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WALTER REED ARMY MEDICAL CENTER

Washington, D.C. 20012

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Unit Summary Sheet

Clinical Investigation Service, WRAMC

FY-77 saw a marked increase in the workload of Clinical Investigation Service, WRAMC. At the start of FY-77, there were 112 ongoing investigative work units. An additional 13 protocols were awaiting approval from the Office of the Surgeon General (OTSG). During 1977, 132 new protocols were approved by the Clinical Investigation Committee, WRAMC; 94 of these projects received OTSG approval and were initiated.

During FY-77, 25 projects were completed and 30 projects were terminated. One hundred sixty two investigative work units were active at the close of FY-77, with approval anticipated from OTSG on 38 additional protocols. This represents a 45% increase in protocol workload in FY-77 compared to FY-76. In addition, preparations were made for the transfer of the Infectious Disease Clinical Research Laboratory from WRAIR to Clinical Investigation Service, WRAMC, effective 1 October 1977. Clinical Investigation Service anticipated gaining four personnel, one military and three civilians; gaining equipment listed at approximately $120,000, and responsibility for $85,000 of operating funds.

Clinical Investigation Service provided support to the program by purchasing reprints of staff authored publications in national journals. These reprints are used for training and distribution and numbered 23. TDY for members of the staff to present their projects at national meetings and to collaborate with other institutions regarding methods and procedures was provided by this Service. These trips numbered 44. Some of the projects receiving International recognition include 1) development of a specific radioimmunoassay for prostatic acid phosphatase; 2) development of radioimmunoassays for reverse T3 and 3,3'T2; 3) further clarification of the nature of thyroidal suppression during acute malaria. Clinical Investigation Service continued to encourage resident research by awarding the Bailey K. Ashford Award to the outstanding graduating resident research project, this year it was awarded to Major William J. Oetgen, MC, Resident, Department of Medicine.

The marked increase in protocols submitted to Clinical Investigation Service provided stimulus for refinement of protocol processing procedures. Extensive use was made of independent disinterested expert review of protocols. Protocols were distributed to Committee members at least two weeks in advance of the meeting. The Committee meeting format was revised so that the bulk of the time was spent critically appraising both the scientific merit of each protocol and the funding implications. At the close of the fiscal year, the Chief and Asst Chief, Clinical Investigation Service were developing a system of prioritization of existing research projects.

In December 1976, a biochemist, LT Rudolfo Bongiovanni, joined the Clinical Investigation Service. In addition to development of a high pressure liquid chromatography method for measurement of theophylline, amino acids, Vitamin D and its metabolites, and hemoglobin A-1-C, he has initiated a workload reporting system that will be used in Clinical Investigation Service laboratories.

In September 1977, the FDA selected Walter Reed as site for an inspection tour of the Clinical Investigation Service and Human Use Committee. During their inspection, the FDA was especially concerned with the function of the Human Use Committee. No deficiencies were identified at the exit briefing.

Objectives: To achieve continuous improvement in the quality of patient care. To provide experience in the mental discipline achieved by participation in such organized inquiries and to provide experience for personnel who will ultimately be teaching chiefs in military hospitals and medical specialty consultants. To maintain an atmosphere of inquiry because of the dynamic nature of health sciences. To maintain high professional standing and accreditation of advanced health programs.

Technical Approach: Provides direction and management as outlined under provisions of AR 40-38, Clinical Investigation Program; AR 40-7, Use of Investigational Drugs in Humans; and WRAMC Regulation 70-1, Clinical Investigation Program, WRAMC. Provides guidance, assistance and support to the housestaff in matters pertaining to the program. Coordinates the WRAMC program with higher headquarters and other facilities.

Manpower: Current and authorized strength is outlined.

Description	Grade	MOS	Br	Actual	Name
C, Clin Inv	06	3000	MC	1	Evans
Asst C, CIS	04	3000	MC	1	Boehm
Biochemist	02	68000	MSC	1	Bongiovanni
Dietitian	02	3420	AMS	1	Walker
Med Lab Tech	E7	92B30	MSC	2	Gaunt
					Hayes
Med Lab SP	E4	92B20	MSC	1	Dickinson
Sup Rsch Chem	14	1320	GS	1	Bruton
Chem	11	1320	GS	1	Smith
Sup Biol	11	0401	GS	1	Davis
Sup Bio Tech	10	0404	GS	1	Young

(continued next page)

Description	Grade	MOS	Br	Actual	Name
Med Tech	09	0645	GS	2	Armstrong
					Burgess
Med Tech	09	1320	GS	1	Dawson
	09	0644	GS	1	Wright
	09	0058	GS	1	Lukes
Biol Lab Tech	08	0404	GS	2	Coleman
					Butler
Rsch Chem	07	1320	GS	1	Maydonovitch
Med Tech	07	0644	GS	2	Battista
					Bongiovanni
Biol Lab Tech	07	0404	GS	1	Barnes
Sec (Steno)	06	0318	GS	1	Ervin
Clk (DMT)	05	0316	GS	2	Laster
					Vacant
Clk-Typist	04	0322	GS	1	Keys
Clk (DMT)	04	0316	GS	1	Roberts
Med Tech (Chem)	04	0645	GS	1	Martin

Funding, FY-77:

Civilian Personnel	$461,700
Travel	9,187
Rental	12,687
Contracts	17,994
Supplies	217,622

TABLE OF PUBLICATIONS AND PRESENTATIONS, FY-77

DEPARTMENT OF MEDICINE

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Burman KD, Dimond RC, Wright FD and Wartofsky L: Sensitivity to lithium in treated Graves' disease: Effects on serum T4, T3 and reverse T3. J Clin Endocrinol & Metab 43:606, 1976.

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Burman KD, Dimond RC, Wright FD, Earll JM, Bruton J, and Wartofsky A: A radioimmunoassay for reverse T3: J Clin Endocrinol & Metab 44:660, 1977.

Burman KD, Djuh Y-Y, Wright FD, Bruton J, and Wartofsky L: Effect of 3,3'T2 on TSH response to TRH stimulation. (In press, provisionally accepted May 1977, Metab).

Smallridge RC, Wartofsky L, and Burman KD: A radioimmunoassay for 3' monoiodothyronine. (To be submitted to J Clin Endocrinol & Metab, 10 Jul 77).

DEPARTMENT OF MEDICINE (continued)

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Tormey DC, Falkson G, Perlin E, Bool J, Blom J, and Lippman M: Evaluation of an intermittent schedule of dibromodulcitol in breast cancer. Cancer Treatment Repts 60(11):1593-1596, Nov 1976.

Oldham RK, et al: Immunological monitoring and immunotherapy in carcinoma of the lung. The results of this study were presented by Dr. Perlin at the Chicago Symposium on Immunotherapy of Solid Tumors in February 1977, the proceedings of which will also be published. An updated presentation was delivered by Dr. Perlin at the Amer Soc of Clin Oncology 13th Annual Meeting, Denver, CO, on 16 & 17 May 1977; and published in the proceedings, p 346. Dr. Herberman of the Natl Cancer Institute presented data of this study at the Second Conference on Lung Cancer Treatment sponsored by the Division of Cancer Treatment, Natl Cancer Institute, Williamsburg, VA, 23 May 1977; in a talk titled "Prospects for immunotherapy of lung cancer with specific immunoadjuvants. Proceedings of this meeting will be published in the Cancer Treatment Repts.

Falkson Dr: Metastatic breast carcinoma study to evaluate the effect of cyclophosphamide, adriamycin and 5-fluorouracil versus adriamycin, dibromodulcitol and vincristine sequentially alternating with cyclophosphamide, methotrexate and 5-fluorouracil. Preliminary results of this study were presented to the Univ of Pretoria at the 68th Annual Meeting of the American Assn of Cancer Rsch, Denver, CO, 1-17 May 1977, page 40 of the published proceedings.

Tarrassoff PG, and Kark JA: Inhibition of erythrocyte pyridoxal kinase by a metabolite of isoniazid. Clin Rsch 24:623A, 1976.

DEPARTMENT OF SURGERY

Rich NM, Hobson RW II, Collins GJ, Jr, and Andersen CA: The effect of acute popliteal venous interruption. Ann Surg 183:365, 1976.

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Rich NM: The Chesapeake Vascular Society: Milit Med 141:874, 1976.

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Spees EK, Davis M, Gibson TP, et al: Impairment of *in vitro* lymphocyte function by a plasticiser, DEHP. Abstract submitted, 1976.

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Oakes DD, Spees EK, Light JA, Flye MN. A three year experience using modified bovine arterial heterografts for vascular access in patients requiring hemodialysis. Abstract submitted, 1977.

Light JA, Annable CA, Spees EK, Oakes DD, Reinmuth B: Comparison of long term kidney survival following cold storage or pulsatile preservation, Transpl Proc, 1977.

ALLERGY-IMMUNOLOGY SERVICE

Casterline CL, and Evans R: Selective IgA Deficiency and PiZ Deficiency Associated with Recurrent Sinopulmonary Infections, Emphysema, and Bronchiectasis. (Has been accepted in CHEST, in press.)

Casterline CL, Evans R, Ward GW Jr: Quantitative immunoglobulin levels in tuberculosis. (Has been accepted in CHEST, in press.)

Evans R: Standardization of the quantitation of total serum IgE. (Presented to the Research Council, Amer Acad Allergy, NYC, March 1977.

Milluncheck E, deShazo R, Levinson AI, Ruymann F, Grogan T: Pneumocystis pneumonia hypogammaglobulinemia and C-chromosomes aberration. (Submitted for publication.)

Levinson AI: Pseudo-DiGeorge Syndrome. Amer Acad of Allergy, 1977.

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Levinson AI, Summers R, Evans R III, et al: Late sequelae to long-term hyposensitization. Am Acad of Allergy, March 1977.

DEPARTMENT OF OBSTETRICS AND GYNECOLOGY

Park RC et al: Microinvasive carcinoma of the cervix: Obstet & Gyn 48:5, Nov 1976.

Klapholz H, Miller FC, Skiba, H: 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. Data from this protocol will be presented to the Armed Forces District meeting in New Orleans in Oct 1977 (Abst).

DEPARTMENT OF OBSTETRICS AND GYNECOLOGY (continued)

Duff P, Kacenga K: Evaluation of gonorrhea screening in a prenatal population of military dependents. Data from this protocol will be presented to the Armed Forces District meeting in New Orleans in Oct 1977.

DEPARTMENT OF RADIOLOGY

Johnson MC, Corcoran RJ: Evaluation of a thyroid fluorescent scanning system of concentric source detector design: J Nuc Med 18:163-167, 1977.

DEPARTMENT OF PEDIATRICS

Maybee DA et al: Granulocyte transfusion therapy in children. Southern Med J 70:320-324, 1977.

DIVISION OF HEMATOLOGY, WRAIR

Kark JA, Haut MJ, McQuilkin CT and Hicks CU: Dissociation of biochemical and hematologic responses to pyridoxine in patients with sideroblastic anemia. Blood 48:966, 1976.

Work Unit No: 1112

Title of Project: Use of Minoxidil in the Treatment of Severe, Uncontrolled or Poorly Controlled Hypertension

Principal Investigator: Donald E. Butkus, MD, COL, MC

Associate Investigators: Daniel A. Nash, MD, LT COL, MC; Joseph Johnson, MD, MAJ, MC; Timothy McNamara, MD, MAJ, MC; Jeffrey Weidig, MD, MAJ, MC; and Joseph Lombardo, MD, LT CMDR, MC.

Objectives: To assess the efficiency and safety of minoxidil in severe hypertension refractory to currently available potent antihypertensive agents.

Progress and Results: Since this protocol was established a total of thirteen patients have been entered into the protocol, four within the last year. As the first nine have been previously described and no complications related to their therapy have been ensued they will not be further defined at present. Of the four patients entered into the protocol during the past year two have been in association with severe hypertension in patients undergoing transplant rejection and a third is a chronic hemodialysis patient with underlying renal ischemia. All three noted improvement of hypertension and stablization of their course. All underwent subsequent nephrectomy when their courses stablized and were subsequently removed from the protocol. The fourth patient, a 4 1/2 year old child with von Recklinghausen's disease and bilateral renal entry stenosis was placed on minoxidil when he failed to respond to adult standard doses of aldomet, apressoline, inderal, catapress and furosemide and had an excellent antihypertensive response. Unfortunately, this patient had presented with a cerebrovascular accident and has severe residual neurologic impairment. The major side effect of therapy continues to be hypertricosis.

Conclusion: Minoxidil is an extremely potent antihypertensive agent which is superior to oral agents currently available.

Funding Utilized: None

Funding Requested: None

Publications: None

Type of Report: Interim

Work Unit No.: 1119

Title of Project: Skin Biopsy Immunofluorescence in Patients with Renal Disease

Investigators:

Principal: Jeffrey Weidig, Nephrology Fellow

Associate: Timothy McNamara, Nephrology Fellow, Samuel Goodlowe, Pathology Department, Daniel A. Nash, Asst. Chief, Nephrology Service, and Donald Butkus, Chief, Nephrology Service, Walter Reed Army Medical Center

Objectives: To determine if skin biopsy immunofluorescence is of predictive value in patients with non diagnosed renal disease.

Progress & Results: Since the onset of this protocol several skin biopsies accompanying renal biopsies were performed but the number done were not enough to use any statistically significant data. In addition, the question of skin biopsy immunofluorescence as it relates to patients with undiagnosed renal disease has been addressed in the literature. Since the main question relative to this project has already been answered no further skin biopsies were performed.

Conclusions: In view of recent publications which answer the question posed by this protocol, no further skin biopsies accompanying renal biopsies were performed. For this reason the protocol was terminated.

Funds Utilized, FY-77: None

Funding Requirements, FY-78: None

Publications: None

Type of Report: Termination

Work Unit No.: 1120

Title of Project: Bone Marrow Reserves and WBC Survival in Patients with Chronic Renal Failure.

Investigators: J.P. Johnson, Staff Nephrologist, Nephrology Service; J.A. Light, Assistant Chief, Organ Transplant Service; Thomas P. Gibson, Assistant Chief, Nephrology Service; William A. Briggs, Chief, Nephrology Service; Everett Spees, Chief, Organ Transplant Service; Patrick Farley, Hematology Fellow, Hematology Service.

Objective: To determine if changes in white blood cell kinetics observed during hemodialysis and those induced by corticosteroids to predict tolerance for immunosuppression post-transplantation and efficacy of splenectomy pre-transplantation.

Technical Approach: As outlined in protocol, patients will be tested for changes in peripheral white count following exposure of blood to hemodialysis coil and following injection of 100mg Hydrocortisone i.v. Patterns of response will be assessed in respect to bone marrow stores as evaluated by bone marrow biopsy and spleen size as evaluated by spleen scan. Patients subjected to splenectomy will be restudied for influence of this procedure. All patients will be compared in terms of white count and mean immunosuppression dosage post-transplantation.

Progress and Results: 12 Patients have been studied since initiation of protocol with 11 coil tests, 12 hydrocortisone tests and 3 hemodialysis tests as outlined in protocol. No untoward effects have been noted. Hemodialysis test has been eliminated from procedure as preliminary results indicated no significantly different response from those obtained with coil tests alone. All patients have received bone marrow biopsy and undergone spleen scans. One patient has received spleenectomy and undergone repeat study post splenectomy One patient has undergone splenectomy but not yet been restudied. Six patients have undergone seven allografts, one patient receiving two allografts during this period. Three allografts have been lost to rejection episodes or complications of therapy during this period. Data obtained from these tests are being analyzed as outlined above and in protocol; however, more sequential observations on all patients post-transplantation will be required before firm assessment of predictive value of white cell kinetic patterns can be established. The pattern of response is not homogeneous in all patients and this observation suggests that the tests may well have discriminative value.

Conclusion: See above. Information at this time is too limited in number of observations to permit firm conclusions.

Funding Requirements, FY-78:

Personnel:	None
Equipment:	None
Supplies:	$709.00, as outlined in original protocol.
Travel:	$600.00

Publications: None

Type of Report: Interim

Addendum: J.P. Johnson, T.P. Gibson, W.A. Briggs, W.H. Whitman, and E.K. Spees should be deleted from the protocol due to reassignment in other areas or departure from WRAMC. J.A. Light, Chief, Organ Transplant Service will become principal investigator. D.A. Nash, Chief, Nephrology Service will become associate investigator.

Work Unit No.: 1121

Project Title: Combined Prednisone and Cytoxan Therapy Coupled with Plasma Exchange in the Treatment of Anti-Glomerular Basement Antibody Mediated Renal Disease.

Investigators: J.P. Johnson, Staff Nephrologist
J. Lombardo, Nephrology Fellow

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

Technical Approach: Patients with confirmed anti GBM antibody mediated renal disease will be randomized to treatment with either prednisone and cytoxan alone or in combination with plasma exchange. Disappearance rates of antibody will be calculated and compared along with clinical outcome and response to therapy.

Progress and Results: Five patients have been treated according to this protocol since inception. Four patients were treated with prednisone and cytoxan alone. One patient treated with prednisone, cytoxan combined with plasma exchange. Disappearance rates of antibody have been observed. Initial observations suggest that rates of disappearance may be similar between the two groups. However the patient experience remains too small at this time for meaningful comparisons.

Conclusions: Only tentative conclusions can be reached at this time. As indicated above, more patients are required in each treatment group for significant comparison of relevant parameters and outcome can be made.

Funding Requirements, F.Y. 78:

Personnel:	None
Equipment:	None
Supplies:	None
Travel:	$600.00

Publications: Johnson, J.P., Whitman, W.H., Briggs, W.A., and C.B. Wilson: Combined Immunosuppression and plasma exchange in the treatment of anti-glomerular basement membrane antibody mediated Goodpasture's Syndrome. American Journal of Medicine in Press. (Accepted December, 1976).

Type of Report: Interim.

Work Unit No.: 1122

Title of Project: Evaluation of urinary creatinine excretion as a reference point for comparing total body potassium determinations

Senior Investigator: Donald E. Butkus-MD Col of M.C.

Objectives: To determine a more reliable reference standard with which to compare total body potassium measurement and to increase the usefulness of this measurement in assessing body potassium stores.

Technical Approach: Ambulatory volunteers who are receiving no medication and who have normal plasma potassium concentrations will have total body potassium measurements performed in a total body counter measuring naturally occuring K^{40} and no radioisotopes will be administered. Volunteers will collect 24 hour urine samples for creatinine and have blood drawn for measurement of plasma and red cell potassium concentrations, total body potassium measurements will be expressed per grams of creatinine exerted and results will be compared with standard references including height, weight, body surface area and standard predictive formuli.

Progress and Results: This project was delayed because of unavailability of laboratory space and equipment until 1 April 1977. Thus far standardization of the total body counter has been accomplished as well as serial measurement in individuals to assess reproducibility. The red cell harvesting procedure has been standardized and percent trapping of plasma in red cell samples has been analyzed and found to be consistantly below 2% which is suitable for performance of red cell cation studies. The creatinine assay is currently being set up and should be ready to initiate the full study within two to three weeks.

Conclusions: No conclusions may be drawn at the present time

Funds Utilized:

Funds Required: FY-78

Supplies: $500

Travel: Presentation at American Federation of Clinical Research $550

Publications: None

Type of Report: Interim

Work Unit No.: #1123

Title of Project: Effect of Acidosis, Nutritional Status and Aldosterone on Potassium Metabolism in Patients with Stable Chronic Renal Failure

Principal Investigator: Donald E. Butkus, MD, Col. MC

Objective: To assess body potassium stores in patients with chronic renal failure and relate deficits to three potential causes - acidosis, nutritional status and status of mineralocorticoid production

Technical Approach: Patients with stable chronic renal failure will be studied in conjunction with routine hospitalization to determine total body potassium status by total body counting of endogenous K^{40}. No radioisotopes will be administered. Total body potassium status will be related to patients' degree of systemic acidosis, nutritional intake and plasma aldosterone levels. Such patients have previously been demonstrated to have a high incidence of total body potassium deficit. Following detection of total body potassium deficits serial measurement will be made to assess the effect of correction of acidosis and/or nutritional status.

Progress and Results: As with project #1122 this project has not yet begun because of lack of laboratory space until recently. It is anticipated that patients will enter into the protocol within 30 days.

Conclusion: None possible at present

Funds Utilized, FY-77: None

Funds Requested:

a) Personnel - Part Time (50%) General Chemist, GS-7, $6,000
b) Supplies - $2,000
c) Travel - $550

Publications: None

Type of Report: Interim

Work Unit No.: 1308

Title of Project: Inderal Kinetics in Hyperthyroidism

Investigators:

Principal: Kenneth D. Burman, MAJ, MC

Associates: L. Wartofsky, LTC, MC; Dave Lowenthal, M.D.

Objectives: To assess Inderal half life in thyrotoxic patients.

Technical Approach: All patients are studied on Ward 30. They are given Inderal and blood samples are obtained to ascertain its disappearance rate.

Progress & Results: About 15 patients have been analyzed and preliminary data indicates that the half life of Inderal may be about 90 minutes which is not different than a group of normal controls. Dr. Lowenthal has moved his laboratory twice in the last 2 years and believes now he can help finish this project.

Conclusions: Inderal half life is about one hour.

Funds Utilized FY 77:

Personnel:	$1,691
Exp. supplies:	1,000
Reprints, printing:	-0-
Audio-Visual:	-0-
Xerox; Office Supplies:	200
Isotopes:	-0-
Lab Contracts:	-0-
Loose Issue, non-exp.:	200
Animals:	-0-
Travel:	-0-
Equipment:	1,995
Total	$5,086

Funds Requested FY 78:

Personnel:	$ 836
Exp. supplies:	500
Reprints, printing:	500
Audio-Visual:	200
Xerox; Office Supplies:	100
Isotopes:	-0-
Lab Contracts:	-0-
Loose Issue, non-exp.:	-0-

CONTINUED

Animals:	$	-0-
Travel:		-0-
Equipment:		750
Total	$	2,886

Publications: None

Type of Report: Interim (Annual)

Work Unit No.: 1310

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

Investigators:

Principal: Leonard Wartofsky, LTC, MC

Associates: R.C. Dimond, MAJ, 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 the injection 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 500 such studies have been completed in approximately 300 subjects. Although much of the data is yet to be analyzed, some appears in the publications listed below.

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

Funds Utilized FY-77:

Personnel:	$2,945
Exp. Supplies:	1,000
Reprints, printing:	1,000
Audio-Visual:	500
Xerox; office supp.:	200
Isotopes:	-
Lab Contracts:	2,000
Loose Issue, non-exp.:	500
Animals:	-
Travel:	800
Equipment:	2,035
TOTAL	$10,980

Funds Requested FY-78:

Personnel:	$2,895
Exp. Supplies:	500
Reprints, printing:	500
Audio-Visual:	250
Xerox;office supp.:	100
Isotopes:	-
Lab Contracts:	2,000

CONTINUED

Loose issue, non-exp:	250
Animals:	-
Travel:	600
Equipment:	500
TOTAL	$7,595

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., 41:484-490, 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.

Type of Report: Interim

Work Unit No.: 1311

Title of Project: Treatment of Thyroid Storm with Anion Exchange Resin.

Investigators:

Principal: Kenneth D. Burman, MAJ, MC

Associates: H. Yeager, MAJ, MC; J.M. Earll, COL, MC; W. Briggs; L. Wartofsky, LTC, MC

Objectives: Thyroid storm is a serious condition characterized by high serum concentrations of triiodothyronine (T3) and thyroxine (T4) and by an exaggeration of the usual manifestations of thyrotoxicosis. Presently accepted modes of therapy for thyroid storm include propylthiouracil or methimazole to decrease thyroid hormone synthesis, iodine to block glandular release, propranolol to decrease tissue sensitivity to T3 and T4, and glucocorticoids to prevent the precipitation of relative adrenal insufficiency and, perhaps, to decrease serum thyroid hormone levels. In spite of the effective glandular blockade permitted by the available forms of chemotherapy, the mortality of thyroid crisis remains high. The high mortality rate may be partly related to the inherent delay in decreasing serum T4 or T3 following inhibition of thyroid hormone synthesis and secretion with usual therapy. A treatment modality that would directly remove these hormones from the circulation and decrease their serum concentrations within several hours would be highly desirable. Previous attempts to develop such therapy for patients with thyroid storm have included plasmapheresis, peritoneal dialysis, and hemodialysis. The purpose of the present study is to evaluate the ability of an extracorporeal resin hemoperfusion (RH) system, employing uncharged Amberlite^{R} XAD-4 resin, to bind thyroid hormone and to rapidly decrease serum T3 and T4 concentrations in thyrotoxic humans.

CONTINUED

Progress & Results: The following results in dogs have been attained:

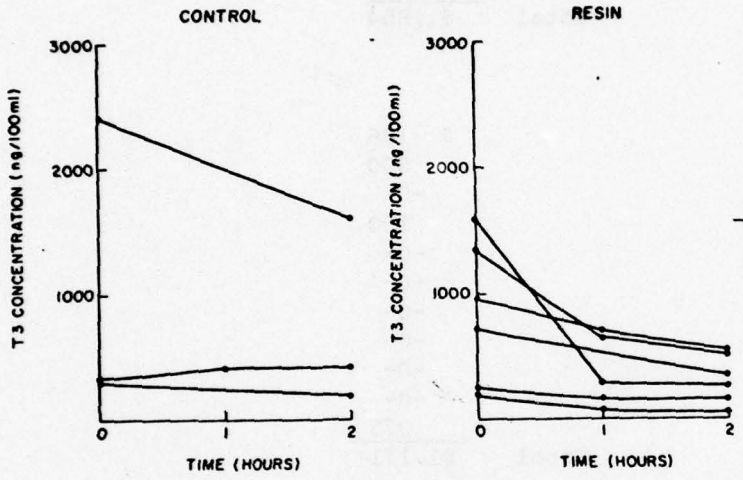


FIG. 3. Serum T3 concentrations during three 2 h control and six 2 h resin hemoperfusion experiments in thyrotoxic dogs.

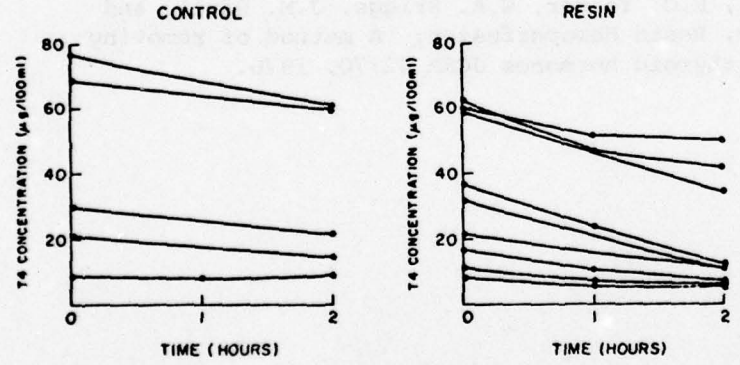


FIG. 4. Serum T4 concentrations during five 2 h control and nine 2 h resin hemoperfusion experiments in thyrotoxic dogs.

To date, no humans have been studied because of the rarity of thyroid storm.

Conclusions: None yet

Funds Utilized FY-77:

Personnel:		$ 184
Exp. Supplies:		200
Reprints, printing:		500
Audio-Visual:		250
Xerox; office supp.:		100
Isotopes:		-0-
Lab Contracts:		-0-
Loose issue, non-exp.:		-0-
Animals (dogs):		400
Travel:		-0-
Equipment:		220
	Total	$1,854

Funds Requested FY-78:

Personnel:		$ 196
Exp. Supplies:		500
Reprints, printing:		-0-
Audio-Visual:		100
Xerox; office supp.:		-0-
Isotopes:		-0-
Lab Contracts:		-0-
Loose issue, non-exp.:		-0-
Animals (dogs):		-0-
Travel:		-0-
Equipment:		375
	Total	$1,171

Publications: Burman, K.D., H.C. Yeager, W.A. Briggs, J.M. Earll, and L. Wartofsky, Resin Hemoperfusion: A method of removing circulating thyroid hormones JCEM 42:70, 1976.

Type of Report: Interim

Work Unit No: 1314

Title of Project: Stimulation and Suppression of Plasma Prolactin in Patients with Pituitary Disease

Investigators:

Principal: Gordon L. Noel, MAJ, MC

Associates: J.M. Earll, COL, MC; A.G. Frantz, M.D.

Objectives:

1. To evaluate the efficacy of various tests now available in stimulating and suppressing the release of prolactin as a means of assessing pituitary function.

2. To study the pathophysiology of abnormal prolactin secretion in various forms of galactorrhea.

3. To ascertain whether prolactin has osmoregulatory properties in patients with disorders of prolactin secretion.

Technical Approach: Patients with pituitary tumors and/or galactorrhea have complete evaluation of their pituitary function by standard methods (thyroid and adrenal function studies, growth hormone stimulation and suppression). Following this, tests of prolactin release (TRH test, chlorpromazine stimulation, breast stimulation, sleep and of prolactin suppression (L-dopa, water loading) are performed. Prolactin is measured in an immunoassay by Dr. A.G. Frantz, Columbia University College of Physicians and Surgeons, New York, N.Y.

Progress & Results: Study of 29 patients with galactorrhea and/or pituitary tumors reveal that basal prolactin determinations correlated better with the presence of a pituitary tumor than all of the stimulatory and suppressive manipulations. A small but statistically significant rise in mean prolactin was found in 10 normal men and 11 normal women one half hour after ingestion of a water load. There was no effect of intravenous infusion of either hypotonic or hypertonic saline. Water loading was shown to also have no effect on elevated TSH and PRL levels or the response to TRH in patients with primary hypothyroidsm.

Conclusions: Basal prolactin concentrations are more useful than other methods of differentiating between tumorous and non-tumorous galactorrhea. TRH and chlorpromazine testing are effective means of establishing the integrity of the pituitary and hypothalamic pituitary interactions. Water loading studies did not support a physiologic role for prolactin in the short term regulation of plasma osmolality in normal or hypothyroid subjects.

Funding Utilized FY 77: None

Funding Requested FY-78:

Personnel:	$ 465
Supplies:	250
Printing, misc.:	250
Nichols Contract:	750
Equipment:	250
TOTAL	$1,965

Publications:

1. Adler, R.A., G.L. Noel, L. Wartofsky, and A.G. Frantz. Failure of Oral Water Loading and Intravenous Hypotonic Saline to Suppress Plasma Prolactin in Man. J. Clin. Endocrinol. & Metab., 41:383-389, 1975.

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.

Type of Report: Interim

Work Unit No.: 1320

Title of Project: Effect of Lilly Compound 83636 on Plasma Prolactin in Humans

Investigators:

Principal: Jerry M. Earll, M.D., COL, MC

Associates: Marcus Schaaf, M.D.
Andrew G. Frantz, Columbia Presbyterian Medical Center,
Chief of Physicians & Surgeons, Columbia University, New York, N.Y.

Objectives: 1) To study the ability of Lilly Compound 83636 (Lergotrile Myselate) to lower growth hormone and prolactin and to improve clinical manifestations in patients with pituitary tumors causing acromegaly.
2) To study the growth hormone & prolactin response to TRH before and during Lergotrile treatment.

Technical Approach: Patients with acromegaly were hospitalized on the Kyle Metabolic Unit on a constant calcium intake. Blood specimens for growth hormone and prolactin measurements were obtained before treatment with Lergotrile during a standard TRH test and on another day every 2 hours for a 24 hour period of unrestricted ward activity. Blood specimens for growth hormone and prolactin measurements were also obtained over a 3 hour period following the initial dose of Lergotrile, 0.5 mg orally, and again 3 and 7 days later as the dose was gradually increased to 1.0 mg and 2.0 mg. TRH test and blood sampling every 2 hours over a 24 hour period was repeated on full dosage, 2.0 mg every 8 hours orally. Clinical parameters of growth hormone activity (Nerve conduction, ring size, hand volume and urinary calcium excretion) were measured before and during Lergotrile. Some patients were discharged to continue the drug as outpatients with re-evaluation at 2 to 4 week intervals.

Progress & Results: Ten acromegalic patients have been studied. Partial or complete results are available on eight. Lergotrile caused a 66 to 96% reduction in growth hormone by 2 1/2 hours at each dosage increment in 5 patients and was ineffective in two. Growth hormone profiles by 2 hour sampling over a 24 hour period showed significant reduction in 4 of 6 patients. TRH response of growth hormone was not modified by Lergotrile. Prolactin was elevated in only 1 patient and this was decreased 79% to normal range by Lergotrile. Chronic out-patient treatment with periodic re-hospitalization was conducted in 5 patients, and showed a sustained drug effect.

Conclusions: Compound 83636 (Lergotrile myselate) is an effective agent to lower growth hormone and prolactin in acromegaly.

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Funds Utilized FY-77:

Personnel:	$1,603
Supplies:	500
Reprints:	-
Audio-Visual:	-
Xerox, misc:	100
Isotopes:	-
Contracts:	-
Consultants:	-
Loose Issue:	-
Non-exp. supplies:	-
Animals:	-
Travel:	-
Equipment:	-
Total	$2,203

Funds Requested FY-77:

Personnel:	$1,767
Supplies:	1,000
Reprints:	-
Audio-Visual:	250
Xerox, misc:	100
Isotopes:	-
Contracts:	-
Consultants:	-
Loose Issue:	-
Non-exp. supplies:	-
Animals:	-
Travel:	-
Equipment:	-
Total	$3,117

Publications: None

Type of Report: Interim

Work Unit Number: 1321

Title of Project: Effects of Cancer Chemotherapy Agents on Endocrine Function

Investigators:

Principal: COL Jerry M. Earll, MC

Associates: None

Objectives: To evaluate the effects of modern cancer chemotherapy on endocrine function.

Technical Approach: Patients receiving standard protocol approved drugs have their endocrine function tested before and after treatment. No change is made in the patients usual management for malignancy.

Progress and Results: Five patients have had evaluation of their adrenal function following completion of either one or two courses of chemotherapy. Two other patients had been entered in the study but became ill with hepatitis. No significant suppression of adrenal function was detected following the early courses of chemotherapy. A pronounced hyperzincuria occurred within 24 hours of the administration of most chemotherapeutic agents while serum zinc levels remained stable.

Conclusions: Preliminary results suggest minimal if any significant impairment of adrenal function following initial courses of chemotherapy. The immediate hyperzincuria following certain chemotherapeutic agents may reflect drug toxicity upon tumor and normal tissue cells at a time much sooner than traditional concepts would suggest. Principal investigator changed duty positions during the last year and there has not been further progress in this project. Further study of the mechanism of changes in zinc and their clinical implications are being considered.

Funds Utilized 1977:

Personnel:	$388
Supplies:	500
TOTAL	$888

Funds Requested 1978:

Personnel:	$660
Supplies:	400
TOTAL	$1,060

Publications: None

Type of Report: Interim

Work Unit No: 1329

Title of Project: Lithium Effects on Thyroid Gland

Investigators:

Principal: Kenneth D. Burman, MAJ, MC

Associates: L. Wartofsky, LTC, MC, R.C. Dimond, MAJ, MC, J.M. Earll, COL, MC

Objective: Lithium and iodine^{3} have been demonstrated to have antithyroid effects in hyperthyoid individuals. Both agents inhibit thyroid secretion and, as a result, produce a decrease in circulating levels of triiodothyronine (T_3) and thyroxine (T_4). Euthyroid subjects are more resistant to the antithyroid effects of these ions, and hence only a small percentage of normal individuals given these drugs will become hypothyroid, a process which usually requires many months of drug administration. Recently it has become apparent that subjects with a history of thyroid abnormalities such as diffuse toxic goiter or Hashimoto's thyroiditis may be extremely sensitive to the antithyroid effects of iodine even though they may be euthyroid prior to the administration of this drug. Braverman et al., demonstrated that a majority of such individuals become hypothyroid after only three to six weeks of therapy and iodine. The purpose of the present study was to determine if patients rendered euthyroid following the treatment of diffuse toxic goiter would be similarly sensitive to the antithyroid effects of lithium. Such a finding might give further insight into the mechanisms of both lithium and iodine induced hypothyroidism, and would delineate a group of patients to whom lithium should be administered with caution. The measurement of 3,3',5'-triiodo-L-thyronine (reverse T_3, rT_3) as well as T_3 and T_4 in the present group of patients was performed to help determine whether lithium was having a direct effect on thyroidal secretion or whether the drug was influencing the peripheral conversion or degradation of T4.

Technical Approach: Seven patients (three men, four women; average age 37 years, range 27-43) who had been euthyroid for an average of eleven months following radioiodine (six patients) or antithyroid (patient 7) treatment of diffuse toxic goiter were studied (number of months euthyroid without medication: 1, 6; 2, 12; 3, 13; 4, 3; 5, 17; 6, 15; 7, 10). Initially, all patients were considered to be euthyroid based upon clinical evaluation, normal serum T_4, and normal radioiodine uptake by the thyroid gland. The thyroid glands of all patients were initially estimated to be less than 40 g. The study protocol was divided into a control period which lasted 1-3 days, a post-treatment period which lasted 1-7 days, and an experimental period which lasted 4-7 weeks. Patients 6 and 7 received lithium for 5 and 4 weeks, respectively; the remaining 5 patients

Technical Approach: 1, 2, 3, 4, 5) were administered lithium for 7 weeks. During the experimental period, 300 mg lithium carbonate was administered orally three times daily, a dose sufficient to maintain the serum lithium level between 0.50 mEq/l and 1.0mEq/l. During the control and post-treatment periods, the patients received no medications. At approximately weekly intervals, blood was drawn 0800 and 1000 h for the determination of serum thyrotropin (TSH), T_3, T_4, and rT_3. After lithium had been discontinued, 500 µg thyrotropin-releasing hormone (TRH) was administered iv to six of the seven subjects. Each hormone measurement for an individual patient was analyzed in a single assay after the termination of the study. Serum TSH was determined in duplicate by radioimmunoassay as previously described (normal range, <1-5 µU/ml); serum T_3 was determined in triplicate by a modification of the method of Chopra et al, utilizing antisera obtained from Dr. D. Mayes, Endocrine Sciences, Tarzana, California (normal range, 60-185 µg/100 ml); and serum T_4 was measured in duplicate by the RIA-MAT™ Circulating T_4 ^{125}I-Kit (Mallinckrodt Inc., St. Louis, Missouri; normal range, 4.5-12.0 µg/100 ml). Serum rT_3 was measured in duplicate by radioimmunoassay utilizing a rabbit antiserum directed against the L form of the hormone which had been kindly supplied by Dr. Hans Cahnmann, National Institutes of Health, Bethesda, Maryland. Serum was analyzed directly without extraction by the addition of 300 µg 8-anilino-1-naphthalene sulfonic acid to each assay tube. This antiserum does not cross react with various thyroid hormone analogues including 1000 ng/100 ml T_3 and 20 µg/100 ml T_4. The intra-assay coefficient of variation throughout the standard curve is less than 3%. The normal range (mean ± 2 SD) in our laboratory is considered to be 36-84 ng/100 ml. Thyroglobulin and microsomal thyroid anti-bodies were measured by use of Sera-Tek Test Kits (Ames Co., Div. of Miles Lab., Inc., Elkhart, Indiana).

Progress & Results:

SENSITIVITY TO LITHIUM

Serum T_3* T_4†, and reverse T_3‡ concentrations before, during, and after lithium administration in 7 patients rendered euthyroid following treatment of diffuse toxic goiter

Patient	Pre-treatment§	Week of lithium administration							Post-treatment¶
		1	2	3	4	5	6	7	
					Triiodothyronine				
1	160	164	99	99	97	104	111	83	108
2	—	150	—	143	128	146	—	170	212
3	123	73	95	100	119	—	87	77	133
4	189	127	118	98	93	90	99	137	162
5	65	102	165	129	120	90	73	111	133
6	73	—	98	100	99	107	—	—	—
7	169	110	91	108	133	—	—	—	174
Mean	130	121	111	111	112	107	92	116	154
SE	21	14	11	7	6	10	8	17	15
					Thyroxine				
1	6.3	4.7	5.4	3.9	2.5	3.1	3.5	—	6.8
2	7.3	—	6.6	6.3	6.4	6.8	—	7.2	7.3
3	7.9	7.6	6.2	5.1	4.8	—	6.1	—	7.3
4	9.4	4.4	4.0	3.4	3.2	3.3	5.5	5.5	9.3
5	6.4	7.6	5.4	4.5	4.6	4.8	4.9	5.3	6.9
6	6.9	—	6.9	6.1	6.9	7.6	—	—	—
7	8.8	7.0	5.9	5.8	5.9	—	—	—	8.7
Mean	7.6	6.3	5.8	5.0	4.9	5.1	5.0	6.0	7.7
SE	0.4	0.7	0.4	0.4	0.6	0.9	0.6	0.6	0.4
					Reverse T_3				
1	65	59	65	41	32	43	50	—	—
2	—	60	—	64	63	67	—	62	60
3	56	47	45	46	16	—	34	44	46
4	68	55	38	31	30	32	39	52	64
5	15	39	38	29	33	—	30	34	56
6	44	—	50	45	34	46	—	—	—
7	41	45	18	16	22	—	—	—	45
Mean	48	51	42	39	33	47	38	48	54
SE	8	3	6	6	6	8	4	6	4

* Normal range, 60–185 ng/100 ml.
† Normal range, 4.5–12.0 μg/100 ml.
‡ Normal range, 36–84 ng/100 ml.
§ 1–3 days duration.
¶ 1–7 days duration.

Conclusions: In the present study, patients rendered euthyroid following treatment of diffuse toxic goiter demonstrated sensitivity to the antithyroid effects of lithium, a finding similar to previous experiments employing iodine.

Funding FY 77:

Personnel:	$2,519
Loose issue, etc.:	500
Supplies:	2,000
Isotopes:	3,000
Xerox, misc.:	200
Printing, Reprints, Page Costs, etc.:	1,000
Nichols Contract:	1,000
Equipment:	1,000
Travel:	-0-
	$11,219

Funding FY 78:

Personnel:	$2,635
Loose issue, etc.:	650
Supplies:	2,200
Isotopes:	2,000
Xerox, misc.:	300
Printing, Reprints, Page Costs, etc.:	1,000
Nichols Contract:	1,000
Equipment:	1,500
Travel:	-0-
	$11,285

Publications: Burman, K.D., Dimond, R.C., Wright, F.D., and L. Wartofsky: Sensitivity to Lithium in Treated Graves' Disease: Effects on serum T4, T3, and reverse T3. JCEM 43:606, 1976.

Burman, K.D., Dimond, R.C., Wright, F.D., and L. Wartofsky. Sensitivity to Lithium, Presented at the 501th annual meeting of the American College of Physicians, Philadelphia, Pennsy. April 1976.

Type of Report: Interim

Work Unit No.: 1330

Title of Project: Thyroid function in patients with Klinefelter's Syndrome.

Investigators:

Principal: Kenneth D. Burman, M.D., MAJ MC

Associates: Leonard Wartofsky, M.D., LTC MC
G.L. Noel, M.D.
Richard C. Dimond, M.D., LTC MC
Jerry M. Earll, M.D., COL MC

Objective: To ascertain if thyroid function is abnormal in patients with Klinefelter's syndrome.

