efficacy of Suppressing Platelet Activity in Patients with Intermittent Claudication

| Starting Date: May 1978 | Estimated Completion Date: Completed |
|---|---|

**Principal Investigator:** George J. Collins, Jr., COL, MC

**Associate Investigators:**
Salvatore Scialla, MAJ, MC
Norman M. Rich, COL, MC
Earl Ferguson, MAJ, MC
C. Patrick Clagett, LTC, MC
Mr. Charles Barr

**Facility:** WRAMC, WRAIR

**Dept/Svc** Peripheral Vascular Surgery

**Key Words:**
Platelets, Intermittent claudication

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: |
|---|---|---|

| FY-80 MEDCASE Cost: | Periodic Review Results: (to be filled in by DCS) |
|---|---|

Study Objective:
1. To determine the relative effect of several platelet active drugs in suppressing in vivo and in vitro platelet function.
2. To determine whether or not these drugs cause a lowering of coagulation factors.
3. To determine if suppression of platelet function in patients with intermittent claudication results in objective improvement in exercise tolerance.

**Technical Approach:** Patients ranging in age from 40 to 70 years of either sex with intermittent claudication documented by lowering of ankle pressure after exercise were randomized into four treatment groups. One treatment group received placebo, one received 600 mg per day of aspirin, one received 600 mg per day of aspirin and 100 mg per day of persantine and one received 200 mg of sulfinpyrazone four times daily. Patients had a full coagulation screening battery including prothrombin time, activated partial thromboplastin time, fibrinogen, factors II, V, VII-X, (Cont'd)

**Progress during FY-80:** A total of 93 patients completed the entire test period, i.e., six months on drugs and all specified laboratory tests.

Number of subjects to be studied before completion of study: Completed

Serious/unexpected side effects in subjects participating in project:
Only one patient withdrew due to a rash from aspirin.

**Conclusions:** Data analysis has not been completed. It should be completed within six months.

Publications or Abstracts, FY-80: None

Appendix G - Detail Summary Sheet

Technical Approach: (Cont'd)
VIII antigen, IX, X, XI, XII, antithrombin III, fibrin split products, and protamine sulfate paracoagulation. The tests were done before taking medicines, after being on medications for two weeks, after being on medications for two months, and after being on medications for six months. In addition to this, patients had arm and ankle pressures before and after treadmill exercise at the same time intervals.

| Date: 8 March 1981 | Protocol No: 2105 | Status: Interim / Final X |
|---|---|---|

Title of Project: Rapid Screening for Coagulation Abnormalities

| Starting Date: May 1979 | Estimated Completion Date: Complete June 1980 |
|---|---|

Principal Investigator: George J. Collins, Jr., COL, MC

| Associate Investigators: | Facility: CTS, WRAMC<br>Hematology, WRAIR |
|---|---|
| Mr. Donald Christopher<br>Daniel Kimball, COL, MC<br>Norman M. Pich, COL, MC<br>Salvatore Scialla, MAJ, MC<br>Mr. Charles Barr | Dept/Svc Peripheral Vascular Surgery |

Key Words:
Coagulation, Thromboelastography

| Accumulative MEDCASE Cost: | Accumulative Contract Cost: | Accumulative Supply Cost: |
|---|---|---|
| | | |

| FY-80 MEDCASE Cost: | Periodic Review Results: (to be filled in by DCT) |
|---|---|
| | |

Study Objective: To develop techniques whereby sizable numbers of patients can be screened for hypercoagulability. The objective of the study is to be able to screen as many as twenty patients per day.

Technical Approach: Patients from the Peripheral Vascular Surgery and Hematology/Oncology Clinics with suspicion of hypercoagulability had coagulation screening batteries and thromboelastography performed. In addition, twenty healthy volunteers were examined. After the determinations were made, the results of thromboelastography and the screening battery were tabulated.

*Progress during FY-80: The study was completed per objective and the results have been tabulated. Statistical analysis should be completed in six months.

There were no side effects or complications.

Number of subjects to be studied before completion of study:

Serious/unexpected side effects in subjects participating in project:

Conclusions:

Publications or Abstracts, FY-80: None

Date: 15 October 1980 | Protocol No: 2810 | Status: Interim X / Final

Title of Project: Comparative Study of High Dose Versus Low Dose Pre-operative Radiation to Radical Cystectomy for Control of Transitional Cell Carcinoma of the Bladder.

Starting Date: | Estimated Completion Date:

Principal Investigator: DAVID G. McLEOD, MD, COL, MC, USA

Associate Investigators: RONALD DORN, MD, MAJOR, MC, USA

Facility:

Dept/Svc Urology & Radiation Therapy

Key Words: Cancer of Bladder, irradiation

Accumulative MEDCASE Cost: 0

Accumulative Contract Cost: 0

Accumulative Supply Cost: 0

FY-80 MEDCASE Cost: 0

Periodic Review Results: (to be filled in by DCI)

Study Objective:

To compare short courses versis long courses of pre-operative radiation therapy in the treatment of invasive cancer of the bladder.

Technical Approach: No deviation from protocol. There are no increased side effects or increased incidence of expected untoward side effects.

Progress during FY-80: To date we have 14 patients in study. Study started in FY 79. No funds required and no funds needed.

Number of subjects to be studied before completion of study: 30

Serious/unexpected side effects in subjects participating in project: To date there have been no serious/unexpected side effects.

Conclusions: No conclusions yet.

30

Publications or Abstracts, FY-80: None

| Date: 31 Oct 80 | Protocol No: 4501 | Status: Interim / Final X |
|---|---|---|

Title of Project: Clinical Evaluation of Fluorescence Scanning of the Thyroid with an Americium Source

| Starting Date: | Estimated Completion Date: |
|---|---|

Principal Investigator: Robert J. Kaminski, LTC, MC

| Associate Investigators: | Facility: Walter Reed Army Medical Center |
|---|---|
| | Dept/Svc Dept of Radiology/Nuclear Med Svc. |

Key Words:

| Accumulative MEDCASE Cost: $19,500 | Accumulative Contract Cost: $19,5[illegible] | Accumulative Supply Cost: [illegible] |
|---|---|---|

| FY-80 MEDCASE Cost: 0 | Periodic Review Results: (to be filled in by hand) |
|---|---|

Study Objective: Clinical evaluation of fluorescent scanning under protocol 4501 were terminated by the resignation from active duty of the principal investigator. Current research ongoing under a new protocol.

Technical Approach:

Progress during FY-80:

Number of subjects to be studied before completion of study:

Serious/unexpected side effects in subjects participating in project:

Conclusions: Final report

Publications or Abstracts, FY-80: None

AUTHOR INDEX

Barr, C.- 27,29
Berenberg, J.L.- 11,13,14,15,16,17,21,22,24
Blom, J. -6,12,18,19,20,23
Booth, B. -10
Burman, K.D.- 2

Christopher, D.- 29
Clagett, G.P.- 27
Collins, G.J.- 27,29

Dorn, R.- 30

Ferguson, E.- 27

Glass, A.R.- 3,4

Herberman, Dr.- 23

Johnson, L.F.- 1

Kaminski, R.J.- 31
Keegan, M.T.- 1
Kimball, D.B. -29

Latham, K.R.- 2,3,4

McLeod, D.G.- 30

Peura, D.A.- 1

Rich, N.M.-27,29
Ruyman, F.B.-5

Scialla, S.- 27,29
Smallridge, R.C.- 2

Tseng, Y.C.L.- 3,4

Wartofsky, L.- 2

DAT
ILM