Technical Approach:

Six patients (average age 33, range 18-59) with chromatin positive Klinefelter's syndrome were studied prior to and after an average of 8 months of testosterone therapy. The karyotype in all patients was 46 XXY as determined in circulating leukocytes. All patients had small testes, evidence of decreased androgenicity, and patients R.D., M.G., and B.K., had gynecomastia. Each patient received monthly injections of 300 to 1,000 mg testosterone enanthate following their initial evaluation, with the last injection approximately 2 weeks prior to reexamination. All patients were clinically euthyroid, had normal thyroid glands by palpation, and were healthy throughout the study, except for patient M.G. who had infectious mononucleosis four weeks prior to his initial TRH test. Patients B.K. and R.S. had each received testosterone therapy previously for one year, but treatment had been discontinued 7 months and 3 months, respectively, prior to this study.

Progress & Results:

Hormone measurements in 6 patients with Klinefelter's Syndrome before and after testosterone therapy

Testosterone therapy	Testosterone (ng/100 ml)	T_3 (ng/100 ml)	RT_3U (%)	T_4 (μg/100 ml)	FT_4 (ng/100 ml)	TBG (mg/100 ml)	Antibodies*	FSH (mIU/ml)	LH (mIU/ml)	Estradiol (pg/ml)
Normal values	>300	80-220	35-45%	5-13	1.5-4.0	2.0-4.8	absent	<1-15†	<1-15†	10-50†
R.D.										
Before	554	172	46	7.0	2.0	2.8	absent	19.3	21.8	47
After	1,216	140	48	5.6	1.4	3.0		1.6	0.8	77
W.B.										
Before	477	132	40	6.8	1.7	3.1	absent	58	5.6	30
After	944	122	42	6.1	1.8	2.9		15.9	16.7	28
N.M.										
Before	538	118	43	5.6	1.5	2.2	absent	23.9	20.7	<20
After	945	124	46	5.6	1.6	2.7		1.8	1.2	24
R.S.										
Before	424	96	41	5.5	2.5	2.6	absent	42.2	55.8	30
After	2,032	116	41	6.0	1.6	2.6		36.4	38.1	48
B.K.										
Before	238	114	33	7.2	2.4	3.2	absent	28.7	14.3	31
After	828	118	35	7.4	1.9	3.6		19.6	10.3	24
M.G.										
Before	609	106	38	9.4	2.6	4.5	absent	65.4	35.2	52
After	2,122	110	40	6.6	1.9	3.4		35.5	31.4	42
Before testosterone										
Mean	473	123	40.2	6.9	2.1	3.0	0/6	39.6	23.6	35.0
SE	± 53	± 10	± 1.8	0.6	± 0.2	± 0.3	—	± 7.7	± 7.2	± 4.9
After testosterone										
Mean	1,351	121	42.0	6.2	1.7	3.0	—	18.5	16.4	40
SE	± 238	± 4	± 1.9	± 0.3	± 0.1	± 0.2	—	± 6.3	± 6.3	± 8.3
Paired t test	<.02	NS	<.025	NS	NS	NS	—	<.02	NS	NS

* Includes results of immunofluorescent analysis for autoantibodies to thyroid gland colloid, cytoplasm, and mitochondria as well as results of analysis by hemagglutination for the presence of autoantibodies to thyroglobulin.

Conclusions:

In the present study, RAIU, TSH stimulation tests, serum T3, T4, FT4, TBG, RT3U, and TSH response to TRH were normal prior to and after long term testosterone therapy. Treatment had no significant effect on any of these parameters except for the RT3U.

Funds Utilized FY-77:

Personnel	$ 184
Expendable supplies	200
Reprints, printing	600
Audio-Visual	-
Xerox; office supplies	100
Isotopes	-
Lab contracts	-
Loose issue, non-expendable	-
Animals	-
Travel	-
Equipment	280
TOTAL	$1,364

Funding Requested FY-78: None

Publications:

1. Burman, K.D., R.C. Dimond, G.L. 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. JCEM 41:1161, 1975.

Type of Report: Final

Work Unit No.: 1331

Title of Project: Effect of Iodine and Lithium on the Release of Thyroxine from the Thyroid Gland of Patients with Thyrotoxicosis

Investigators:

Principal: Timothy M. Boehm, MAJ MC

Associates: K. D. Burman, MAJ MC, L. Wartofsky, LTC MC

Objective: Both lithium and iodine block thyroidal secretion and lead to clinical improvement in patients with thyrotoxicosis. This study is designed to examine whether a synergistic effect can be demonstrated by administration of both agents.

Technical Approach: ^{125}I and T_4 ^{131}I are given to label the thyroid and peripheral pools respectively. Blood is drawn bidaily and urines collected 12 hourly during 5 day control periods and during two 5 day treatment periods with either lithium or iodine followed by both drugs.

Progress and Results: 18 patients have completed study; lithium and iodine are comparably efficacious agents in blocking thyroidal release. Additional therapeutic benefit was observed if lithium was added to iodine therapy but not if iodine was added to lithium. This "Conditional" synergism was observed regardless of whether methimazole was employed. Further studies are underway to ascertain whether this "synergism" is a cumulative benefit of iodine administration.

Conclusions: Lithium and iodine appear to be conditionally synergistic and may mechanistically affect different aspects of thyroidal release.

Funds Utilized, FY-77:

1. Personnel	$ 1,700.00
2. Supplies	1,000.00
3. Audio-Visual	500.00

4. Xerox, Misc.	$	200.00
5. Isotopes		2,500.00
6. Loose Issue		250.00
7. Travel		500.00
Total:	$	6,650.00

Funding Requested, FY-78:

1.. Personnel		2,844.00
2. Supplies		800.00
3. Printing		600.00
4. Audio-Visual		250.00
5. Xerox, Misc		200.00
6. Isotopes		500.00
Total:	$	5,194.00

Publications: Manuscript currently submitted to Journal of Clinical Investigation.

Type of Report: Interim

Work Unit No.: 1332

Title of Project: Differentiation of Benign from Malignant Thyroid Nodules: Assessment of New Diagnostic Techniques.

Investigators:

Principal: Charles Smith, MAJ, MC

Associates: Leonard Wartofsky, LTC MC, Robert Corcoran, MAJ, MC

Objectives: To attempt to differentiate benign from malignant thyroid nodules by use of the routine I^{131} and Technetium ^{99}m scans plus newer diagnostic techniques including ultrasonography, fluourescent scanning and needle biopsy.

Technical Approach: 50-75 patients with solitary thyroid nodules will have the diagnostic tests mentioned under objectives which will be correlated with findings at surgery in hope of preventing the number of patients requiring the latter.

Progress & Results: 52 patients have been included in the study thus far with 31 having gone to surgery. Thus, there are too few patients to draw meaningful conclusions. Reassignment of principal investigator has slowed progress.

Conclusions: None

Funds Utilized FY-77:

Personnel:	$ 184
Exp. Supplies:	250
Reprints, printing:	-
Audio-Visual:	-
Xerox; office supp.:	100
Isotopes:	-
Lab Contracts:	500
Loose Issue, non-exp.:	250
Animals:	-
Travel:	-
Equipment:	-
Total	$1,284

Funds Requested FY-78:

Personnel:	$ 280
Exp. Supplies:	250
Reprints, printing:	500
Audio-Visual:	500
Xerox; office supp.:	100
Isotopes:	-
Lab Contracts:	500
Loose Issue, non-exp.:	250
Animals:	-
Travel:	-
Equipment:	250
Total	$2,630

Publications: None

Type of Report: Interim

Work Unit No.: 1334

Title of Project: The Regulation of Extrathyroidal Conversion of Thyroxine (T4) to Triiodothyronine (T3).

Investigators:

Principal: Kenneth D. Burman, M.D., MAJ MC

Associate: Leonard Wartofsky, M.D., LTC MC

Objective: To determine if T4 regulates its own conversion rates.

Technical Approach:

Patients who have been thyroidectomized for thyroid cancer and who are on fixed replacement doses of T4 will be studied. Conversion of T4 to T3 is calculated from the kinetics of disappearance of injected doses of ^{131}I-T4 and ^{125}I-T3. Conversion will be quantitated and compared while patients are receiving varied doses of T4 and/or T3 replacement.

Progress and Results:

9 patients have been studied and conversion rates are constant regardless of the T4 level.

Conclusion: T4 does not regulate T4 conversion.

Funds Utilized FY-77:

Personnel	$1,691
Supplies	1,000
Reprints-Audio Visual	500
Xerox, office	250
Isotopes	1,000
Nichols contract	500
Loose issue	250
Non-expendable supplies	200
Animals	0
Travel	1,000
Equipment	1,915
TOTAL	$8,306

Funds Requested FY-78:

Personnel	$1,714
Supplies	1,200
Reprints-Audio Visual	500
Xerox, office	200
Isotopes	800
Nichols contract	0
Loose issue	200
Non-expendable supplies	200
Animals	0
Travel	0
Equipment	750
TOTAL	$5,564

Publications:

1. Burman, K.D., R.C. Dimond, R.A. McGuire, J.M. Earll, D. Strum, and L. Wartofsky. The effect of varying serum T4 concentrations on extrathyroidal production of T3, reverse T3, and 3,3' diiodothyronine. Clin Res 24:270A, 1976.

Type of Report: Interim

Work Unit No.: 1335

Title of Project: Intestinal Bile Salt Clearance in Thyrotoxic Patients With and Without Diarrhea

Investigators:

Principal Investigator: MAJ Mark Donowitz, MC

Associate Investigator: MAJ Dean Kinsey, MC; LTC Leonard Wartofsky, MC; and MAJ Kenneth Burman, MC; MAJ Tim Boehm, MC

OBJECTIVES: To determine nature and quantity of bile salts in serum, jejunum (both fasting and post-prandially) and in stool in patients with and without diarrhea and hyperthyroidism.

TECHNICAL APPROACH: Serum was obtained fasting; stool is collected and frozen over a 3 day period; bile is collected by passing a single lumen tube overnight and in the morning prior to ingestion of food; fasting jejunal contents and jejunal contents following Freamine injection are obtained. These samples are extracted and studied quantitatively for bile salts by gas liquid chromatography.

PROGRESS AND RESULTS: (See abstract published in Gastroenterology 70: 902, 1976 and presented at annual meeting of American Gastroenterology Association, Miami, Florida, May 28, 1976 and manuscript submitted 5/77 to Lancet.

A sensitive and specific radioimmunoassay for conjugates of chenodeoxycholic acid was developed. Antiserum was developed in rabbits injected at weekly intervals for 8 weeks with glycochenodeoxycholic acid conjugated to Bovine Serum Albumin by the carbodiimide method. The displacement curve over the range of 4 to 80 p moles was linear when the percent binding was plotted against the natural log of the added concentration utilizing a 1:250 dilution of antibody.

The specificity of the RIA is illustrated by the relative amounts of pure conjugated bile acid standards required to displace 50% of bound ^{3}H-glycochenodeoxycholic acid with glycochenodeoxycholate as reference. The antibody has 400 times less affinity for glycocholate and 3000 times less affinity for glycodeoxycholate. There was equal reactivity between glycine and taurine conjugates and only 1 log difference with free chenodeoxycholic acid. The assay is thus capable of sensitive and specific measurements of conjugates of chenodeoxycholic acid in serum.

Ten patients with hyperthyroidism with pruritus and 5 without pruritus have been studied and compared to normal volunteers. 10 patients with hyperthyroidism without diarrhea and 2 with diarrhea have been studied. Patients with hyperthyroidism have a shift in their primary biliary bile acid from cholic acid to chenodeoxycholic acid. Patients with pruritus and hyperthyroidism have elevated serum chenodeoxy acid levels compared to controls which exceed that of normals. Hyperthyroid patients without pruritus have normal serum chenodeoxycholic acid levels. Following conventional treatment for hyperthyroidism with propylthiouracil, pruritus stops and serum chenodeoxycholic acid levels return towards normal. Patients with hyperthyroidism without diarrhea have normal total 72 hour stool salt excretion; patients with hyperthyroidism and diarrhea have an increased fecal bile salt excretion and cholestyramine dramatically caused a decrease in the diarrhea.

CONCLUSIONS:

a). Serum chenodeoxycholic levels can be measured by a sensitive specific radioimmunoassay.

b). Patients with hyperthyroidism have an increase in biliary chenodeoxycholic acid.

c). Pruritus is a common symptom in hyperthyroidism.

d). Serum chenodeoxycholic levels are increased in hyperthyroid patients with pruritus.

e). Medical treatment of hyperthyroidism is associated with resolution of pruritus and return of serum chenodeoxycholic levels towards normal.

f). An increase in colonic dihydroxy bile salts may be the cause for the diarrhea seen in hyperthyroidism.

FUNDING REQUIREMENTS:

Personnel: None

Equipment: All supplied by Investigator's laboratories at WRAIR.

FUNDING REQUESTED:

None

PUBLICATION: Gastroenterology 70: 902, 1976; Lancet - submitted (1) and in preparation (1)

TYPE OF REPORT: Completed - due to principal investigator leaving military.

Work Unit No.: 1336

Title of Project: Effects of Continuous Infusion of TRH on Growth Hormone Secretion in Acromegaly.

Investigators:

Principal: Richard C. Dimond, M.D., LTC, MC

Associates: D. Corrigan, M.D., LTC, MC, L. Wartofsky, M.D., LTC, MC

Objectives: To examine the pattern of growth secretion in patients with acromegaly during continuous infusion of TRH.

Technical Approach: TRH is administered intravenously by constant infusion at a rate of 1 microgram/min for 4 hours and then by a 500 microgram bolus injection with blood samples obtained serially. Total growth hormone concentration is measured by radioimmunoassay; components of circulating growth hormone are measured by gel chromatography and radioimmunoassay.

Progress & Results: TRH was unavailable for clinical studies during the last 1 1/2 years and only recently has again become available for such studies. Only four patients have been studied. Therefore, the data is incomplete and insufficient to draw any conclusions.

Conclusions: None

Funds Utilized FY-77:

Personnel:	$ 600
Supplies:	250
Reprints:	-
Audio-Visual:	-
Xerox, Misc.	-
Isotopes:	-
Contracts:	-
Consultants:	-
Loose Issue:	-
Non-exp. supplies:	-
Animals:	-
Travel:	-
Equipment:	-
Total	$ 850

CONTINUED

Funds Requested FY-78:

Personnel:	$1,432
Supplies:	500
Reprints:	-
Audio-Visual:	300
Xerox, misc:	100
Isotopes:	150
Contracts:	600
Consultants:	-
Loose issue:	150
Non-exp. supplies:	-
Animals:	-
Travel:	-
Equipment:	-
Total	$3,232

Publications: None

Type of Report: Interim

Work Unit No.: 1337

Title of Project: Growth Hormone Responses to TRH in Acromegaly

Investigators:

Principal: Richard C. Dimond, M.D., LTC, MC

Associates: D. Corrigan, M.D., LTC, MC, L. Wartofsky, M.D., LTC, MC, M. Schaaf, M.D., and J.M. Earll, M.D., COL, MC

Objective: Assess the inhibitory effects of thyroid hormone, glucose and L-Dopa on the abnormal growth hormone response to TRH in acromegaly.

Technical Approach: Standard TRH stimulation tests after administration of thyroid hormone, during a constant infusion of glucose, and after the administration of L-Dopa.

Progress & Results: TRH was unavailable for clinical studies during the last 1 1/2 years and only recently has again become available for such studies. Only five patients have been studied. Therefore, the data is incomplete and insufficient to draw any conclusions.

Conclusions: None

Funds Utilized FY-77:

Personnel:	$ 600
Supplies:	200
Reprints:	-
Audio-Visual:	-
Xerox, misc:	-
Isotopes:	-
Contracts:	-
Consultants:	-
Loose Issue:	-
Non-exp. supplies:	-
Animals:	-
Travel:	-
Equipment:	-
Total	$ 800

CONTINUED

Funds Required FY-78:

Personnel:	$1,432
Supplies:	500
Reprints:	-
Audio-Visual:	300
Xerox, misc:	100
Isotopes:	150
Contracts:	600
Consultants:	-
Loose issue:	-
Non-exp. supplies:	150
Animals:	-
Travel:	-
Equipment:	-
	Total $3,232

Publications: None

Type of Report: Interim

Work Unit Number: 1338

Title of Project: Hormonal and Metabolic Changes in Hypertension

Investigators:

Principal: Jerry M. Earll, M.D.

Associate: Marcus Schaaf, M.D.

Objectives: Normal and low renin group of hypertensive patients would be studied metabolically to determine if there were any alterations of body composition suggestive of "Unidentified" mineral corticoid substances.

Technical Approach: Hypertension patients would receive a standard workup with careful screening to categorize them as to whether they were normal or low renin groups. The low renin patients were to be matched carefully by age to a normal renin hypertension patient. Whole body composition with emphasis on potassium determinations in a whole body counter were to be made. Five hypertension patients have been studied. Difficulty has been encountered in obtaining the low renin hypertension group for study. Six patients had basal prolactin levels studied while on low salt and high salt diets and following diuretic stimulation. There was no significant change in basal prolactin during these manipulations. Difficulty with operation of the whole body counter and changing priorities in the department restricted any further progress.

Conclusion: In spite of some animal evidence to indicate that prolactin may be an important hormone in manipulating salt and water metabolism, major changes in sodium intake have failed to stimulate or surpress prolactin. In addition, therapy with a potent diuretic failed to stimulate prolactin. No data is available for additional conclusions at this time.

Funds Utilized 1977:

Personnel:		$184
Supplies:		600
Isotopes:		150
	TOTAL	$934

Funds Requested 1978:

Personnel:		$660
Supplies:		600
Isotopes:		250
	TOTAL	$1,510

Publications: None

Type of Report: Interim

Work Unit No.: 1339

Title of Project: Effect of Lithium on Intrathyroidal Iodine Content

Investigator:

Principal: Timothy M. Boehm, MAJ MC

Objective: To ascertain whether chronic lithium therapy in psychiatric patients alters intrathyroidal iodine

Technical Approach: To utilize the fluorescent scanner to measure intrathyroidal iodine content in patients receiving lithium therapy.

Progress and Results: Preliminary studies have been completed in 3 patients; apparently some patients receiving chronic lithium have elevated intrathyroidal iodine. The pace of the study has been slowed because of the geographic separation of Forest Glen from the Main Hospital and limited availability of psychiatric patients. Because of unavailability of patients, no further patients were entered onto study in FY-77. An attempt will be made to reinstitute the study when the new hospital is opened.

Conclusions: None

Funds Utilized, FY-77: None

Funding Requested, FY-78:

1. Personnel	$	660.00
2. Supplies		400.00
3. Non-expendible		100.00
4. Printing, etc.		300.00
Total:		1,460.00

Publications: None

Type of Report: Interim

Work Unit No.: 1340

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

Principal Investigator: Charles Smith, MAJ, MC

Associate Investigators: Leonard Wartofsky, LTC, MC, Kenneth D. Burman, MAJ, MC, Robert Corcoran, 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: Ten to 20 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 iodide (I_s), thyroidal ^{127}I (I_t) by flourescent scan. In addition, two twenty four hour hour urines/week will be collected and twenty four 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: Only 3 patients have been studied to date largely due to the transfer of the former principal investigator. Studies will be resumed in August 1977 and should be completed within 2 years.

Conclusions: None yet.

Funds Utilized FY-77:

Personnel:	$ 277
Supplies:	350
Reprints:	-
Audio-Vis:	-
Xerox, Misc:	100
Isotopes:	-
Lab Contracts:	-
Consultants:	-
Loose Issue:	-
Non-exp. supplies:	-
Animals:	-
Travel:	-
Equipment:	-
TOTAL	$ 727

Funds Requested FY-78:

Personnel:	$ 660
Supplies:	400
Reprints:	300
Audio-Vis:	250
Xerox, Misc:	100
Isotopes:	500
Lab Contracts:	-
Consultants:	-
Loose Issue:	250
Non-exp. supplies:	-
Animals:	-
Travel:	400
Equipment:	-
TOTAL	$2,860

Publications: None

Type of Report: Interim

Work Unit Number: 1342

Title of Project: Dietary Influence on Prolactin Secretion

Investigators:

Principal: Jerry M. Earll, COL, MC

Associates: Marcus Schaaf, M.D., Kenneth Burman, MAJ, MC

Objectives: To evaluate changes in hormone secretion during alterations of carbohydrate and fat in the diet. Emphasis is being placed upon prolactin, growth hormone and thyroid hormone changes.

Technical Approach: Obese patients will be admitted to the metabolic ward where baseline studies will be performed prior to a high fat and low carbohydrate diet. Following these dietary manipulations, some patients will undergo fasting episodes.

Progress and Results: Principal investigator changed duty positions forcing this project into a very low priority. No progress has been made during the past year. Request project be kept open for one more year.

Conclusions: No laboratory data has been completed yet.

Funds Utilized 1977:

Personnel:	$184
Supplies:	200
TOTAL	$384

Funds Requested 1978:

Personnel:	$660
Supplies:	400
TOTAL	$1,060

Publications: None

Type of Report: Interim

Work Unit No.: 1345

Title of Project: Conversion of Testosterone to Estradiol

Investigators:

Principal: Kenneth D. Burman, M.D., MAJ, MC

Associates: A.G. Glass, M.D., MAJ, MC, D. Lynn Loriaux, M.D., R. Vigersky, M.D., MAJ, MC and L. Wartofsky, M.D., LTC, MC

Objectives: To determine if conversion of Testosterone to Estradiol is unvaried in Klinefelters Syndrome.

Technical Approach: Injection of Radiolabeled testosterone and estradiol.

Progress & Results: No patients yet studied.

Conclusions: None

Funds Utilized FY-77: None

Funds Requested FY-78:

Personnel:	$2,244
Exp. Supplies:	500
Reprints, printing:	-
Audio-Visual:	-
Xerox, office supp.:	100
Isotopes:	350
Lab Contracts:	2,000
Loose Issue, non-exp.:	-
Animals:	-
Travel:	300
Equipment:	3,000
TOTAL	$8,494

Publications: None

Type of Report: Interim

Work Unit No.: 1346

Title of Project: Thyroid Function Tests in Cord Blood, Maternal Sera and Amniotic Fluid.

Investigators:

Principal: Kenneth D. Burman, M.D., MAJ, MC

Associates: J. Read, M.D., MAJ MC
W. Patow, M.D., COL MC
Frances D. Wright
Leonard Wartofsky, M.D., LTC MC

Objectives:

In order to assess fetal function at term, we have investigated parameters of thyroid hormone secretion and degradation in human amniotic fluid and in cord and maternal sera at delivery. The parameters measured included 3,3' L-diiodothyronine (3,3'T2), 3,3',5'-triiodothyronine (rT3), 3,3',5-triiodothyronine (T3), thyroxine (T4), dialyzable T3 and T4, thyroxine binding globulin (TBG), and total iodine.

Technical Approach:

Maternal sera was obtained from healthy euthyroid pregnant women within 15 minutes from delivery. Throughout their pregnancy, none of the subjects had taken medications known to influence thyroid hormone parameters, all deliveries were transvaginal and uncomplicated and all patients were in their thirty-eighth to fortieth week of pregnancy. This study was approved by the hospital medical research review committee and each patient gave informed consent. Furthermore, only patients who were going to require iatrogenic rupture of their amniotic fluid sac were studied. Sterile amniotic fluid was obtained prior to delivery by aspiration with an #18 gauge needle under direct vision. Rupture of the amniotic fluid sac was usually performed between 2 and 6 h prior to delivery. Thyroid hormone parameters in cord serum were measured in the same samples that were routinely obtained to determine blood type incompatibility.

T4 measurements were determined in duplicate by a radioimmunoassay which utilized 10 ul of unknown sample and polyethylene glycol for phase separation; 10 ul of hypothyroid sera were incorporated in the standard curve. T3 concentrations were determined by three radioimmunoassay systems. The assay performed at the Nichols Institute for Endocrinology, San Pedro, CA, employed the method of Chopra, et al. and utilized 250 ul of unknown sample or standard, 250 ul of hypothyroid sheep serum in each tube of the standard curve, and goat anti-rabbit antibody for phase separation. Samples for T3 determinations were assayed in duplicate. T3 was also measured in our laboratory in all unknown samples utilizing either the RIA-MAT™ Circulating T3 ^{125}I Kit (Mallinckrodt, Inc., St. Louis, MO) or a system employing T3 antiserum obtained from Dr. D. Mayes, Tarzana, California.

Reverse T3 concentrations were determined by the use of a rabbit antiserum (#152) generated in our laboratory against a bovine serum albumin and L-3,3',5'-triiodothyronine conjugate. The rT3 assay utilized 100 ul unknown or serum, 200 ul "premix", 100 ul serum rendered low in rT3, and 100 ul antiserum (working dilution 1:1000; final dilution 1:5000). The "premix" contains 75 mg ANS, 50 ml 0.2M borate

buffer (pH 8.5) containing 0.5% (w/v) bovine serum albumin, and approximately 10-15 pg/200 ul ^{125}I-rT3. The bound and free fractions of radioiodinated tracer were separated by ammonium sulfate precipitation.

3,3'T2 levels were measured by a radioimmunoassay which was performed in a manner similar to that of rT3, with the exception that 3,3'L-T2 was utilized in the standard solutions, ^{125}I-3,3'L-T2 was utilized as a radioactive antigen, and a specific antiserum to 3,3'L-T2 generated in our laboratory was employed in a final dilution of 1:1500.

The percent binding of ^{125}I-3,3'T2 to antiserum was similar regardless of whether 100, 200, or 300 ug ANS was added into each tube comprising the standard curve or into unknown serum samples.

The process of removing iodothyronines from serum was accomplished by the addition of 500 mg of Amberlite IRA-400 resin (Mallinckrodt, Inc., St. Louis, MO) per ml of sample, allowing this mixture to stir at room temperature overnight, and then decanting and freezing the serum. The efficiency of this procedure was evaluated by observing that serum treated in this manner after the addition of ^{125}I-T3, ^{125}I-L-rT3 or ^{125}I-L-3,3'T2 had final concentrations of these isotopes which were less than 1% of the original concentrations.

Dialyzable T3 and T4 were determined as described by Sterling and Brenner and TBG concentrations were measured by radioimmunoassay. Total iodine and RT3U determinations were performed by routine procedures.

When iodothyronine measurements were performed on amniotic fluid, resin-treated amniotic fluid rather than the customary hypothyroid human or sheep serum was incorporated into the standard curve. Alternatively, amniotic fluid specimens were lyophilized and then diluted to their original volume with buffer, distilled water, or serum rendered hypothyroid. Both of these methods resulted in similar final concentrations being obtained. Because large dilutions (approximately 1:2000) were required in the TBG radioimmunoassay, and because RT3U and iodine determinations were not thought to be affected by the nonspecific effects of amniotic fluid, the determinations of TBG in sera and amniotic fluid were performed at Nichols Institute in their customary fashion. All determinations for each measurement were performed in a single assay. For comparison, serum samples from 21 euthyroid healthy subjects (15 males, 6 females; mean age 33) on no medications were also analyzed.

Progress and Results:

TABLE 1. Amniotic fluid and maternal and cord serum levels (mean ± SE) of various thyroid hormone parameters

	Normal range in the serum of euthyroid adults (mean ± 2 SD)	Amniotic fluid	Cord serum	Maternal serum
Total T4 (μg/100 ml)	5–13	0.54 ± 0.07 (n = 5)	9.4 ± 0.5 (n = 12)	10.8 ± 0.4 (n = 12)
Per cent dialyzable T4 (%)	.020–.040	0.225 ± .02 (n = 4)	—	—
Total T3 (ng/100 ml)	60–220	30 ± 2 (n = 5)	30 ± 3 (n = 21)	150 ± 8 (n = 21)
Per cent dialyzable T3 (%)	0.238–0.418	1.72 ± 0.35 (n = 3)	—	—
Reverse T3 (ng/100 ml)	36–84	82 ± 25 (n = 9)	315 ± 16 (n = 5)	79 ± 5 (n = 7)
3-3'T2 (ng/100 ml)	7–29	20 ± 2 (n = 10)	20 ± 1 (n = 5)	27 ± 3 (n = 11)
Total iodine (μg/100 ml)	4–8	3.4 ± 0.2 (n = 9)	7.6 ± 0.4 (n = 10)	7.2 ± 0.7 (n = 9)
TBG (mg/100 ml)	2.0–4.8	0.3 ± 0.04 (n = 5)	5.1 ± 0.4 (n = 5)	8.6 ± 1.0 (n = 5)
Resin T3 uptake	0.85–1.10	0.55 ± .01 (n = 5)	—	—

Conclusions:

In the present study, amniotic fluid concentrations of T3, T4, and TBG were low, iodine and 3,3'T2 were relatively normal, and reverse T3 and per cent dialyzable T3 and T4 were increased when compared to serum levels in euthyroid adults. These results for T4, TBG, and per cent dialyzable T4 levels are similar to measurements obtained in previous studies. The elevations of amniotic fluid reverse T3 concentrations in the present study were comparable to those reported by Chopra and Crandall (93 ng/100 ml).

Funds Utilized, FY-77:

Personnel	$ 4,406
Supplies	1,500
Reprints	500
Audio-Visual	400
Xerox, miscellaneous	200
Isotopes	2,400
Contracts	1,800
Consultants	-
Loose issue	250
Non-expendable supplies	-
Animals	500
Travel	-
Equipment	4,675
TOTAL	$16,631

Funding Requirements FY-78:

Personnel	$ 3,695
Supplies	2,000
Reprints	400
Audio-Visual	250
Xerox, misc.	100
Isotopes	1,800
Contracts	1,500
Consultants	-
Loose issue	250
Non-expendable supplies	250
Animals	250
Travel	-
Equipment	7,000
TOTAL	$17,495

Publications:

1. Burman, K.D., J. Read, R.C. Dimond, D. Strum, F.D. Wright, W. Patow, and J.M. Earll, Measurements of reverse T3, 3,3'T2, T3, and T4 in human amniotic fluid and in cord and maternal serum. JCEM 43:1351, 1976.

2. Burman, K.D., J. Read, R.C. Dimond, D. Strum, F.D. Wright, W. Patow, and J.M. Earll, Measurements of reverse T3, 3,3'T2, T3, and T4 in human amniotic fluid and in cord and maternal serum. Presented, American College of Obstetricians, Dallas, TX, May 76. It was presented an award as the second best paper on the program.

Type of Report: Interim

Work Unit No.: 1347

Title of Project: Investigations into the Physiology of L-Reverse T3 (rT3) and L-3-3'-Diiodothyronine

Investigators:

Principal: Kenneth D. Burman, M.D., MAJ, MC

Associate: F.D. Wright, L. Wartofsky, M.D., LTC, MC

Objectives:

Although thyroxine (T4) metabolism may occur through several pathways, apparently the majority of this iodothyronine is degraded by peripheral deiodination. Through this process, T4 is monodeiodinated directly either to 3,5,3'-triiodothyronine (T3) or to 3,3',5'-triiodothyronine (reverse T3; rT3), and subsequently these triiodothyronines themselves may be degraded to less iodinated compounds. While the peripheral metabolism of T4 and T3 have been extensively studied, few kinetic studies have analyzed the metabolism of reverse T3 in euthyroid subjects and, to date, there are no published studies examining reverse T3 degradation in hyper- or hypothyroidism. With the recent development of sensitive radioimmunoassays for reverse T3, considerable interest has been generated in understanding the role of this hormone in thyroid physiology. The present study was therefore designed to examine the production rates, metabolic clearance rates, and serum half-lives of reverse T3 in euthyroid individuals and in patients with altered states of thyroid function.

Technical Approach:

Subjects

After written informed consent was obtained, nineteen patients participated in the study and were hospitalized on the Kyle Metabolic Unit. Six patients with untreated active hyperthyroidism, six hypothyroid patients, and seven clinically and biochemically euthyroid patients who were receiving appropriate replacement doses of L-thyroxine for treatment of underlying hypothyroidism were studied. No patient in any of these categories was receiving any medications known to affect thyroid hormone metabolism.

Materials

^{125}I-labelled reverse T3 (specific activity approximately 400-500 μCi/μg) was obtained from Abbott Laboratories, North Chicago, Illinois, through the courtesy of Mr. B.J. Green. Before administration, the ^{125}I-rT3 was diluted in normal saline containing 1% human serum albumin, and was then passed through a 0.22 μ Millipore filter. Unlabelled 3,3',5'-triiodothyronine, 3,3'-diiodothyronine, and 3'-monoiodothyronine were obtained through the courtesy of Dr. Hans Cahnmann, National Institutes of Health, Bethesda, Maryland.

Thin layer chromatography was performed using Eastman Kodak Silica Gel coated Chromagram sheets, with a solvent system containing acetone:tert-amyl alcohol:tert-butanol:NH_4OH:H_2O (80:10:10:10:10).

Kinetic Studies

In order to block uptake and secondary release of radioactive iodine by the thyroid gland, the hyperthyroid patients were given perchlorate, 200 mg every 8 hours for the duration of the experiment.

Approximately 25-50 μCi of ^{125}I-rT3 were administered as an intravenous bolus injection after baseline thyroid function tests had been obtained. Serum specimens were drawn every 30 minutes for 3 hours, and then every 2-3 hours for a total of 30 hours.

Processing of Samples

Serum samples were treated with Iobead™ Resin (Technicon Company, Tarrytown, NY) to remove free iodide and one ml of serum was counted in an Autogamma Spectrometer to obtain protein bound (PB-^{125}I) counts. One ml of serum was then mixed with 4 ml of acidified butanol, vortexed, and centrifuged (1000 x g for 10 minutes). The tubes were decanted and the precipitable radioactivity (non-extractable iodoproteins), was determined and subtracted from the PB-^{125}I counts to result in an estimate of radioactive iodothyronines in each sample. The radioactive counts were then expressed as percent of administered dose per liter of serum. All samples were counted to a statistical efficiency of < 5%.

Hormone Studies

Serum reverse T3 was measured in unextracted serum as previously described (14). Serum T4 and T3 were determined by the RIA-MAT™ Circulating T4 ^{125}I and T3 ^{125}I Kits (Mallinckrodt Inc., St. Louis, Missouri) and T3 resin uptake by the Thyrostat® -3 Diagnostic Test Kit (E.R. Squibb & Sons, Princeton, N.J.).

Data Analysis

In each case a plot of the percent administered dose at each sampling time was fit to a biexponential function using a weighted nonlinear regression program based on the Marquardt algorithm (16). The program was adapted for use in a Tektronix 4051 Graphics Calculator System. Several nonlinear functions were evaluated and that which most consistently "fit" the data from our subjects was the sum of two exponential terms:

$$C = Ae^{-\alpha t} + Be^{-\beta t}$$

where C = concentration (percent dose administered per liter of serum)
t = Time
A, B, α, β are parameters of the model equation

Parameter estimates obtained in this way were used to calculate metabolic clearance rates for each individual as follows:

$$MCR = \frac{D}{\int C dt} = \frac{D}{\frac{A}{\alpha} + \frac{B}{\beta}}$$

Production rates for rT3 were then computed by multiplying the metabolic clearance rate times the measured serum concentration.

$$PR = MCR \times rT3$$

Comparison of group means for clearance rates was made by simple one-way analysis of variance.

Progress and Results: See Table

Metabolic Clearance Rates in Hyperthyroid, Euthyroid, and Hypothyroid Subjects.

Subject	Age	Sex	Weight (kg)	T4 μg/dl	RT3U %	T3 ng/dl	rT3 ng/dl	Clearance Rate L/day	Clearance Rate L/day/70 kg	Production Rate μg/day	Production Rate μg/d/70 kg
Hyperthyroid											
1	27	F	57.3	22.1	41	510	239	126.4	154.4	302.0	368.9
2	26	M	77.1	16.7	40	470	121	236.2	214.4	285.8	259.5
3	36	F	49.4	23.0	43	415	162	153.2	217.0	248.1	351.6
4	27	F	56.0	26.6	37	490	252	108.2	135.3	272.8	341.0
5	20	F	77.8	14.7	42		90	213.1	191.8	191.8	172.6
6	45	F	70.0	15.2	33	155	58	232.0	232.0	134.6	134.6
Mean				19.7	39.3		153.7	178.2	190.8	239.2	271.4
± SE				±2.0	±1.5		±32.4	±22.9	±15.6	±26.1	±40.6
Euthyroid											
1	31	F	55.6	8.9	32	78	45	88.2	111.0	39.7	50.0
2	48	F	80	11.0	33	108	85	121.9	106.7	103.6	90.7
3	20	F	58.6	9.0	29	115	38	136.8	163.4	52.0	62.1
4	60	M	70.6	6.3	35	84	26	117.6	116.6	30.6	30.3
5	46	F	102.8	9.4	28	108	35	71.5	48.7	25.0	17.0
6	43	M	107.5	7.7	29	108	65	152.4	99.2	99.1	64.5
7	21	M	100	5.4	34	110	35	193.7	135.6	67.8	47.4
Mean				8.2	31.4	101.6	47	126.0	111.6	59.7	51.7
± SE				±0.7	±1.0	±5.4	±7.8	±15.3	±13.3	±12.0	±9.1
Hypothyroid											
1	63	F	62.3	2.6	20	70	<6	64.1	72.0	3.8	4.3
2	29	F	43.5	1.2	28	10	<6	38.9	62.6	2.3	3.8
3	53	F	70.0	1.1	30	52	7	104.4	104.4	7.3	7.3
4	54	F	71.3	<1	28	10	<6	53.3	52.8	3.2	3.2
5	48	F	80.6	<1	25	19	<6	80.6	70.0	4.8	4.2
6	29	F	58.6	2.0	20	20	<6	58.1	69.4	3.5	4.2
Mean				1.5	25.2	30.2	<6	66.6	71.9	4.2	4.5
± SE				±0.3	±1.8	±10.2		±9.4	±7.1	±0.7	±0.6

Conclusions:

The mean MCR of 111.6 L/day/70 kg in our euthyroid subjects is similar to the values of 97.1 L/day/70 kg recently reported by Gavin et al. and 96 L/day/70 kg reported by Einsenstein et al., although it is higher than the MCR reported by Chopra for both adult sheep (73.7 L/M^2/day) and humans (76.7 L/day/70 kg). The production rate of 51.7 µg/day/70 kg is higher than that reported by Gavin et al. (34.3 µg/day), probably due to the fact that our mean serum rT3 concentration was greater (47 ng/dl vs. 36.6 ng/dl). Chopra also reported a lower PR of 36.5 µg/day due to a lower MCR since mean serum rT3 concentration was comparable (48 ng/dl).

Previous studies have shown that serum concentrations of reverse T3 are elevated in hyperthyroid and decreased in hypothyroid patients and this was confirmed in this study (mean rT3=154 ng/dl and < 6 ng/dl, respectively). Kinetic studies demonstrated that both the MCR (191 L/day/70 kg) and PR (271.4 µg/day/70 kg) were increased in hyperthyroidism, whereas both the MCR (71.0 L/day/70 kg) and PR (4.5 µg/day/70 kg) were decreased in hypothyroid subjects. These results are in accord with the well documented alterations in clearance and production rates of T4 and T3 in these two disorders.

The rapid disappearance of ^{125}I-reverse T3 from serum makes accurate estimates of kinetic parameters more difficult, particularly if there is equally rapid metabolism of rT3 in vivo. Rudolph et al., using column chromatography, demonstrated that approximately 10-16% of the radioactive serum counts were not reverse T3, but were diiodo- and monoiodothyronine derivatives. Gavin et al., using a constant infusion model, found that < 5% of the radioactivity could be attributed to other iodothyronines. The limited thin layer chromatography studies reported herein are largely in agreement with these observations but do indicate that reverse T3 was being assessed, especially in the early hours after injection. And although proportionally more counts were attributable to free iodide at 8 hours, the total radioactivity remaining by then was so small that it was not felt to appreciably affect the metabolic clearance rate.

The present study has demonstrated that the elevated serum levels of reverse T3 in hyperthyroidism are associated with an increase in both the clearance and production rates of this hormone; likewise, the low levels of reverse T3 in hypothyroidism are associated with a decreased MCR and PR. These changes parallel those seen for T4 and T3 in the same conditions.

Funds Utilized, FY-77:

Personnel		$12,340
Supplies		3,000
Isotopes		5,000
Printing, Audio Visual, Xerox		1,800
Animals (24 rabbits)		600
Nichols contract		5,000
Travel		500
Consultants		250
Equipment ½ freezer @2,000		1,000
	TOTAL	$29,390

Funding Requirements, FY-78:

Personnel	$11,864
Supplies; reagents	4,000
Reprints	1,500
24 rabbits	600
Travel	400
Nichols contract	4,000
Isotopes	6,000
Equipment	1,675
TOTAL	$30,039

Publications:

1. Smallridge, RC, L Wartofsky, RE Desjardins, and KD Burman, Reverse T3 production rates in thyrotoxic, euthyroid, and hypothyroid subjects. Clin. Research 25:302A, 1977.

2. Smallridge, RC, L Wartofsky, RE Desjardins, and KD Burman, Reverse T3 production rates in thyrotoxic, euthyroid, and hypothyroid subjects. To be submitted to Journal of Clinical Endocrinology and Metabolism, July 1, 1977.

3. Burman, KD, D Strum, Y-Y Djuh, FD Wright, and L Wartofsky, A radioimmunoassay for 3,3' diiodothyronine. Presented to the Annual Meeting, American Thyroid Association, Toronto, Canada, Sept. 76.

4. Burman, KD, D Strum, Y-Y Djuh, FD Wright, and L Wartofsky, A radioimmunoassay for 3,3' diiodothyronine. In press, JCEM, Aug. 77.

5. Burman, KD, RC Dimond, FD Wright, JM Earll, J Bruton, and L Wartofsky, A radioimmunoassay for reverse T3. JCEM 44:660, 1977.

6. Burman, KD, Y-Y Djuh, FD Wright, J Bruton, and L Wartofsky, Effect of 3,3'T2 on TSH response to TRH stimulation. In press (provisionally accepted 5/77), Metabolism.

7. Smallridge RC, L Wartofsky, and KD Burman, A radioimmunoassay for 3' monoiodothyronine. To be submitted to JCEM, July 10, 1977.

Type of Report:

Interim approval has been given for the development of 3'5'T2 and 3'T1 assays and investigations into their physiology.

Work Unit No.: 1348

Title of Project: Correlation of Dose and Duration of Exogenous Steroid Therapy with Recovery of Hypothalamic-Pituitary-Adrenal Function

Investigators:

Principal: Timothy M. Boehm, MAJ MC

Associate: Joseph Bruton, Ph.D.

Objectives: To investigate the effect of high dose steroid therapy of less than one month duration in inducing hypothalamic pituitary suppression, as reflected by ACTH responsiveness.

Technical Approach: To use metyrapone and insulin tolerance testing, with measurement of plasma cortisol and ACTH, as a measure of hypothalamic-pituitary suppression.

Progress and Results: Preliminary studies have been completed in one patient, and laboratory verification of the ACTH assay is pending. Insufficient accrual of patients was obtained, and resources are not available now on Kyle Metabolic Unit to perform the necessary assays.

Date of Approval at WRAMC: 25 Nov 75

Date of Approval at OTSG Required: 20 May 76

Conclusions: None at present

Funds Utilized, FY-77: None

Funding Requested, FY-78: None unless project is reactivated.

1. Travel, mission: $600.00

Publications: None

Type of Report: Interim

Work Unit No.: 1349

Title of Project: Evaluation of the Use of a Specific Radioimmunoassay for Compound S in the Interpretation of the Results of Metyrapone Testing

Investigator:

Principal: Timothy M. Boehm, MAJ MC

Objective: To compare values for compound S with urinary 17 hydroxycorticosteroid measurements in the interpretation of the results of metyrapone testing.

Technical Approach: Normal ranges for response to metyrapone will be obtained. The percentage abnormals in both compound S response and urine response will be compared and the concordance and discordance assessed.

Progress and Results: Approximately 100 patients and 10 normals are under study. Data is presently under analysis.

Conclusions: None

Funds Utilized, FY-77:

1. Personnel	$ 23,043.00
2. Supplies	3,400.00
3. Xerox, Misc.	100.00
4. Isotopes	300.00
5. Loose Issue	250.00
Total:	$ 27,093.00

Funding Requested, FY-78:

1. Personnel:		$ 21,822.00
2. Supplies:		1,200.00
3. Printing:		500.00
4. Audio-Visual:		500.00
5. Xerox, Misc:		200.00
6. Isotopes:		150.00
7. Loose Issue:		200.00
8. Travel, Mission:		600.00
	Total:	$ 25,172.00

Publications: None

Type of Report: Interim

Work Unit No.: 1350

Title of Project: Effect of Cholestyramine and Phenobarbital on T4 and T3 Degradation and Excretion in Thyrotoxicosis

Investigator:

Principal: Timothy M. Boehm, MAJ MC

Objective: To assess whether cholestyramine or phenobarbital enhanced T4 and T3 degradation and excretion in thyrotoxicosis.

Technical Approach: This project involved isotopic kinetic studies as well as triple lumen biliary perfusion.

Progress and Results: One patient was studied. Other patients have been unable to tolerate the triple lumen perfusion study on multiple occasions. Isotopic counts in bile were too low to provide meaningful results.

Date of Approval at WRAMC: 27 April 76

Date of Approval at OTSG Required: 1 Sept 76

Conclusions: None

Funds Utilized, FY-77: None

Funding Requested, FY-78: None

Publications: None

Type of Report: Terminated

Work Unit No.: 1351

Title of Project: Effects of Cyproheptadine on Pituitary Secretion

Investigators:

Principal: Richard C. Dimond, M.D., LTC, MC

Associates: Robert C. Smallridge, M.D., MAJ, MC, Leonard Wartofsky, M.D., LTC, MC, Jerry M. Earll, M.D., COL, MC

Objective: To examine the role of serotonin on the regulation of prolactin and TSH secretion in patients with hyperprolactinemia, galactorrhea, or hypothyroidism.

Technical Approach: Standard TRH stimulation tests before and after three days of treatment with cyproheptadine, 4 mg p.o. tid.

Progress & Results: TRH was unavailable for clinical studies during the last 1 1/2 years and only recently has again become available for such studies. Therefore, no patients have been studied to date.

Conclusions: None

Funds Utilized FY-77:

Personnel:	$ 380
Supplies:	300
Reprints:	-
Audio-Visual:	-
Xerox, misc:	-
Isotopes:	-
Contracts:	-
Consultants:	-
Loose issue:	-
Non-exp. supplies:	-
Animals:	-
Travel:	-
Equipment:	-
Total	$ 680

Funds Requested FY-78:

Personnel:	$1,530
Supplies:	800
Reprints:	300
Audio-Visual:	200
Xerox, misc:	100
Isotopes:	200
Contracts:	750
Consultants:	-
Loose issue:	-
Non-exp. supplies:	-
Animals:	-
Travel:	400
Equipment:	-
Total	$4,280

CONTINUED

Publications: None

Type of Report: Interim

Work Unit No.: 1352

Title of Project: Echocardiographic Findings in Acromegaly

Investigators:

Principal: Robert C. Smallridge, M.D., MAJ, MC

Associates: Sol Rajfer, M.D., MAJ, MC, A. Anderson, M.D., LTC, MC, James Davia, M.D., LTC, MC, Marcus Schaaf, M.D.

Objectives: To evaluate the incidence of cardiac septal hypertrophy

Technical Approach: Echocardiograms were performed on each subject in the usual fashion in the cardiology department. Endocrine studies were performed on each patient on Ward 30.

Progress & Results: The study has been completed, and the manuscript is in preparation. A copy will be forwarded upon its completion.

Conclusions: To be outlined in detail in manuscript.

Funds Utilized FY-77:

Personnel:	578
Supplies:	350
Reprints:	-
Audio-Vis:	200
Xerox, Misc:	100
Isotopes:	-
Contracts:	-
Consultants:	-
Loose issue:	-
Non-exp. supplies:	250
Animals:	-
Travel:	-
Equipment:	-
Total	$1,478

Funds Required FY-78:

Personnel:	673
Supplies:	500
Reprints:	500
Audio-Vis:	350
Xerox, Misc:	100
Isotopes:	-
Contracts:	-

CONTINUED

Consultants:	-
Loose Issue:	-
Non-exp. Supplies:	100
Animals:	-
Travel:	-
Equipment:	-
Total	$2,223

Publications: Manuscript in preparation

Type of Report: Interim

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Work Unit No.: 1353

Title of Project: The Regulation of T4 Conversion.

Investigators:

Principal: Kenneth D. Burman, M.D., MAJ MC

Objective:

To determine the factors regulating extrathyroidal conversion and affecting T3 receptors. Recent studies have indicated that T4 may be peripherally converted to both T3 and to reverse T3 (rT3) and that relative shifts in the pathways of thyroxine degradation may occur in various conditions which, in general, are catabolic in nature. For example, fasting has been associated with relative decreases in serum T3 levels and increases in serum rT3 concentration.

Separate areas of investigation have documented that high affinity T3 receptors exist in various tissues, including liver, and that T3 administration may be associated with a dose-dependent depletion of its own nuclear receptors. It is presently speculated that metabolic actions of T3 are mediated through its interaction with the receptor. Therefore, in an effort to determine if receptor kinetics remain normal in conditions associated with altered serum T3 and rT3 levels and also to gain insight into the mechanisms of decreased T3 action (e.g., basal metabolic rate) during fasting, the present study examined T3 receptor binding affinity and capacity in rats from whom food was withheld for several days.

Technical Approach:

Nuclei Preparation. Liver from 150-250 g male rats (Sprague-Dawley) was rapidly obtained following cervical dislocation and the nuclei were isolated and prepared essentially as described by Spindler, et al.

Incubation Studies. 0.5 ml of nuclei (representing 0.4 g/ml liver) were incubated with 0.2 ml diluted 125 I-T3 (specific activity approximately 600 $\mu Ci/_{10}g$; Abbott Laboratories, Chicago, IL), and 0.1 ml of T3 standards ranging from 10^{-10} to 10^{-6}M (Sigma Chemical Co., St. Louis, MO). The total incubation volume was brought to 1 ml and all incubations, unless stated otherwise, were at 37°C for 30 minutes. Following incubation, samples were removed from the water bath and the nuclear pellet was washed, and the remaining radioactivity determined, as described by Spindler, et al. Specific binding was ascertained in each study by subtracting the radioactivity in the tubes with excess competing T3 from the radioactivity determined in the appropriate tubes without excess competing T3. Individual samples were determined in duplicate.

Data Analysis. Scatchard plots were constructed from which apparent affinity equilibrium constants (Ka) and maximal binding capacities (MBC) were calculated.

Experimental Design. Euthyroid litter mates were allowed a regular diet (G.L. Baking Co., Frederick, MD) and water ad lib until the start of the experiment. At that time, one rat was placed in an individual cage with continued access to food and water ad lib whereas another rat was placed in a separate cage from which all food was removed but free access to tap water was permitted. Both cages were constructed and separated such that no undesired edible material (e.g. feces, urine) was allowed into these cages. Both rats were maintained in their respective cages for approximately 72

hours when they were sacrificed and their hepatic nuclei isolated. Studies utilizing both fasting and fed rats were always performed on the same day and employed identical reagents (i.e., buffer, standards, radioisotope) in order to minimize external factors that might influence interpretation of comparative results.

Measurements. DNA determinations were performed by a modification of the method of Burton, et al. Customarily, DNA analysis was performed on a 1 ml aliquot of nuclei (approximately 0.4 g/ml liver) that had not been incubated at 37°C but had been aliquotted and then maintained at -20°C for less than 2 weeks prior to extraction and analysis. Serum T3 and T4 levels were determined by radioimmunoassay.

Progress and Results:

Preliminary studies had suggested that the time course of binding of fed and fasting rats did not differ and that equilibrium was established for both groups at 30 minutes of incubation. The mean (± SE) maximal percent binding of 125 I-T3 to its receptor was 13.4 ± 1.2%/mg DNA in the fasted rats and 26.7 ± 2.9%/mg DNA in the fed rats ($p < .001$). The mean MBC was also decreased being .30 ± .05 nM/mg DNA in fasting and .46 ± .07 nM/mg DNA ($p < .01$) in the fed state. Nevertheless, the Ka values were similar in both groups being 5.2 ± 1.0 X $10^8 M^{-1}$ and 6.2 ± 1.1 X $10^8 M^{-1}$ in the fed and fasted state, respectively. The mean DNA concentration/200 mg liver was 341 ± 16 µg during food restriction and 313 ± 13 µg during feeding and the mean weight of the total liver was 2.4 g/100 g rat during fasting and 3.1 g/100 g rat in the fed state. The ability to recover DNA from whole liver as well as the rate of loss of DNA from the nuclear pellet during incubation were similar in fed and fasted rats; dialysis estimations of receptor loss from the nuclear pellet during incubation also indicated no differences between the two study groups. Moreover, the apparent rate dissociation constants were .0170 min^{-1} during fasting and .0179 min^{-1} during feeding. Lastly, preliminary rat studies in vivo have confirmed these results concerning decreased MBC in fasting. In the fed state, the mean (± SE) serum T3 concentration was 124 ± 8 ng/dl and the mean serum T4 level was 6.6 ± 0.4 µg/dl; during fasting, mean (± SE) serum T3 and T4 concentrations were 65 ± 9 ng/dl and 4.2 ± 0.3 µg/dl, respectively.

Comparison of binding characteristics and affinity equilibrium constants (Ka) in hepatic nuclear T3 receptors isolated from fasting and fed rats.[2]

	Fasting Rats			Fed Rats		
	^{125}I-T3 Binding[3]	MBC[4]	Ka[5]	^{125}I-T3 Binding	MBC	Ka
1	15.1	.27	5.7	27.4	.35	7.4
2	10.1	.28	4.1	11.6	.34	2.9
3	8.7	.22	5.1	25.5	.64	4.1
4	13.4	.20	2.2	18.9	.35	2.7
5	13.8	.25	5.1	21.6	.23	12.7
6	18.0	.29	4.9	34.5	.37	10.4
7	9.9	.21	7.5	27.8	.29	9.6
8	19.9	.73	1.6	34.4	.88	3.5
9	14.6	.41	2.4	44.0	.66	3.9
10	10.1	.11	13.6	20.4	.46	4.3
Mean	13.4	.30	5.2	26.7	.46	6.2
SE	1.2	.05	1.0	2.9	.07	1.1

[2]Nuclei were incubated for 30 minutes at 37°C.
[3]Maximal ^{125}I-T3 Binding is expressed as % per mg DNA.
[4]MBC is expressed as nM/mg DNA.
[5]Ka is expressed as (X $10^8 M^{-1}$).

Conclusions:

In the present study, reduction in the maximal binding capacity of the hepatic T3 receptor in fasting rats was observed compared to normal rats although the mean affinity equilibrium constant in each group remained essentially unaltered. The mechanism by which this alteration occurs is unknown. Nevertheless, it can be speculated that the decrement in maximal binding capacity could alter the normal relationship existing between T3 and its receptor as well as the metabolic actions mediated through this interaction.

Funds Utilized FY-77:

Personnel	$18,586
Expendable Supplies	3,000
Reprints, printing	500
Audio-Visual	250
Xerox; office supplies	100
Isotopes	2,500
Consultants	200
Loose issue, non-expendable	200
Animals	2,000
Travel	-
Equipment	2,785
TOTAL	$30,121

Funds Requested FY-78:

Personnel	$19,809
Expendable Supplies	3,000
Reprints, printing	500
Audio-Visual	500
Xerox; office supplies	100
Isotopes	2,200
Consultants	-
Loose issue, non-expendable	200
Animals (rats)	2,400
Travel	200
Equipment	3,485
TOTAL	$32,594

Publications: Work is in progress as grant has only recently been approved.

Burman, K.D., Y. Lukes, F.D. Wright, and L. Wartofsky, Reduction in hepatic T3 binding capacity induced by fasting, Submitted, Endocrinology, June 20, 1977.

Type of Report: Interim

Work Unit No.: 1354

Title of Project: Purification of Testosterone-Estradiol Binding Globulin

Investigators:

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

Objectives:

To purify and characterize estradiol binding globulin in order to 1) study physiologic effects of steroid binding on target tissue function; and 2) develop a radioimmunoassay.

Technical Approach:

Use of serial purification methods e.g., preparative polyacrylamide gel electrophoresis, affinity chromatography, temperature dependent affinity chromatography, and isotachophoresis.

Progress & Results:

Due to lack of funding, this project has not been started.

Conclusions: None.

Funds Utilized FY-77: None

Funding Requirement FY-78:

Personnel	$ 3,393
Supplies, general	1,800
Non-expendable; loose-issue	300
Printing, publication	500
Xerox, office supplies	200
Animals	600
Isotopes	350
Equipment	8,325
Travel	600
TOTAL	$16,068

Publications: None

Type of Report: Interim

Work Unit No.: 1355

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

Investigator:

Principal: Timothy M. Boehm, MAJ MC

Objective: To assess the effect of high dose prednisone upon thyroidal kinetics in thyrotoxicosis

Technical Approach: A double isotope technique is utilized to assess thyroidal release and aspects of the peripheral metabolism of T4.

Progress and Results: Three patients have completed study.

Date of Approval at WRAMC: 23 Nov 76

Date of Approval at OTSG Required: 29 Mar 77

Conclusions: None at present

Funds Utilized, FY-77:

1. Personnel		$ 1,920.00
2. Supplies		1,500.00
3. Xerox		100.00
4. Isotopes		480.00
	Total	$ 4,000.00

Funding Requested, FY-78:

1. Personnel	$ 4,080.00
2. Supplies	2,250.00
3. Printing	500.00

4. Audio Visual		250.00
5. Isotopes		1,200.00
6. Contract Svcs.		1,000.00
7. Loose Issue		200.00
	Total:	9,480.00

Publications: None

Type of Report: Interim

Work Unit No.: 1356

Title of Project: The Pituitary-Gonadal Axis and Testicular Function in Hyperthyroidism

Investigators:

Principal: Robert A. Vigersky, M.D., MAJ, MC
Gerald S. Kidd, M.D., MAJ, MC

Associates: Kenneth D. Burman, M.D., MAJ, MC
Joseph Bruton, Ph. D.
Leonard Wartofsky, M.D., LTC, MC
Allan R. Glass, M.D., MAJ, MC

Objective:

To assess the status of the pituitary-gonadal axis and the status of spermatogenesis in men with hyperthyroidism.

Technical Approach:

Measurement of basal levels of total and free testosterone and estradiol, LH, FSH and testosterone-estradiol binding globulin while hyperthyroid and after euthyroidism has been maintained for 3 months. Semenanalysis is performed on 3 occasions at both time periods. The pituitary reserve of LH and FSH is determined by their response to 100 ug of LRH at both time periods and the testosterone synthetic reserve is determined at both time periods by a 4 day hCG (human chorionic gonadotropin - 4000 U, intramuscularly a day) test.

Progress and Results:

3 patients have been entered into the study. The sperm counts on all are markedly lower than normal. For the purpose of minimizing interassay variation, analysis of all hormones, binding proteins and their responses is being deferred until the full number of patients has been entered into the study. One patient refused to have the hCG test.

Conclusions:

Testicular function, as determined by spermatogenesis, appears to be decreased in hyperthyroidism.

Funds Utilized FY-77:

Personnel		$4,373
Supplies		800
Isotopes		150
Misc., Xerox, etc.		200
Travel		400
Equipment		1,885
	TOTAL	$7,808

Funds Requested FY-78:

Personnel		$4,118
Supplies		2,500
Printing, Audio-Visual		1,000
Misc., Xerox, etc.		250
Contract Labs.		2,000
Consultants		250
Non-exp. supplies		250
Equipment		7,125
Travel		0
	TOTAL	$17,493

Publications (FY-77): None

Type of Report: Interim

Work Unit No.: 1357

Title of Project: Effect of T3 and rT3 on Extracellular Cyclic Nucleotide Levels in Humans.

Investigators:

Principal: H. Linton Wray, M.D., LTC MC

Associates: Kenneth D. Burman, M.D., MAJ MC
Robert C. Smallridge, M.D., MAJ MC
Leonard Wartofsky, M.D., LTC MC

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 (T3) and 3,3',5' triiodothyronine (reverse T3, rT3).

Technical Approach:

Hypothyroid patients will be studied before, during and after taking T3, rT3 or both T3 and rT3. Hyperthyroid patients will be studied only with rT3. 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 T3, rT3 and T4 will be measured on days 1-5 and 8-12.

Progress and Results:

No patients have been studied yet because suitable volunteers have been used in other research protocols.

Funds Utilized FY-77: None

Funds Requested FY-78:

Personnel	$ 7,596
Expendable supplies	2,000
Reprints, printing	450
Audio-Visual	250
Xerox; office supplies	100
Isotopes	0
Lab contracts	0
Loose issue, non-expendable	250
Animals	0
Travel	400
Equipment	875
TOTAL	$11,921

Publications: None

Type of Report: Interim

Work Unit No: 1358

Title of Project: The Effect of Obesity and Fasting on T_3 Receptors in Circulating Mononuclear Cells.

Investigators:

Principal: Kenneth D. Burman, MAJ, MC

Associates: L. Wartofsky, Y. Lukes, and G. Harvey

Objectives: To ascertain if T3 receptors are altered in fasting

Approach: To quantitate T3 receptors in white cells by constructing Scatchard plots.

Progress & Results: Protocol just approved and study being started.

Conclusions: None yet.

Funds Utilized FY-77:

Personnel:	$1,815
Exp. supplies:	250
Reprints, printing:	-0-
Audio-visual:	-0-
Xerox; office supp.:	-0-
Isotopes:	250
Lab Contracts:	-0-
Loose issue, non-exp.:	100
Animals:	-0-
Travel:	-0-
Equipment:	400
Total	$2,815

Funds Requested FY-78:

Personnel:	$2,047
Exp. supplies:	2,000
Reprints, printing:	500
Audio-visual:	250
Xerox; office supp.:	100
Isotopes:	2,000
Lab Contracts:	250
Loose issue, non-exp.:	200
Animals:	-0-
Travel:	-0-
Equipment:	1,175
Total	$8,522

Publications: None

Type of Report: Interim

Work Unit No.: 1359

Title of Project: The Effect of Reverse T3 and 3,3'T2 on Thyroid Secretion, T4 Degradation, and Iodide Leak in Thyrotoxic Patients.

Investigators:

Principal: Kenneth D. Burman, M.D., MAJ MC

Objective:

To determine if reverse T3 administration effects thyroidal secretion or T4 disappearance.

Technical Approach:

Sample Processing. 1.5 mls of serum is aliquotted and 100 mg. of Iobeads are added. The sera is centrifuged and the supernatent is extracted with 95% ethanol. The remaining precipitate is counted for radioactivity and the results are expressed as percent administered dose per liter.

Isotope Technique. Approximately 25 microcuries ^{131}I-T4 are injected I.V. and sera are sampled approximately every hour for 3 hours and then every 4 hours for 24 hours. The ^{131}I-T4 is chromatographically pure. The obtained sera are processed as above.

Data Analysis. Results are expressed as percent administered dose per liter and are analyzed by a non-compartmental approach. Metabolic Clearance Rates and Production Rates are determined from the slope of the curve.

Reverse T3 Administration. 80 micrograms pure reverse T3 are administered four times a day and serum levels of reverse T3 are determined by radioimmunoassay. Reverse T3 is obtained from Dr. Schaefele, Henning-Berlin.

Progress and Results:

Since the protocol was only recently approved, no results have yet been obtained.

Conclusions: None yet.

Funds Utilized FY-77:

Personnel	$1,510
Expendable supplies	2,000
Reprints, printing	0
Audio-Visual	0
Xerox; office supplies	100
Isotopes	500
Consultants	100
Loose issue, non-expendable	100
Animals	-
Travel	-
Equipment	520
TOTAL	$4,830

Funds Requested FY-78:

Personnel	$ 2,150
Expendable supplies	3,000
Reprints, printing	500
Audio-Visual	500
Xerox; office supplies	100
Isotopes	2,000
Consultants	250
Loose issue, non-expendable	150
Nichols contract	1,000
Travel	600
Equipment	1,050
TOTAL	$11,300

Publications: None

Type of Report: Interim

Work Unit No.: 1361

Title of Project: Postoperative Changes in Free Testosterone and Sex-Hormone-Binding-Globulin

Investigators:

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

Associates: Jerry Kidd, M.D., MAJ, MC, Joseph Bruton, Ph.D.

Objective: To evaluate changes in serum total testosterone, free testosterone, LH, and sex-hormone-binding-globulin in the postoperative period.

Technical Approach: Blood samples are obtained before and for 3 days after surgery in men under age 50 undergoing elective operation. Serum testosterone will be measured by radioimmunoassay, free testosterone by equilibrium dialysis, and sex-hormone-binding-globulin by ammonium sulfate precipitation. Serum LH will be measured by radioimmunoassay through contractual agreement.

Progress and Results: Blood samples have been obtained from 5 patients for this study, and further patient recruitment is underway. This pace is slower than expected due to a relatively low percentage of elective surgery performed on patients on age 50. Establishment of assays for free testosterone and sex-hormone-binding-globulin has begun, while validation of serum testosterone assay has been completed.

Conclusions: No conclusions have been reached since no patient samples have yet been assayed. The experimental design calls for accumulation of all required blood samples from all subjects prior to any assay so that hormones may be assayed in a single run.

Funds Utilized, FY 77:

Personnel:	$2167	$2,167
Equipment:	none	
Supplies:	approx. $350	350
Travel:	approx. $400	400
Other:	mis. services & supplies $200	200
	TOTAL	$3,117

Funding Requirements FY-78:

Personnel:	$3890
Equipment:	Shaking water bath $1450
Supplies:	$800
	$150 (isotopes: 3H-testosterone and 3H-dihydrotesterone)
Travel:	$365.00
Other:	page charges and reprints $400
	audio-visual, Xerox, etc. $400
TOTAL:	$7,855

Publications: None in FY-77

Type of Report: Interim

Work Unit No.: 1362

Title of Project: Medical Treatment of Amenorrhea-Galactorrhea Syndromes with Vitamin B_6 (pyridoxine)

Investigators:

Principal: Gerald S. Kidd, M.D., MAJ, MC

Associates: Robert A. Vigersky, M.D., MAJ, MC
Richard C. Dimond, M.D., LTC, MC
Thomas Klein, M.D., LTC, MC

Objectives: To evaluate the effects of pyridoxine on the elevated levels of prolactin and on the symptoms of Amenorrhea-Galactorrhea Syndromes.

Progress & Results: This project was just recently approved. The second patient is now being studied. No results have become available. No adverse effects have occurred.

Conclusions: This project is just beginning. It is hoped that all patients will have completed the study by February 1977 and that the study will contribute significant physiologic and theraputic information.

Funds Utilized FY-77:

Personnel:	$ 790
Supplies:	300
Reprints:	-
Audio-Visual:	-
Xerox, misc.:	100
Isotopes:	-
Contracts:	-
Consultants:	-
Loose Issue:	-
Non-exp. supplies:	100
Animals:	-
Travel:	-
Equipment:	-
Total	$1,290

Funds Required FY-78:

Personnel:	838
Supplies:	450
Reprints:	400
Audio-Visual:	250
Xerox, misc.:	100
Isotopes:	-
Contracts:	3,000
Consultants:	-
Loose Issue:	-
Non-exp. supplies:	-

CONTINUED

Animals:	-
Travel:	-
Equipment:	-
Total	$5,038

Publications: None

Type of Report: Interim

Work Unit No.: 1363

Title of Project: Effect of T3 and rT3 on Plasma Cyclic Nucleotide Levels on Sheep.

Investigators:

Principal: H. Linton Wray, LTC, MC

Associates: Kenneth D. Burman, MAJ, MC, John P. Alford, CPT, V.C., Leonard Wartofsky, LTC, MC

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 T3, rT3).

Technical Approach: Plasma cyclic AMP, cyclic GMP and serum T3, rT3 and T4 will be measured before, during and after 6 days of intramuscular administration of placebo, T3, rT3 or both T3 and rT3 together. Six animals will comprise each treatment group. The 12 day study period consists of 3 days of baseline, 6 days of treatment with thyronine given every 8 hours and 3 days of recovery. Morning blood samples will be obtained on days 1-5 and 8-12. The first dose of each hormone will be given intravenously and blood collections made at 0, 60, and 180 minutes. Blood samples will be obtained 7 hours after the morning treatment on day 8. Pretreatment thyroid stimulating hormone (TSH) levels will be determined on days 1-3 in each 12 day study period. After the last dose of each hormone at 0700 on day 9, a thyrotropin releasing hormone (TRH) test will be performed with an intravenous bolus injection of 400 µg of TRH and blood collections at -30, 0, 30, 60, 90, and 120 minutes for TSH.

Progress & Results: Five groups of sheep have completed the study protocol with the following treatments (1) placebo, (2) 1.5 µg T3/kg body weight, (3) 4.5 µg T3/kg body weight, (4) 4 µg rT3/kg body weight, and (5) 1.5 µg T3/kg body weight and 4 µg rT3/kg body weight. Measurement of the experimental parameters is only partially completed. Analysis of the cyclic nucleotide data for the placebo, 1.5 µg T3, and 4 µg rT3 groups show that these doses of thyronines had only minimal effects on plasma cyclic AMP and cyclic GMP. T3 treatment for 6 days caused only a marginal increase in cyclic AMP (<35% higher than placebo) and no change in cyclic GMP. Reverse T3 treatment for 6 days caused no change in either cyclic nucleotide when compared to placebo.

Conclusions: Short-term elevations of serum T3 or rT3 to levels associated with hyperthyroidism cause only minimal changes in plasma cyclic AMP and cyclic GMP.

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Funds Utilized FY-77:

Personnel:	$6,028
Exp. Supplies:	2,500
Reprints, printing:	-
Audio-Visual:	-
Xerox; office supp.:	100
Isotopes:	250
Lab Contracts:	-
Loose issue, non-exp.:	2,300
Animals:	300
Travel:	-
Equipment:	815
Total	$12,293

Funds Requested FY-78:

Personnel:	$8,599
Exp. Supplies:	2,400
Reprints, printing:	500
Audio-Visual:	300
Xerox; office supp.:	100
Isotopes:	250
Lab Contracts:	2,800
Loose issue, non-exp.:	-
Animals:	300
Travel:	600
Equipment:	3,000
Total	$18,849

Publications: None

Type of Report: Interim

Work Unit No.: 1368

Title of Project: Effect of Dietary Phosphate on Serum Levels of Vitamin D Metabolites in Hypoparathyroidism

Investigators:

Principal: H. Linton Wray, LTC, MC

Associate: Marcus Schaaf, M.D., Joseph Bruton, Ph.D.

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

Technical Approach: Eight hypoparathyroid patients will be studied during changes in phosphate intake to determine the effect on serum levels of 25-OH-D, 24, 25-$(OH)_2$-D and 1, 25-$(OH)_2$-D. 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 phorphorus). During the period of phosphate restriction, phosphate-binding antacids will be given (aluminum hydroxide gel with magnesium hydroxide (Maalox), 60 ml at 0800, 1200, 1500 and 2000 and aluminum hydroxide gel suspension (Amphojel), 30 ml at 1000, 1400, 1800 and 2200). During the period of phosphate excess, supplemental sodium-potassium phosphate will be given (1.0 g of phosphorus per day, (Neutro-Phos solution), 100 ml at 0900, 1400 and 1700). Adjustments will be made in the dosage of antacids and phosphate supplements as necessary to prevent either constipation or diarrhea. Caloric and calcium intakes as well as all medications including vitamin D will remain constant throughout the study. Twenty-four urine collections will be made daily for determination of inorganic phosphate, calcium, magnesium and creatinine. A 45 ml blood specimen will be obtained approximately every other day for a total of 9 blood collections. 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. A 10 ml blood specimen for serum PTH will be collected on the last day of each of the three study periods.

Progress & Results: Several patients have volunteered for this protocol but will not be studied until the Vitamin D assays have been set-up at WRAMC. The equipment to modify the high pressure liquid chromatography system has been ordered.

Conclusions: None

Funds Utilized FY-77:

Personnel:		$1,513
Supplies:		400
Reprints:		-
Audio-Vis:		-
Xerox, misc.:		100
Isotopes:		-
Contracts:		-
Consultants:		-
Loose Issue:		-
Non-exp. supplies:		9,200
Animals:		-
Travel:		-
Equipment:		1,800
	Total	$13,013

Funds Requested FY-78:

Personnel:		$8,259
Supplies:		4,000
Reprints:		500
Audio-Vis:		400
Xerox, misc.:		200
Isotopes:		3,000
Contracts:		3,600
Consultants:		250
Loose Issue:		500
Non-exp. supplies:		1,200
Animals:		500
Travel:		-
Equipment:		15,625
	Total	$38,034

Publications: None

Type of Report: Interim

PROTOCOL: 1408

TITLE: Bile Salt Clearance in Chronic Active Hepatitis

LOCATION: Gastroenterology Service, Department of Medicine, Walter Reed Army Medical Center

PRINCIPAL INVESTIGATORS:

Principal Investigators: Lawrence F. Johnson, M.D., LTC, MC
Edgar C. Boedeker, M.D., Major, MC

MANAGEMENT DATA: Project 3A672760A822, In-House Independent Research
Task 00
Work Unit 130 Gastrointestinal diseases of military importance

OBJECTIVE: To ascertain if the clearance rate of intravenously administered cholyl glycine (a) can reliably determine those patients with chronic active hepatitis who require corticosteroid therapy; and (b) can determine the end-point of such therapy in those patients who are treated.

TECHNICAL APPROACH:

(a) Development of radioimmunoassay (RIA) for conjugates of cholic acid.

(1) Antibody to cholyl glycine will be developed in rabbits by linking cholyl glycine covalently bound to bovine serum albumin by the carbodimide method (9). After separating the free from the bound bile acid by dialysis, the albumin-cholyl glycine complex is emulsified with an equal volume of Freund's complete adjuvant and injected into rabbits at weekly intervals. Antibody titers will be assessed at two months or until an adequate titer is obtained for RIA.

(2) Assay (10): The assay is performed on 0.1 ml aliquots of unextracted serum. The reaction mixture contains: 0.1 ml of human gamma globulin diluted (1:25 v/v dilution); 0.1 ml of ^{3}H-cholyl glycine (10^{5} cpm); 0.1 ml of unlabeled cholyl glycine (to prepare standard curves) or unknown serum for bile acid assay; 0.1 ml of antibody to cholyl glycine (1:60 titer); and 0.01M potassium phosphate buffer, pH 7.4 to a final volume of 1.0 ml. The mixture is incubated for 1 hour at $37^{\circ}C$, and then placed at $4^{\circ}C$ for 10 minutes. The free antigen is separated from bound antigen by polyethylene glycol and 1 ml of the supernatant pipeted into scintillation vials containing 10 ml of Hydromix for counting. Each human serum sample will be run in triplicate with simultaneous determination of a known standard curve.

(b) Patient selection:

(1) Controls: A group of 30 healthy volunteers with no apparent liver disease will establish the range of normal cholyl glycine clearance. Informed consent will be obtained.

(2) Patients: All patients in whom the diagnosis of chronic active hepatitits, minimal change type, is established by clinical and histologic parameters will be entered into the study. Informed consent will be obtained. Each patient will have an evaluation of cholyl glycine clearance before initiation of therapy which will be repeated at 6 month intervals, in conjunction with routine clinical and histologic follow-up, until histologic remission occurs.

(c) Cholyl glycine clearance: Following an overnight fast and baseline 2 cc blood sample for cholic acid determination, cholyl glycine (5 M/kg) will be administered intravenously. From another vein, 2 cc blood samples will be drawn at 1 minute intervals for 10 minutes and then at 5 minute intervals for an additional 20 minutes (total blood sample - 30 cc's). A disappearance curve will then be constructed and the half-line of intravenously administered cholyl glycine determined.

The clearance rate of cholyl glycine will be related to the clinical and histologic findings at each evaluation. The relationship of cholyl glycine half-life to both response to corticosteroid treatment and to histologic status will be determined. It is anticipated that this liver function test will be capable of determining those patients who will require corticosteroid therapy. Furthermore, in group so treated, it should be capable of determining the endpoint of such therapy. This may obviate the need for repetitive liver biopsy and, thus, reduce hospitalization time and expense.

PROGRESS AND RESULTS:

In order to develop an antibody to cholyl glycine, we have made some modifications in the injection of the rabbits since August 1976.

Currently, three rabbits are being innoculated for cholate antibody and three for chenodeoxycholate antibody. It is thought that a freshly prepared glycine - BSA conjugate gives a better antibody response than a stock mixture. Rabbits are innoculated Im weekly and bleed after 8 injections. A rabbit is terminated if it shows no antibody response after the initial 8 injections. If there is a response, rabbits are injected once weekly for an additional month and then bled. When a good antibody is obtained, the serum is lyophilized and stored at -20°C. We found that lyophilization is a much safer method of storing the antibody after we lost a stock of frozen antibody when a freezer malfunctioned. Lyophilization of an antibody does not seem to alter its sensitivity or specificity. At present, we have a good stock of chenodeoxycholate antibody but need to work on obtaining a stock of cholyl antibody.

Serum samples from normal, hepatitis, and hyperthyroid patients are being collected and stored in -20°C. The normal range for serum chenodeoxycholate has been determined a .5 to 1.0 Eg/1. Hyperthyroid patients are being studied under protocol 34411 and show a wide range of elevation of serum chenodeoxycholate.

Work on obtaining a safe preparation of cholyl glycine for humans needs to be continued.

CONCLUSIONS:

A good radioimmunoassay was developed for conjugates of chenodeoxycholate acid. This development prompted a separate protocol #1411 and publication of an abstract[1] and a subsequent publication[2]. We continue our work to develop an antibody for conjugates of cholyl glycine.

FUNDING IMPLICATIONS:	YEARLY TOTAL
(a) Personnel:	
Chemist - Corinne Maydonovitch	$13,482.00
(b) Equipment:	
No additional equipment needed	
(c) Consumable Supplies:	
(1) Rabbits #20 @ $20.00	400.00
(2) ^{3}H-cholyl glycine (New England Nuclear) 1.5 mC @ $104.00 per 250 uC	624.00
(3) Scintillation vials #9 cases case of 500 @ $45.00	405.00
(4) Hydromix #12 gallon gallon @ $36.00	432.00
(5) Glycocholic acid 50 grams 25 grams @ $160.00	320.00
(6) Eppendorf Pipette Tips #5000 1000 @ $48.00	240.00
(7) Animal Maintenance $.33/day Average 6 rabbits maintained/year	712.80
(d) Travel to present paper (TDY):	550.00
(e) Consultation Fees:	1,000.00
	$18,165.80

TYPE OF REPORT: Interim

Work Unit No.: 1410

Title of Project: Percutaneous (Blind) vs Laparoscopic (Direct Vision) Liver Biopsy in Assessing Chronic Active Hepatitis

Investigators:

Principal: Howard A. Heit, MAJ MC

Associate: Lawrence F. Johnson, MAJ MC

Objective: To ascertain if the diagnosis and management of chronic active hepatitis can be adequately monitored by percutaneous (blind) liver biopsy or whether laparoscopic (direct vision) liver biopsy should be utilized.

Technical Approach: Patients with chronic active hepatitis are currently evaluated by percutaneous liver biopsy. This means of biopsy often fails to establish the presence of cirrhosis. Under the guidelines of this study, patients with chronic active hepatitis who have equivocal percutaneous biopsies will be further evaluated by laparoscopy with biopsy under direct vision, and the combined diagnostic accuracy of observation and direct vision biopsy will be compared to that of percutaneous biopsy alone. This will establish the best method of diagnosis and management for our patients with chronic active hepatitis.

Progress and Results: To date, eight patients have been part of the study. In five patients, percutaneous biopsy was as accurate as laparoscopy in defining the presence of extensive fibrosis without cirrhosis. One patient had cirrhosis established only by laparoscopy with direct vision biopsy. Two patients had the diagnosis of chronic active hepatitis changed to chronic persistent hepatitis after the laparoscopy. To date, 33% of the patients had a significant change in their diagnosis as a result of this study.

Conclusion: We need to continue to evaluate all appropriate patients until an adequate number for statistical significance have been accessioned.

Funds Utilized: None

Funds Requested, FY-78:		
	Travel	$400.00
	Publication	200.00

Publications (FY-77): None

Type of Report: Interim

Work Unit No.: 1411

Title of Project: Intestinal Bile Salt Clearance In Thyrotoxic Patients With and Without Diarrhea.

Investigators:

Principle Investigator: MAJ Mark Donowitz, M.D.

Associate Investigator: MAJ Dean Kinsey, M.D.; LTC Leonard Wartofsky, M.D.

OBJECTIVE: To determine bile salt kinetics in patients with hyperthyroidism as a possible cause of pruritus and diarrhea which are frequent complain in hyperthyroidism.

TECHNICAL APPROACH: Triple lumen perfusions have been obtained on 3 patients with hyperthyroidism without diarrhea and 2 patients with diarrhea and bile salt excretion and water and electrolyte transport have been measured. Bile salt half lives were measured by Iv injection of radiolabelled bile salts and measurement of these radiolabelled bile salts in the duodenum.

PROGRESS AND RESULTS: Bile salt secretion from the gall bladder is normal in both patients with hyperthyroidism with and without diarrhea. The total bile salt excretion is increased only in patients with hyperthyroidism with diarrhea. Patients with hyperthyroidism without diarrhea have normal jejunal water and electrolyte transport. Patients with hyperthyroidism with diarrhea have a shorter T 1/2 of bile salts than normal while the T 1/2 is normal in hyperthyroid patients without diarrhea. This may be due to either rapid transit of bile salts past the terminal ileum or a defect in ileal function.

CONCLUSION: a). Patients with hyperthyroidism secrete normal amounts of bile salts from the liver whether or not diarrhea is present.

b). Fecal bile salt excretion is increased in patients with hyperthyroidism with diarrhea and not in patients with hyperthyroidism without diarrhea.

c). Jejunal salt and water transport are normal in hyperthyroid patients without diarrhea.

FUNDING REQUIREMENT:

Personnel: Nurses Ward 30 plus Ms. Debbie Riggins, Laboratory Technician.

FUNDING REQUESTED FOR NEXT YEAR: None

Publications: None

Type of Report: Completed due to principal investigator leaving military.

Work Unit Number: 1412

Title: Laparoscopic, Histologic, and Electron Microscopic Evaluation of the Liver in Patients with Alcoholic Liver Disease

Investigators: Howard A. Heit, Maj, MC
Lawrence F. Johnson, LTC, MC

Objective: 1) To determine if disproportionate enlargement of the left hepatic lobe is a characteristic, reproducible, physical and laparoscopic finding in patients with alcoholic liver disease. 2) To define the histologic and electron microscopic alterations of hepatic tissue which are determinants for the disproportionate enlargement of the left hepatic lobe.

Progress and Results: The first four patients who were entered into the protocol who had a history of alcoholic liver disease did not have a disproportionate enlargement of the left hepatic lobe as observed and measured during laparoscopy. Biopsies were obtained of the left and right lobes in order to see if there was any difference in the histology between the two lobes. On H&E studying of the biopsy sections, there was no difference. There were technical problems preparing EM studies of the tissues, and these were never done.

Because the initital patients in the protocol did not show a difference in the size of their left lobe as compared to their right lobe, it was decided to terminate this project in its preliminary stages, because it was felt that the objective of the study would not be fulfilled. This project has now been terminated as far as clinical investigation, and no other patients will be entered into this study.

Conclusions: The final conclusion in our preliminary data is that the observation of the left lobe being enlarged more than the right lobe in alcoholic liver disease is not substantiated by laparoscopic and physical findings.

Type of Report: Termination

Work Unit No: 1414

Title: The Effect of Cimetidine on Gastric Ulcer Healing, A Double Blind Study.

Investigators: David A. Peura, Maj, MC
Lawrence F. Johnson, LTC, MC

Location of Study: Gastroenterology Service, Walter Reed Army Medical Center, Washington, D.C.

Objective: To determine if Cimetidine will diminish symptoms and improve the rate of gastric ulcer healing in hospitalized patients.

Technical Approach: See attached protocol, section PLAN, pages 2-7.

Progress and Results: Two patients were assessed to study and were evaluated a outlined in the protocol. Neither patient had any adverse effects that might be related to the investigational drug, Cimetidine. Both patients showed evidence of gastric ulcer healing with no evidence of recurrence. The study was terminated by Smith, Kline and Franch Laboratories, and data obtained was submitted to Smith, Kline and French and is currently undergoing statistical analysis.

Conclusions: No definite conclusions can be drawn from the study at this time since the data is currently undergoing statistical analysis.

Funds Utilized FY-77: None

Funds Requested FY-78: None

Publications FY-77: None
FY-78: Pending Smith, Kline and French's statistical analysis data.

Type of Report: Terminated

Resume of Direction of Future Studies: No further patients will be assessed into this study since the national study has been terminated. No further use of Cimetidine will be made under this protocol.

Unused Supplies: All unused supplies of Cimetidine were returned to Smith, Kline and French.

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-MH	Annual Progress Report - Clinical Investigation Program of the Oncology Section, Hematology-Oncology Service

TO C, Clin Invest Svc FROM C, Onc Sec, Hem-Onc Svc DATE 25 Jul 77 CMT 1

1. The Oncology Section, Hematology-Oncology Service, continued to participate in studies of the Cancer and Acute Leukemia Group B of experimental and standard drugs, singly and in combinations, in patients with various neoplastic diseases. New WRAMC protocols were initiated during FY 1977 and others were continued from previous years. Several studies in cooperation with the National Cancer Institute were completed; several new studies in cooperation with the Oncology Service of Georgetown Medical Center were begun.

2. All diagnoses of malignancy were substantiated by histological examination of biopsy material. All patients were informed of the experimental nature of the therapy and were provided information related to the toxicity which might be expected from therapy. The informed consent was signed by each patient, parent or guardian.

3. All protocols were reviewed by the Walter Reed Army Medical Center Research Advisory Committee and Human Use Committee prior to use and forward to the Human Use Review Office, Office of the Surgeon General, for approval in compliance with Army Regulation 40-7. All protocols were also forwarded to the Chief, Investigational Drug Branch, Cancer Therapy Evaluation, Division of Cancer Treatment, National Cancer Institute, National Institutes of Health, for approval.

4. Because of the uncertainty of financial support through transfer of funds from the National Institutes of Health and support through the chairman's office of the Cancer and Acute Leukemia Group B an application for support for the clinical investigation program of the Oncology Section was submitted to the WRAMC Clinical Investigation Committee for FY 1977. However, adequate funds were made available through the extension of the existing agreement with the National Cancer Institute for support of 50% of the salary of the principal investigator and 100% of the salaries of a hematology technician, a secretary-data manager, plus funds for patient travel and physician travel to attend meetings of the Cancer and Acute Leukemia Group B.

JOHANNES BLOM, M.D.
Chief, Oncology Section
Hematology-Oncology Service

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DA FORM 1 FEB 62 2496 REPLACES DD FORM 96, EXISTING SUPPLIES OF WHICH WILL BE ISSUED AND USED UNTIL 1 FEB 63 UNLESS SOONER EXHAUSTED.

☆ U.S. GPO: 1974-559-130/5058

Work Unit No.: 1516

Title of Project: ALGB Protocol #7291 - Add. #2: Intergroup rhabdomyosarcoma study; role of postoperative radiotherapy and combinations of dactinomycin, vincristine, cyclophosphamide and adriamycin in childhood rhabdomyosarcoma by Acute Leukemia Group B, Southwestern Cancer Chemotherapy Study Group and Childrens Cancer Study Group A.

Investigators:

Principal: Johannes Blom, M.D.

Associate: Frederick B. Ruymann, M.D., LTC, MC

Objectives: 1. To determine whether postoperative radiotherapy prevents local recurrence and improves the survival rate after what appears to be complete surgical removal of the localized tumor.

2. To compare duration of remission, recurrence and survival of patients treated with vincristine and dactinomycin with those treated with vincristine, dactinomycin and daily oral cyclophosphamide.

3. To compare in terms of response to treatment, length of remission, percentage exhibiting recurrence and survival of the effectiveness of vincristine, dactinomycin and high pulse doses of cyclophosphamide to the same drug combination plus adriamycin for the treatment of patients with gross residual disease at the time of diagnosis.

Technical Approach: Patients are divided into four groups:

Group 1 - localized disease completely removed

Group 2 - grossly removed tumor with microscopic residual disease

Group 3 - incomplete removal of tumor or biopsy with gross residual disease

Group 4 - distant spread of disease present at onset

Patients are randomized according to their disease group and treatment started within 72 hours of surgery.

The patients in group 1 will be randomized between regimen A and B, patients in group 2 will be randomized between regimen C and D (regimen D is the same as regimen B), and patients in group 3 and 4 will be randomized between regimen E and F.

Regimen A: vincristine, 2 mg/M^2 (maximum dose 2.0 mg) IV weekly for 12 doses plus
dactinomycin 0.015 mg/kg/day (max. 0.5 mg) IV for 5 days to be repeated 12, 24, 36 and 48 weeks plus
cytoxan 2.5 mg/kg/day orally starting on day 42 and continuing it up through 24 months.

Regimen B: radiotherapy to the tumor bed after surgery plus
chemotherapy as outlined in regimen A

Regimen C: radiotherapy to the tumor bed after surgery plus
dactinomycin 0.015 mg/kg/day (max. 0.5 mg) IV for 5 days to be repeated at 9, 18, 27, 36 and 45 weeks plus
vincristine 2 mg/M^2 (max. 2 mg) IV weekly for six doses

Regimen E: vincristine 2 mg/M^2 (max. 2 mg) IV weekly for 12 doses plus
dactinomycin 0.015 mg/kg/day (max. 0.5 mg) IV for 5 days to be repeated 18, 30, 42 and 54 weeks plus
cytoxan 10 mg/kg/day IV for 7 days, a second seven day course to be given by mouth at 13 weeks-
cytoxan 2.5 mg/kg/day p.o. from 21st week through the 24th month of therapy plus
radiotherapy to the tumor bed as well as to the areas of spread to be started at six weeks.

Regimen F: vincristine 2 mg/M^2 (max. 2.0 mg) IV weekly for 12 doses plus
dactinomycin 0.015 mg/kg/day (max. 0.5 mg) in the vein for 5 doses to be repeated at 21, 33, 45 and 57 weeks plus
cytoxan 10 mg/kg/day IV for 7 days. A second 7 day course by mouth to be started at 13 weeks.
cytoxan 2.5 mg/kg/day by mouth from the 24th week to the 24th month of therapy plus
adriamycin 50 mg/M^2 IV at 5, 18, 27, 39 and 51 weeks. This will be reduced to 30 mg/M^2 if a large bone marrow volume is to be irradiated (maximum total dose 600 mg/M^2) plus
radiotherapy to the tumor bed as well as to the areas of spread to be started in six weeks.

Progress & Results: WRAMC entered one patient, who was followed for 127 days and then lost to followup.

The Group entered 371 patients. The most recent report is of March 1976. The study continues.

Funding Requirements: See introductory remarks to Annual Research Report.

Publications: None.

Work Unit No.: 1517

Title of Project: ALGB Protocol 7331 - Add. 0: Hydroxyurea (NSC 32065), 6-Mercaptopurine (NSC 755), and Prednisone (NSC 10023) with or without Vincristine (NSC 67574) and Daunorubicin (NSC 84151) in the Treatment of the Resistant Phase of Chronic Granulocytie Leukemia. A Phase III Study.

Investigators:

Principal: Johannes Blom, M.D.

Objectives:

1. To assess the effectiveness of the combination of hydroxyurea, 6-MP and prednisone with or without vincristine in the resistant phase of chronic granulocytic leukemia for remission induction and maintenance.

2. To assess the effectiveness of daunorubicin as a consolidation agent.

Technical Approach:

1. Induction:

   Regimen I - Hydroxyurea 30 mg/kg/day p.o. in one dose plus
   6-MP 3 mg/kg/day p.o. in two divided doses plus
   Prednisone 0.75 mg/kg/day p.o. in two divided doses

   Regimen II- Hydroxyurea 30 mg/kg/day p.o. in one dose plus
   6-MP 3 mg/kg/day p.o. in two divided doses plus
   Prednisone 0.75 mg/kg/day p.o. in two divided doses plus
   Vincristine 1.5 mg/m^2 I.V. every week for four doses

2. Consolidation:

   Regimen A - Daunorubicin 60 mg/m^2 daily for two days plus
   Prednisone 0.25 mg/kg/day p.o. in two divided doses

   Regimen B - No consolidation

3. Maintenance: Will continue until there is recurrence of disease.

   Regimen I - Hydroxyurea 7 mg/kg/day p.o. one daily dose in a.m. plus
   6-MP 0.7 mg/kg/day p.o. one daily dose in a.m. plus
   Prednisone 0.25 mg/kg/day p.o. in two divided doses

   Regimen II- Hydroxyurea 7 mg/kg/day p.o. one daily in a.m. plus
   6-MP 0.7 mg/kg/day p.o. one daily in a.m. plus
   Prednisone 0.25 mg/kg/day p.o. in two divided doses plus
   Vincristine 1.5 mg/m^2 in the vein once a month.

Progress & Results: WRAMC has entered four patients. One patient was disqualified, one expired on day 39, and one expired on day 65. One patient went into complete remission, but had prolonged hypocellularity of the bone marrow. After recovery, she was placed on non-random maintenance regimen and has remained in complete remission for 555 days.

ALGB has entered 109 patients, 90 of whom are presently evaluable. At the most recent analysis in March 1976, complete and partial bone marrow remissions are 26% and 32% for the two regimens, and an overall response, which includes liver, spleen, and lymph nodes, of 26% and 34%.

Conclusions: There is no difference between the two induction regimens and responses are unsatisfactory and rather short. This protocol was replaced by CALGB Protocol 7531 on 20 August 1975.

Funding Requirements: See introductory remarks to the Annual Research Report.

Publications: None

Type of Report: Interim

Work Unit No.: 1518

Title of Project: ALGB Protocol 7383 - Add. 0: Clinical Trial of VP-16-213 (NSC 141540)(4'-dimethyl-epipodophyllotoxin-B-D-ethylidene-glucoside) in Advanced Neoplastic Disease. A Phase II Study.

Investigators:

Principal: Johannes Blom, M.D.

Objectives: To examine the antitumor effect (remission induction and maintenance) of VP-16-213 in a broad spectrum of metastatic tumors.

Technical Approach:

Regimen I - VP-16 60 mg/m^2 twice weekly for four weeks

Regimen II - VP-16 90 mg/m^2 twice weekly for four weeks.

Progress & Results: WRAMC entered six patients. One was found dead at home five days after he was entered on the study. The other five patients did not respond and had progressive disease and subsequently expired.

ALGB has entered 382 patients, 346 were evaluable at the last analysis in September 1976. Complete and partial response rates with 60 mg and 90 mg were 9% and 12% respectively. The response rate with the 135 mg regimen was 6%. Lymphomas and GI malignancies are still the most responsive tumors. The protocol was discontinued in September 1976.

Conclusions: This drug has some activity in lymphomas and malignancies of the GI tract.

Funding Requirements: See introductory remarks to the Annual Research Report.

Publications: None

Type of Report: Interim

Work Unit No.: 1519

Title of Project: ALGB Protocol 7361: Multiple Myeloma Resistant to l-phenylalanine Mustard Treated with Cyclophosphamide (Cytoxan)(NSC 26271), Prednisone (NSC 10023) and 1,3-bis-(2-chloroethyl-l-nitrosourea)(BCNU)(NSC 409962).

Investigators:

Principal: Johannes Blom, M.D.

Objectives: To determine whether patients previously treated with l-phenylalanine mustard but with recurrent active disease will respond to other alkylating agents (cyclophosphamide and BCNU) and prednisone.

Technical Approach:

Regimen I - Cyclophosphamide 600 mg/m^2 I.V. on day 1 plus
Prednisone 0.6 mg/kg orally daily for 14 days (in 3 equally divided doses beginning on day 1)
0.4 mg/kg orally daily for 14 days
0.25 mg/kg orally daily for 14 days

Then every 6 weeks:

Cyclophosphamide 600 mg/m^2 I.V. x1 plus
Prednisone 0.6 mg/kg/day x7

Regimen II - Cyclophosphamide 300 mg/m^2 I.V. on day 1 plus
BCNU 100 mg/m^2 I.V. on day 1 plus
Prednisone 0.6 mg/kg orally daily for 14 days (in 3 equally divided doses beginning on day 1)
0.45 mg/kg orally daily for 14 days
0.25 mg/kg orally daily for 14 days

Then every 6 weeks:

Cyclophosphamide 300 mg/m^2 I.V. x1 plus
Prednisone 0.6 mg/kg/day x7
BCNU 100 mg/m^2 I.V. x1

Progress & Results: WRAMC has entered seven patients; three patients had responses, two had progressive disease on day 308 and day 394, the third patient is still in response on day 376. Two patients had no response and went off study on day 88 and day 111. One patient is still on study. One patient had no change and subsequently expired.

ALGB has entered 95 patients, 79 of whom were evaluable at the March meeting in 1977. The percentages of good response in both regimens were 7% and 19% respectively with P=.0526. Numbers of limited response and no response were 33% and 25% and 60% and 56% respectively. Toxicity was tolerable. The protocol was discontinued on 3 December 1976.

Conclusions: Responses with cytoxan and prednisone and BCNU are possible in patients who are resistant to l-phenylalanine mustard and seem to be somewhat better than responses to cytoxan and prednisone alone.

Funding Requirements: See introductory remarks to the Annual Research Report.

Publications: None

Type of Report: Interim

Work Unit No.: 1520

Title of Project: ALGB Protocol #7411 - Add. #2: Combination chemotherapy in induction for standard risk and combination chemotherapy plus cranial irradiation plus daunorubicin for increased risk followed by maintenance with continuous vs. intermittent 6-MP plus methotrexate reinforcement and subsequent immunotherapy. Activated 18 April 1974.

Investigators:

Principal: Johannes Blom, M.D.

Associate: Frederick Ruymann, M.D., LTC, MC

Objectives: 1. To assess the role of early cranial radiation in the control of CNS and systemic leukemia by randomly allocating its use.

2. To introduce the concept of more vigorous induction and reinforcement therapy for a group of children considered to be at increased risk; older or younger age (after the 8th birthday or before the 2nd) and/or high leukocyte count (over 30,000), and test whether the addition of daunorubicin will favorably affect the frequency and/or the duration of complete remission in such patients.

3. To compare the effectiveness of three reinforced maintenance regimens:

A. Continuous combined oral 6-MP daily and oral MTX weekly.

B. Intensification with 5-day courses of combined oral MTX weekly.

C. Intensification with 5-day courses of oral MTX alone.

4. To be prepared to introduce immunotherapy in maintenance phase regimens at random.

Technical Approach: Patients are stratified in two risk categories:

Standard Risk: age is after the 2nd and before the 8th birthday and a total white count of less than 30,000.

Increased Risk: age is before the 2nd or after the 8th birthday or the total white blood count is equal to or greater than 30,000.

Patients at standard risk will be allocated to regimens 1 or 2. Patients at increased risk will be allocated to regimens 2 or 3.

Regimen I: vincristine 2.0 mg/M^2/week IV for 4 weeks on days 1, 8, 15 and 22
plus
prednisone 40.0 mg/M^2/day p.o. for 4 weeks (days 1-28), then taper to 20.0 mg/M^2/day for 2 days, 10 mg/M^2/day for 2 days, 5.0 mg/M^2/day for 2 days, 2.5 mg/M^2/day for 2 days, then stop prednisone
plus
methotrexate 12.0 mg/M^2 q 2 weeks IT for six doses on days 1, 15, 22, 43, 50 and 57
plus
l-asparaginase 1000 IU/kg/day IV for ten consecutive days from day 29 through 38

Regimen II: vincristine 2.0 mg/M^2/week IV for 4 weeks on daysl, 8, 15 and 22
plus
prednisone 40.0 mg/M^2/day p.o. for 4 weeks (days 1-28), then taper as Regimen I.
plus
methotrexate 12.0 mg/M^2 q 2 weeks IT for six doses on days 1, 15, 22, 43, 50 and 57 (last three injections coincide with cranial irradiation)
plus
l-asparaginase 1000 IU/kg/day IV for ten consecutive days from day 29 through 38
plus
cranial irradiation beginning on day 43 (after completion of l-asparaginase) 2400 rads of cranial irradiation over 16 days to day 58.

Regimen III: vincristine 2.0 mg/M^2/week IV for 4 weeks on days 1, 8, 15 and 22
plus
prednisone 40.0 mg/M^2/day p.o. for 4 weeks (days 1-28) and then taper as in Regimen I
plus
methotrexate 12.0 mg/M^2 q 2 weeks IT for six doses on days 1, 15, 22, 43, 50 and 57 (last three injections coincide with cranial irradiation)
plus
daunorubicin 45.0 mg/M^2/day IV for 3 days on days 1, 2 and 3 for those 2 years and over and 22.5 mg/M^2/day IV for 3 days on days 1, 2 and 3 for those under 2 years of age
plus
l-asparaginase 1000 IU/kg/day IV for ten consecutive days from day 29 through 38
plus
cranial irradiation beginning on day 43 (after completion of l-asparaginase) 2400 rads of cranial irradiation over 16 days to day 58.

Maintenance phase:

Regimen A: continuous oral 6-MP and MTX:
6-MP 90.0 mg/M^2/day orally
plus
MTX 15.0 mg/M^2/week orally on the 1st day of each week
reinforce with vincristine and prednisone at monthly intervals for five months, thereafter two week reinforcement treatments are given after the sixth month and every three months thereafter. The doses are as follows:

vincristine 2.0 mg/M^2 IV
plus
prednisone 40.0 mg/M^2/day p.o. for one week beginning with the vincristine injections - (do not taper). When two week reinforcements are given, prednisone continues for two weeks and then is tapered.
Patients induced on regimen 3 with daunorubicin will receive daunorubicin as part of the reinforcement course at the 13th and 25th week of maintenance, 45.0 mg/M^2/day IV x 2 beginning on the 1st day of the vincristine plus prednisone reinforcement.

Regimen B: intermittent intensification oral 6-MP and oral MTX:
6-MP 200 mg/M^2/day orally for five days
plus
MTX 7.5 mg/M^2/day orally for five days
wait nine days and then repeat,
wait nine days and then repeat for a third course

reinforce with vincristine and prednisone after every third course:
vincristine 2.0 mg/M^2 IV on days 1 and 8 for two week reinforcement treatment
plus
prednisone 40.0 mg/M^2/day p.o. for 2 weeks and then taper with each vincristine reinforcement

Patients induced on regimen 3 with daunorubicin should receive daunorubicin as part of the reinforcement course at the 15th and 31st weeks of maintenance, 45.0 mg/M^2/day IV x 2 beginning on the first day of vincristine and prednisone reinforcement

Regimen C: Intermittent intensification oral MTX alone:
MTX 15.0 mg/m^2/day orally for 5 days
Wait 9 days and repeat
Wait 9 days and repeat for a third course
Reinforce with vincristine and prednisone after every third course:
Vincristine 2.0 mg/m^2 I.V. on days 1 and 8 for 2-week reinforcement treatment, plus
Prednisone 40.0 mg/m^2/day p.o. for 2 weeks and tapered with each vincristine reinforcement
Patients induced on regimen 3 with Daunorubicin should receive Daunorubicin as part of the reinforcement course at the 15th and 31st weeks of maintenance, 45.0 mg/m^2/day I.V. x2 beginning on the first day of vincristine plus prednisone reinforcement.

Progress & Results: WRAMC entered 16 patients. One patient was invalidated because review of the material was more in favor of AML rather than ALL. Ten patients had a complete remission, one of whom relapsed on day 56 and the other on day 738. Two were not evaluable for maintenance. The remaining six patients are still in remission from 329 to 973 days. One patient had a partial remission, and then moved to another area where he is being followed by another member of the CALGB. Three patients had progressive disease.

CALGB has entered 513 patients, 455 of whom were evaluable in June 1977. Bone marrow remissions varied from 84 to 98 per cent in the four treatment regimens. Presently there is no significant difference in the various induction and maintenance treatment regimens nor any difference in duration of complete remission. Entry of patients was discontinued on 12 November 1976.

Conclusions: The remission induction duration and CNS relapse are essentially equivalent in the various treatment regimens.

Funding Requirements: See introductory remarks to Annual Research Report.

Publications: None

Type of Report: Interim

Work Unit No.: 1528

Title of Project: ALGB Protocol 7391 - Add. 0: Clinical Trial of Radiotherapy and Chemotherapy (Cyclophosphamide (NSC 26271), Vincristine (NSC 67574) and Actinomycin-D (NSC 3053)) in Managing Non-Metastatic Ewing's Sarcoma.

Investigators:

Principal: Johannes Blom, M.D.

Associate: Frederick B. Ruymann, M. D., LTC, MC

Objectives:

1. Compare the time interval from clinically localized tumor to appearance of metastases using (a) irradiation of the primary tumor only, (b) irradiation of the primary tumor plus systemic chemotherapy (cyclophosphamide, vincristine and dactinomycin)

2. Compare the time interval from clinically localized tumor to appearance of metastases using: (a) localized irradiation of the primary tumor plus chemotherapy, (b) irradiation of the primary tumor plus chemotherapy plus bilateral pulmonary irradiation.

3. Document the incidence and time of appearance of local recurrence in all patients included in the protocol regimens.

4. Document the total survival time of patients treated by all protocol regimens.

5. Document and evaluate the pattern of organ metastases for all protocol patients who develop metastases so future studies will result in programming improved means of therapy.

Technical Approach:

Initial Plan:

Regimen I - Vincristine 15 mg/m^2/week I.V. x6 plus
Cyclophosphamide 500 mg/m^2 I.V. x6 plus
Radiotherapy to the lesion

Regimen II - Vincristine 1.5 mg/m^2/week x6 plus
Cyclophosphamide 500 mg/m^2/week I.V. x6 plus
Radiotherapy to the lesion and both lung fields

Continuation Plan: Actinomycin-D 15 mcg/kg daily I.V. x5 at 3 months; after one weeks rest vincristine and prednisone are given from the third through the seventh week. These 7-week courses are repeated every 3 months for a total of 6 in 18 months.

Progress & Results: WRAMC entered four patients. One relapsed on day 582. One went off study shortly after entry, and a third patient relapsed. Follow-up on one patient is pending. Most recent analysis is of February 1977 reported at the March ALGB meeting. Seventy-five of the 225 evaluable patients represent CALGB input. The arms employing adriamycin and bilateral pulmonary radiotherapy are both superior to the arm with vincristine, actinomycin-D, cyclophosphamide and radiation of the primary tumor site alone. Delayed pulmonary toxicity from radiation therapy may occur only in patients who receive actinomycin-D in addition to radiation therapy. The sites of greatest risk appear to be the pelvis and proximal lesions.

Conclusions: As above.

Funding Requirements: See introductory remarks to Annual Research Report.

Publications: None

Type of Report: Interim

Work Unit No.: 1532

Title of Project: ALGB Protocol #7451 - Add. #0: Combination radiotherapy and chemotherapy of stage III Hodgkin's disease. (Phase III)

Investigators:

Principal: Johannes Blom, M.D.

Associate: Henry Keys, MAJ, MC, USA

Objectives: 1. To compare long-term, multiple-agent chemotherapy either alone or in combination with total nodal radiotherapy with total nodal radiation therapy alone.

2. To compare tolerance of patients to these treatments of various intensities.

3. To compare the quality of response, duration of response and survival rates of the therapeutic groups.

4. To compare tolerance of therapy for patients with and without prior splenectomy for staging.

5. To study patterns of relapse in the various study groups.

Technical Approach: Regimen I: total nodal radiation therapy with the mantle port above the diaphragm and inverted "Y" below the diaphragm plus the spleen or splenic pedicle area and optionally the porta hepatis.

Regimen II: chemotherapy consisting of:

vincristine 1.4 mg/M^2/week IV x 2 with a maximum dose of 2.0 mg

plus

procarbazine 50.0 mg on day 1 p.o.
100.0 mg on day 2 p.o.
100.0 mg/M^2/day on days 3-14 p.o.

plus

BCNU 80.0 mg/M^2 IV on day 1

Each course will consist of 2-weeks treatment and 2-weeks rest.

The 2nd and 3rd course will be as described above with the deletion of prednisone.

The 4th course is the same as the 1st course with prednisone included.

The 5th and 6th course is the same as the 2nd and 3rd course - vincristine/procarbazine/BCNU with the prednisone.

Maintenance therapy will be given for 3 years consisting of:

chlorambucil 6.0 mg/M^2/day p.o.

Regimen III: Chemotherapy followed by radiation therapy.

Six cycles of chemotherapy as outlined under regimen II will be followed by a 2-month rest period and then total nodal radiation as described under regimen I.

No maintenance drugs will be given.

Progress & Results: WRAMC has entered 10 patients, 3 of whom obtained complete remission, 5 a partial remission and 2 patients were disqualified. One patient with a complete remission relapsed on day 203. The other 2 complete remissions remain in remission 293 and 642 days respectively. Duration of partial remissions continues from 57 to 157 days.

CALGB has entered 121 patients, 102 of whom were evaluable in June 1977. Response rates do not seem to be significantly different in the four treatment arms. Remission duration is also similar in the different treatment arms.

Conclusions: Too early

Funding Requirements: See introductory remarks to Annual Research Report

Publications: None

Type of Report: Interim

Work Unit No.: 1533

Title of Project: ALGB Protocol 7461 - Add. 3: Primary Treatment of Multiple Myeloma: Comparison of L-PAM (NSC 8806) plus Prednisone (NSC 10023) and BCNU (NSC 409962) plus Prednisone and CCNU (NSC 79037) plus Prednisone with or without Intermittent Vincristine (NSC 67574) and Prednisone. A Phase III Study.

Investigators:

Principal: Johannes Blom, M.D.

Objectives: 1. To compare the relative response inducing capabilities of CCNU plus prednisone, BCNU plus prednisone, and L-PAM plus prednisone in multiple myeloma.

2. To study the effectiveness of intermittent reinforcement doses of vincristine and prednisone added to the therapies described under 1 in multiple myeloma.

Technical Approach:

Regimen I - L-PAM 150 mcg/kd/day x7 p.o. plus
Prednisone 0.8 mg/kg/day x14 p.o. beginning on day 1
0.4 mg/kg/day x14 p.o.
0.2 mg/kg/day x14 p.o.

3-4 weeks after the loading dose of L-PAM when the peripheral counts are rising daily maintenance with L-PAM will be started in a dose of 50.0 mcg/kg/day p.o.

Regimen II - BCNU 150 mg/m^2 I.V. every 6 weeks plus
Prednisone as described under Regimen I

Regimen III - CCNU 100 mg/m^2 p.o. every 6 weeks plus
Prednisone as described under Regimen I

On day 154 (at the end of week 22) all patients who have not shown relapse or progressive disease will be randomized again.

Regimen A indicates that the patient should continue with initial therapy and receive no additional therapy.

Regimen B indicates that the patient should continue with his initial therapy and in addition receive
Vincristine 1.0 mg/m^2 I.V. x1 on day 154 and every 8 weeks therafter plus
Prednisone 0.6 mg/kg/day p.o. x7 beginning on day 154 and every 8 weeks thereafter

During maintenance phase the interval between doses of BCNU or CCNU is increased from 6 to 8 weeks.

Addendum #1 dated 24 January 1975 adds

Regimen IV - L-PAM 16.0 mg/m^2 I.V. every 2 weeks for 6 weeks and then every 4 weeks plus
Prednisone as outlined under Regimen I

Addendum #2 dated 23 March 1976 provides for modification of the I.V. L-PAM dose in patients with impaired renal function.

Addendum #3 dated 29 April 1977 discontinues Regimen II and III, BCNU and CCNU.

Progress & Results: WRAMC entered five patients. One had progressive disease, one had improvement of the serum proteins but developed extensive myopathy and subsequently expired, one patient obtained a good remission but relapsed on day 593, one patient had response but was disqualified because of erroneous maintenance, and the fifth patient is in response by day 47.

CALGB entered 484 patients, 447 of whom were evaluable in June 1977. The responses to the intravenous l-phenylalanine mustard is considerably better than responses in the other three regimens.

Conclusions: As above.

Funding Requirements: See introductory remarks to Annual Research Report.

Publications: None

Type of Report: Interim

Work Unit No.: 1534

Title of Project: ALGB Protocol #7521. Add. 3 : A comparative study of the value of immunotherapy with MER as adjuvant to induction and two maintenance chemotherapy programs in acute myelocytic leukemia. A Phase III Study.

Investigators:

Principal: Johannes Blom, M.D.

Objectives: 1. To determine whether early immunotherapy with MER in conjunction with a primary chemotherapeutic induction program will increase the probability of achieving complete remission.

2. To compare remission duration and survival with respect to two types of maintenance chemotherapy, one using monthly courses of Ara-C and 6-thioguanine, the other using alternating monthly courses of Ara-C and thioguanine with vincristine, dexamethasone and Ara-C.

3. To determine by concurrent comparative controlled trial if MER immunotherapy will prolong remission duration and increase the survival time of patients with AML receiving either of two plans of concomitant chemotherapy.

4. To determine if the frequency of CNS leukemia and of toxicity to chemotherapy is different in patients randomly assigned to receive maintenance chemotherapy with or without vincristine and dexamethasone and with or without MER.

5. In two programs of maintenance chemotherapy, to assess the morbidity and toxicity of MER immunotherapy.

Technical Approach: Induction Regimen is the same for all patients, consisting of:

cytosine arabinoside 100 mg/M^2/day by continuous infusion from day 1 thru day 7

plus

Daunorubicin 45 mg/M^2/day by rapid IV injection on days 1, 2 and 3.

If the bone marrow contains more than 5% leukemic cells, patient will receive a second course of cytosine arabinoside, this time for 5 days plus daunorubicin for 2 days.

Patients will be randomized for MER or no MER during the Induction Phase.

The Maintenance Phase consists of:

Regimen A: 5-day courses repeated every 4 weeks, consisting of:

cytosine arabinoside 100 mg/M^2 s.c. every 12 hrs for 10 injections
plus
thioguanine 100 mg/M^2 p.o. every 12 hrs for a total of 10 doses
plus
MER

Regimen B: cytosine arabinoside 100 mg/M^2 s.c. every 12 hrs for a total of 10 injections
plus
thioguanine 100 mg/M^2 p.o. every 12 hrs for a total of 10 doses

Alternate with Second five day course:

cytosine arabinoside 100 mg/M^2 s.c. injection every 12 hrs, total of 10 injections on days 1 thru 5
plus
vincristine 2 mg/M^2, 2 mg max., on day 1 of this course
plus
dexamethasone 8 mg/M^2, not to exceed 16 mg p.o. in 3 divided doses daily on day 1 thru 5
plus
intradermal MER

Regimen C: 5-day course repeated every 4 weeks
cytosine arabinoside 100 mg/M^2 s.c. every 12 hrs, total of 10 injections
plus
thioguanine 100 mg/M^2 p.o. every 12 hrs for a total of 10 doses

In all 3 regimens, the 3rd, 7th, 11th and 15th courses are substituted for cytosine arabinoside 100 mg/M^2 s.c. every 12 hours, total of 10 injections
plus
daunorubicin 45 mg/M^2/day by rapid IV injection on days 1 and 2.

Progress & Results: WRAMC has entered 27 patients. Eleven patients obtained a complete remission, 4 of whom relapsed from 114 to 250 days, 4 patients had a partial remission 2 of whom relapsed, and 12 patients did not respond and had progressive disease, 11 of whom subsequently expired. Seven patients remain in complete remission from 40 to 517 days. CALGB has entered 634 patients, 430 of whom were evaluable in June 1977. Fifty-one per cent in the regimen with the MER obtained an M1 marrow and 43% in the regimen without MER. This is not a statistically significant difference. Patients with negative skin tests prior to treatment seem to have a somewhat better response with MER than without MER. Patients with positive skin tests do not seem to benefit from the addition of MER to the treatment regimen.

Conclusions: It seems that MER in the induction phase may benefit patients who have negative skin tests prior to treatment. It is too early for evaluation of duration of response.

Funding Requirements: See introductory remarks to Annual Research Report.

Publications: None

Type of Report: Interim

Work Unit No.: 1535

Title of Project: ALGB Protocol #7581 - Add. #1: Long term surgical adjuvant systemic chemotherapy with or without adjuvant immunotherapy in mammary carcinoma. A comparative study of cytoxan, vincristine, methotrexate, 5-fluorouracil, prednisone vs. cytoxan, methotrexate, 5-fluorouracil vs. cytoxan, methotrexate, 5-fluorouracil, MER. A Phase III Study.

Investigators:

Principal: Johannes Blom, M.D.

Objectives: 1. 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 given 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 mastectomy. A corollary comparison to the historical information 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.

2. The duration of the disease free interval in each treatment will be evaluated for its impact upon survival, as well as serving the principle measure of therapeutic effect.

3. Patient tolerance to the therapeutic regimens will be evaluated.

4. The site of first recurrence of disease will be evaluated to determine any differential action of the regimens.

5. An attempt will be made to determine if patient age, primary lesion size, or the utilization of postoperative radiotherapy influenced the recurrence or survival rates, as well as the location of the site of first recurrence.

Technical Approach: Induction Phase Treatment Schedules

Regimen I: cytoxan 80 mg/M^2/day orally for 42 consecutive days
plus
methotrexate 40 mg/M^2/week IV for 6 consecutive weeks
EXCEPT patients 60 years of age are to receive 30 mg/M^2/week IV

plus
5-FU 500 mg/M^2/week IV for 6 consecutive weeks
plus
vincristine 1.0 mg/M^2/week IV for 6 consecutive weeks (max. dose 1.5 mg per dose)
plus
prednisone 40 mg/M^2/day orally daily in 3 divided doses for 21 consecutive days followed by half dose for 2 consecutive days; followed by quarter dose for 2 consecutive days; followed by one-eighth dose for 2 days, then discontinue

Treatment will begin no sooner than two weeks and not later than four weeks following mastectomy in those patients not receiving postoperative radiotherapy. If postoperative radiotherapy is given, chemotherapy will begin no sooner than 4 weeks and not later than 8 weeks following completion of radiotherapy (and not later than 16 weeks from mastectomy)

Regimen II: cytoxan 80 mg/M^2/day orally for 42 consecutive days
plus
Methotrexate 40 mg/M^2/week IV for 6 consecutive weeks, EXCEPT patients 60 years or older are to receive 30 mg/M^2/week IV
plus
5-FU 500 mg/M^2/week IV for 6 consecutive weeks

Regimen III: cytoxan 80 mg/M^2/day orally for 42 consecutive days
plus
methotrexate 40 mg/M^2/week IV for 6 consecutive weeks EXCEPT patients 60 years or older are to receive 30 mg/M^2/week IV
plus
5-FU 500 mg/M^2/week IV for 6 consecutive weeks
plus
MER 200 ug intradermally in each of 5 sites (total 1 mg) at weeks 1, 3 and 5

MER should be swirled in the vial and repeatedly tilted in the tuberculin syringe to assure its homogeneous suspension. Injection sites should be chosen to drain into different node groups. Do not inject lymphadematous arm.

Maintenance Phase Treatment Schedules for First Year of Maintenance

Regimen I: cytoxan 100 mg/M^2/day orally days 1-14 of each cycle
plus
methotrexate 40 mg/M^2 IV day 1 and day 8 of each cycle EXCEPT patients 60 years or older are to receive 30 mg/M^2
plus
5-FU 500 mg/M^2 IV day 1 and day 8 of each cycle
plus
vincristine 1.0 mg/M^2 IV day 1 and day 8 of each cycle (max. dose 1.5 mg/dose)
plus
prednisone 40 mg/M^2/day orally days 1-14 of each cycle DO NOT TAPER

Each cycle of therapy is 28 days in length and recycle begins on day 29. This regimen should be given for 10 cycles, after which patients enter the Second Year of Maintenance (see below)

Regimen II: cytoxan 100 mg/M^2/day orally days 1-14 of each cycle
plus
methotrexate 40 mg/M^2 IV days 1 and day 8 of each cycle EXCEPT patients 60 years or older are to receive 30 mg/M^2
plus
5-FU 500 mg/M^2 IV day 1 and day 8 of each cycle

Each cycle of therapy is 28 days in length and recycle begins on day 29. This regimen should be given for 10 cycles, after which patients enter the Second Year of Maintenance

Regimen III: cytoxan 100 mg/M^2/day orally days 1-14 of each cycle
plus
methotrexate 40 mg/M^2 IV days 1 and day 8 of each cycle EXCEPT patients 60 years or older are to receive 30 mg/M^2
plus
5-FU 500 mg/M^2 IV day 1 and day 8 of each cycle
plus
MER 200 ug intradermally in each of 5 sites (total 1 mg) on day 8 of each cycle.

Each cycle of therapy is 28 days in length and recycle begins on day 29. This regimen should be given for 10 cycles, after which patients enter the Second Year of Maintenance.

Maintenance Phase Treatment Schedule for Second Year of Maintenance

At the scheduled time for the 11th cycle of maintenance therapy, patients in all 3 regimens will begin a uniform treatment schedule. Vincristine and prednisone are dropped from regimen I; MER is dropped from regimen III and the length of a treatment cycle is increased to 56 days.

In the second year of maintenance, <u>all patients</u> will receive:

cytoxan 100 mg/M^2/day orally days 1-14 of each cycle
plus
methotrexate 40 mg/M^2 IV on day 1 and day 8 of each cycle EXCEPT patients 60 years or older are to receive 30 mg/M^2
plus
5-FU 500 mg/M^2 IV on day 1 and day 8 of each cycle

Each cycle of therapy is 56 days in length and recycle begins on day 57. Treatment should continue for 6 cycles, after which, all treatment is discontinued and the patient should be observed indefinitely at 3 month intervals without further therapy.

Progress & Results: WRAMC has entered 16 patients, one of whom has relapsed. All other patients remain in complete remission from 92 to 612 days.

CALGB has entered 307 patients, 273 of whom were evaluable in June 1977. Toxicity in all arms has been acceptable and MER toxicity has been tolerable although several patients have had their treatment interrupted to allow healing of local MER lesions. Patients with prior radiation had more severe depression of white counts than patients without prior radiation. Number of failures in the coded treatment regimens are 5, 9 and 7, at times varying from 69 to 620 days.

Conclusions: Too early

Funding Requirements: See introductory remarks to Annual Research Report

Publications: None

Type of Report: Interim

Work Unit No.: 1536

Title of Project: ALGB Protocol 7531 - Add. 0: Treatment of Chronic Myelocytic Leukemia with the Aim of the Prevention of Myeloblastic Transformation. A Phase III Study.

Investigators:

Principal: Johannes Blom, M.D.

Objectives: To determine whether longer courses of CCNU and Ara-C, begun at time of diagnosis and without Busulfan, can postpone or prevent myeloblastic transformation.

Technical Approach:

Regimen I - Busulfan 4 mg/m^2 daily for induction and maintenance

Regimen II - CCNU 35 mg/m^2 orally every 6 weeks plus Ara-C 50 mg/m^2 s.c. q 12 hours on days 1-5 of each 6-week cycle

Progress & Results: WRAMC has entered three patients. One had progressive disease on day 84, one patient refused treatment after he was randomized and the third patient was disqualified because of prior treatment.

ALGB has entered 92 patients, 81 of whom were evaluable in June 1977. Control of the disease with CCNU and Ara-C is more difficult to obtain. The study has not progressed long enough to determine any difference in blastic transformation in the two treatment regimens, however sufficient patients have been entered and therefore the study was discontinued on 16 June 1977.

Conclusions: CML is easier to control with busulfan than with the combination of CCNU and Ara-C. Any difference in the development of blastic crisis cannot be evaluated at the present time.

Funding Requirements: See introductory remarks to Annual Research Report.

Publications: None

Type of Report: Terminated

Work Unit No.: 1537

Title of Project: ALCB Protocol #7551, Add. #0: Combination chemotherapy and radiotherapy for stage IV Hodgkin's disease, no prior treatment.

Investigators:

Principal: Johannes Blom, M.D.

Objectives: 1. To compare the response rates and remission durations observed with 6 or 12 monthly cycles of chemotherapy.

2. To determine the effectiveness of a combined approach by radiotherapy and multiple drug chemotherapy in the control of Stage IV Hodgkin's Disease as compared to multiple drug chemotherapy alone.

3. To explore whether early reduction of bulk disease by radiotherapy is beneficial in controlling the disease.

4. To explore the ability of radiotherapy to eradicate residual microscopic disease in patients with apparent complete remission after a full course of multiple drug chemotherapy.

5. To explore the ability of radiotherapy to eradicate disease in patients with apparent partial remission after a full course of multiple drug chemotherapy.

Technical Approach: Regimen I: CCNU 75 mg/M^2 p.o. day 1
vinblastine 4 mg/M^2 IV day 1 and 8
procarbazine 100 mg/M^2 p.o. day 1 thru 14
prednisone 40 mg/M^2 p.o. day 1 thru 14

Prednisone is given on course 1 and 4 only.

After each course of treatment, there is a 2 week rest period. This treatment is given for a total of six courses.

Regimen II: Is the same as Regimen I, but the therapy should continue for a total of twelve courses.

The prednisone is given on courses 1, 4, 7 and 10 only.

Regimen III: Consists of six months of chemotherapy, as outlined in Regimen I, plus radiation therapy.

Regimen IV: Is the same chemotherapy as outlined in Regimen I, to be given for three courses, after which radiation therapy will be administered. Four weeks after the completion of radiation, another three courses of chemotherapy will be administered.

The radiation therapy will consist of 2500 rads to be given in 4 weeks to areas of gross disease known to exist prior to the start of chemotherapy.

All patients will be placed on maintenance therapy which will consist of:

chlorambucil 6 mg/M^2 given daily for a total of 3 years, or until progressive disease.

Progress & Results: WRAMC has entered one patient who had a partial remission on day 258 and subsequently expired.

CALGB has entered 101 patients, 82 of whom were evaluable in June 1977. Complete and partial remissions in the four treatment regimens vary from 82% to 91%. It is too early for any reliable relapse figures.

Conclusions: Too early

Funding Requirements: See introductory remarks to Annual Research Report

Publications: None

Type of Report: Interim

Work Unit No.: 1538

Title of Project: CALGB Protocol #7552. Add. #2: Combination chemotherapy and immunotherapy for previously treated Stage III and IV Hodgkin's Disease.

Investigators:

Principal: Johannes Blom, M.D.

Objectives: 1. To compare remission rates and the remission duration of two, four drug chemotherapy regimens employing completely different agents in previously treated patients with Stage IV Hodgkin's Disease.

2. To compare the response rates and remission durations of the repetitive use of the four drug combination regimens with alternating cycles of the two entirely different regimens, thus exposing the patient to eight drugs.

3. To compare the efficacy of chemotherapy and chemo-immunotherapy with respect to response rates, remission durations, and toxicity.

4. To assess immunological tests of delayed MER hypersensitivity as prognostic indices, and to compare the effects of different combined chemotherapies and of immunotherapy upon them.

Technical Approach: Regimen IA or Regimen IB

CCNU 75 mg/M^2 p.o. on day 1
plus
vinblastine 4 mg/M^2 IV on days 1 and 8
plus
procarbazine 100 mg/M^2 p.o. on days 1 thru 14
plus
prednisone 40 mg/M^2 p.o. on days 1 thru 14

Prednisone is included in courses 1, 4, 7, and 10 only.

Patients randomized to Regimen IA will receive in addition to this chemotherapy, immunotherapy with MER 200 ug intradermally in each of 5 sites, to be administered on the first day of each course.

Patients randomized to Regimen IB will receive chemotherapy only.

Regimen IIA bleomycin 5 units/M^2 I.V. on days 1
or Regimen IIB and 8
plus
adriamycin 50 mg/M^2 I.V. on day 1
(max. total dose 550 mg/M^2)
plus
vincristine 1.4 mg/M^2 I.V. on days 1
and 8
plus
streptozotocin 1500 mg/M^2 I.V. on
days 1 and 8

After each 2 week treatment period, there will be a 2 week rest period. Patient will receive a total of 12 courses.

Patients randomized to Regimen IIA will receive in addition to this chemotherapy, immunotherapy with MER, 200 ug intradermally in each of 5 sites, to be administered on the first day of each course.

Patients randomized to Regimen IIB will receive Regimen II chemotherapy only.

Regimen IIIA Will consist of 12 courses of induction
or Regimen IIIB therapy. Each course will consist of
2 weeks of chemotherapy, and a course
will be given every 4 weeks.

Regimen III will be alternate courses of Regimen I and Regimen II chemotherapy.

Patients randomized to Regimen IIIA will receive in addition to this chemotherapy, immunotherapy with MER, 200 ug intradermally in each of 5 sites, to be administered on the first day of each course.

Patients randomized to Regimen IIIB will receive Regimen III chemotherapy only.

Maintenance Therapy: At the end of 12 courses of induction therapy, all patients who are in complete or partial remission status will receive: chlorambucil 6 mg/M^2/day

Addendum 2 : Decrease in dose of Streptozotocin.

Progress & Results: WRAMC entered four patients, all of whom obtained a complete remission and remain in remission from 93 to 540 days.

CALGB entered 121 patients, 102 of whom were evaluable in June 1977. Complete and partial remissions are fairly equal in all three treatment regimens varying from 76 to 96%. Presently there is no difference in response rate between regimens with and without immunotherapy.

Conclusions: Too early

Funding Requirements: See introductory remarks to Annual Research Report.

Publications: None

Type of Report: Interim

Work Unit No: 1539

Title of Project: CALGB Protocol 7541 - Add. 0: Combination Chemotherapy and Immunotherapy in Previously Untreated Stage III and IV Neuroblastoma. A Phase III Study.

Investigators:

Principal: Johannes Blom, M.D.

Objectives:

1. To evaluate the role of triple drug (vincristine, cyclophosphamide, adriamycin) combination chemotherapy in previously untreated Stage III and IV neuroblastoma.

2. To evaluate the immunological responsiveness of patients with disseminated neuroblastoma, both prior to and during therapy.

3. To evaluate the role of an agent (MER) thought capable of stimulating immunological responsiveness both in terms of the patient's immunological reactivity (to skin tests) and in terms of possible contribution to prolongation of median survival.

Technical Approach:

Regimen I - Vincristine 1.5 mg/m^2 I.V. on days 1, 8, 29, 36, 57, 64, 85, 92 and for a similar schedule (two weeks out of every four) for a total of one year plus
Cyclophosphamide 500 mg/m^2 on days 1, 57 and every two months thereafter for one year, and 1,000 mg/m^2 on days 29, 85 and every two months thereafter for one year plus
Adriamycin 25 mg/m^2/day x3 I.V. beginning on days 1, 57 and every two months thereafter

Regimen II - Vincristine 1.5 mg/m^2 I.V. on days 1, 8, 29, 36, 57, 64, 85, 92, and for a similar schedule (two weeks out of every four) for a total of one year plus
Cyclophosphamide 500 mg/m^2 on days 1, 57 and every two months thereafter for one year, and 1,000 mg/m^2 on days 29, 85 and every two months thereafter for one year plus
Adriamycin 25 mg/m^2/day x3 I.V. beginning on days 1, 57 and every two months thereafter plus
MER 200 ug in each of 5 sites (total 1 mg) intradermally on days 8, 36, 64 and every fourth week thereafter.

Treatment Procedure:

1. Laparotomy and tumor resection will be performed as appropriate.

2. Patients with Stage III disease will have scheduled radiotherapy beginning 5 weeks after the first course of chemotherapy, providin hematologic thresholds are satisfied

3. Patients with Stage IV disease will have radiotherapy used electively, beginning 5 weeks after the first dose of chemotherapy providing hematologic thresholds are satisfied, unless emergency indicated appearance beforehand. The radiation therapy will be given in 180-200 rad fractions at a rate of one fraction per day for a total schedule of five fractions per week.

Progress & Results: Two patients have been entered at WRAMC. One patient is in a complete remission and the second patient has had considerable regression in tumor size.

CALGB entered 24 patients, 14 of whom were evaluable in June 1977. Five of nine on one regimen had a complete remission and two of five in the other regimen had a complete remission and one of five a partial remission. Two patients relapsed at 12 and 14 months.

Conclusions: Both regimens demonstrate responses. It is too early for any comparison.

Funding Requirements: See introductory remarks to Annual Research Report.

Publications: None

Type of Report: Interim

Work Unit No.: 1540

Title of Project: CALGB Protocol 7582 - Add. 0: Procarbazine, Vinblastine and Dactinomycin in Stage III and IV Melanoma with or without MER. (A Comparative Phase II Study.)

Investigators:

Principal: Johannes Blom, M.D.

Objectives:

1. To assess the effectiveness of a combination of procarbazine, vinblastine and dactinomycin against metastatic melanoma.

2. To assess the effectiveness of the addition of MER to the above program.

3. To informally assess the effectiveness of radiation therapy in those patients who develop CNS metastasis during the course of treatment with procarbazine, vinblastine and dactinomycin with or without MER.

Technical Approach:

Regimen I - Vinblastine 5 mg/m^2 I.V. on days 1 and 8
Dactinomycin 0.5 mg/m^2 I.V. on days 1 and 8
Procarbazine 100 mg/m^2 p.o. on days 1 thru 10

This treatment regimen is repeated every 28 days.

Regimen II - The chemotherapy regimen is the same as Regimen I, plus 1 mg of MER intradermally on day 1 of each cycle. The 1 mg of MER will be divided in 5 equal doses, and injected at 5 different sites.

Progress & Results: WRAMC entered one patient who had progressive disease.

CALGB has entered 115 patients, 102 of whom were evaluable in March 1977. Response rates are disappointingly low, 5% and 8% complete remissions and 17% and 8% partial remissions respectively; with most responses in patients with only skin and/or nodal involvement. The arm with MER did not confer any advantage. This study was closed to entry on 18 September 1976.

Conclusions: Results with this regimen disappointingly low. MER does not offer any advantage.

Funding Requirements: See introductory remarks to Annual Research Report.

Publications: None

Type of Report: Terminated

Work Unit No.: 1541

Title of Project: CALGB Protocol #7542. Add. #0: Protocol for the treatment of Non-Hodgkin's lymphomas in children. Methotrexate, Vincristine, Dexamethasone, Cyclophosphamide, 6-Mercaptopurine plus radiation therapy to involved areas. A Phase III Study.

Investigators:

Principal: Johannes Blom, M.D.

Associate: Frederick B. Ruymann, M.D., LTC, MC

Objectives: 1. To develop a combined radiotherapy/chemotherapy regimen which will increase the survival and cure rate in children with non-Hodgkin's lymphoma not previously treated.

2. To determine the efficacy of the addition of daily oral 6-MP and weekly oral MTX to standard lymphoma-type maintenance with high dose intermittent Cyclophosphamide and Vincristine-steroid reinforcements in Stage I, II and III disease.

3. To test the efficacy of high dose Methotrexate (500 mg/M^2) in a maintenance program for patients with Stage IV disease.

Technical Approach: Stages I, II and III Induction Treatment will consist of:
vincristine 2 mg/M^2 IV x 4 doses given on days 1, 8, 15 and 22
plus
dexamethasone 6 mg/M^2 p.o. daily x 4 weeks and then taper
plus
methotrexate 12 mg/M^2 IT given on days 1, 8, 15 and 22
Radiation therapy will begin on day 15.

Maintenance:

Regimen I: cyclophosphamide 500 mg/M^2 IV push x 1 beginning on day 36 of study and every 4 weeks thereafter
plus
vincristine 2 mg/M^2 IV push x 1 beginning on day 36 and every 4 weeks thereafter
plus

dexamethasone 6 mg/M^2 p.o. daily x 7 days every 4 weeks beginning on day 64 of study
plus
methotrexate 15 mg/M^2 p.o. once weekly
plus
6-MP 75 mg/M^2 p.o. daily

Regimen II: cyclophosphamide 1,000 mg/M^2 IV push x 1 beginning on day 36 and every 4 weeks thereafter
plus
vincristine 2 mg/M^2 IV push x 1 beginning on day 36 and every 4 weeks thereafter
plus
dexamethasone 6 mg/M2 p.o. daily x 7 days every 4 weeks beginning on day 64

Treatment of Stage IV Disease - Induction

All Stage IV patients will receive the same therapy, consisting of:

vincristine 2 mg/M^2/week IV x 4 doses given on days 1, 8, 15 and 22
plus
dexamethasone 6 mg/M^2 p.o. daily x 4 weeks and then taper
plus
methotrexate 12 mg/M^2 IT given on days 1, 8, 15 and 22

Radiation therapy will begin on day 15.

Intensification

Regimen III: vincristine 2 mg/M^2/week IV x 3 doses given on days 36, 57 and 78 of study
plus
dexamethasone 6 mg/M^2 p.o. daily x 1 week beginning on days 57 and 78
plus
methotrexate 12 mg/M^2 IT given on days 36, 57 and 78. IT MTX should be given between 1/2 and 2 hours after the start of the high dose MTX (500 mg/M^2)
plus

methotrexate 500 mg/M^2 1/3 IV push and 2/3 IV drip over 24 hours given on days 36, 57 and 78
plus
leucovorin twenty-four hours after completion of each course of MTX (500 mg/M^2), leucovorin will be given at 12 mg/M^2 IV or IM once only as "rescue"

Maintenance therapy will begin on day 85 after the completion of the Intensification

Regimen IV: cyclophosphamide 500 mg/M^2 IV push x 1 beginning on day 36 of study and every 4 weeks thereafter
plus
vincristine 2 mg/M^2 IV push x 1 beginning on day 36 and every 4 weeks thereafter
plus
dexamethasone 6 mg/M^2 p.o. daily x 7 days every 4 weeks beginning on day 64
plus
methotrexate 15 mg/M^2 p.o. once weekly
plus
6-MP 75 mg/M^2 p.o. daily
plus
IT Methotrexate 12 mg/M^2 IT given on days 36, 43 and 50

The radiation dose is 3500 rads in 3-1/2 to 4 weeks, given in 180 to 200 rad fractions.

Progress & Results: WRAMC entered three patients. One had improvement, but rapidly recurrent disease; the second patient has no evidence of disease on day 133 and the third patient is presently on treatment.

CALGB entered 21 patients, 16 of whom were evaluable in June 1977. Fifteen of these 16 patients had either complete or partial remission with remission durations from 58 to 442 days. Two patients relapsed on day 74 and day 222.

Conclusions: These are active regimens, however no comparison can be made at the present time.

Funding Requirements: See introductory remarks to Annual Research Report.

Publications: None

Type of Report: Interim

Work Unit No.: 1542

Title of Project: CALGB Protocol 7583. Adjuvant Chemotherapy in Osteogenic Sarcoma, Adriamycin vs. Sequential Adriamycin, High Dose Methotrexate - Citrovorum Factor vs. Sequential Adriamycin - Cyclophosphamide. Addendum 1, dated 17 June 1976, entries to Regimen III were temporarily suspended pending further pilot observation.

Investigators:

Principal: Johannes Blom, M.D.

Associate: Frederick B. Ruymann, M.D., LTC, MC

Objectives:

1. To determine the relative duration of disease-free interval and survival for patients treated with six courses of adriamycin alone, or sequential adriamycin and high dose methotrexate, followed with citrovorum factor rescue, or sequential adriamycin and high dose cyclophosphamide after radical operation of either primary lesion, or complete resection of pulmonary metastasis or osteogenic sarcoma.

2. To determine the patient's tolerance to these different therapeutic regimens.

Technical Approach:

Regimen I - Adriamycin 30 mg/m^2 daily for 3 days I.V. to be repeated every 4 weeks for 6 courses. The treatment will begin no sooner than 4 days and not later than 4 weeks following operation.

Regimen II:
Day 1 to 3, adriamycin 30 mg/m^2 I.V. daily
Day 28 to 30, adriamycin 30 mg/m^2 I.V. daily
Day 56, high dose methotrexate 200 mg/kg body weight I.V. infusion for 6 hours. Two hours after completion of the high dose MTX infusion, administer citrovorum factor 12 mg I.M. every 6 hours for 12 doses.
Day 77, high dose methotrexate 200 mg/kg I.V. infusion for 6 hours. Two hours after completion of infusion, administer citrovorum factor 12 mg I.M. every 6 hours for 12 doses.
Day 105, repeat the above adriamycin, high dose MTX plus citrovorum factor sequence at the same dose and interval for a total of 6 courses for each agent.

Regimen III - Day 1 to 3, adriamycin 30 mg/m^2 I.V. daily
Day 28 to 30, adriamycin 30 mg/m^2 I.V. daily
Day 56, cyclophosphamide 25 mg/kg I.V. every other day for 5 doses over a 10-day period
Day 98, repeat the above adriamycin, cyclophosphamide sequence for a total of 6 courses for adriamycin and 3 courses for cyclophosphamide.

Progress & Results: WRAMC entered two patients, both of whom are presently on treatment.

CALGB entered 22 patients, 20 of whom were evaluable in June 1977. Two patients on regimen II have relapsed on day 75 and day 118 before completing treatment. The remaining 18 patients continue on protocol from one to ten months.

Conclusions: Too early

Funding Requirements: See introductory remarks to Annual Research Report.

Publications: None

Type of Report: Interim

Work Unit No.: 1543

Title of Project: CALGB Protocol #7651. A Phase III Study. Combination chemotherapy of Stage III and IV lymphocytic lymphoma (lymphosarcoma) in adults with or without radiotherapy consolidation. Induction: Vincristine, Streptonigrin, Prednisone Maintenance: Cyclophosphamide. Addendum 1.

Investigators:

Principal: Johannes Blom, M.D.

Objectives: 1. To confirm the improvement of remission induction in advanced lymphocytic lymphoma by adding streptonigrin to vincristine and prednisone in this phase.

2. To explore the therapeutic potential of radiation therapy in advanced lymphocytic lymphoma following an initial remission induction with combination chemotherapy by comparing identical chemotherapy maintenance arms, one of which adds radiotherapy to initially involved areas.

Technical Approach: Induction vincristine 1 mg/M^2 IV on days 1, 8, 15, 22, 29 and 36
plus
streptonigrin 1 mg/M^2 p.o. spaced over 1 hr on days 1, 8, 15, 22, 29 and 36
plus
prednisone 40 mg/M^2 p.o. daily in one dose for 42 days, then tapered by halving the dose every 2 days until the patient is receiving 5 mg/M^2/day, after 3 days of which it should be stopped

Consolidation and Maintenance Regimens for Patients Who Have Obtained at Least a Partial Remission

Regimen I: Maintenance should begin immediately with:
cyclophosphamide 1 gm/M^2 IV
plus
vincristine 1 mg/M^2 (max. 2 mg) IV
plus
prednisone 40 mg/M^2 p.o. daily (in one dose) x 7 days

Regimen II: Patients will receive an interim consolidation phase with chemotherapy and radiotherapy to the areas initially involved at the time of entry to the study, to be followed by maintenance chemotherapy. The map of disease distribution prepared on entry will be used to define the sites of radiotherapy.

Radiation therapy will be given in a dose of 3500 to 4000 rads in 4 weeks to the sites of involvement. The daily dose will vary from 180 to 200 rads.

Progress & Results: WRAMC entered nine patients; four obtained complete remission, and are in remission from 50 to 427 days; two patients had progressive disease; three are too early for evaluation.

CALGB entered 109 patients, 67 of whom were evaluable in June 1977. Complete and partial response rate is 85%.

Conclusions: Too early

Funding Requirements: See introductory remarks to Annual Research Report

Publications: None

Type of Report: Interim

Work Unit No.: 1544

Title of Project: CALGB Protocol #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
Addendum 1

Investigators:

Principal: Johannes Blom, M.D.

Objectives: 1. To confirm the improvement of remission induction in advanced histiocytic lymphoma by adding streptonigrin to vincristine and prednisone in this phase.

2. To explore the therapeutic potential of radiation therapy in advanced histiocytic lymphoma following initial remission induction with combination chemotherapy.

3. To evaluate the benefits of a consolidation phase with Adriamycin.

Technical Approach: The induction program for all patients will consist of:

vincristine 1 mg/M^2 IV on days 1, 8, 15, 22, 29 and 36
plus
streptonigrin 1 mg/M^2 p.o. spaced over 1 hour on days 1, 8, 15, 22, 29 and 36
plus
prednisone 40 mg/M^2 p.o. daily in one dose for 42 days, then tapered by halving the dose every 2 days until the patient is receiving 5 mg/M^2 per day, after 3 days of which it should be stopped.

Consolidation and Maintenance will be begun on all patients who have obtained at least a partial remission after 6 weeks of induction.

Regimen I: Patients are begun on maintenance chemotherapy immediately, consisting of
cyclophosphamide 1 gm/M^2 IV
plus
vincristine 1 mg/M^2
plus
prednisone 40 mg/M^2 p.o. daily for 7 days.

The first 4 courses are to be given at 3 week intervals, after the 4th course continued every 4 weeks.

Regimen II: Patients will receive consolidation phase with 3 courses of adriamycin, vincristine and prednisone after completion of the 6 week induction phase. Consolidation phase consists of:
adriamycin 60 mg/M^2 IV q 3 weeks x 3
plus
vincristine 1 mg/M^2 IV q 3 weeks x 3
plus
prednisone 40 mg/M^2/day p.o. x 7 days q 3 weeks.

Maintenance phase is to be started 3 weeks after the last consolidation course, and will consist of: cyclophosphamide, vincristine and prednisone every 4 weeks, as outlined under Regimen I.

Regimen III: The patient is to receive an interim consolidation phase with chemotherapy and radiotherapy to the areas initially involved at the time of entry into the study, to be followed by maintenance chemotherapy.

The radiotherapy shall be delivered to all areas with known initial involvement which were greater than 2 cm in diameter at time of entry into study. If the total aggregate field area is under 300 sq cm the dose will be 4000 rads in 4-5 weeks. If the fields required measure greater than 300 sq cm, the dose will be 3000 rads in 4-5 weeks. This dose will be delivered in 180 to 200 rad fractions daily.

Progress & Results: WRAMC entered three patients, one of whom obtained a complete remission; the other two patients did not respond and are off the study.

CALGB entered 63 patients, 36 of whom were evaluable in June 1977. Complete and partial responses were 67%. Because newer treatment modalities have become available in histiocytic lymphomas, this study was closed on 16 June 1977.

Conclusions: Although responses are adequate newer treatments have become available, and therefore the study was closed.

Funding Requirements: See introductory remarks to Annual Research Report.

Publications: None

Type of Report: Final

Work Unit No.: 1545

Title of Project: CALGB Protocol 7382 - Add. 2. Chemotherapy of Metastatic or Recurrent Inoperable Carcinoma of the Breast Following Ovariectomy in Pre-Menopausal Patients: Vincristine (NSC 67574), 5-Fluorouracil (NSC 19893), Methotrexate (NSC 740), Cyclophosphamide (NSC 26271), and Prednisone (NSC 10023). A Phase III Study. Both addenda were dose modifications.

Investigators:

Principal: Johannes Blom, M.D.

Objectives: To determine if combination chemotherapy is better than single drug chemotherapy following oophorectomy.

To determine if oophorectomy plus chemotherapy is more effective than oophorectomy alone as the first treatment following the appearance of metastasis in pre-menopausal women.

To determine whether prolonged survival is dependent on the institution of chemotherapy within two weeks following oophorectomy.

Technical Approach: Patients with good risk or a poor risk will be randomized separately.

Regimen I - To be instituted within 14 days following oophorectomy
Vincristine .025 mg/kg I.V. weekly x8
5-Fluorouracil 12 mg/kg I.V. weekly x8
Methotrexate .75 mg/kg I.V. weekly x8
Cyclophosphamide 2 mg/kg p.o. daily x8 weeks
Prednisone .75 mg/kg p.o. daily x 3 weeks, then taper over one week
.50 mg/kg p.o. daily x 3 weeks, then taper over one week
.50 mg/kg p.o. daily x4 days
.25 mg/kg p.o. daily x3 days

If less than 50% regression has been obtained within the 8 weeks, 4 additional weeks of treatment will be given.

Maintenance Regimen:
Vincristine .025 mg/kg I.V. every 6 weeks
5-Fluorouracil 12 mg/kg I.V. every 3 weeks
Methotrexate .75 mg/kg I.V. every 3 weeks
Cyclophosphamide 2 mg/kg p.o. daily
Prednisone .75 mg/kg p.o. daily for 7 days every 6 weeks with vincristine dose

Regimen II - Treatment to be initiated within 14 days following oophorectomy
Cyclophosphamide 15 mg/kg I.V. twice weekly for a maximum of 8 doses or to toxicity

Maintenance:
Cyclophosphamide 2 mg/kg p.o. daily for 5 consecutive days every week until relapse

Regimen III - Following oophorectomy the patient will be observed for response without further treatment if the patient is in remission or has no further regression. Any time there is evidence of progression of disease the patient will be treated with chemotherapy as outlined in Regimen I.

Progress & Results: WRAMC entered one patient who did not respond.

CALGB entered 139 patients, 123 of whom were evaluable in June 1977. The time to response and the survival particularly of good risk patients is better with chemotherapy than with the oophorectomy followed by observation until relapse. The study was closed to entry on 1 May 1977.

Conclusions: Pre-menopausal patients with recurrent inoperable carcinoma of the breast benefit from oophorectomy followed immediately by chemotherapy.

Funding Requirements: See introductory remarks to Annual Research Report.

Publications: None

Type of Report: Final

Work Unit No.: 1546

Title of Project: CALGB Protocol 7611, Add. 0: Treatment of Primary Untreated Acute Lymphocytic Leukemia in Patients under 20 Years with Vincristine (NSC 67574), Prednisone (NSC 10023), Methotrexate (NSC 740), L-Asparaginase (NSC 109229), and 6-Mercaptopurine (NSC 755), plus Cranial Irradiation. A Phase III Study.

Investigators:

Principal: Johannes Blom, M.D.

Associate: Frederick B. Ruymann, M.D., LTC, MC

Objectives:
1. To test whether the substitution of high dose methotrexate with leucovorin rescue for cranial irradiation decreases the frequency of occurrence of CNS leukemia.
2. To test whether remission consolidation with 3 courses of high dose methotrexate with leucovorin rescue prolongs complete remission duration.

Technical Approach:

Induction Phase: Vincristine 2 mg/m^2 I.V. x4 on days 1, 8, 15 and 22 (maximum dose 2 mg)
Prednisone 40 mg/m^2/day p.o. daily x4 weeks and then tapered over 10 days
Methotrexate 12 mg/m^2 IT x3 on days 15, 22, 29 (maximum dose 15 mg)
L-Asparaginase 1000 iu/kg/day I.V. on days 29 thru 38

After completion of the L-asparaginase treatment patients will be randomized between:

Regimen A - High dose Methotrexate 500 mg/m^2 over 24 hours on days 43, 64 and 85
Leucovorin 24 hours after completion of each course of methotrexate at a dose of 12 mg/m^2 plus
Methotrexate 12 mg/m^2 IT x3 doses on days 43, 64 and 85
Vincristine 2 mg/m^2 I.V. on day 78
Prednisone 40 mg/m^2 p.o daily x7 days beginning on day 78

Regimen B - Methotrexate 12 mg/m^2 IT x3 on days 43, 50 and 57 (maximum dose of IT MTX 15 mg)
Cranial Irradiation 2400 rads over a period of 16 days beginning on day 43

Upon completion of this so-called sanctuary phase of treatment patient will be placed on

Maintenance Phase: 6-Mercaptopurine 90 mg/m^2 /day p.o.
Methotrexate 15 mg/m^2/week p.o. on the first day of each week, plus
Reinduction courses of vincristine plus prednisone at 6, 12, 16, 20 and 24 weeks. Beginning 28 weeks after L-asparaginase two doses of vincristine one week apart and 14 days of prednisone will be given every 12 weeks until relapse.

Progress & Results: WRAMC has entered no patients.

CALGB has entered 46 patients, 31 of whom were evaluable in June 1977. 97% of these patients obtained a bone marrow remission which is higher than on several previous protocols. Results of other objectives of the study are too early.

Conclusions: Too early

Funding Requirements: See introductory remarks to Annual Research Report.

Publications: None

Type of Report: Interim

Work Unit No.: 1547

Title of Project: CALGB Protocol 7682, Add. 0: Combination Chemotherapy or Chemoimmunotherapy for Metastatic Recurrent or Inoperable Carcinoma of the Breast. Three Treatment Regimens: Cyclophosphamide (NSC 26271), Adriamycin (NSC 123127), 5-Fluorouracil (NSC 19893) vs. Cyclophosphamide, Adriamycin, 5-Fluorouracil, Vincristine (NSC 67574), Prednisone (NSC 10023) vs. Cyclophosphamide, Methotrexate (NSC 740), 5-Fluorouracil, All with or without MER (NSC 143769). A Phase III Study.

Investigators:

Principal: Johannes Blom, M.D.

Objectives:
1. To compare the remission induction frequency and duration of the CAF and the CMF combination individually with the five-drug combination, CAFVP, which appears to be the best combination program in CALGB study 7482.
2. 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.
3. To determine whether MER alters the tolerance of normal tissues to these combination chemotherapeutic programs.
4. To establish the initial immunocompetence of patients with metastatic breast cancer as determined by skin testing; to assess whether the administration of MER alters that initial status, and to test whether any such changes are associated with a prolongation of disease control.
5. To determine the influence of metastatic disease patterns at time of first recurrence following mastectomy and at onset of protocol upon the remission induction frequency and remission duration.

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.

Regimen IA - Cyclophosphamide 100 mg/m^2/day p.o. days 1-14
Methotrexate 40 mg/m^2 I.V. days 1 and 8; for patients >60 years 30 mg/m^2 I.V. days 1 and 8
5-Fluorouracil 500 mg/m^2 I.V. days 1 and 8

This cycle is to be repeated every 28 days.

Regimen IB - Same as Regimen IA plus MER.

Regimen IIA - Cyclophosphamide 100 mg/m^2/day p.o. days 1-14
Adriamycin 25 mg/m^2 I.V. days 1 and 8 to a total dose of 450 mg/m^2
5-Fluorouracil 500 mg/m^2 I.V. days 1 and 8

This cycle is to be repeated every 28 days.

Regimen IIB - Same as Regimen IIA plus MER.

Regimen IIIA - Cyclophosphamide 100 mg/m^2 p.o. days 1-14
Adriamycin 25 mg/m^2 I.V. days 1 and 8 to a total dose of 450 mg/m^2
5-Fluorouracil 500 mg/m^2 I.V. days 1 and 8
Vincristine 1.0 mg/m^2 I.V. days 1 and 8 with maximum dose of 2 mg
Prednisone 40 mg/m^2/day p.o. days 1-14

Each cycle is to be repeated every 28 days.

Regimen IIIB - Same as Regimen IIIA plus MER.

Progress & Results: WRAMC has entered 7 patients on study. One had progressive disease on day 179; one patient expired on day 130; one patient has had a partial response and has been on study for 145 days; one patient is in a complete remission on day 127; the remaining three patients are too early for evaluation.

CALGB entered 67 patients, 55 of whom were evaluable in June 1977. No complete remissions were observed. Partial remissions and improvements are approximately equal in all treatment regimens. Presently there is no evidence of any difference between regimens with MER or without.

Conclusions: Too early

Funding Requirements: See introductory remarks to Annual Research Report.

Publications: None

Type of Report: Interim

Work Unit No.: 1548

Title of Project: CALGB Protocol 7681, Add. 0: Investigation of the Effects of Adriamycin with and without Added MER in Soft Tissue Sarcomas. A Phase III Study.

Investigators:

Principal: Johannes Blom, M.D.

Objectives:
1. To compare the effectiveness of adriamycin alone and adriamycin together with MER in the induction of remission in inoperable soft tissue sarcomas.
2. To compare the effectiveness of single monthly doses and three consecutive daily doses/month of adriamycin.
3. To determine whether the addition of MER to adriamycin treatment affects the duration of remission in patients with inoperable soft tissue sarcomas.

Technical Approach:

Regimen IA - Adriamycin 75 mg/m^2 I.V. every four weeks to a maximum dose of 550 mg/m^2

Regimen IB - Adriamycin plus MER 1 mg intracutaneously on day 1 and 8 to be repeated every four weeks

Regimen IIA - Adriamycin 25 mg/m^2 on days 1, 2 and 3, to be repeated every four weeks to a maximum dose of 550 mg/m^2

Regimen IIB - Adriamycin plus MER 1 mg intracutaneously on day 1 and 8 every four weeks.

Patients who are in a remission or who have no evidence of progressive disease and who have received the maximum dose of 550 mg/m^2 of adriamycin will be placed on cyclophosphamide 750 mg/m^2 day 1 only, vincristine 1.5 mg/m^2 I.V. daily day 1 and weekly thereafter for a total of 8 doses, plus DTIC 250 mg/m^2 I.V. days 1 thru 5. Cyclophosphamide and DTIC will be repeated every four weeks. Patients who are on MER should be continued on MER.

Progress & Results: WRAMC entered one patient who had progressive disease and expired.

CALGB has entered 11 patients, 11 of whom were evaluable in June 1977. Two patients had a partial remission, three remained unchanged and six had progressive disease.

Conclusions: Too early

Funding Requirements: See introductory remarks to Annual Research Report.

Publications: None

Type of Report: Interim

Work Unit No.: 1551

Title of Project: CALGB Protocol 7612, Add. 1: Therapy of Acute Lymphocytic Leukemia in Adults: A Comparison of Vincristine, Prednisone and L-Asparaginase with or without Daunorubicin for Induction with Central Nervous System Prophylaxis with Radiotherapy and Intrathecal Methotrexate and Maintenance with 6-Mercaptopurine and Methotrexate with or without Immunotherapy with MER. A Phase III Study.

Investigators:

Principal: Johannes Blom, M.D.

Objectives:
1. To test whether the addition of daunorubicin to vincristine and prednisone followed by L-asparaginase will increase the frequency of complete remission in adults with acute lymphocytic leukemia.
2. To test whether the addition of immunotherapy in the form of MER to maintenance therapy prolongs remission durations.
3. To assess the efficacy of employing CNS prophylaxis with intrathecal methotrexate plus cranial irradiation immediately following remission induction.

Technical Approach:

Regimen I - Vincristine 2 mg I.V. once weekly x3 plus
Prednisone 40 mg/m^2 p.o. daily for 21 days plus
L-asparaginase 500 i.u./kg M.V. daily for 10 days beginning on day 22

Regimen II - Vincristine 2 mg I.V. weekly x3
Prednisone 40 mg/m^2 p.o. daily for 21 days
Daunorubicin 45 mg/m^2 I.V. daily for 3 days followed by
L-asparaginase 500 i.u./kg I.V. daily for 10 days starting on day 22
Prednisone will be tapered over 10 days

Progress & Results: WRAMC entered one patient who is too early for evaluation.

CALGB entered 22 patients, 15 of whom were evaluable in June 1977. Responses in the coded treatment arms are 33% and 67%.

Conclusions: Too early

Funding Requirements: See introductory remarks to Annual Research Report.

Publications: None

Type of Report: Interim

Work Unit No.: 1552

Title of Project: CALGB Protocol 7632, Add. 0: Chemotherapy in Indolent Chronic Lymphocytic Leukemia. A Phase III Study. (Chlorambucil (Leukeran) NSC 3088)

Investigators:

Principal: Johannes Blom, M.D.

Objectives:
1. To test whether the administration of intermittent chlorambucil in patients with indolent CLL of categories 2 and 3 delays or possibly prevents the development of aggressive CLL in comparison to a no treatment group.
2. To test whether the administration of intermittent chlorambucil prolongs survival with the disease in comparison to a no treatment group.

Technical Approach: Patients will be kept for 12 weeks in an observation period. Afterwards they will be randomized to Regimen I, which is no treatment, or Regimen II, which is treatment with intermittent chlorambucil 0.5 mg/kg p.o. every 28 days.

Progress & Results: WRAMC has entered no patients.

CALGB entered two patients in June 1977.

Conclusions: Too early

Funding Requirements: See introductory remarks to Annual Research Report.

Publications: None

Type of Report: Interim

Work Unit No.: 1553

Title of Project: CALGB Protocol 7661, Add. 0: Multiple Myeloma Resistant to Melphalan Treated with Cyclophosphamide (NSC 26271), Adriamycin (NSC 123127), BCNU (NSC 409962), and Prednisone (NSC 10023). A Phase III Study.

Investigators:

Principal: Johannes Blom, M.D.

Objectives:
1. To test whether patients previously treated with melphalan but with recurrent disease will respond to the combination of adriamycin, cyclophosphamide and prednisone.
2. To test whether patients previously treated with melphalan but with recurrent active disease will respond to the combination of adriamycin, BCNU and prednisone.

Technical Approach:

Regimen I -
Adriamycin 30 mg/m^2 I.V. on day 1
Cyclophosphamide 400 mg/m^2 I.V. on day 1
Prednisone 0.6 mg/kg p.o. daily for 7 days (in 3 equally divided doses beginning on day 1)

Then, every 3 weeks:
Adriamycin 30 mg/m^2 I.V. x1
Cyclophosphamide 400 mg/m^2 I.V. x1
Prednisone 0.6 mg/kg/day x7 (in 3 equally divided doses)

Regimen II -
Adriamycin 30 mg/m^2 I.V. on day 1
BCNU 75 mg/m^2 I.V. on day 1
Prednisone 0.6 mg/kg p.o. daily for 7 days (in 3 equally divided doses beginning on day 1)

Then every 3 weeks:
Adriamycin 30 mg/m^2 I.V. x1
Prednisone 0.6 mg/kg p.o. daily for 7 days (in 3 equally divided doses)

Then every 6 weeks:
BCNU 75 mg/m^2 I.V. x1

Progress & Results: WRAMC has entered no patients.

CALGB has entered two patients in June 1977.

Conclusions: Too early

Funding Requirements: See introductory remarks to Annual Research Report

Publications: None

Type of Report: Interim

Work Unit No.: 1601

Title of Project: WRAMC Protocol 7207 - Add. 0: Use of pentamidine isethionate in pneumonia caused by or suspected to be caused by pneumocystis carinii.

Investigators:

Principal: Johannes Blom, M.D.

Objectives: Treatment of pneumonia caused by or suspected to be caused by pneumocystis carinii with pentamidine isethionate.

Technical Approach: Pentamidine isethionate 4 mg/kg I.V. for 12-14 days.

Progress and Results: Six patients have been entered, five of whom had good clearing of the infiltrative process. The sixth patient had pulmonary hemorrhage at autopsy and no evidence of pneumocystis.

Conclusions: As has been demonstrated by many investigators, pentamidine is an effective drug in the treatment of pneumocystis carinii pneumonia. No new patients have been placed on study during FY 1977, as other drugs have become available. However, pentamidine isethionate remains a very useful agent.

Funding Requirements: See introductory remarks to Annual Research Report.

Publications: None

Type of Report: Interim

Work Unit No.: 1602

Title of Project: WRAMC Protocol 7301 - Add. 0: The Use of Cholestyramine in Metastatic Carcinoma of the Prostate and Ovary and Other Malignancies.

Investigators:

Principal: Johannes Blom, M.D.

Objectives: To observe response in metastatic carcinoma of the prostate and ovary and other malignancies.

Technical Approach: Cholestyramine (questran) 4 mg (one packet) placed in a preferred beverage three times daily. Because of interference with the absorption of lipid soluble vitamins, 2 ml of polyvisol will be administered daily.

Progress & Results: Four patients have been entered on study. Three had no response or progressive disease. One has had minimally progressive disease for about 18 months. One patient was recently entered who had subjective improvement.

Conclusions: No new patients were entered on study during FY 1977, however we remain interested in this study and attempts will be made to place suitable patients on study.

Funding Requirements, FY-78: See introductory remarks to Annual Research Report.

Publications: None

Type of Report: Interim

Work Unit No.: 1603

Title of Project: WRAMC Protocol 7206 - The Use of Methyl-CCNU (1-(2-chloroethyl)-3-(4-methylcyclohexyl)-1-nitrosourea-1)(NSC 95441) in the Treatment of Brain Tumors.

Investigators:

Principal: Johannes Blom, M.D.

Associate: Patrick R. Bergevin, MAJ, MC

Objectives: 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: Patients are divided into good risk and poor risk groups. The good risk group will receive adriamycin 60 mg/m^2 and DIC 250 mg/m^2 for 5 days. The poor risk group will receive adriamycin 45.0 mg/m^2 and DIC 200 mg/m^2 for 5 days.

Progress & Results: Forty-nine patients have been entered on study, 3 of whom are too early for evaluation, 9 are lost to follow-up or no recent information is available, 1 is not evaluable, 11 patients had progressive disease and subsequently expired, 5 patients remain stable or had no response. One patient had an improvement of his clinical condition. Nineteen patients were entered on study after surgery and radiation therapy when their condition was stable. Twelve patients relapsed from 19 to 770 days after entry on the study. Seven patients remain on study from 33 to 520 days.

Conclusions: The efficacy of this treatment for patients with active disease is very minimal. The efficacy of the chemotherapy after surgery and radiation therapy will need further evaluation.

Funding Requirements: See introductory remarks to Annual Research Report.

Publications: None

Type of Report: Interim

Work Unit No.: 1604

Title of Project: WRAMC Protocol 7205 - Phase II Protocol Combination Chemotherapy with Dimethyl-Triazeno Imidazole Carboxamide (DIC) and Adriamycin in Soft Tissue and Bone Sarcomas.

Investigators:

Principal: Johannes Blom, M.D.

Associate: A. Richard Miskoff, MAJ, MC

Objectives:
1. To determine the efficacy of combination chemotherapy with DIC and adriamycin in patients with soft tissue and bone sarcomas.
2. To evaluate the toxicity of this combination of agents.

Technical Approach: Treatment regimen for good risk patients:
Adriamycin 60 mg/m^2 on day 1 in rapid I.V. infusion
DIC 250 mg/m^2 I.V. daily for 5 days

Treatment regimen for poor risk patients:
Adriamycin 45 mg/m^2 on day 1 in rapid I.V. infusion
DIC 200 mg/m^2 I.V. daily for 5 days

Progress & Results: Thirty-six patients have been entered on the study, 5 of whom are still on study and too early for evaluation, 9 patients are lost to follow-up or no recent follow-up is available, 2 patients are not evaluable, 1 patient had a complete remission, 2 a partial remission, 6 had progressive disease, 1 had an improvement, 6 had stable disease or no response. Three patients remain on the study disease free.

Conclusions: Although patients with a variety of sarcomas have been entered on this study, the overall response rate is rather low. However, many of these patients had far-advanced disease.

Funding Requirements: See introductory remarks to Annual Research Report

Publications: None

Type of Report: Interim

Work Unit No.: 1605

Title of Project: WRAMC Protocol 7204 (EST 2372), Add. 2 - Comparison of the Treatment of Metastatic Testicular Tumors with Actinomycin-D, or Actinomycin-D, Bleomycin and Vincristine

Investigators:

Principal: Johannes Blom, M.D.

Objectives: To evaluate the response rate and duration of response to intensive chemotherapy consisting of actinomycin-D, vincristine and bleomycin, or actinomycin-D alone.

Technical Approach:

Regimen A - Actinomycin-D 0.65 mg/m^2 I.V. days 1 through 5
Bleomycin 15 mg/m^2 I.V. days 1, 8 and 15
Vincristine 1 mg/m^2 I.V. days 1 and 8

This cycle is to be repeated every 21 days

Regimen B - Actinomycin-D 0.65 mg/m^2 I.V. days 1 through 5

This cycle to be repeated every 21 days

For maintenance this treatment is given every 30 days for 6 courses and then every 60 days for a total of 2 years.

Progress & Results: WRAMC entered 7 patients, 4 of whom obtained a complete remission. Two of these have relapsed, 2 patients are still in complete remission and being followed at another institution. Two patients had partial remissions and subsequently relapsed. Another patient had progressive disease and subsequently expired. Members of the Eastern Cooperative Oncology Group entered 110 patients.

Conclusions: Although the response rate is better with the combination treatment, survival and duration of response was not any better with the combination treatment. The study was closed to entry on 25 November 1975.

Funding Requirements: See introductory remarks to Annual Research Report

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Publications: Results of this study were presented to the meetings of the American Society of Clinical Oncology in May 1975 in San Diego and May 1976 in Toronto. Publication is presently in preparation.

Type of Report: Final

Work Unit No.: 1608

Title of Project: WRAMC Protocol 7302, Add. 1 - Treatment of Metastatic Malignant Melanoma with a Combination of Imidazole Carboxamide Dimethyl Triazeno (ICDT)(NSC 45388), Methyl-CCNU (NSC 95441) and Vincristine

Investigators:

Principal: Johannes Blom, M.D.

Associate: Patrick R. Bergevin, MAJ, MC

Objectives: 1. To evaluate the response rate to a combination of ICDT, methyl-CCNU and vincristine in the treatment of metastatic melanoma.
2. To evaluate the survival of patients treated in this fashion.

Technical Approach: ICDT 600 mg/m^2 I.V. every 6 weeks
MeCCNU 100 mg/m^2 p.o. every 6 weeks
Vincristine 2.0 mg I.V. every other week

Progress & Results: Twenty patients have been entered on study. Two were unevaluable, one was lost to follow-up, three patients had a complete remission, one had a partial remission, six had no change, four had progressive disease, one had an improvement and one remained stable. One patient has remained in remission for 34 months. This study was closed to entry on 31 May 1977.

Conclusions: Complete and partial remissions are 20% which is not better than with ICDT alone.

Funding Requirements: See introductory remarks to Annual Research Report

Publications: None

Type of Report: Final

Work Unit No.: 1609

Title of Project: WRAMC Protocol 707, Add. 5 - Comparative Study of Synchronizing Chemotherapy in Adult Solid Tumors Utilizing MTX (with CF Reversal) Followed by Ara-C and Bleomycin.

Investigator:

Principal: Johannes Blom, M.D.

Technical Approach:

0-18 hrs:	MTX 240 mg/m^2 in a constant infusion
18 hrs:	Citrovorum factor 340 mg/m^2 in a 5-minute infusion
20-42 hrs:	Ara-C, from 750 to 1250 mg/m^2, in a constant infusion
44 hrs:	Citrovorum factor 360 mg/m^2 in a 5-minute infusion

These courses are repeated as necessary.

Progress & Results: Twenty-seven patients have been entered, 25 of whom were evaluable; 12 patients with acute myelocytic leukemia were entered, 1 had a complete remission, 1 had a partial remission, and 9 had no response. Eight patients with acute lymphocytic leukemia were entered, 1 had a complete remission, 2 had a partial remission, 1 had an improvement, and 4 had no response. Five patients with lymphosarcoma cell leukemia were entered, 1 was not evaluable, 1 had a complete remission, 1 had an improvement and 2 had progressive disease. Two patients with acute erythroblastic leukemia were entered, 1 was not evaluable and 1 had no response.

Conclusions: This is an effective regimen for patients who are resistant to methotrexate or cytosine arabinoside given in a more conventional schedule. Because presently other effective chemotherapeutic agents are available entry of patients onto this study was discontinued on 31 May 1977.

Funding Requirements: See introductory remarks to Annual Research Report

Publications: None

Type of Report: Final

Work Unit No.: 1610

Title of Project: WRAMC Protocol 7307, Add. 1 - Phase I-II Evaluation of Dibromodulcitol in Previously Treated Patients with Metastatic Carcinoma of the Breast. (NCI B-134)

Investigator:

Principal: Johannes Blom, M.D.

Objectives: Evaluation of dibromodulcitol in patients who have been treated with and are resistant to standard modes of therapy.

Technical Approach: Patients will be treated with dibromodulcitol by mouth on days 1-10 of each 21 day cycle.

Progress & Results: Ten patients have been entered on the study, one of whom is too early for evaluation, one patient was not evaluable, eight patients had progressive disease.

Conclusions: Twenty-nine patients were entered by all participating institutions. In four patients a response was observed.

Funding Requirements: See introductory remarks to Annual Research Report

Publications: Tormey, D.C., Falkson, G., Perlin, E., Bool, J., Blom, J., and Lippman, M. Evaluation of an intermittent schedule of dibromodulcitol in breast cancer. Cancer Treatment Reports 60(11):1593-1596, November 1976.

Type of Report: Interim

Work Unit No.: 1611

Title of Project: WRAMC Protocol 7403, Add. 1 - Treatment of Advanced Lung Cancer with a Combination of 1,2-di (3, 5-dioxylpiperazine-1yl-propane)(ICRF-159) and Adriamycin with Cyclophosphamide Maintenance

Investigators:

Principal: Johannes Blom, M.D.

Associate: J. Phillip Olmert, Jr., MAJ, MC

Objectives:
1. To evaluate the combination of ICRF-159 and adriamycin in the treatment of carcinoma of the lung.
2. To measure survival in patients so treated.
3. To evaluate the combination of cyclophosphamide and ICRF-159 in the maintenance phase.

Technical Approach: Adriamycin 50 mg/m^2 I.V. on day of each 28-day cycle
ICRF-159 300 mg/m^2 p.o. every 8 hours on days 4, 5 and 6 of each 28-day cycle

Addendum 1 decreased the dose of ICRF-159 from 300 to 200 mg/m^2 p.o. every 8 hours on days 4, 5 and 6 of each 28-day cycle.

Progress & Results: WRAMC has entered 32 patients on study, 2 had a partial response but have subsequently relapsed after 2 and 6 months of response respectively. Twenty-seven patients have expired.

Conclusions: The combination of adriamycin and ICRF-159 is an ineffective treatment regimen in patients with advanced lung cancer.

Funding Requirements: See introductory remarks to Annual Research Report

Publications: A manuscript is ready to be presented to Cancer Chemotherapy Reports for publication.

Type of Report: Final

Work Unit No.: 1612

Title of Project: WRAMC Protocol 7401 - Treatment of Advanced Lung Cancer with a Combination of Emetine (NSC 33669) and Cyclophosphamide or 1-(2-chlorethyl)-3-cyclohexyl-1-nitrosourea (CCNU)(NSC 79037).

Investigators:

Principal: Johannes Blom, M.D.

Associate: Patrick R. Bergevin, MAJ, MC

Objectives: 1. To evaluate the effectiveness of cyclophosphamide or CCNU and emetine in the treatment of advanced lung cancer.
2. To measure survival in patients so treated.

Technical Approach: Patients who have received no prior treatment with cyclophosphamide will receive:
Cyclophosphamide 1.2 gm/m^2 I.V. every 3 weeks
Emetine 2 mg/kg I.V. every week for 6 weeks

Patients who have received prior treatment with cyclophosphamide will receive:
CCNU 100 mg/m^2 p.o. every 6 weeks
Emetine 2 mg/kg I.V. every week for 6 weeks

Progress & Results: Twelve patients were entered on study. Three were not evaluable, one was disqualified, six had progressive disease, and two had no change. All these patients had previous chemotherapy and were in the final stage of their disease. Because of these disappointing results, the study was discontinued in January 1976.

Conclusions: Combination of emetine and cyclophosphamide or CCNU is ineffective in the treatment of advanced lung cancer.

Funding Requirements: See introductory remarks to Annual Research Report.

Publications: None

Type of Report: Final

Work Unit No.: 1613

Title of Project: WRAMC Protocol 7402 - Protocol for Adjuvant Therapy of Stage II Testicular Carcinoma with Chemotherapy (Actinomycin-D and Chlorambucil), Radiation Therapy or Chemotherapy plus Radiation Therapy after Retroperitoneal Lymph Node Dissection.

Investigators:

Principal: Anthony Borski, COL, MC
Stanley Chism, MAJ, MC
Johannes Blom, M.D.

Objectives: To determine which is the best form of therapy in patients with stage II carcinoma of the testicle after radical lymphadenectomy.

Technical Approach: Patients who had all tumor removed at the time of radical retroperitoneal lymph node dissection are randomly assigned to one of three forms of therapy, radiation therapy, chemotherapy or chemotherapy plus radiation therapy. The chemotherapy will be continued intermittently for three years and will consist of actinomycin-D and chlorambucil. Patients who have residual tumor in the abdomen after radical retroperitoneal dissection are randomized between two forms of therapy, radiation therapy and chemotherapy plus radiation therapy.

Progress & Results: This study was activated in January 1974. Four patients have been entered at WRAMC. Two patients had chemotherapy and two patients had radiation therapy. Both patients who received chemotherapy relapsed. No follow-up is presently available on the patients who had radiation therapy. This was a national study under the auspices of the National Cancer Institute in which several institutions participated, however because of lack of entry of patients onto the study it was discontinued on 26 January 1976.

Conclusions: None

Funding Requirements: See introductory remarks to Annual Research Report

Publications: None

Type of Report: Interim

Work Unit No.: 1617

Title of Project: WRAMC Protocol 7105 - Phase II Study of the Combined Use of Bleomycin and Adriamycin in the Treatment of Adult Malignancies

Investigators:

Principal: Johannes Blom, M.D.

Associate: Patrick Bergevin, MAJ, MC

Objectives: To determine the effectiveness of the combination of bleomycin and adriamycin in patients with hepatomas.

Technical Approach: Adriamycin 15 mg/m^2 I.V. daily for 4 consecutive days
Bleomycin 15 mg/m^2 I.V. on days 1 and 4 of each week

This course is to be repeated every 21 days.
Maximum dose of bleomycin 200 mg/m^2
Maximum dose of adriamycin 550 mg/m^2

Progress & Results: Six patients have been entered on the protocol. One was not evaluable, 2 had no response, 3 had partial remissions and subsequently progression of disease. Entry of patients on this study was discontinued on 31 May 1977.

Conclusions: Although the number of patients is small this combination does have activity in hepatoma which is a tumor very resistant to chemotherapy.

Funding Requirements: See introductory remarks to Annual Research Report

Publications: None

Type of Report: Final

Work Unit No.: 1620

Title of Project: WRAMC Protocol 7305 - Study to Evaluate the Effect of Estrogen Therapy with and without Additive Chemotherapy in the Management of Recurrent Mammary Carcinoma in Post-Menopausal Women (B124). Cooperative study by the National Cancer Institute, WRAMC and Bethesda Naval Hospital.

Investigators:

Principal: Johannes Blom, M.D.

Objective: To determine whether drugs given together with hormones is more effective than the sequential use of hormones and drugs.

Technical Approach: All patients receive diethylstilbesterol (DES) 5 mg tid p.o.

Patients with a CR or PR at 8-12 weeks are randomly allocated to receive:

I DES 5 mg tid p.o. continuously

II DES 5 mg tid p.o. continuously
Cytoxan 100 mg/m^2 q.d. p.o. on days 1-14 of each cycle
Methotrexate 40 mg/m^2 I.V. on days 1 and 8 of each cycle
5-Fluorouracil 600 mg/m^2 I.V. on days 1 and 8 of each cycle

Each cycle is 28 days long.

Progress & Results: Four patients were entered at WRAMC, three of whom had progressive disease and one remained stable. A total of 23 patients were entered on the study, 2 of whom had a partial remission, 13 had progressive disease, 2 were disqualified, 4 were too early, on 2 no evaluation was available at the most recent analysis in June 1977. Entry of patients on this study was discontinued in May 1977.

Conclusions: None available.

Funding Requirements: See introductory remarks to Annual Research Report

Publications: None

Type of Report: Final

Work Unit No.: 1621

Title of Project: WRAMC Protocol 7208 - Phase II Protocol 5-Azacytidine in Acute Leukemia

Investigators:

Principal: Johannes Blom, M.D.

Associate: A. Richard Miskoff, MAJ, MC

Objectives: To determine the effectiveness of 5-azacytidine in the treatment of acute leukemia.

Technical Approach: 5-azacytidine 250 mg/m^2 I.V. daily x5 in 3 divided infusions every 8 hours
This course to be repeated every 2 weeks.

Progress & Results: Thirteen patients have been entered on the study, 2 patients are lost to follow-up, 1 had an inadequate treatment, 1 had a complete remission, 1 a partial remission and 8 had no response.

Conclusions: 5-azacydidine is a moderately active agent in patients with advanced acute leukemia. Experiences in other institutions indicate a somewhat better response rate in combination with other agents.

Funding Requirements: See introductory remarks to Annual Research Report

Publications: None

Type of Report: Interim

Work Unit No.: 1625

Title of Project: WRAMC Protocol 7304 - Study to Evaluate the Effect of Oophorectomy with and without Adjuvant Chemotherapy in the Management of Recurrent Mammary Carcinoma in Pre-Menopausal Women. (B-123)

Investigators:

Principal: Johannes Blom, M.D.

Objectives: To determine any difference in duration and quality of response between the use of chemotherapy in sequence and starting it 12 weeks after the removal of the ovaries.

Technical Approach: All patients receive oophorectomy by laparotomy. Patients who have no change or a CR or PR are randomly allocated to receive either:

I No further treatment or

II Cytoxan 100 mg/m^2 p.o. q.d. on days 1-14 of each cycle
5-Fluorouracil 600 mg/m^2 I.V. on day 1 and 8 of each cycle

Each cycle is 28 days long.

Progress & Results: This is a cooperative study with the National Cancer Institute, National Naval Medical Center and WRAMC. WRAMC has entered 3 patients, none of whom had response. Twenty-seven patients have been entered in total by the cooperating institutions, 3 of whom had a complete remissions, 2 an improvement and 14 had progressive disease as analyzed in June 1977. Entry of patients into the study was discontinued on 31 May 1977.

Conclusions: As above

Funding Requirements: See introductory remarks to Annual Research Report

Publications: None

Type of Report: Final

Work Unit No.: 1626

Title of Project: WRAMC Protocol 7405, Add. 1 - Treatment of Advanced Renal Cell Carcinoma with a Combination of 1-(chlorethyl)-3-cyclohexyl-1-nitrosourea (CCNU)(NSC 79037) and Bleomycin (NSC 125066).

Investigators:

Principal: Johannes Blom, M.D.

Associate: Ivan P. Law, MAJ, MC
Daniel H. Cox, MAJ, MC
Bernhard T. Mittemyer, COL, MC

Objectives: 1. To evaluate the effectiveness of CCNU and bleomycin in the treatment of advanced renal cell carcinoma.
2. To measure survival in patients so treated.

Technical Approach:

Induction: All patients will receive
CCNU 130 mg/m^2 p.o. every 6 weeks
Bleomycin 15 mg I.V. once a week

Maintenance: All patients who are in complete remission or a partial remission after three courses of induction regimen will receive:
CCNU 130 mg/m^2 p.o. every 6 weeks
Bleomycin 15 mg I.V. every three weeks, not to exceed the maximum total dose of 210 mg/m^2

Progress & Results: Twenty-six patients have been entered on the study, on 6 of these patients no recent follow-up is available. Eight patients were entered for adjuvant treatment, 2 of whom relapsed at 165 and 222 days. The remaining 6 patients remain without evidence of disease from 227 to 995 days. All 12 patients who had metastatic disease had no response to the treatment, had progressive disease and subsequently expired.

Conclusions: The number of patients entered in the adjuvant group is too few to make any conclusions at this time.

Funding Requirements: See introductory remarks to Annual Research Report

Publications: None

Type of Report: Interim

Work Unit No.: 1627

Title of Project: WRAMC Protocol #7404 - Add. #1: Immunological evaluation and immunotherapy of patients with carcinoma of the lung.

Investigator:

Principal: Johannes Blom, M. D.

Associate: William J. Heim, MAJ, MC, USA
Robert K. Oldham, M. D.
Robert B. Herberman, M. D.

Objectives: 1. To investigate the therapeutic efficacy of BCG given be dermal scarification in patients with carcinoma of the lung.

2. To investigate the therapeutic efficacy of the combination of BCG and allogeneic tumor cells in patients with carcinoma of the lung.

3. To correlate *in vitro* and *in vivo* measurements of cellular immunity with the clinical status of the patient.

Technical Approach: Patients are put into three broad groups based on the extent of disease:

A patients - surgically resectable disease (no clinically detectable tumor after surgery)

B patients - 1) surgically treatable for the bulk of tumor but not completely locally resectable (palliative resection) or 2) residual disease treatable by local radiotherapy (after 1) or primary disease treatable by radiotherapy (patients in whom surgery is contraindicated)

C patients - patients with metastatic disease.

Radiotherapy: A) "Curative Intent" - B patients: When no distant metastases are clinically detectable, 5000 rads delivered at 900-1000 rads weekly in divided doses to the primary tumor, adjacent mediastinum and hilar region followed by an additional 1000-1500 rads to the primary tumor only.

Progress & Results: Thirty-six patients have been entered on the study. Two patients were not evaluable, 7 patients are lost to follow-up or no recent information is available. One A patient on BCG relapsed at 14½ months, 3 patients are still on study from 12 to 27½ months. Six A patient controls relapsed from 2½ to 30 months, 1 patient is still on study at 12 months. Seven B patients on BCG and chemotherapy relapsed from 1 to 9 months, 1 patient is still on study at 30 months. Two B patients on chemotherapy alone relapsed at 2 and 4 months, 1 patient died at 9 months without any evidence of disease. Three C patients on BCG and chemotherapy had progressive disease and expired at 2, 6 and 6½ months. One patient on chemotherapy with the syndrome of inappropriate ADH secretion went into complete remission and expired 7 months later from a pulmonary embolus without any clinical evidence of disease. Another patient expired 6½ months after entry on the protocol. On 1 January 1977 entry of B and C patients to the study was terminated. Entry of A patients will continue.

Conclusions: Based on the data of all 70 patients entered by all participating institutions it could be concluded that BCG or BCG plus allogeneic tumor cells were unable to prevent recurrences or improve survival in B and C patients, however it is too early to evaluate the effectiveness in Stage A patients, and therefore the study will continue on this category of patients.

Funding Requirements: See introductory remarks to Annual Research Report

Publications: "Immunological Monitoring and Immunotherapy in Carcinoma of the Lung," R.K. Oldham, et al. The results of this study were presented by Dr. Perlin at the Chicago Symposium on Immunotherapy of Solid Tumors in February 1977, the proceedings of which will also be published. An updated presentation was delivered by Dr. Perlin at the American Society of Clinical Oncology 13th Annual Meeting, Denver, held on 16 and 17 May 1977, and published in the proceedings, page 346. Dr. Herberman of the National Cancer Institute presented data of this study at the Second Conference on Lung Cancer Treatment sponsored by The Division of Cancer Treatment, National Cancer Institute, Airlie House, Virginia on 23 May 1977, in a talk titled "Prospects for Immunotherapy of Lung Cancer with Specific Immunoadjuvants." Proceedings of this meeting will be published in the Cancer Treatment Reports.

Type of Report: Interim

Work Unit No.: 1628

Title of Project: WRAMC Protocol 7406 - Chemoimmunotherapy of Carcinoma of the Large Bowel. Revised December 1976.

Investigators:

Principal: Johannes Blom, M.D.

Associate: William J. Heim, MAJ, MC
Richard Miskoff, MAJ, MC
Robert Muir, LTC, MC
Salvatore Scialla, MAJ, MC

Objectives: 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 and MeCCNU.

Technical Approach:

Patients eligible for this protocol can be put into four broad groups based on the extent of disease:

Type II Patients (Stage B_1) - Extension into but not through muscularis
(Stage B_2) - Extension to or through serosa; negative nodes

III Patients (Stage C_1) - Limited to serosa; positive nodes
(Stage C_2) - Extension through serosa; positive nodes

IV Patients - 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 Patients (Stage D) - Distant metastases

Surgery Protocol - Surgical resection of colon and rectal cancer is undertaken when there are no medical or surgical contraindications and the patient consents to surgery.

Radiotherapy Protocol - "Curative intent" for type IV2 patients
"Palliative intent" for type V patients

Chemotherapy Protocol -
Type II and III - Starting about 3 weeks after surgery, but no later than 6 weeks, or when in the judgement of the physician the patient can tolerate chemotherapy,

these patients will receive 5-FU 10 mg/kg p.o. day 1 through 5 each 28 days. If the first two courses are well tolerated without toxicity, this dose will be increased to 15 mg/kg. Chemotherapy will continue at least 2 years.

Type IV2 - After 2 weeks (10 doses) of radiation, these patients will be treated as V patients.

Type IV1 - About 3 weeks after surgery, these patients will be treated as V patients.

Type IV3 - If after radiotherapy the patient is operable and the tumor is completely resectable, the patient will begin chemotherapy as a type II patient. If the tumor is not completely resectable, they will be treated as type V patients. If after radiotherapy the patient is felt to be inoperable he will be treated as a type V patient.

Type V - Will be treated with combined 5-FU and MeCCNU instead of 5-day 5-FU infusion:
5-FU 325 mg/m^2 daily I.V. days 1-5 and 36-40 (1 cycle)
MeCCNU 150 mg/m^2 p.o. day 1

Each cycle is repeated every 10 weeks (day 71).

Immunotherapy Protocol -

Type II and III - Patients randomized to receive BCG will have it administered on days 8, 15, 22 of the chemotherapy cycle for three courses then every 2 weeks (days 8 and 22) thereafter for at least 2 years.

Type IV and V - Patients randomized to receive BCG will have it administered on day 22, 27, 57, etc.

The BCG will be a lyophilized preparation (Phillip Roxane high viability Pasteur BCG). It will be administered as directed on the BCG procedure sheet. For severe local reactions, the next dose of BCG will not be given.

Progress & Results: Fifty-six patients have been entered on study, 14 of whom have no recent follow-up available. Of 19 patients entered for adjuvant treatment, 9 received BCG, 1 of whom has relapsed at 11 months. Ten patients received no BCG, 2 of these relapsed at 13 and 17 months. Of 21 evaluable patients with metastatic disease 5 have expired, 2 have

obtained a response, 1 a complete remission and 1 a partial response, 7 had progressive disease, but patients are still alive and 5 patients could not be evaluated because of protocol violations.

Conclusions: Addition of BCG does not add to the response rate or duration of response of patients with metastatic disease, in fact the results of the chemotherapy are rather poor. For the evaluation of the value of adjuvant treatment, more patients will be studied over a longer period of time.

Funding Requirements: See introductory remarks to Annual Research Report.

Publications: None

Type of Report: Interim

Work Unit No.: 1629

Title of Project: WRAMC Protocol 7407, Add. 3 - Chemoimmunotherapy of Malignant Melanoma

Investigators:

Principal: Johannes Blom, M.D.

Associate: William J. Heim, MAJ, MC
A. Richard Miskoff, MAJ, MC

Objectives: The purpose of this study is to determine if nonspecific immunotherapy with BCG given by dermal scarification is of value in the treatment of malignant melanoma when used after surgery in stage I melanoma and in combination with ICDT (imidazole carboxamide dimethyl triaena) or MeCCNU in stage II-IV melanoma.

Technical Approach:

Patient categories:

Stage I - No metastatic disease. Primary penetrates beyond the immediate subepidermal zone.

Stage II - Local recurrence or metastases within 3 cm of the primary. No distant metastases, no lymph node involvement.

Stage III - Regional metastases more than 3 cm from the primary site.
- A - Intradermal
- B - Regional lymph nodes
- AB - Intradermal and regional nodes. No distant metastases.

Stage IV - Distant metastases

Treatment schedules:

Stage I - Within 2 weeks following surgery, the patient will be treated with BCG by dermal scarification weekly for 3 months and then every other week for 21 months.

Stage II - ICDT 700 mg/m^2 on day 1 of each 21-day cycle. BCG on day 7, 12 and 17 of the 21-day cycle. This treatment will be continued for at least 2 years after complete remission is achieved until there is evidence of progressive disease.

Stage III - These patients will be treated as stage II within 2 weeks of surgery. Therapy will continue for at least 2 years or until there is progression of disease.

Stage IV - As soon as the diagnosis has been established, these patients will receive chemoimmunotherapy as described under stage II. Therapy is continued until there is evidence of disease progression.

Progress & Results: Thirty patients have been entered, 14 of whom have been lost to follow-up or on whom there is no recent data available. Four patients had stage I disease, 1 of whom relapsed at day 284; the remaining 3 remain in remission from 162 to 245 days. Five stage III patients were entered, 1 of whom obtained a complete remission, but relapsed at day 694; a second patient relapsed at day 400; the remaining 3 have progressive disease. Of 7 stage IV patients, 1 is in a partial remission at 61 days, the remaining 6 have progressive disease.

Conclusions: It is too early for conclusions concerning the value of BCG in stage I melanoma, however in far advanced disease this regimen is minimally active.

Funding Requirements: See introductory remarks to Annual Research Report.

Publications: None

Type of Report: Interim

Work Unit No.: 1630

Title of Project: WRAMC Protocol 7408, Add. 1 - Comparative Trial of Tamoxifen and Fluoxymesterone plus Tamoxifen in Metastatic Breast Cancer. (NCI B132)

Investigator:

Principal: Johannes Blom, M.D.

Objectives:
1. Response rates and durations will be compared to assess the relative therapeutic benefit of the two regimens.
2. The quality of survival will be assessed in the two regimens.
3. Prognostic importance of a variety of pretherapy stratification factors will be evaluated.

Technical Approach:

Regimen A - Tamoxifen 2.0 mg/m^2 p.o. t.i.d.

Regimen B - Fluoxymesterone 7.0 mg/m^2 p.o. b.i.d.
Tamoxifen 2.0 mg/m^2 p.o. t.i.d.

The dose of tamoxifen will gradually be increased.

Progress & Results: Fourteen patients have been entered, 3 of whom were lost to follow-up or no recent follow-up was available, 3 patients are too early for evaluation, 5 had no response or progressive disease, 1 patient remains in partial remission at 776 days, 1 patient had improvement and subsequently progressive disease by day 146.

Conclusions: Although the response rates are rather low these are all patients who have far advanced carcinoma of the breast and who have not necessarily proven hormone dependency.

Funding Requirements: See introductory remarks to Annual Research Report.

Publications: *None*

Type of Report: Interim

Work Unit No.: 1631

Title of Project: WRAMC Protocol 7409 - Phase I-II Evaluation of a Combination of BCNU and Methotrexate in Metastatic Breast Cancer

Investigator:

Principal: Johannes Blom, M.D.

Objectives:
1. The dosage of both drugs will be escalated to that which causes moderate reversible side effects.
2. The response rate and duration of response will be evaluated.
3. The impact of age, disease-free interval, metastatic site, response to previous therapy and other potential prognostic factors will be evaluated for their effect upon response rate and duration.
4. The plasma levels of methotrexate following oral administration will be evaluated and this date correlated with tumor response.

Technical Approach: Initial doses at onset of study:
BCNU 50 mg/m^2 I.V. every 28 days
Methotrexate 20 mg p.o. on days 1, 4, 7, 11 and 14 of each 28-day cycle

The dose of BCNU and methotrexate will be increased in a stepwise fashion after each third patient.

Progress & Results: WRAMC has not entered any patients. Entry of patients into the protocol was discontinued on 31 May 1977.

Conclusions: This is a study in cooperation with the National Cancer Institute and results are presently not available.

Funding Requirements: See introductory remarks to Annual Research Report

Publications: None

Type of Report: Final

Work Unit No.: 1632

Title of Project: WRAMC Protocol 7410 - Combination of MeCCNU plus VP 16-213 in the Treatment of Metastatic Adenocarcinoma of the Gastrointestinal Tract and the Pancreas

Investigator:

Principal: Johannes Blom, M.D.

Objectives: To examine the antitumor effect (remission induction and maintenance) of MeCCNU plus VP 16-213 in previously treated and untreated patients with metastatic malignancies of the gastrointestinal tract and of the pancreas.

Technical Approach: MeCCNU 150 mg/m^2 p.o. in a single dose every 6 weeks
VP 16-213 60 mg/m^2 I.V. twice weekly

Progress & Results: Two patients have been entered at WRAMC. One patient died on day 18 of the study; he had marked necrosis of a cutaneous tumor. The second patient had progressive disease. This was a pilot study in cooperation with other members of the Cancer and Acute Leukemia Group B. The combined experience of several other members did not indicate any activity of this combination. The study was discontinued on 20 September 1976.

Conclusions: MeCCNU and VP-16 was not more effective than MeCCNU alone.

Funding Requirements: See introductory remarks to Annual Research Report

Publications: None

Type of Report: Final

Work Unit No.: 1633

Title of Project: WRAMC Protocol 7411, Add. 4 - Evaluation of a Combined Modality Approach to Therapy in Mammary Carcinoma Patients with Tc 1, 2, ea, 4b N+ lesions: A Comparativ Study of Radical Mastectomy, Cyclophosphamide, Methotrexate, 5-Fluorouracil, C. Parvum versus Radical Mastectomy (B135). This is a study in cooperation with the National Cancer Institute.

Investigator:

Principal: Johannes Blom, M.D.

Objectives:

1. It is the specific aim of this study to ascertain if intermittent chemotherapy with or without immunotherapy is superior to no therapy in prolonging the disease-free interval of breast cancer patients who are at high risk for relapse.
2. The relative benefit of chemotherapy alone versus the addition of immunotherapy will also be evaluated with respect to the effect of immunotherapy on the disease-free interval.
3. The duration of the disease-free interval in each regimen will be evaluated for its impact upon survival.
4. Patient tolerance to the therapeutic regimens will be evaluated.
5. The site of first recurrence of disease will be evaluated within each regimen.
6. The study will be integrated with other studies involving the measurement of tumor markers, pathologic staging, clinical parameters and immunologic status.

Technical Approach:

Regimen A - No chemotherapy or immunotherapy

Regimen B - Cyclophosphamide 100 mg/m^2/day p.o. days 1-14 of each 28-day treatment cycle, plus
Methotrexate 40 mg/m^2 I.V. days 1 and 8 of each 28-day cycle
5-fluorouracil 600 mg/m^2 I.V. days 1 and 8 of each 28-day treatment cycle

This regimen is given for 20 cycles. No further chemotherapy will be given.

Regimen C - C. parvum 2.4 mg/m^2 subcutaneous days -7, -6, -5, -4 and -3, followed by no therapy on days -2 and -1. The next day, day 1, initiate therapy with
Cyclophosphamide 100 mg/m^2/day p.o. days 1-14 of each 28-day treatment cycle
Methotrexate 40 mg/m^2 I.V. days 1 and 8 of each 28-day treatment cycle
5-fluorouracil 600 mg/m^2 I.V. days 1 and 8 of each 28-day treatment cycle
C. parvum 2.4 mg/m^2 subcutaneous days 15 and 22 of each 28-day treatment cycle

This regimen is given for 20 cycles. No further chemotherapy or immunotherapy will be given.

Addendum 4 discontinued Regimen A - observation and replaced it with l-phenylalanine mustard 0.15 mg/kg/day x5 days every 6 weeks.

Progress & Results: One patient was entered at WRAMC who developed progressive disease. Entry of patients in this study was discontinued on 31 May 1977.

Conclusions: Results of the study are presently not available.

Funding Requirements: See introductory remarks to Annual Research Report

Publications: None

Type of Report: Final

Work Unit No.: 1634

Title of Project: WRAMC Protocol 7412, Add. 1 - Metastatic Breast Carcinoma Study to Evaluate the Effect of Cyclophosphamide, Adriamycin and 5-Fluorouracil versus Adriamycin, Dibromodulcitol and Vincristine Sequentially Alternating with Cyclophosphamide, Methotrexate and 5-Fluorouracil. This is a study in cooperation with the National Cancer Institute and the National Naval Medical Center.

Investigator:

Principal: Johannes Blom, M.D.

Objectives:
1. The response rates obtained with the two induction regimens will be compared for their value as primary induction therapy.
2. Both programs will be compared for their impact upon response duration.
3. The prognostic importance of selected pre-therapy stratification factors will be assessed as to their impact upon response rates, response durations and survival within each program.

Technical Approach:

Induction Therapy -

Regimen A - Cytoxan 100 mg/m^2 p.o. every day as a single daily dose on days 1-14 of each cycle
Adriamycin 20 mg/m^2 I.V. over 5 minutes on days 1 and 8 of each cycle
5-FU 500 mg/m^2 I.V. push on days 1 and 8 of each cycle

All drugs are recycled to day 1 of the next cycle on day 29 of each cycle, each cycle is 28 days long. Treatment will be continued for 2 full cycles and thereafter until either patient has progressive disease or no change, at which time they will be removed from protocol, or a total dose of 500 mg/m^2 of adriamycin is obtained after which the patient enters the maintenance phase.

Regimen B - Adriamycin 45 mg/m^2 I.V. day 1 of each cycle
Dibromodulcitol 150 mg/m^2 p.o. every day as a single daily dose on days 1-10 of each cycle
Vincristine 1.2 mg/m^2 I.V. days 1, 8 and 15 of each cycle

Each cycle is 28 days long. This regimen is given for 3 consecutive cycles after which the patient is switched to the following Program:

Cytoxan 100 mg/m^2 p.o. every day as a single daily dose on days 1-14 of each cycle
Methotrexate 40 mg/m^2 I.V. push or days 1 and 8 of each cycle
5-FU 600 mg/m^2 I.V. push on days 1 and 8 of each cycle

Each cycle is 28 days long. Treatment on this regimen is continued for 3 full cycles after which the patient undergoes sequential therapy with adriamycin, dibromodulcitol, vincristine alternating with cytoxan, methotrexate, 5-FU after each 3 cycles until either the patient has progressive disease or no change and is removed from protocol or a total dose of 500 mg/m^2 of adriamycin is attained after which the patient enters the maintenance phase.

Maintenance Therapy - This is attained after a cumulative dose of 500 mg/m^2 of adriamycin has been given in both regimens A and B:

Cytoxan 100 mg/m^2 p.o. every day as a single daily dose on days 1-14 of each cycle
Methotrexate 40 mg/m^2 I.V. push on days 1 and 8 of each cycle
5-FU 600 mg/m^2 I.V. push on days 1 and 8 of each cycle

Each cycle is 28 days long.

Progress & Results: Eleven patients were entered on the study, 1 of whom has no recent information available, 2 patients remain in complete remission at 738 and 426 days. Seven patients obtained an improvement, 6 of whom relapsed from 354 to 930 days, 1 patient remains in an improved status at 289 days. One patient had progressive disease. This study was closed to entry on 31 May 1977.

Conclusions: Based on 90 evaluable patients entered by participating institutions there was no significant difference between responses and duration of response in the two treatment regimens.

Funding Requirements: See introductory remarks to Annual Research Report.

Publications: Preliminary results of this study were presented by Dr. Falkson of the University of Pretoria at the 68th Annua Meeting of the American Association of Cancer Research, Denver, Colorado, 1-17 May 1977, page 40 of the published proceedings.

Type of Report: Interim

Work Unit No.: 1642

Title of Project: An Investigation Conducted by the Microbiology Department of the University of Maryland

Investigators:

Principal: Lynn Wilson, Graduate Student, University of Maryland

Associate: Johannes Blom, M.D.

Objectives: This study was undertaken to look at the degree of immunologic recognition invoked in peripheral lymphocytes from infectious mononucleosis, Hodgkin's disease, and American Burkitt's lymphoma patients on challenge by EBV antigen.

Technical Approach: The level of immunologic recognition will be measured by inhibition of macrophage migration from capillary tubes (MIF), i.e. the level of MIF produced by the challenge cells. Preliminary data from infectious mononucleosis challenges indicates an average level of inhibition of 25%, which is significantly greater than normal controls.

Progress & Results: Since the previous report Mr. Wilson has not returned despite several telephone calls. Therefore, this project will be terminated.

Conclusions: None

Funding Requirements: None

Publications: None

Type of Report: Final

Work Unit No.: 1643

Title of Project: The Use of Auto Factor IX Concentrate Dried in the Treatment of Patients with Bleeding due to Factor VIII Inhibitors and the Treatment of Factor VIII Inhibitors

Investigator:

Principal: Daniel B. Kimball, Jr., LTC, MC

Objectives: To study the usefulness, efficacy and safety of auto-factor IX concentrate in the treatment of inhibitors to factor VIII.

Progress & Results: Since the activation of this study no patients with factor VIII inhibitors have been entered on the protocol since none have been identified.

Conclusions: I would like to keep this protocol active in the event that either our Service or the Pediatric Service sees a patient with a factor VIII inhibitor, which prior to the time of activation of the protocol was occurring at the rate of about one to two per year.

Funds Utilized, FY-77: None

Funding Requirements, FY-78: None

Publications: None

Type of Report: Interim

Work Unit No.: 1644

Title of Project: WRAMC Protocol 7501 - Evaluation of Adriamycin and Cis-Platinum Combination Chemotherapy in Treatment of Malignant Disease. A Phase II Study.

Investigators:

Principal: Johannes Blom, M.D.

Associate: William Babcock, MAJ, MC
Salvatore Scialla, MAJ, MC

Objectives: To evaluate the antitumor activity of the combination of adriamycin and cis-platinum in previously untreated malignancies that have a low order or response to conventional modes of therapy such as head and neck carcinoma, squamous and adenocarcinoma of the lung, metastatic transitional cell carcinoma of the bladder and renal cell carcinoma.
To evaluate the antitumor activity of this combination in malignancies that have become refractory to conventional modes of therapy such as ALL, AML, Hodgkin's disease and non-Hodgkin's lymphoma, oat cell carcinoma of the lung, adenocarcinoma of the prostate, soft tissue sarcoma, and multiple myeloma.

Technical Approach: Adriamycin 60 mg/m^2 I.V. day 1 every 21 days
Cis-platinum 60 mg/m^2 I.V. day 1 every 21 days

Progress & Results: Twenty-four patients with a variety of malignancies have been entered on the study. So far an insufficient number of patients have been entered to make any conclusions as far as activity of this regimen.

Conclusions: None

Funding Requirements: See introductory remarks to Annual Research Report

Publications: None

Type of Report: Interim

Work Unit No.: 1645

Title of Project: WRAMC Protocol 7502 - A Pre-Test Trial of 2,5-Piperazinedione, 3,6-Bis-(5-Chloro-2-Piperidyl)-, Dihydrochloride in the Treatment of Advanced Renal Cell Carcinoma

Investigators:

Principal: Johannes Blom, M.D.

Objectives: To study the effect of piperazinedione in patients with advanced renal cell carcinoma.

Technical Approach: Piperazinedione 12 mg/m^2 I.V. every 28 days.

Progress & Results: Two patients were entered at WRAMC both of whom did not have any response. Subsequent experience at other institutions indicated the resistance of renal cell carcinoma to this drug, therefore further entry of patients in this protocol was discontinued on 20 September 1976.

Conclusions: Piperazinedione is not effective in the treatment of metastatic renal cell carcinoma.

Funding Requirements: See introductory remarks to Annual Research Report

Publications: None

Type of Report: Final

Work Unit No.: 1646

Title of Project: WRAMC Protocol 7503 - Clinical Evaluation of Galactitol 1,2:5,6-Dianhydro-(NSC 132313) in the Treatment of Metastatic Renal Cell Carcinoma. A Phase II Study.

Investigators:

Principal: Johannes Blom, M.D.

Associate: William J. Heim, MAJ, MC

Objectives: To determine the efficacy of galactitol in the treatment of metastatic renal cell carcinoma.

Technical Approach: Galactitol 60 mg/m^2 I.V. once weekly

Progress and Results: WRAMC entered one patient who had no response. Because experience obtained in other institutions demonstrated the resistance of this tumor to galactitol the entry of patients was discontinued in September 1976.

Conclusions: Galactitol is not effective in the treatment of metastatic renal cell carcinoma.

Funding Requirements: See introductory remarks to Annual Research Report.

Publications: None

Type of Report: Final

Work Unit No.: 1647

Title of Project: Inhibition of red cell pyridoxal kinase by the carbonyl reagents, isoniazid and hydralazine

Investigators:

Principal: MAJ John A. Kark, MD,MC

Associate: Peter G. Tarassoff, George Washington University School of Medicine
LTC Michael J. Haut

Objectives: To elucidate the mechanism of the anti-B_6 side effects of these drugs and to define the time-course of these effects.

Technical Approach: Methods have been described in detail in previous protocols and interim reports. This year we have synthesized the putative inhibitor of pyridoxal kinase, the pyridoxal hydrazone derivative. We have shown that inhibition of red cell pyridoxal kinase occurs at the expected low concentration (10^{-6}M in pyridoxal-isonicotinyl hydrazone, PL-INH). We are in the process of devising an assay for this compound in red cells.

Progress and Results: Purified PL-INH inhibited red cell pyridoxal kinase with an apparent K_I of 10^{-6}M. The mechanism appears to be non-competitive. PL-INH was measured in red cell hemolysates at concentrations of 10^{-7}M. Future patient studies will include determination of red cell PL-INH levels during administration of isoniazid.

Conclusions: If PL-INH can be successfully measured in red cells taken from patients on INH, it will be possible to determine the clinical significance of inhibition of pyridoxal kinases in product of the anti-B_6 side effects of INH.

Publications: Peter G. Tarrassoff and John A. Kark. Inhibition of erythrocyte pyridoxal kinase by a metabolite of isoniazid. Clinical Research 24: 623A, 1976.

Funds Utilized, FY-77: none (funded by WRAIR).

Funding Requirements, FY-78: none.

Type of Report: Interim.

Work Unit No.: 1648

Title of Project: WRAMC Protocol 7601, Add. 2 - The Treatment of Unresectable Bronchogenic Carcinoma with CCNU (1-(2 Chlorethyl)-3-Cyclohexyl-1-Nitrosourea)(NSC 79037), Cyclophosphamide, Procarbazine, and Hexamethylmelamine (NSC 13875)

Investigators:

Principal: Johannes Blom, M.D.

Associate: William J. Heim, MAJ, MC

Objectives: To determine the efficacy of combination chemotherapy with cyclophosphamide, CCNU, procarbazine and hexamethylmelamine in remission reduction and prolongation of survival of patients with unresectable bronchogenic carcinoma.

Technical Approach:

1. No prior chemotherapy or radiotherapy:

   CCNU 100 mg/m^2 p.o. day 1 of every 42-day cycle
   Cyclophosphamide 500 mg/m^2 I.V. day 1f of every 42-day cycle
   Procarbazine 100 mg/m^2 p.o. days 8 through 18 of every 42-day cycle
   Hexamethylmelamine 6 mg/kg p.o. days 8 through 22 of every 42-day cycle

2. Prior chemotherapy or radiotherapy:

   It must be at least 3 to 4 weeks since the last dose of prior chemotherapy or 2 weeks from the last dose of radiation before patients should be started on this protocol. For these patients the first and second course will be:

   CCNU 50 mg/m^2 p.o. day 1 of every 42-day cycle
   Cyclophosphamide 250 mg/m^2 I.V. day 1 of every 42-day cycle
   Procarbazine 50 mg/m^2 p.o. day 8 through 18 of every 42-day cycle
   Hexamethylmelamine 6 mg/kg p.o. day 8-22 of every 42-day cycle

   If this dose is tolerated without a nadir WBC of less than 3,500 or a nadir platelet count of less than 75,000 the third and fourth courses will be given in the following doses:

   CCNU 75 mg/m^2 p.o. day 1 of every 42-day cycle
   Cyclophosphamide 375 mg/m^2 I.V. day 1 of every 42-day cycle
   Procarbazine 75 mg/m^2 p.o. day 8 through 18 of every 42-day cycle
   Hexamethylmelamine 6 mg/kg day 8 through 22 of every 42-day cycle

If these four courses are well tolerated by the above criteria, full doses will be given subsequently.

3. Previous treatment with cyclophosphamide:

   Patients who have previously received cyclophosphamide will not receive this drug, but will be treated with CCNU, procarbazine and hexamethylmelamine as outlined above in the same doses.

4. Preferably, radiotherapy will be used only for palliation of local symptoms that do not respond to chemotherapy, e.g., intractable pain due to bone metastasis, brain metastasis, etc.

Progress & Results: WRAMC entered 15 patients, all of whom had progressive disease. Because of this poor result the protocol was changed to 7601-A.

Funding Requirements: See introductory remarks to Annual Research Report.

Publications: None

Type of Report: Final

Work Unit No.: 1649

Title of Project: WRAMC Protocol 7602, Add. 1 - Chemoimmunotherapy of Prostatic Carcinoma

Investigators:

Principal: Johannes Blom, M.D.

Associate: Charles F. Miller, MAJ, MC
William McDonald, MAJ, MC
Bernhard Mittemeyer, COL, MC

Objectives: 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 $6x10^8$ units on day 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.

Progress & Results: WRAMC entered eight patients on the study. One patient remains in a partial remission at day 279. One had stable disease for 10 months and subsequently progression. Four had progressive disease. Two are on study and it is too early to evaluate results.

Funding Requirements: See introductory remarks to Annual Research Report

Publications: None

Type of Report: Interim

Work Unit No.: 1650

Title of Project: WRAMC Protocol 7603 - Evaluation of Galactitol 1,2: 5,6-Dianhydro in the Treatment of Advanced Neoplastic Disease

Investigators:

Principal: Johannes Blom, M.D.

Associate: William J. Heim, MAJ, MC

Objectives: To determine the antitumor effect of galactitol in a broad spectrum of metastatic tumors.

Technical Approach: Galactitol 60 mg/m^2 I.V. every 7 days

Progress and Results: WRAMC entered 19 patients with a variety of tumors, none of whom had any significant response. Based on experience by others it seems that further investigation of this drug is warranted in patients with resistant carcinoma of the lung and melanoma. For this purpose this protocol was adapted for a pilot study for members of the Cancer and Acute Leukemia Group B. Therefore, WRAMC 7603 was closed to entry of new patients on 30 June 1977. Four patients are presently still on study.

Conclusions: Galactitol does not seem to be an active agent, but requires further study in melanoma and carcinoma of the lung.

Funding Requirements: See introductory remarks to Annual Research Report.

Publications: None

Type of Report: Interim

Work Unit No.: 1651

Title of Project: WRAMC Protocol 7604, Add. 1 - Combination Chemotherapy Protocol 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. Addendum 1 eliminated the use of Ftorafur. This is a study in cooperation with the Oncology Service, Georgetown University Hospital.

Investigators:

Principal: Johannes Blom, M.D.

Associate: J. Phillip Olmert, MAJ, MC

Objectives: 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. daily for 5 days during week 1 and 5 of each 8 week cycle
Adriamycin 30 mg/m^2 I.V. on day 1 and day 29
Mitomycin-C 10 mg/m^2 I.V. on day 1 of each 8-week cycle

5-fluorouracil 600 mg/m^2 I.V. on days 1 and 8 and days 29 and 36 of each 8-week cycle
Adriamycin 30 mg/m^2 I.V. on days 1 and 29 of each 8-week cycle
Mitomycin-C 10 mg/m^2 I.V. on day 1 of each 8-week cycle

Progress and Results: WRAMC entered nine patients. Four patients are still on study from 35 to 550+ days.

Funding Requirements: See introductory remarks to Annual Research Report

Publications: None

Type of Report: Interim

Work Unit No.: 1652

Title of Project: WRAMC Protocol 7605 - Combination Chemotherapy of Advanced Pancreatic Carcinoma with 5-Fluorouracil, Mitomycin-C and Streptozotocin. This is a study in cooperation with the Oncology Service, Georgetown University Hospital.

Investigators:

Principal: Johannes Blom, M.D.

Associate: J. Phillip Olmert, MAJ, MC

Objectives: To examine the efficacy of the combination of three active single agents, 5-fluorouracil, mitomycin-C and streptozotocin, in advanced pancreatic carcinoma.

Technical Approach: 5-fluorouracil 15 mg/kg I.V. weekly plus
Streptozotocin 1 gm/m^2 I.V. weekly plus
Mitomycin-C 10 mg/m^2 I.V. every 6 weeks

Progress & Results: WRAMC has entered 12 patients. Five patients are still on study from 49 to 309+ days, six had progressive disease and expired. One patient was not evaluable because patient refused further therapy.

Funding Requirements: See introductory remarks to Annual Research Report

Publications: None

Type of Report: Interim

Work Unit No.: 1653

Title of Project: WRAMC Protocol 7606 - Phase I-II Study of High Dose Methotrexate (MTX) with Citrovorum Factor Rescue for Children and Adults with Metastatic Osteosarcoma and Advanced Gliomas of the Brain.

Investigators:

Principal: Johannes Blom, M.D.

Associate: Alan D. Mease, MAJ, MC
Frederick B. Ruymann, LTC, MC

Objectives: To evaluate the efficacy and kinetics of high dose methotrexate in the treatment of malignant neoplasms in adults and children.

Technical Approach: Vincristine 2 mg/m^2; maximum dose 2 mg, to be followed by
Methotrexate infusion in doses varying from 100-500 mg/kg I.V. over 6 hours and followed by
Citrovorum rescue 15 mg/m^2 I.V. every 6 hours for 12 doses beginning 2 hours after completion of the methotrexate infusion.

Progress & Results: WRAMC entered two patients, one with the extra-osseous Ewings sarcoma and another with osteogenic sarcoma, both of whom had progressive disease and subsequently expired.

Conclusions: Too early

Funding Requirements: See introductory remarks to Annual Research Report.

Publications: None

Type of Report: Interim

Work Unit No.: 1654

Title of Project: WRAMC Protocol 7601-A, Add. 1 - The Treatment of Unresectable Bronchogenic Carcinoma with CCNU (1-(2-Chlorethyl)-3-Cyclohexyl-1-Nitrosourea)(NSC 79037), Cyclophosphamide, Adriamycin, Procarbazine, Hexamethylmelamine (NSC 13875), Methotrexate and Irradiation

Investigators:

Principal: Johannes Blom, M.D.

Associate: William J. Heim, MAJ, MC

Objectives: To determine the efficacy of combination chemotherapy with CCNU, cyclophosphamide, adriamycin, procarbazine, hexamethylmelamine and methotrexate and radiotherapy in remission induction and prolongation and survival of patients with unresectable bronchogenic carcinoma.

Technical Approach:

No prior chemotherapy or radiotherapy:

CCNU 65 mg/m^2 p.o. day 1 each 56 days
Cytoxan 500 mg/m^2 I.V. push day 1 each 56 days
Adriamycin 30 mg/m^2 I.V. push day 2 each 56 days
Hexamethylmelamine 6 mg/kg p.o. days 8 to 22 each 56 days
Procarbazine 100 mg/m^2 p.o. days 8 to 18 each 56 days
Methotrexate 40 mg/m^2 I.V. push on day 50 each 56 days

Prior chemotherapy or radiotherapy:

It must be at least 3 weeks since the last dose of prior chemotherapy or 2 weeks from the last dose of radiation before patients are started on this protocol. For these patients, the first and second course of therapy will be:

CCNU 35 mg/m^2 p.o. day 1 each 56 days
Cytoxan 250 mg/m^2 I.V. push day 1 each 56 days
Adriamycin 15 mg/m^2 I.V. push day 2 each 56 days
Hexamethylmelamine 6 mg/kg p.o. days 8 to 22 each 56 days
Procarbazine 50 mg/m^2 p.o. days 8 to 18 each 56 days
Methotrexate 20 mg/m^2 I.V. push day 50 each 56 days

If this dose is tolerated without a nadir WBC of less than 2500 or a nadir platelet count of less than 75,000, the third and fourth courses will be given in the following doses:

CCNU 50 mg/m^2 p.o. day 1 each 56 days
Cytoxan 375 mg/m^2 I.V. push day 1 each 56 days
Adriamycin 25 mg/m^2 I.V. push day 2 each 56 days
Hexamethylmelamine 6 mg/kg p.o. days 8 to 22 each 56 days
Procarbazine 75 mg/m^2 p.o. days 8 to 18 each 56 days
Methotrexate 30 mg/m^2 I.V. push day 50 each 56 days

If these four courses are well tolerated by the above criteria, full doses will be given subsequently.

Progress & Results: WRAMC entered 35 patients, two of whom obtained a complete remission and 6 a partial remission. Four of these patients have relapsed. Twenty-three patients had no response at all. The median survival of the responders was 215 days. This study was closed to entry on 31 May 1977.

Conclusions: Response rate of approximately 25% is not significantly dissimilar from response rates with less intense chemotherapeutic programs. Further entry of patients is, therefore, not warranted.

Funding Requirements: See introductory remarks to Annual Research Report.

Publications: None

Type of Report: Interim

Work Unit No.: 1655

Title of Project: WRAMC Protocol 7607 - Chemoimmunotherapy of Carcinoma of the Lung using High-Dose Methotrexate and Citrovorum Factor with or without BCG. This is a study in cooperation with the National Cancer Institute and Bethesda National Naval Medical Center.

Investigators:

Principal: Johannes Blom, M.D.

Associate: Charles F. Miller, MAJ, MC

Objectives:
1. To evaluate the response obtained with high dose methotrexate plus citrovorum factor rescue and radiation therapy in patients with residual carcinoma of the lung restricted to the thorax.
2. To evaluate the effect of BCG immunotherapy both in regard to clinical response to high dose methotrexate and also to immunologic function.
3. To have this investigation function as a pilot study for eventual use of chemoimmunotherapy as an adjuvant therapy regimen in patients with no residual tumor at the time of operation.

Technical Approach:

Regimen A - High dose methotrexate to begin with 17 mg/kg I.V. over 6 hours, followed by calcium leucovorin rescue 9 mg every 6 hours for a total of 12 doses. Doses of methotrexate will be increased to 50 mg/kg, 100 mg/kg, 200 mg/kg and 300 mg/kg. Subsequent to this radiation therapy 1500 rads will be given to large ports including the resected area and the mediastinum. Subsequent to this courses of high dose methotrexate will be continued.

Regimen B - Consists of the same high-dose methotrexate plus BCG.

Progress & Results: WRAMC has entered two patients.

Conclusions: Too early

Funding Requirements: See introductory remarks to Annual Research Report.

Publications: None

Type of Report: Interim

Work Unit No.: 1656

Title of Project: WRAMC Protocol 7608 - The Use of Thymosin (F5) in Patients with Carcinoma of the Esophagus. A Phase I Study.

Investigators:

Principal: Johannes Blom, M.D.

Associate: Charles F. Miller, MAJ, MC
Howard Heit, MAJ, MC
Lawrence Johnson, LTC, MC

Objectives:
1. To determine if doses of thymosin that have not been toxic thus far in patients with solid malignancies are toxic when given in combination with radiation therapy.
2. To determine if thymosin alters the progressive decline in peripheral blood T cells that occurs in patients receiving radiation therapy.
3. To determine if thymosin improves the clinical response of patients receiving radiation therapy.
4. To determine if thymosin affects the disease-free interval and survival when used as an adjuvant to radiation therapy.

Technical Approach: All patients will receive conventional radiation therapy to a total tumor dose of 5000 rads via opposed anterior and posterior fields covering the width of the mediastinum and the ipsilateral supraclavicular area on all patients. Patients will be assigned randomly to receive low dose thymosin 20 mg/m^2, high dose thymosin 60 mg/m^2 or placebo daily during the entire period of radiation therapy. This is a study in cooperation with the National Cancer Institute.

Progress & Results: WRAMC has entered one patient.

Conclusions: Too early.

Funding Requirements: See introductory remarks to Annual Research Report

Publications: None

Type of Report: Interim

1. Work Unit No.: 1801

2. Title of Project: Direct Immunofluorescence in MCTD

3. Investigators:
   a. Principal: ROBERT A. DAVIS, MAJ, MC, USA
   b. None

4. Objectives: (Goal of Research)
To determine the immunofluorescence pattern in mixed connective tissue disease and its relationship to lupus erythematosus, scleroderma and dermatomyositis and attempt to correlate the immunofluorescence with the ENA titers in these patients.

5. Technical Approach: Perform 4 mm punch biopsies of skin on patients suspected of having mixed connective tissue disease. Direct immunofluorescent tests were performed on these biopsies and examined for any abnormal fluorescence, specifically looking at the dermal epidermal junction and looking at the nuclei of epidermal cells.

6. Progress and Results: Between July 1, 1976 and June 30, 1977, 120 biopsies were performed on patients for direct immunofluorescence. The diagnosis of lupus erythematosus, dermatomyositis, scleroderma or mixed connective tissue disease was suspected on 100 of these biopsies. The direct immunofluorescence was positive at the dermal epidermal junction in 28 of these biopsies. Twenty-four of these were from involved skin and 4 were from normal skin. Of the 24 positive biopsies from involved skin 19 were positive at the dermal epidermal junction for DLE or SLE; 2 were positive at the dermal epidermal junction compatible with MCTD; 1 was positive at the intercellular areas throughout the epidermis compatible with pemphigus vulgaris; 1 was positive at the intercellular area of the upper epidermis compatible with pemphigus foliaceus; 1 biopsy was positive at the dermal epidermal junction and in the dermal blood vessels compatible with porphyria cutanea tarda. Negative immunofluorescence studies were performed on patients suspected of having erythema multiforme, herpes gestationes, dermatomyositis, scleroderma, linear morphea, chronic meningococcemia, urticaria, erythropoietic protoporphyria, dermatitis herpetiformis, drug eruptions, seborrheic dermatitis and panniculitis. Five of the 120 biopsies were from patients with mixed connective tissue disease. Three of these patients had a positive nuclear staining in the epidermis. Two of these three patients had a positive band test at the dermal epidermal junction of involved skin. The ENA titer was not available in three of these five patients. In the two patients in whom the ENA titer was available, it was very high (i.e. 1×10^5) in both patients and they both had a positive staining of their nuclei in epidermal skin. One of these two patients had a positive band test of involved skin and the other had a negative band test of involved skin.

7. Conclusions: At the present time, it appears that patients with epidermal nuclear staining have very high ENA titers, possibly not related to whether the ENA is sensitive or resistant to RNase. However, no definitive conclusion can be drawn from this data at the present time. It will take a larger number of patients. Hopefully the ENA test with titers and whether it is sensitive or resistant to RNase will become more readily available over the next 2-3 years, so that this information can be correlated with the direct immunofluorescence.

8. Funds Utilized - FY-77:

a. Personnel:	ROBERT A. DAVIS, MAJ, MC
b. Equipment:	None
c. Supplies:	$1,409.65
d. Travel:	None
e. Other:	None
f. Funds not Utilized:	$824.35

9. Funds Requested - FY-78:

a. Personnel:	ROBERT A. DAVIS, MAJ, MC
b. Equipment:	None
c. Supplies:	Immunologic reagents, glassware and miscellaneous Items - $1,500.00
d. Travel:	$600.00
e. Other:	None

10. Publications: None

11. Type of Report: Interim

Work Unit No.: 1991

Title of Project: The Efficacy of Antisera to Gram Negative Endotoxin in the Treatment of Gram Negative Sepsis

Investigators:

Principal: John L. Carpenter, MD

Associate: Jerald Sadoff, MD

Objective: To evaluate the efficacy of antisera which is made against a "common antigen" in the core of the endotoxin of gram negative rods in treating suspected or documented gram negative sepsis.

Technical Approach: Patients with documented or suspected gram negative sepsis were given antisera in addition to standard antibiotic and supportive therapy. The antiserawere administered in a double blind fashion in that two units had been prepared from each donor; one obtained pre-immunization and one post-immunization. An individual patient would receive either the pre or post-immunization sera. The patients were clinically evaluated pre and post therapy by the investigators and the data recorded on standard flow sheets. This clinical information was then relayed to Dr. Elizabeth Ziegler at the University of California at San Diego, who is coordinating this multi-center study.

Progress and Results: During FY 77, 2 units of antisera were given without significant complications. The efficacy of the antisera has not been determined as the code in this double blind study has not yet been broken.

Conclusions: Deferred at present.

Funds Utilized, FY 77: None.

Funding Requirements, FY 78, None.

Publications: None.

Type of Report: Interim - Annual Progress Report

Work Unit No.: 1903

Title of Project: Persistence of T. Pallidum in Neurosyphilis

Investigators:

Principal Investigator: Robert A. Davis, MAJ MC

Associate Investigator: Edmund C. Tramont, LTC MC

Objective: To determine the frequency with which Treponema pallidum can be isolated from the cerebrospinal fluid (CSF) of patients who have received the recommended course of treatment for 1 or 2 syphilis, and to examine the CSF of these patients to determine whether improved procedures for detecting early neurosyphilis can be devised.

Progress and Results: Annual report project not commenced due to lack of USUHS funding.

Conclusions: None

Funding Requirement, FY-77: None

Funding Required, FY-78: None

Publications: None

Type of Report: Interim

Work Unit No.: 2101

Title of Project: Investigation of Vascular Injuries, Vascular Disease, Vascular Grafts and Operating Procedures.

Investigators:

Principal: COL Norman M. Rich, MC

Associate: LTC George J. Collins, Jr., MC, LTC Charles A. Andersen, MC and LTC Paul T. McDonald, MC.

Objectives: To establish the best possible diagnosis of vascular injury and disease, to evaluate the methods of management currently used for these problems, and to determine the long term results of current methods of therapy.

Technical Approach: Monthly reports are analyzed and specific topics of interest are investigated in detail. All patients are repeatedly examined on a routine evaluation basis in the Vascular Blood Flow Laboratory.

Progress and Results: The long term follow-up effort continues in the Peripheral Vascular Surgery Clinic and Vascular Blood Flow Laboratory in evaluating patients with vascular disease. The fate of various methods of vascular reconstruction remains a challenge. Since establishment of Walter Reed Army Medical Center as the Army's vascular treatment facility 27 years ago, considerable progress has been made. On the other hand, because of our long term follow-up, we are now beginning to question the true value of our most important arterial substitute, namely the greater saphenous vein. The stimulating professional challenge remains because we still do not have the "ideal graft" for either arterial or venous reconstruction. Vascular surgery not only remains a relatively new field, the tremendous proliferation in the diagnostic area for vascular disease within the past 12 to 18 months has been phenomenal. Medical-engineering advances have established many new modalities that enable us to better determine regional blood flow, including intra-cerebral blood flow.

The value of the Vascular Blood Flow Laboratory is just being realized in the civilian community with a great deal of interest in university medical centers to establish vascular blood flow laboratories. Our Vascular Blood Flow Laboratory is now in its eleventh year of operation. Yet, in this past year, we have added three new electronic devices which enable us to improve our diagnostic acumen and established improved patient follow-up care. Because of the current situation facing the Army Medical Department, our work load in the Vascular Clinic and Blood Flow Laboratory has essentially doubled within the past year. Obviously, this has given us an opportunity to evaluate many additional and unusual vascular problems.

Our Vascular Registry contains the copies of medical records of nearly 7,500 Vietnam casualties, approximately 300 Korean casualties, a scattered number of World War II casualties, and more than 10,000 patients with vascular disease. This Registry continues to be expanded.

Patients are encouraged to return for routine follow-up visits and many former Vietnam casualties have visited our Clinic from all over the United States. When follow-up visits are not possible, questionnaires are sent by mail and assistance of other doctors from both military and civilian hospitals is solicited.

We continue to enjoy the excellent exchange with the research effort at Walter Reed Army Institute of Research where two of our staff hold Associate Investigator positions. Three surgeons assigned in the Division of Surgery at Walter Reed Army Institute of Research also work on a part time basis in our Vascular Clinic and Blood Flow Laboratory. Our exchange with the Cardiovascular Branch of the Armed Forces Institute of Pathology continues. We also maintain close liaison with the Biophysics Laboratory at Edgewood Arsenal, Maryland and with George Washington University School of Medicine.

Progress continues similar to previous years reflected by an outstanding quality of patient care with the accomplishment documented for both clinical and research vascular projects as outlined in the references of published reports. Numerous presentations including scientific papers, scientific exhibits, and scientific movies have reflected positive reaction to our program. The unofficial recognition of vascular fellowship training is given to our program which is now completing its eleventh year. Dr. Rich continues to work on a number of important committees for the American College of Surgeons, the Society for Vascular Surgery, the Society of University Surgeons, the Trauma Societies, and the International Cardiovascular Society. Dr. Collins joins Dr. Rich as the only two active duty members of the Society for Vascular Surgery and Dr. Andersen joins Dr. Rich and Dr. Collins in the International Cardiovascular Society. This is all recognition of the clinical and experimental vascular research that has been accomplished. The Fourth Annual Walter Reed Vascular Surgery Seminar and Meeting of Military Vascular Surgeons in December, 1976 continues to demonstrate the leadership in postgraduate education in vascular surgery that has been established by the Army Medical Department. Because of this continued investigation, the Peripheral Vascular Surgery Service is able to maintain its leadership position in vascular surgery, both nationally and internationally.

Conclusions: The results of the project are reflected by the accomplishments of the investigators and the recognition given these investigators by their peers and by the vascular societies. It is obvious that peripheral vascular surgery remains in a strong position representing a very favorable posture for Walter Reed Army Medical Center and the Army Medical Department.

It is of paramount importance that this investigation continue because this is the foundation for all of the accomplishments that have been possible. The cost factor to the Army Medical Department is extremely small compared to the positive exposure and publicity that is gained. Continuing medical education and postgraduate training are also made possible.

Funds Utilized, FY-77: Because FY-77 continues through 30 September 1977, we have not yet spent all of the money allotted us, however, the $40,000 given for our project will be spent by the end of this period.

Funding Requirements, FY-78:

Personnel: COL Rich will continue to be the Principal Investigator, LTC Andersen will be deleted from the project because of PCS and MAJ Louis Kozloff will become part of the project as the new Fellow in Peripheral Vascular Surgery. Funding requirements for FY-78 will be similar to FY-77 at approximately $40,000 with essentially the same breakdown for equipment, supplies, travel and other expenses. However, this will not be calculated until it is submitted to Research and Development Command, Office of The Surgeon General, probably within the next two months. This will also be submitted to Clinical Investigation Service, WRAMC at that time.

Publications:

Rich, NM, Hobson, RW, II, Collins, GJ, Jr and Andersen, CA: The effect of acute popliteal venous interruption. Ann Surg 183:365, 1976.

Jarstfer, BS and Rich, NM: The continuing challenge of major injury secondary to disk surgery. J Trauma 16:726, 1976.

Hobson, RW, II, Rich, NM and Wright, CB: Concepts in venous trauma and reconstruction. In Hobbs, JT (Ed), TREATMENT OF VENOUS DISORDERS. Medical and Technical Publishing Company, Ltd., Lancaster, England, 1976.

Jarstfer, BS and Rich, NM: Renal artery false aneurysm: An unusual complication of prosthetic patch angioplasty. Am J Surg 132:657, 1976.

Hobson, RW, II, Wright, CB, Rich, NM and Collins, GJ, Jr: Assessment of chronic ischemia during aortic surgery by Doppler ultrasound. J Surg Res 20:231, 1976.

Collins, GJ, Jr, Rich, NM, Hobson, RW, II and Andersen, CA: Fibromuscular dysplasia of the internal carotid arteries. Surgery 81:105, 1976.

Collins, GJ, Jr, Rich, NM, Hobson, RW, II and Andersen, CA: Ultrasound diagnosis of popliteal arterial aneurysms. Amer Surg 42:853, 1976.

Wright, CB, Hobson, RW, II, Giordano, JM, DeWitt, PL and Rich, NM: Acute femoral venous occlusion: Management by segmental venous replacement. J Cardiovasc Surg 17:435, 1976.

Rich, NM: Modern war wounds. In Mason, JK (Ed), THE PATHOLOGY OF VIOLENCE. Edward Arnold Publishers, Ltd., London, 1976.

Andersen, CA, Collins, GJ, Jr and Rich, NM: Axillo-axillary bypass for complications of axillary artery aneurysm: A case report. Amer Surg 43:212, 1977.

Collins, GJ, Jr, Rich, NM, Hobson, RW, II and Andersen, CA: Ectopic kidney: An unusual indication for extra-anatomic bypass grafting. Amer Surg 43:123, 1977.

Rich, NM: The Chesapeake Vascular Society. Milit Med 141:874, 1976.

Rich, NM, Hobson, RW, II and Collins, GJ, Jr: Elective vascular reconstruction after trauma (Abst). Rev Surg 33:280, 1976.

Rich, NM, Collins, GJ, Jr and Andersen, CA: Infected grafts: Clinical presentation and diagnosis. In Duma, RJ (Ed), INFECTIONS OF PROSTHETIC VALVES AND VASCULAR GRAFTS. University Park Press, Baltimore, 1977.

Rich, NM: Regional vascular societies. Amer Surg 42:803, 1976.

Rich, NM, Hobson, RW, II, Collins, GJ, Jr and Andersen, CA: The effect of acute popliteal venous interruption (Abst). Rev Surg 33:424, 1976.

Collins, GJ, Jr, Rich, NM and Andersen, CA: Limb salvage procedures for lower extremity ischemia. Am J Surg 132:707, 1976.

Collins, GJ, Jr, Ahr, DJ, Rich, NM and Andersen, CA: Detection and management of hypercoagulability. Am J Surg 132:767, 1976.

Rich, NM: The evidence that carotid endarterectomy will prevent stroke. Manual, Postgraduate Course, Peripheral Vascular Disease, American College of Surgeons, Chicago, 1976.

Rich, NM: Complications of peripheral vascular injuries to the extremities. In Epps, CH, Jr (Ed), COMPLICATIONS OF ORTHOPEDIC SURGERY. J.B. Lippicott Co., Philadelphia, 1977.

Wright, CB, Hobson, RW, II, Swan, KG and Rich, NM: The pathophysiology of extremity venous occlusion. In Bergan, JJ and Yao, JST (Eds), SYMPOSIUM ON VENOUS PROBLEMS IN HONOR OF GEZA de TAKATS. Year Book Medical Publishers, Inc., Chicago, 1977.

Hobson, RW, II, Rich, NM and Wright, CB: Clinical experience with direct venous reconstruction and acute trauma. In Bergan, JJ and Yao, JST (Eds), SYMPOSIUM ON VENOUS PROBLEMS IN HONOR OF GEZA de TAKATS. Year Book Medical Publishers, Inc., Chicago, 1977.

Rich, NM, Hobson, RW, II and Wright, CB: Historical aspects of direct venous reconstruction. In Bergan, JJ and Yao, JST (Eds), SYMPOSIUM ON VENOUS PROBLEMS IN HONOR OF GEZA de TAKATS. Year Book Medical Publishers, Inc., Chicago, 1977.

Collins, GJ, Jr, Rich, NM, Andersen, CA and McDonald, PT: Stroke after carotid endarterectomy (Abst). Stroke 8:14, 1977.

Rich, NM: Major extremity arterial injury. Syllabus, THE FIFTH ANNUAL SYMPOSIUM ON VASCULAR SURGERY, UCLA, Department of Continuing Education, Palm Springs, 1977.

Rich, NM: Venous trauma. Syllabus, THE FIFTH ANNUAL SYMPOSIUM ON VASCULAR SURGERY, UCLA, Department of Continuing Education, Palm Springs, 1977.

Rich, NM: Hemodynamic studies of vascular trauma. Syllabus, THE FIFTH ANNUAL SYMPOSIUM ON VASCULAR SURGERY, UCLA, Department of Continuing Education, Palm Springs, 1977.

Rich, NM: Carotid artery trauma. Syllabus, THE FIFTH ANNUAL SYMPOSIUM ON VASCULAR SURGERY, UCLA, Department of Continuing Education, Palm Springs, 1977.

Rich, NM and Collins, GJ, Jr: Problems and resolution of lower extremity vein disease. In Nuhus, LM (Ed), SURGERY ANNUAL, VOLUME X. Appleton-Century-Crofts, New York, 1977.

Type of Report: Interim.

Work Unit No.: 2103

Title of Project: Heparin Dosage during Peripheral Vascular Reconstruction

Investigators:

Principal: LTC George J. Collins, Jr.

Associate: MAJ David J. Ahr
MAJ William Armstrong
COL Norman M. Rich
MAJ Charles A. Andersen

Objective: To determine the safe and effective dose of heparin for use during peripheral vascular reconstructive procedures.

Technical Approach: Thirty one patients undergoing peripheral vascular reconstructive procedures were randomly assigned to two groups to receive either 100 or 150 units/Kgm. of body weight (u/kgm.) of heparin intravenously just prior to cross clamping.

Progress & Results: We used a sensitive thrombin clotting time assay to determine plasma heparin levels. Group 1 (n=16) was given 100 u/kgm of heparin prior to cross clamping while group 2 (n=15) was given 150 u/kgm. Plasma levels (u/ml± S.E.M.) before heparinization (BH), at 5, 20, 35, 50, and 65, min (H+5, H+20, H+----) after heparinization, and after reversal with 0.5 mgm of protamine sulfate/per 100 u heparin given (AR) are recorded below.

Plasma Heparin Levels (u/ml ± S.E.M.)

Dose	BH	H+5	H+20	H+35	H+50	H+65	AR
100u/kgm	0	1.83±.17	1.49±.13	1.05±.11	0.89±.07	0.76±.07	0.04±.03
150u/kgm	0	2.38±.20*	1.89±.13*	1.64±.14*	1.43±.14*	1.26±.18*	0.01±.13

*Significantly different than mean at lower dose.

Conclusions: These studies show that therapeutic heparin levels are achieved with either dose. Heparin need not be repeated with cross clamp times in the range of one hour. Heparin reversal is mandatory with these doses and is satisfactorily accomplished using 0.5 mgm protamine sulfate/100 u of initial heparin dose. We need to study nine more patients to complete our goal of 40 patients.

Funds Utilized, FY-77: $812.00

Funding Requirements, FY $500.00

Publications: None, Abstract sent to Association for Academic Surgery

Type of Report: Interim

Work Unit No.: 2204

Title of Project: Causalgia: A Study of Sympathetic Activity in Affected Patients

Investigators:

Principal: Albert J. Tahmoush, LTC MC

Associate: John R. Jennings, Ph.D, CPT MC
Frederick W. Hegge, Ph.D
Albert N. Martins, LTC MC

Objectives: To determine if abnormalities in sympathetic activity are consistently associated with causalgia.

Technical Approach: Indirect estimates of local sympathetic nervous system activity were obtained through measurements of skin conductance (SC), skin temperature (ST), and an index of skin blood flow (SBFI). Skin conductance was determined by the constant voltage method. SBFI was determined by an optical method developed for this study. Measurements were performed in a controlled environmental chamber on two consecutive days in the two 30-minute periods following an AB-BA design. For each measure, the affected and non-affected extremities were compared.

Progress and Results: The results from eight patients with causalgia and eight control subjects (age and sex-matched) are presented in Figures 1 and 2. In the control group, marked asymmetry of ST did not occur; one subject (#7) had an asymmetry of SC; and one subject (#2) had an asymmetry of SBFI. In the patient group, three subjects (3#, #6, and #8) had asymmetry in ST; three subjects had marked asymmetry in SC (#5, #6, and #8); and four subjects had marked asymmetry in SBFI (#1, #2, #6, and #7). However, the asymmetries were not consistent in the patient group and did not fit the pattern of sympathetic nervous system hyperactivity.

Conclusions: Although sympathetic nervous system innervated variables are more frequently asymmetric in patients with causalgia, the pattern is not consistent with a state of local sympathetic nervous system hyperactivity. A review of the verbal and behavorial descriptors associated with these patients suggests that causalgia is a local disorder of sensory information processing.

Funding Requirements: None

Publications: Manuscript in preparation

Type of Report: Interim

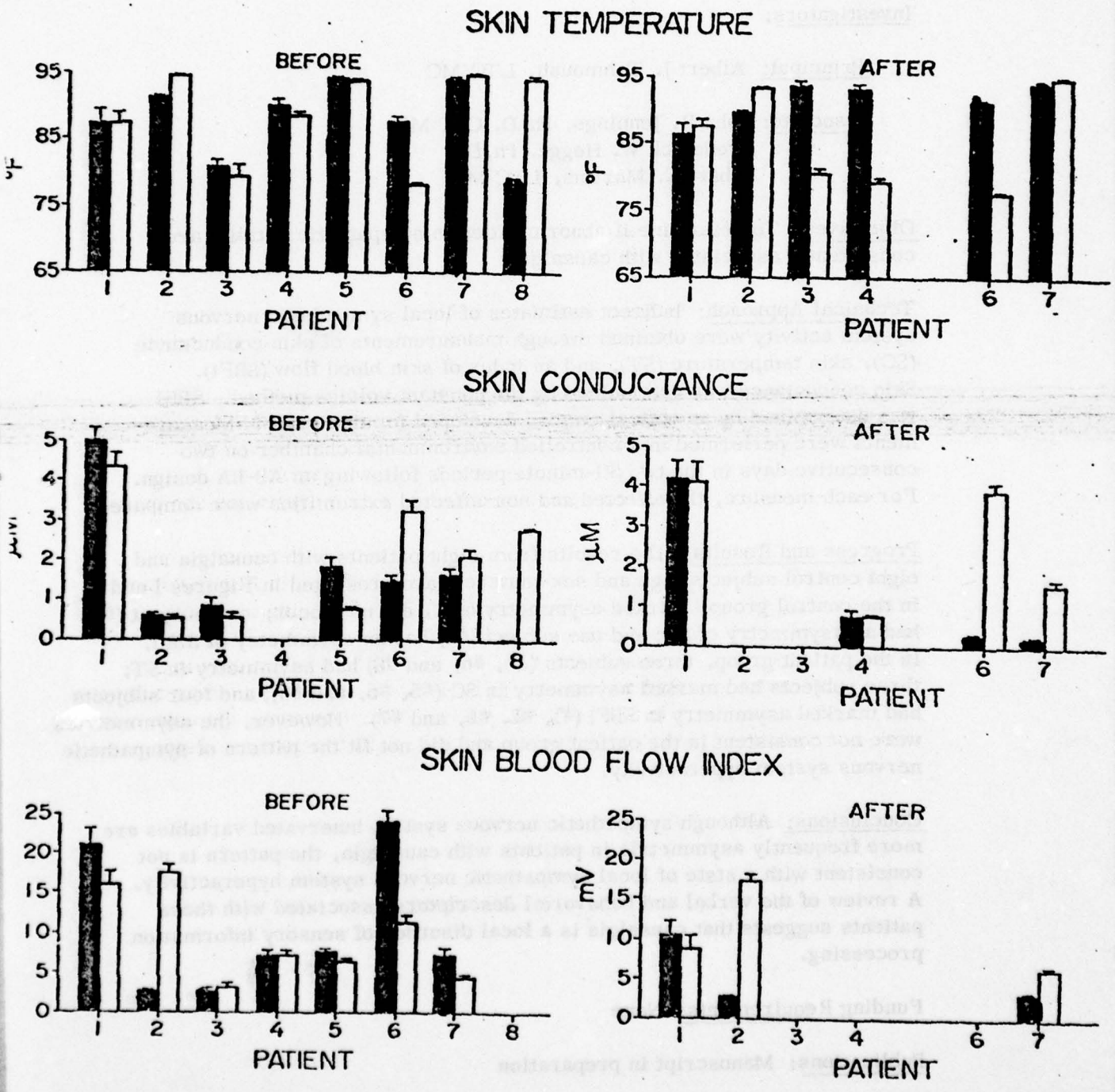


FIGURE 2. RESULTS FROM PATIENTS BEFORE AND AFTER THERAPY.

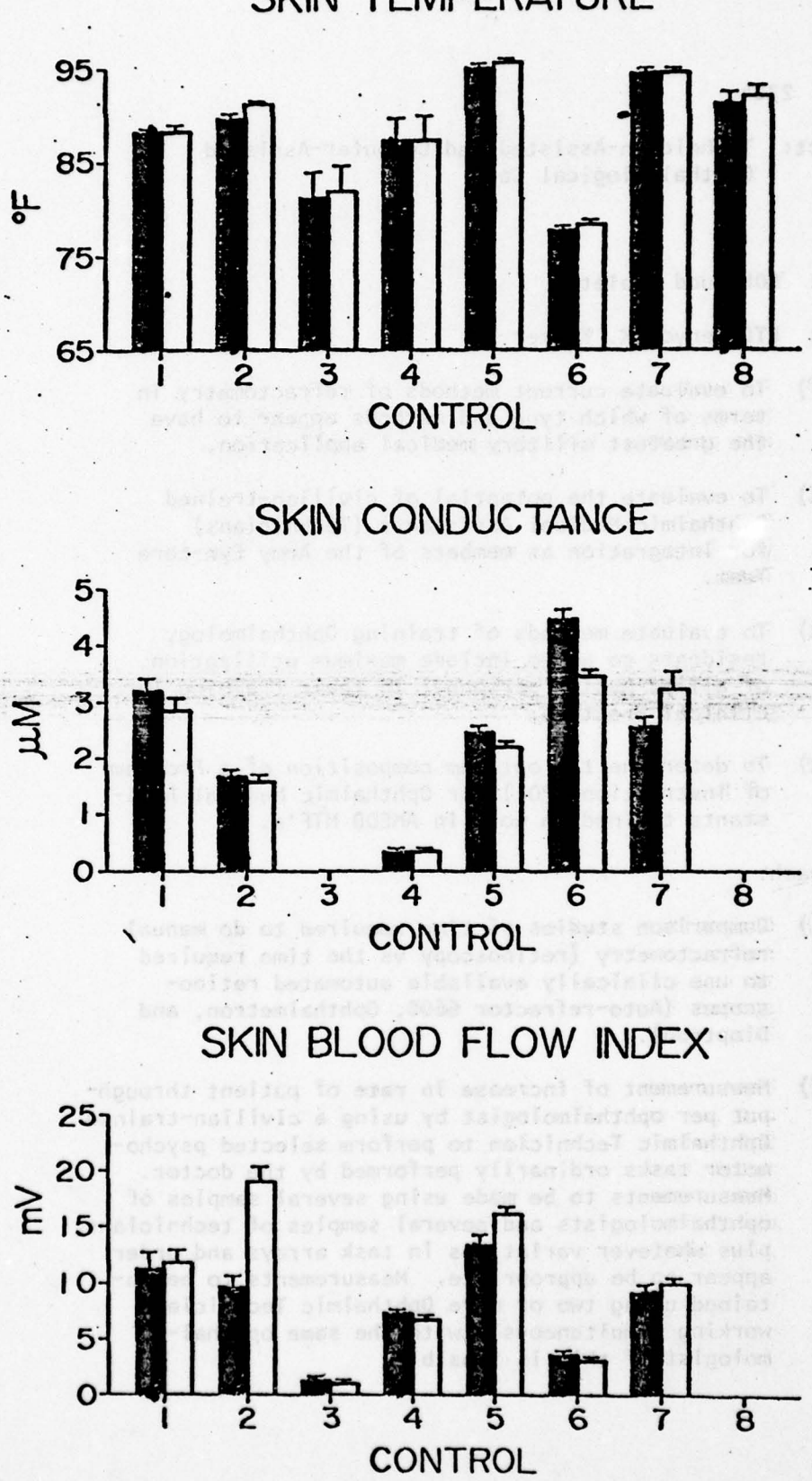


FIGURE 1. RESULTS FROM CONTROLS.

Work Unit No.: 2304

Title of Project: Technician-Assisted and Computer-Assisted Ophthalmological Care

Investigators:

Principal: COL Budd Appleton

Associate: LTC Kenyon K. Kramer

Objectives: (1) To evaluate current methods of refractometry in terms of which type and methods appear to have the greatest military medical application.

(2) To evaluate the potential of civilian-trained Ophthalmic Medical Assistants (Technicians) for integration as members of the Army Eye-care Team.

(3) To evaluate methods of training Ophthalmology residents so as to include maximum utilization of allied health personnel in their training for clinical practice.

(4) To determine the optimum composition of a Program of Instruction (POI) for Ophthalmic Medical Assistants trained to work in AMEDD MTF's.

Technical Approach:

(1) Comparison studies of time required to do manual refractometry (retinoscopy vs the time required to use clinically available automated retinoscopes (Auto-refractor 6600, Ophthalmetron, and Dioptron).

(2) Measurement of increase in rate of patient throughput per ophthalmologist by using a civilian-trained Ophthalmic Technician to perform selected psychomotor tasks ordinarily performed by the doctor. Measurements to be made using several samples of ophthalmologists and several samples of technicians, plus whatever variations in task arrays and order appear to be appropriate. Measurements to be obtained using two or more Ophthalmic Technicians working simultaneously with the same ophthalmologist if this is feasible.

(3) Establishment of proposed SOP's for:

a. Use of one or more Ophthalmic Technicians by an ophthalmologist in an AMEDD MTF Eye Clinic.

b. A Program of Instruction for Army-trained Ophthalmic Medical Assistants trained specifically to do work in AMEDD MTF's.

c. Integration of training in utilization of Ophthalmic Medical Assistants into the POI's for Ophthalmology residents trained in AMEDD MTF's.

Progress & Results: Project has been under way twenty-one (21) months, of which approximately two (2) months were required for task partition and familiarization with clinical procedures. The remaining time has been devoted to Objective 2. and Objective 3. and their technical approaches. The performance levels of six Ophthalmology residents have been evaluated as of this date. Their increases over base-line performance have ranged from approximately 50% to approximately 300%, using an Ophthalmic Technician in the format originally devised by the Investigators. Additional preliminary efforts have been made to evaluate a different (triage) format utilizing an Ophthalmic Technician, but thus far no attempt has been made to produce data utilizing this system comparatively.

Conclusions: As far as the Investigators are concerned Contractor has been fulfilling the terms of his contract, and the project has been conducted to the maximum extent that integration with clinical activities in this Service will allow. The Investigators believe that progress has been quite satisfactory, and it is recommended that the project be continued with a gradual shifting of emphasis from Objective 2. to Objectives 3. and 4.

Funding: Funding was accomplished contractually with the Educational Study Association of St. Paul, Minnesota, in conjunction with the University of Minnesota Medical School at a price of $18,500. The Educational Study Association has stated that they are willing to enter into a new similar contract for an additional year at the same funding level. This funding appears reasonable and has been recommended as such through Clinical Investigation Service, WRAMC, to Headquarters, US Army Medical R&D Command.

Publications: N/A

Type of Report: Interim Annual Progress Report

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
HSW-SQ	Clinical Research Project

TO: C, Clinical Research Svc FROM: C, Ophthalmology Svc DATE: 12 May 76 CMT 1

BA/mc/63537

SUBJECT: Project "Technician-Assisted and Computer-Assisted Ophthalmological Care" (#a162110A816). Progress Report Period 1 March - 30 April 1976

1. Contractor's representative has continued to participate in execution of subject protocol.

2. Major Marvin E. Leedy continued as the resident participating in the protocol during this period. The task partition remained as described in the previous report.

3. The base-line figure was 12 patients per day. During the first half of this 60 day period, Major Leedy saw an average of 24 patients per day. This is an increase of 100% over his base-line figure.

4. During the second portion of this 60 day period, Major Leedy's average number of patients seen per day was 28. This is an increase of 133% over the base-line figure.

5. The Principal Investigators and team members continuously monitored the quality of care during this period and saw no decrease. Patient response has been favorable.

6. Contractor is fulfilling all terms of subject contract as far as provision of requested expert participation is concerned.

BUDD APPLETON, MD
Colonel, MC, USA
Chief, Ophthalmology Service

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
HSW-SQ	60 Day Progress Report, Contract #DADA 15-76-C-0014

TO: C, Clin Invest Svc
FROM: C, Ophthalmology Svc
DATE: 1 July 1976
CMT 1
BA/mc/63537

1. Contractor's representative has continued to participate in execution of subject protocol.

2. As previously decided, a new resident has been assigned. During this period the resident has been Major F. Denton Wertz. The task partition has remained as previously described.

3. The base-line figure was 12 patients per day. During the first half of this 60 day period Major Wertz saw an average of 29 patients per day, an increase of 142% over his base-line figure.

4. During the second portion of this 60 day period, Major Wertz saw an average of 36 patients per day. This is an increase of 300% over his base-line figure.

5. During this period the quality of care was continuously monitored by the Principal Investigators and team members; no decrease was seen. Expressions of patient response have been extremely favorable and have been volunteered without any formal solicitation in the form of an interview or questionnaire.

6. Contractor is fulfilling all terms of subject as far as provision of requested expert participation is required.

BUDD APPLETON, MD
Colonel, MC, USA
Chief, Ophthalmology Service

DA FORM 1 FEB 62 2496 REPLACES DD FORM 96, EXISTING SUPPLIES OF WHICH WILL BE ISSUED AND USED UNTIL 1 FEB 63 UNLESS SOONER EXHAUSTED

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
HSW-SQ	Clinical Research Project: Technician- and Computer Assisted Ophthalmological Care" (3A16211)A816) Bimonthly Progress Report

TO C, Clinical Research Svc FROM C, Ophthalmology Svc DATE 15 Sep 76 CMT 1

BA/mc/63537

1. Preliminary investigations of techniques for use in handling eye patients in a triage (problem-oriented) configuration were carried out during this period. Use of the previous configuration was not feasible because of scheduling difficulties resulting from the annual turn-over of personnel as third-year residents are phasing out, second-year residents are phasing into the third year, and first-year residents are away for 11-week academic ophthalmic basic sciences phase of their training.

2. The triage configuration was used by the senior staff member and contractor's representative on patients selected randomly on the basis of routine patient scheduling overflow (doctors absent, patients arriving too late to be seen as previously scheduled, administrative emergencies, etc.). The initial impression on the part of both the staff member and contractor's representative was that triage management shows significant promise in achieving the objectives of the project, at least equal to that of patient management by the configuration studied previously.

3. Contractor is fulfilling all terms of subject contract as far as provision of expert participation is concerned.

BUDD APPLETON, MD
Colonel, MC
Chief, Ophthalmology Service

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DA FORM 2496 FEB 63 REPLACES DD FORM 96, EXISTING SUPPLIES OF WHICH WILL BE ISSUED AND USED UNTIL 1 FEB 63 UNLESS SOONER EXHAUSTED

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
HSW-SQ	60 Day Progress Report Contract #DADA 15-76-C-0014

TO C, Clinical Research Svc FROM C, Ophthalmology Svc DATE 15 Nov 76 CMT 1

BA/mc/63537

1. Contractor's representative has continued to participate in execution of subject protocol.

2. Patients continue to be processed in accordance with the previously described triage configuration. Because of personnel turbulence among the Ophthalmology Staff and some apparent lack of patient enthusiasm for being "screened" by the Chief, it has not been feasible to load the schedule sufficiently to develop meaningful data. The investigators' subjective impression, however, is that this system provides much more flexibility in evaluating the individual patient, as well as leaving our patients feeling better about the quality of services (as opposed to care) they receive in the triage configuration as compared with the initial configuration studied.

3. Contractor is fulfilling all terms of subject contract with respect to provision of expert participation.

BUDD APPLETON, MD
Colonel, MC
Chief, Ophthalmology Service

DA FORM 1 FEB 62 2496 REPLACES DD FORM 96, EXISTING SUPPLIES OF WHICH WILL BE ISSUED AND USED UNTIL 1 FEB 63 UNLESS SOONER EXHAUSTED.

GPO : 1969 OP—382-529

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
HSW-SQ	60 Day Progress Report Contract #DADA 15-76-C-0014

TO C, Clinical Research Svc FROM C, Ophthalmology Svc DATE 15 Jan 77 CMT 1

BA/mc/63537

1. Contractor's representative has continued to participate in execution of subject protocol.

2. Patients continue to be processed in accordance with the triage configuration. New visual field testing equipment has been received (an automated static perimetric apparatus), and contractor's representative has spent some of this period gaining familiarity and facility with it. In addition, contractor's representative has begun draft plans for the audio-visual segments of the proposed Program of Instruction for Ophthalmic Medical Assistants trained to work in AMEDD Medical Treatment Facilities.

3. Contractor is fulfilling all terms of subject contract with respect to provision of expert participation.

BUDD APPLETON, MD
Colonel, MC, US Army
Chief, Ophthalmology Service

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DA FORM 1 FEB 62 2496 REPLACES DD FORM 96, EXISTING SUPPLIES OF WHICH WILL BE ISSUED AND USED UNTIL 1 FEB 63 UNLESS SOONER EXHAUSTED.

* GPO : 1969 OP—302-529

Work Unit No.: 2306

Title of Project: Clinical Quantification of Intraocular Malignant Melanoma Volume

Investigators:

Principal: Kenyon K. Kramer, LTC, MC, USA

Objectives: To develop a technique to quantitate the size of intraocular malignant melanomas in vivo, since this is an important prognostic parameter.

Technical Approach: B Scan water-bath ultrasonography after the method of Jackson Coleman, M.D., will be used to measure malignant melanomas in vivo, both volume and single largest dimension.

Progress & Results: Three additional lesions have been measured in vivo and come to histopathology with the following combined results:

		Vol % Error	Single Largest Dimension
1st Report	#1	-14%	+11%
	#2	+80%	+71%
	#3	+40%	+22%
	#4	+84%	+45%
2nd Report	#5	+180%	+36%
	#6	+131%	+28%
	#7	+ 15%	-15%

Conclusions: Five other lesions have been measured in vivo. No histopathology is yet available. Certain trends have been observed, i.e. the A-Scan measurement for height is usually within 1.5mm; frequently within 1mm, whereas the horizontal and vertical measurements are frequently 2mm greater than true. With this in mind I believe further improvement is possible.

Funds Utilized, FY-77: $0

Funding Requirements: FY-78: $0

Publications: None

Type of Report: Interim

Work Unit No.: 2307

Title of Project: Evaluation of Dipivalyl Epinephrine in the Treatment of Glaucoma

Investigators: William Rimm, CPT, MC, USA
Lee Jampol (former MAJ, MC, USA)

Objectives: To evaluate Dipivalyl Epinephrine and its efficacy in the treatment of chronic open angle glaucoma

Technical Approach: Unchanged; to treat patients with chronic open angle glaucoma using Dipivalyl Epinephrine in lieu of all Epinephrine-type medications or in addition to and concurrent use of non Epinephrine-type medications.

Progress & Results: To date 13 patients have been instituted on the protocol with the result that nine (9) have maintained adequate intraocular pressure control to date. Four patients have been eliminated from the protocol due to inadequate intraocular pressure control.

Conclusions: None at this time

Funds Utilized, FY-77: $0

Funding Requirements, FY-78: $500.00 requested for travel to present anticipated paper at scientific meetings

Publications: None

Type of Report: Interim

WORK UNIT NUMBER: 2501

TITLE: An Aerodynamic Evaluation of the Speech of Patients with Voice Disorders

INVESTIGATORS:
Principal: Robert A. Prosek, Ph.D.
Associate: Brian E. Walden, Ph.D.
Allen A. Montgomery, Ph.D.

OBJECTIVE: To determine how the breath stream is controlled by patients with voice disorders during speech tasks, and to determine if the aerodynamic parameters of speech may be used to distinguish among groups of patients having different voice disorders.

TECHNICAL APPROACH: Measurements of intraoral air pressure (in cm H_2O), air flow rate (in cc/sec), consonant duration (in milliseconds), fundamental vocal frequency (in Hertz), and sound pressure level (in decibels) were made during the production of words and sentences, and during a psychophysical scaling task. During this latter task, the patients were asked to systematically vary the vocal effort used to produce the syllables /pa ba sa za/.

Intraoral air pressure was sensed by means of a 12 French catheter placed in the mouth of the subject. The catheter was connected to a pressure transducer whose output was amplified and recorded on one channel of an optical oscillograph. The frequency response of the pressure transducer was flat to 100 Hz, and the pressure system was calibrated by means of a U-tube water manometer. Peak intraoral air pressure was taken as the maximum pressure developed in the mouth during the production of consonants. Consonant duration measurements were obtained from the intraoral air pressure tracings by measuring the time elapsed between the onset and offset of the consonant. Consonant onset was defined as the point in time when the pressure tracing first rose above baseline, and consonant offset was the point in time when the intraoral air pressure assumed a value consistent with the following vowel.

Air flow rate was measured by means of a pneumotachograph. The pneumotachograph is a fine-wire screen, placed within a face mask, which presents a slight resistance to the flow of air from the mouth and nose. A differential pressure transducer is used to sense the pressure drop across the screen during speech. The output of the transducer, which is proportional to the air flow rate, was amplified and recorded on a second channel of the oscillograph. The air flow system was calibrated by means of a rotometer.

Overall sound pressure level (SPL) was recorded by placing an audio microphone at the distal end of the pneumotachograph. The speech signal was recorded on a high-quality tape recorder. These recordings were then played into a graphic level recorder which plotted SPL as a function of time during the speech activities. The SPL peaks were measured and averaged to obtain mean overall SPL for an utterance.

Measurements of fundamental vocal frequency were obtained using the spectrographic technique described by Fry (1970). Briefly, narrow-band spectrograms were made from the tape recordings and the tenth harmonic was measured and divided by 10 at 20 msec intervals. These measurements were averaged to obtain mean fundamental vocal frequency for an utterance.

Each subject performed three speech tasks during the experiment. First, the subject read a list of monosyllabic words containing the phonemes / p b t d f v s z/ in initial and final position using his normal rate, loudness and pitch. Second, the subject read a list of sentences containing these words, again using normal pitch, loudness and rate. The third task involved the psychophysical scaling of vocal effort. The subject was told to produce one of four syllables, /pa/ /ba/ /sa/ or /za/, using the vocal effort he would normally employ in conversational speech. This production was assigned an arbitrary value of 10. The subject was then instructed to produce the syllable with vocal efforts of 5, 10, 20, and 30 relative to the standard production. The procedure was then repeated for the remaining three syllables.

PROGRESS AND RESULTS: Three patients with vocal nodules, one patient with contact ulcers of the vocal folds, one patient with bilateral vocal polyps, and one patient with unilateral vocal fold paralysis have been tested. The ages of the patients ranged between 29 and 53 years, with a mean age of 39 years. None of the patients had any respiratory disorders nor any speech problems other than a voice disorder.

In general, the analysis of the data revealed that the patients produced speech with intraoral air pressures, air flow rates and fundamental vocal frequencies which were different from those expected for normal talkers. Sound pressure level and consonant durations were within normal limits for each of the patients. None of the measures used in this study, however, was sufficiently sensitive to differentiate among the patients. The results for intraoral air pressure, air flow rate and fundamental vocal frequency will be discussed.

Intraoral air pressures produced by the patients in words and sentences ranged from 2 to 5 cm H_2O. Hutchinson and Putnam (1974) and Prosek and House (1975) have reported that intraoral air pressure during consonant production for normal talkers was between 6 and 8 cm H_2O. Thus, the patients produced consonants with lower intraoral air pressures than normal talkers. However, five of the patients used intraoral pressures that were between 4 and 5 cm H_2O. Since most of the subjects were clustered in a narrow range, intraoral air pressure was insensitive to differences among subjects caused by differing vocal pathologies. The psychophysical scaling data was analyzed by plotting vocal effort as a function of intraoral air pressure in log-log coordinates, and computing the slope of this function. The range of these slopes varied from .85 to 2.23 for the six patients, with a mean slope of 1.29. These values are in excellent agreement with those reported by Ringel, House and Montgomery (1967) and Prosek and House (1975) for normal talkers. These data indicate that adult patients with voice disorders vary intraoral air pressure in the same manner as normals, even though the absolute values are lower for the voice patients.

The air flow rates produced during word and sentence utterances for the voice patients varied from 300 cc/sec to 850 cc/sec which is substantially greater than the mean air flow rate for normal talkers (140 cc/sec) reported by Isshiki and von Leden (1964). The values are in close agreement, however, with the values reported for hoarse talkers by the same authors. Four of the six patients used air flow rates which clustered in the 300-400 cc/sec range while the remaining two patients used flow rates between 650 and 850 cc/sec. Once again, the clustering of data points does not permit air flow rate to be used to distinguish among the patients. The slopes obtained from the psychophysical data varied from .40 to .76 with a mean of .64. These data indicate that equal changes in effort are accompanied by greater changes in air flow rate. That is, as these patients increase the effort used to produce speech, air wastage increases.

The fundamental vocal frequency of the patients varied from 90 to 120 Hz with a mean of 105 Hz. These values are lower than the mean fundamental frequencies expected for normal talkers (Fairbanks, 1960). Fundamental frequency separated the voice patients better than the other parameters in that the contact ulcer and unilateral paralysis patients were, on the average, 20 Hz below the vocal nodule patients. The nodule patients, in turn, were consistently 10 Hz below the polyps patient. The use of fundamental frequency as the sole criterion for distinguishing among groups of voice disorders is not advisable, however, since Cooper (1971) reported considerable overlap in fundamental frequency for voice patients.

Intraoral air pressure, air flow rate and fundamental vocal frequency data were combined to determine if various combinations of these parameters would distinguish among the subjects better than any one of them. The clustering effect found in both the air pressure and air flow data, however, limited the usefulness of this approach. When consonant duration and SPL were added to the analysis, no significant increase in the distances among subjects was obtained.

CONCLUSIONS: One goal of the present project was to determine if aerodynamic and acoustic measurements could be used to distinguish among types of voice disorders. Intraoral air pressure and air flow rate measured at the lips are the simplest aerodynamic parameters to measure clinically. However, the data indicate that these parameters are not sufficiently sensitive to uniquely classify voice patients. Thus, therapy programs designed to treat voice patients according to etiology are not feasible at the present time. Future research in this area probably should concentrate on estimates of subglottal pressure, glottal volume velocity, and glottal resistance. These measurements, although difficult to obtain, are more directly related to vocal pathology.

The second goal of this project was to determine the manner in which the breath stream is controlled by voice patients during speech production. The data indicate that the voice patients consistently produce speech with higher air flow rates and lower intraoral air pressures than normal talkers. Both of these effects have their origin in the inability of the vocal folds of these patients to make

complete glottal closures (Isshiki and von Leden, 1964). Since the vocal folds do not completely approximate, air flows through the glottis at a higher rate than normal, accounting for the high flow rates observed for each of the voice patients. This phenomenon would also account for the lower intraoral air pressures observed in this study. Since a great amount of air is wasted during vowel production, less air is available for consonant production. It is possible that a therapy program based on monitoring air flow rate may be effective in improving the voice quality of patients with incomplete glottal closures. That is, treatment procedures, using a biofeedback paradigm, which provide a patient with information on his air flow rate during vowel production may improve voice quality in less time than traditional therapy approaches.

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FUNDS UTILIZED, FY-77: NONE

FUNDING REQUIREMENTS, FY-78: NONE

PUBLICATIONS: N/A

TYPE OF REPORT: Terminated. Although 30 patients were to be tested, the data gathered to date indicate that simple aerodynamic measurements are not sufficient to uniquely categorize voice patients, and that measurements more directly related to glottal functioning must be used.

Work Unit No.: 2508

Title of Project: An Experimental Analysis of Aural Rehabilitation Using Programmed Instructions.

Investigators: Edward B. Muth, M.A.
Supervisor
Aural Rehabilitation Section

Charlene K. Scherr, M.A.
Aural Rehabilitation Section

Objectives: To provide three programmed presentations for orientation to effective hearing aid use.

Technical Approach: Utilization of recorded 3-voice narration 20 minute duration. Use of 80 - 2 X 2 35 mm slides for each sound - slide presentation.

Progress and Results: The single presentation on hearing aid orientation that has been in great use during the past year has been very successful with an audiologist's lecture. Programs will be developed for new hospital use as future needs become clear.

Conclusion: The project indicates that programmed materials of this sort will become more beneficial as the Aural Rehabilitation Program evolves.

Fund Requirements: N/A - No funding as of now.

WORK UNIT NUMBER: 2510

TITLE: A Multidimensional Assessment of Stuttering Severity

INVESTIGATORS:
Principal: Robert A. Prosek, Ph.D.
Associate: Allen A. Montgomery, Ph.D.
Brian E. Walden, Ph.D.
Daniel M. Schwartz, Ph.D.

OBJECTIVE: To determine the parameters of stuttered speech that are used by speech pathologists to rate the severity of stuttering.

TECHNICAL APPROACH: Measurements of instances of stuttering, instances of part word repetitions, instances of word repetitions, instances of phrase repetitions, instances of prolongations, instances of interjections, number of part word repetitions, number of word repetitions, number of phrase repetitions, number of prolongations, number of interjections, mean prologation duration, mean pause duration, total reading time, mean fundamental vocal frequency and mean sound pressure level (SPL) are made from tape recorded samples of stuttered speech. The taped samples are to be paired and used to obtain judgments of stuttering similarity from a group of speech pathologists. The similarity judgments will be analyzed by means of a multidimensional scaling routine (INDSCAL) in order to obtain perceptual dimensions of stuttering behavior. The output of INDSCAL will be compared with measurements of stuttering behavior to determine which physical parameters form the basis of stuttering severity.

PROGRESS AND RESULTS: Thirty stutterers have been recorded and the samples of 15 of these subjects have been selected for use in the project. An intercorrelation matrix of the measurements listed in the previous section revealed high correlations between instances of prolongations and number of prolongations (.96) and between instances of interjections and number of interjections (.99). In addition, the data showed very little variation in mean fundamental vocal frequency and mean overall SPL. Therefore, number of prolongations, number of interjections, fundamental vocal frequency and SPL have been eliminated from the study. The measurement data reveal two important characteristics of the stutterers used in the project. First, the parameter having the greatest frequency of occurrance varies across stutterers. That is, while one subject may repeat words most often, other stutterers use interjections, part word repetitions, or prolongations most often. Second, each of the stutterers demonstrates more than one type of stuttering in their speech. These observations lend face validity to the underlying assumption of this study that stuttering is a multidimensional phenomenon.

The second phase of the project, obtaining similarity judgments from speech pathologists, is in progress. Pilot studies have been conducted to determine the best manner of presentation of the taped

speech samples. In the first pilot study, the entire 300-word passage of each stutterer's speech was paired with the passage of every other stutterer. This resulted in a test tape requiring four and a half hours to obtain one set of judgments. This tape was considered much too long to obtain reliable similarity judgments. In the second pilot study, the listeners were asked to judge the severity of each of the taped samples on a seven-point scale. The severity judgments were subtracted from each other to obtain a lower-triangular matrix which estimated the similarity of the stuttering behavior between pairs of stutterers. The INDSCAL analysis of these data, however, resulted in a unidimensional output. That is, since the listeners were asked to rate the stutterers along a single dimension, INDSCAL recovered only this dimension. The pilot study demonstrated that the speech samples must be paired to obtain reliable similarity judgments.

Currently, a procedure is being followed to select a sample of each stutterer's speech which accurately reflects his stuttering behavior and which will be paired with a sample of every other stutterer's speech. In this procedure, the measurements for each sentence of the 300-word passage are converted to standard scores and summed across the measurements. The sentence which yields the highest summed standard score will be selected for use in the listening task. This procedure should result in a test tape requiring only one hour for obtaining a set of judgments from the listeners.

CONCLUSIONS: Not applicable at the present time.

FUNDS UTILIZED, FY-77: NONE

FUNDING REQUIREMENTS, FY-78: NONE

PUBLICATIONS: N/A

TYPE OF REPORT: Interim

WORK UNIT NO.: 2511

TITLE: Memory for Consonants of Normal and Hearing-Impaired Observers

INVESTIGATORS:

Principal: Brian E. Walden, Ph.D.

Associate: Allen A. Montgomery, Ph.D.
Robert A. Prosek, Ph.D.
Daniel M. Schwartz, Ph.D.

OBJECTIVE: To determine the influence of hearing loss on the processing and coding of speech stimuli in memory.

TECHNICAL APPROACH: Pairs of consonant-vowel stimuli were presented to subjects for similarity judgments. Five of the subjects had normal hearing, five had moderate adventitious hearing losses, and five had severe congenital hearing impairments. Using an equal-appearing interval scale, the subjects rated the similarity of the consonant pairs presented auditorily and via an orthographic display. The resulting data were analyzed to reveal differences between the groups and between the modes of presentation.

PROGRESS AND RESULTS: All phases of the experiment have been completed with the exception of some minor data analysis and the preparation of the final manuscript for publication. The results revealed that the psychological spaces of consonant similarity are interpretable in terms of traditional articulatory features. This is true for all three subject groups and for both presentation modalities. The strength of feature usage, however, differed between the two modalities for the hearing-impaired subjects. Under the auditory condition of presentation, "acoustic" features such as voicing and sonorancy emerged as dominant dimensions for the hard-of-hearing subjects, if auditory confusions were ignored. If the auditory confusions were considered into the analysis, however, manner-of-articulation features dominated the psychological spaces. With this form of analysis, the auditory and orthographic modes of presentation yielded very similar psychological spaces. The spaces of the normal-hearing subjects were dominated by manner-of-articulation features under all condition.

CONCLUSIONS: The following conclusions appear justified by these data:

1. Consonant phonemes appear to be coded in memory by hearing-impaired subjects similarly to that by normal-hearing persons.

2. Consonant confusions must be considered in the analysis of similarity judgments by hearing-impaired listeners.

3. The frequently reported dominance of voicing and sonorancy features in the perception of hearing-impaired subjects appears to be a result of the signal degradation, rather than to any inherent perceptual importance of these features to hearing-impaired listeners.

4. Both normal-hearing and hearing-impaired listners appear to make similarity judgments among speech sounds based upon some abstract internal representation of the phonemes as identified (either correctly or incorrectly), rather than rating the similarity of the acoustic images per se.

FUNDS UTILIZED FY-77: None

FUNDS REQUESTED FY-78: None

PUBLICATIONS: A paper based upon this work will be presented at the Annual Convention of the American Speech and Hearing Association, Chicago, Illinois, November, 1977. A manuscript is being prepared for submission to the Journal of Speech and Hearing Research.

TYPE OF REPORT: Completed

WORK UNIT NO.: 2512

TITLE: Effects of Hearing Impairment and Acoustic Filtering on the Perception of Speech

INVESTIGATORS:

Principal: Brian E. Walden, Ph.D.

Associate: Daniel M. Schwartz, Ph.D.
Allen A. Montgomery, Ph.D.
Robert A. Prosek, Ph.D.

OBJECTIVE: The objective of this experiment is to describe those effects of hearing loss on speech perception which cannot be accounted for on the basis of the frequency distortion imposed by reduced auditory sensitivity. Specifically, the purpose is to determine which speech sounds (or classes of sounds) are perceived similarly and differently through an impaired ear and a normal ear listening through a filter network which has been matched to the impaired ear's audiometric configuration.

TECHNICAL APPROACH: Consonant confusion matrices will be constructed for 20 adults with unilateral hearing impairments. For the impaired ear, the consonants will be presented without any external distortion. For the normal ear, however, the stimuli will be presented through a multifilter network which is adjusted to match the configuration of the hearing loss in the impaired ear. In addition, pairs of consonants will be presented sequentially to the two ears for judgments of consonant similarity using an equal-appearing interval scale. The resulting data will be analyzed to reveal which consonants (or classes of consonants) are perceived differently through the impaired ear and the filter network.

PROGRESS AND RESULTS: Both the 400-item confusion matrix test tape and the 80-item paired-comparison tape recording have been prepared and dubbed. The Spectrum Shaper was received from Bruel and Kjaer Instruments, Inc. during FY-77. It did not meet the Government's specifications, however, having several electrical problems. It has been returned to B & K three different times and is there at the present time. Each time it was returned to the Company, they have kept it several weeks. They have yet to satisfactorily repair it. A consultation with the Legal Department of Purchasing and Contracting, WRAMC, indicates that the Government has no recourse since Material Branch indicated in writing that the instrument was received in good working condition upon delivery. Personnel of Material Branch, however, did not inspect the equipment upon receipt.

CONCLUSIONS: N/A

FUNDS UTILIZED FY-77: None

FUNDS REQUESTED FY-78: None

PUBLICATIONS: N/A

TYPE OF REPORT: Interim

WORK UNIT NUMBER: 2514

TITLE: The Use of EMG Biofeedback in the Treatment of Hypertensive Voice Disorders

INVESTIGATORS:
Principal: Robert A. Prosek, Ph.D.
Associate: Allen A. Montgomery, Ph.D.
Brian E. Walden, Ph.D.
Daniel M. Schwartz, Ph.D.

OBJECTIVE: To determine if proportional EMG biofeedback, recorded from the laryngeal region, can effectively improve the voice quality of patients with hyperfunctional voice disorders.

TECHNICAL APPROACH:

Subjects

Six adult patients, three males and three females, participated in the study. The only criterion for inclusion in the project was a speech pathologist's judgment that the voice was produced with excessive laryngeal tension. Laryngological examinations revealed that two patients had vocal nodules, one patient had contact ulcers of the vocal folds, and one patient had a small carcinoma surgically removed from one vocal fold. The fifth patient was diagnosed as recurrent traumatic laryngitis and the sixth as spastic dysphonia. In addition to the six patients, eight normal talkers, four males and four females, served as a comparison group. The normal talkers did not participate in the biofeedback training, but rather, their EMG activity was recorded for comparison with the data obtained from the voice patients.

Equipment

Electromyographic activity was recorded from the laryngeal area using bipolar surface electrodes placed over the cricothyroid region with a third (indifferent) electrode on the earlobe. One electrode was placed over the cricothyroid approximately one centimeter on each side of the midline. Pilot investigations determined that this site yielded EMG recordings during phonation and during approximation of the vocal folds without phonation. Less than 10 microvolts of activity was observed during head turning, head retroflexion, and silent mandibular movements. Although the electrodes were placed over the cricothyroid muscles, the EMG activity recorded was actually the sum of all the EMG activity occurring in this region.

Figure 1 is a block diagram of the equipment used for biofeedback training. The subject was seated in a sound-treated room with the electrodes in place, and a microphone was positioned three feet in front of the subject. The speech signal was recorded on audio tape and on one channel of an optical oscillograph. The EMG signal was amplified and recorded on a second channel of the oscillograph. Additionally, the amplified EMG signal was rectified and averaged over a 100 msec interval by means of a contour-following integrator. The output of the integrator was displayed on a third channel of the

oscillograph. Measurements of EMG activity (in microvolts rms) were made from this tracing.

The output of the contour-following integrator was also used to drive a voltage controlled oscillator (VCO) and a voltage comparator. The output of the VCO was a pure tone whose frequency was increased and decreased as the integrator output increased and decreased. Thus, as the laryngeal EMG activity increased, the tone produced by the VCO increased in frequency, and, as the EMG activity decreased, the tone decreased in frequency. The VCO output was amplified and fed to a pair of earphones in the sound-treated room.

The voltage comparator served as a threshold device during the biofeedback training. When the EMG activity exceeded the value selected on the comparator, a broadband noise generator was activated. The output of the noise generator was amplified and fed to the subject's earphones. When the EMG activity was below the voltage comparator level, the VCO was activated. This arrangement provided two types of information to the subject. First, the VCO informed the subject of increases and decreases in laryngeal tension. Second, the threshold-controlled noise generator provided a specific goal for the subject, i.e., keeping the noise off. In general, the experimenter set the level of the voltage comparator to a high value during the first training session, and the level was gradually reduced during the course of training.

Two AND gates were used to join the outputs of the microphone and the voltage comparator. When the subject was speaking and the EMG activity was below the threshold of the comparator, the VCO was activated. When the subject was speaking and above the level of the comparator, the noise generator was activated. This arrangement resulted in an absence of tone and noise when the subject was not talking. Not shown in Figure 1 are two cumulative timers, one associated with each AND gate. The timers measured the amount of time the subject spent above and below the threshold during periods of speech.

In addition to measurements of EMG activity, the fundamental vocal frequency used by the patients was determined from the tape recordings using the spectrographic technique described by Fry (1970). Also, graphic level recordings were made from the audio tapes to obtain measurements of overall sound pressure level (SPL).

Procedures

Each of the normal talkers was seated in the sound-treated room with the electrodes in place. The subjects were instructed to read the Amplifier Passage (Fairbanks, 1960) using their normal pitch, loudness and rate. The averaged EMG activity was measured from the oscillographic tracings, and frequency distributions of EMG activity were prepared from these data.

The six patients with voice disorders participated in a baseline session, fourteen 30-minute training sessions, and a final session. During the baseline and final sessions, the patients received no biofeedback, and the procedures were identical to those described above for the normal talkers. During the fourteen training sessions, the patients received EMG biofeedback while producing isolated vowels,

isolated words, reading sentences or paragraphs, or while engaged in conversation. The level of the voltage comparator typically was set to a relatively high level (70-90μV, depending upon the initial EMG measurements) during the first training session. When the cumulative timers indicated that the subject was producing 80% of his speech below the threshold, the level was lowered by 5μV until the mean EMG activity, averaged across an entire session, approached the mean level obtained for normal talkers. The subjects were instructed to keep the noise off and the tone on while producing speech. In addition, the subjects were told that the pitch of the tone would indicate if the laryngeal tension were increasing or decreasing. Judgments of voice quality were made following each session by at least one of the experimenters.

PROGRESS AND RESULTS:

Figures 2a and 2b present the frequency distributions of EMG activity for normal male and normal female talkers, respectively. The mean for the male talkers was 48μV with a modal value of 30μV. For female talkers, the mean was 37μV with the mode occurring at 20μV. These data provided descriptive information concerning the amount and range of EMG activity to be expected during normal speech production using our electrode site. These distributions served to indicate when the voice patients were producing speech with EMG levels approaching those used by normal talkers. It must be noted, however, that individual differences in the distribution of adipose tissue, mobility of the vocal folds, placement of the electrodes, and edema of the vocal folds preclude the comparison of individual data to strict normative values. The distributions were used as guidelines by the experimenters to adjust threshold levels during the biofeedback training.

Figure 3 presents the data obtained from a 22 year-old female with contact ulcers of the vocal folds. The baseline distribution has a mean of 45μV and a mode of 50μV. In addition, the baseline measurements show no activity below 30μV. The distribution of EMG activity for the final session has a mean of 28μV and a mode of 30μV. Judgments of voice quality made during the final session indicated that speech was produced with a normal voice, and acoustic measurements revealed a decrease in fundamental vocal frequency of approximately 15 Hz and a decrease of 5 dB in overall SPL. A subsequent laryngeal examination revealed that the contact ulcers were no longer present. During the course of the biofeedback training, the subject was not treated with medication or vocal rest.

The baseline and final distributions of EMG activity obtained from a 47 year-old male with traumatic laryngitis are shown in Figure 4. The vocal symptoms of the patient were periodic hoarseness accompanied by edema of the vocal folds and, occasionally, complete loss of voice. The baseline distribution has amean of 76μV and a modal value of 90μV. The mean of the final distribution is 48μV with the mode occurring at 50μV. The patient has not experienced any episodes of hoarseness or aphonia since completing the biofeedback training. Follow-up data, obtained two, four and eight weeks after the final session, show essentially no change from the final distribution shown in Figure 4.

The acoustic measurements revealed a decrease of approximately 10 Hz in fundamental vocal frequency, but overall SPL remained unchanged.

Figure 5 presents the data obtained from a 36 year-old female with bilateral vocal nodules. The mean of the baseline distribution is 52μV and the mode is 50μV. The distribution of EMG activity for the final session has a mean of 36μV and a mode of 35μV. The acoustic data showed an increase in fundamental vocal frequency of approximately 10 Hz and a decrease of 6 dB in overall SPL. After some training, this patient could produce speech with normal voice quality with and without biofeedback in the clinical setting. The use of good voice quality in situations removed from the clinic, however, was inconsistent. The two patients described above had no difficulty in applying normal voice quality to all situations.

In Figure 6, mean EMG activity is shown as a function of the fourteen training sessions for the remaining voice patients. Measurements made during the initial sessions for these patients indicated that the mean EMG activity was at or below the mean level recorded for the normal talkers. Figure 6a presents the data of a 46 year-old female with bilateral vocal nodules. The mean EMG activity was lowered by 5μV as a result of the biofeedback training, but voice quality did not improve. The data obtained from a 54 year-old male with spastic dysphonia are shown in Figure 6b. The first and last training sessions show no change in mean EMG activity, and the pattern of activity across the sessions is irregular. No improvement in voice quality was consistently achieved, although the subject did produce speech with a normal voice quality during several sessions.

Figure 6c summarizes the data of a 46 year-old male who had had a small carcinoma removed from one vocal fold. A laryngeal examination revealed the presence of edema of both the true and false vocal folds. The voice of this patient was very low in intensity and extremely hoarse, and the patient could not speak for more than 15 minutes without experiencing some discomfort. Despite a reduction in mean EMG activity from 30μV to approximately 15μV, there was no improvement in voice quality. The acoustic measurements revealed no change in fundamental vocal frequency, but there was an increase in overall SPL of approximately 10 dB. Although there was no perceptible improvement in voice quality, the patient reported that speech production was more comfortable following the biofeedback training, even when speaking for prolonged periods of time.

CONCLUSIONS:

The data in Figures 3-5 demonstrate that EMG biofeedback can be used to alter the level of muscular activity used to produce speech with a concomitant improvement in voice quality. Hirano, Koike and Joyner (1969) have shown that a hyperfunctional voice can be accompanied by increased activity of the cricothyroid, lateral cricoarytenoid, vocalis and sternohyoid muscles. The electrode site used in this study probably was summing the activity of these muscles, and thus, provided the subjects with sufficient information concerning laryngeal tension during speech production.

Although biofeedback training did improve the voice quality of three patients, the data shown in Figure 6 indicate that EMG biofeedback will not be successful with every patient who sounds hypertense. Factors in addition to the level of EMG activity, such as the mobility of the vocal folds and the presence of edema, also may influence the success to be expected from biofeedback training. Moore and Thompson (1965) have listed several modes of abnormal vocal fold vibration which are perceived as hoarseness. These modes of vibration may or may not be accompanied by excessive laryngeal tension. It appears, then, that the perception of a deviant voice quality is not sufficient to determine if biofeedback training will be beneficial.

The use of biofeedback in this study was primarily experimental in nature, and therefore, the instrumentation and procedures were established prior to data acquisition. However, our experience with biofeedback has led to some observations which can simplify the technique for routine clinical use. First, the apparatus shown in Figure 1 provided two types of information to the patient: 1) the frequency-varying tone indicated that laryngeal tension was either increasing or decreasing, and 2) the broadband noise indicated that the EMG activity had exceeded threshold. Comments elicited from the patients showed that they concentrated their efforts on keeping the noise off and did not attend to the frequency variations of the tone. Therefore, it is likely that threshold EMG biofeedback is as effective in altering voice quality as analog EMG biofeedback and that two sources of feedback signals are unnecessary.

The second observation concerns joining the outputs of the microphone and the voltage comparator, via the AND gates. Although this arrangement insured that the patient received feedback only during speech production, indications of pre-phonatory laryngeal activity were not presented to the subjects. All of the patients produced some speech with hard glottal attacks during which the laryngeal EMG activity exceeded the threshold prior to the onset of the acoustic signal. Since the feedback signal was contingent upon phonation, the subjects were not made aware of this activity. Thus, feedback which was independent of an acoustic signal would have been preferable in these instances.

Third, our experience showed that the measurement of the amount of time spent below threshold provided adequate documentation of the progress made by the patient. Although measurements of mean EMG activity are more directly related to changes in laryngeal tension, the amount of time below threshold indicates the extent to which the subject is achieving his goal of producing speech without excessive laryngeal activity. Measuring the amount of time below threshold allows the clinician to document progress while avoiding the time consuming process of measuring ascillographic tracings.

The three observations mentioned above may be combined to simplify the instrumentation used for biofeedback training. All that is required is a high-gain differential amplifier, an integrator, a voltage comparator, a timer and a noise generator (or other suitable source of a feedback signal). Such an array provides all the elements needed to measure the EMG signal, control the feedback signal, and document progress.

The final observation is that the biofeedback technique appears to facilitate the vocal re-education process. When perceptual analysis is used to alter voice quality, the patient must be taught to use the auditory system to monitor the voice continuously. Further, the patient must be trained to recognize auditorily examples of the desired voice quality when they occur and to generalize this quality to all situations. In contrast, the biofeedback instrumentation provides an accurate external monitor of laryngeal tension which places fewer demands on the auditory system. The patient is free to concentrate on developing methods of reducing laryngeal tension. Our experience with EMG biofeedback indicates that it is an effective tool for treating some patients with hyperfunctional voice disorders.

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Moore, P. and Thompson, C.L. Comments on the physiology of hoarseness. Arch. Otolaryng., 81, 97-102 (1965).

FUNDS UTILIZED, FY-77: $593.50

FUNDING REQUIREMENTS, FY-78: NONE

PUBLICATIONS: Manuscript is being prepared for publication in the Journal of Speech and Hearing Disorders.

TYPE OF REPORT: Completed.

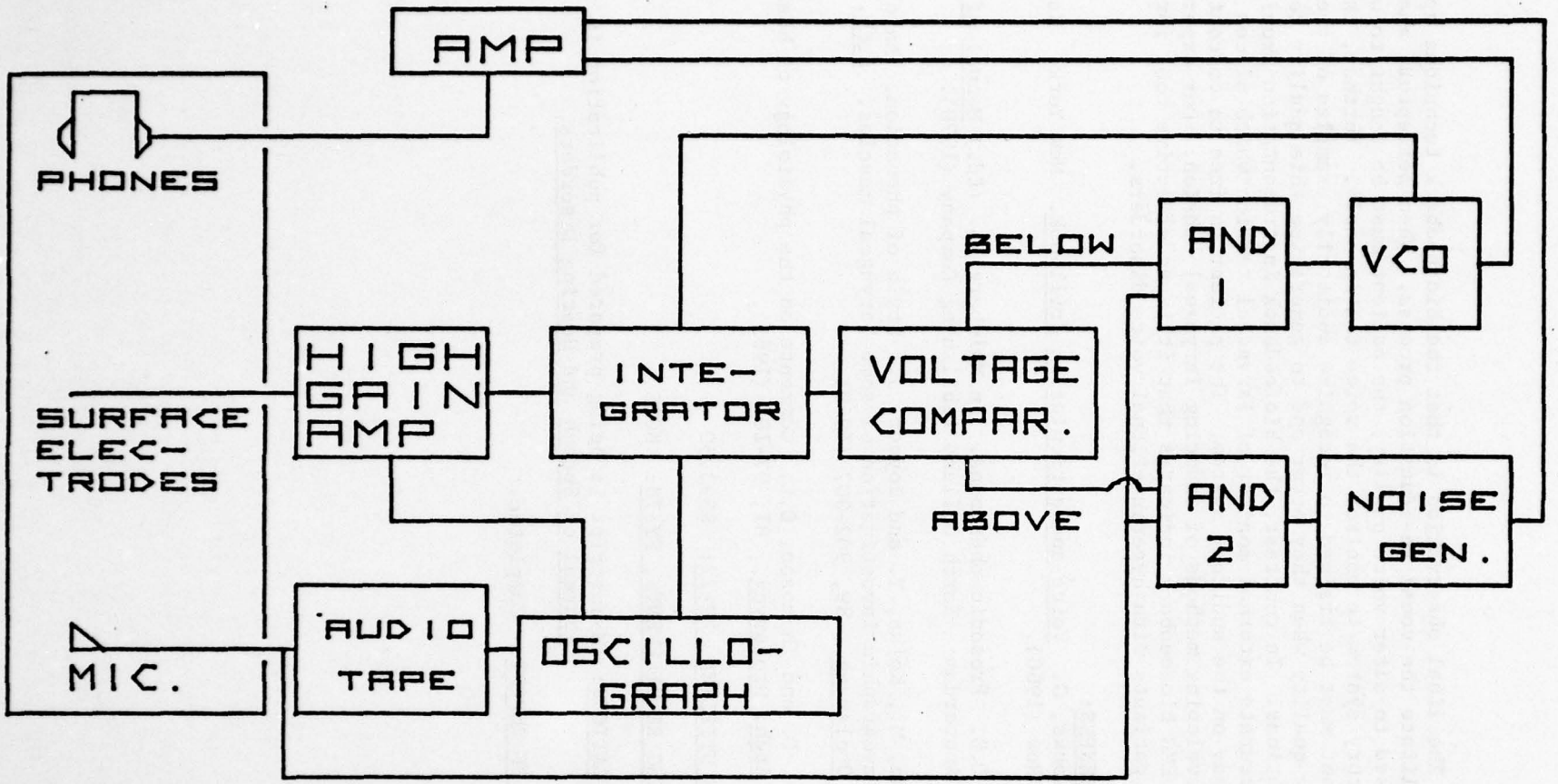


Figure 1. Block diagram of the equipment used for biofeedback training.

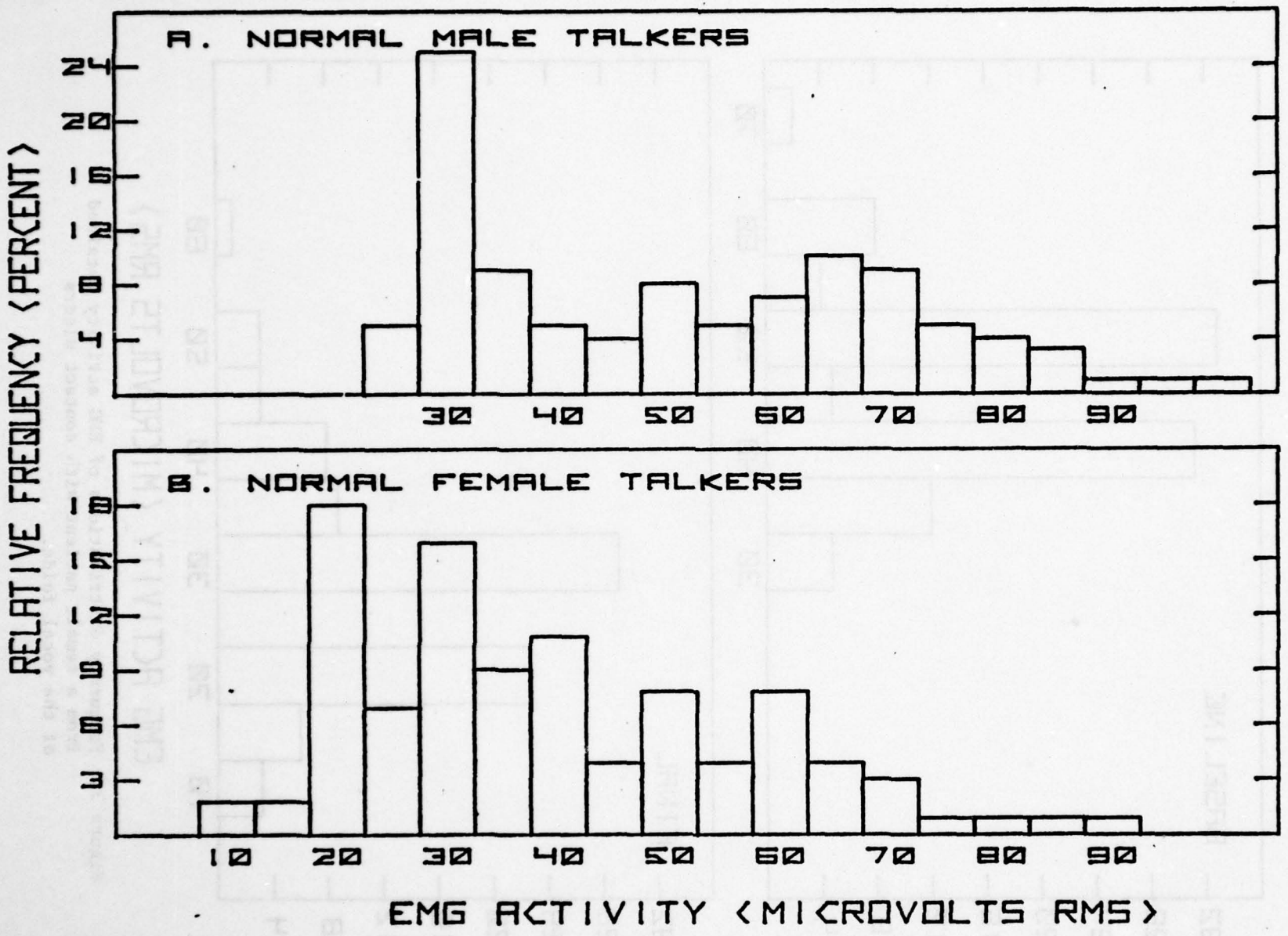


Figure 2. Frequency distributions of EMG activity obtained from A.) normal male talkers and B.) normal female talkers.

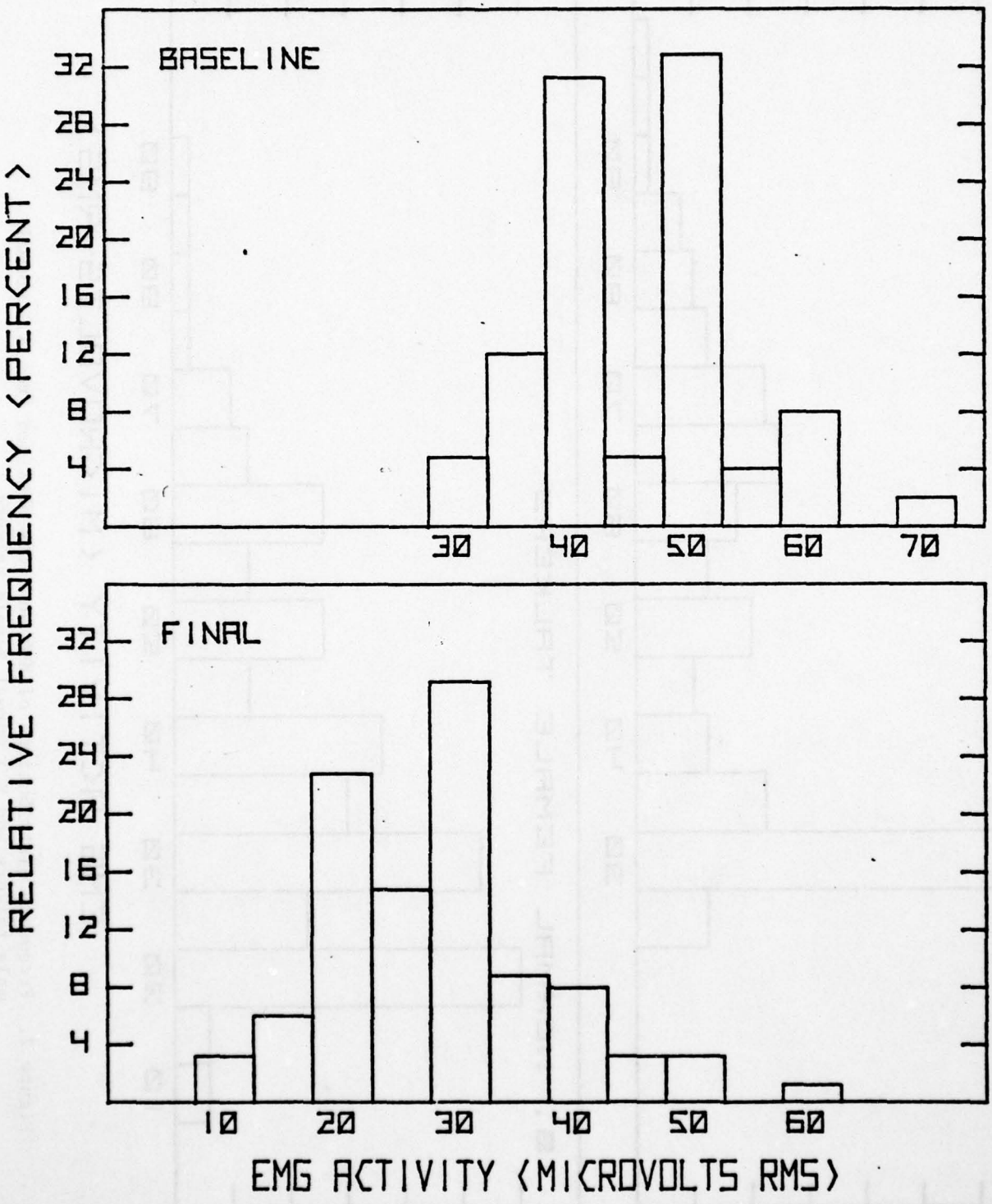


Figure 3. Frequency distributions of EMG activity obtained from a female patient with contact ulcers of the vocal folds.

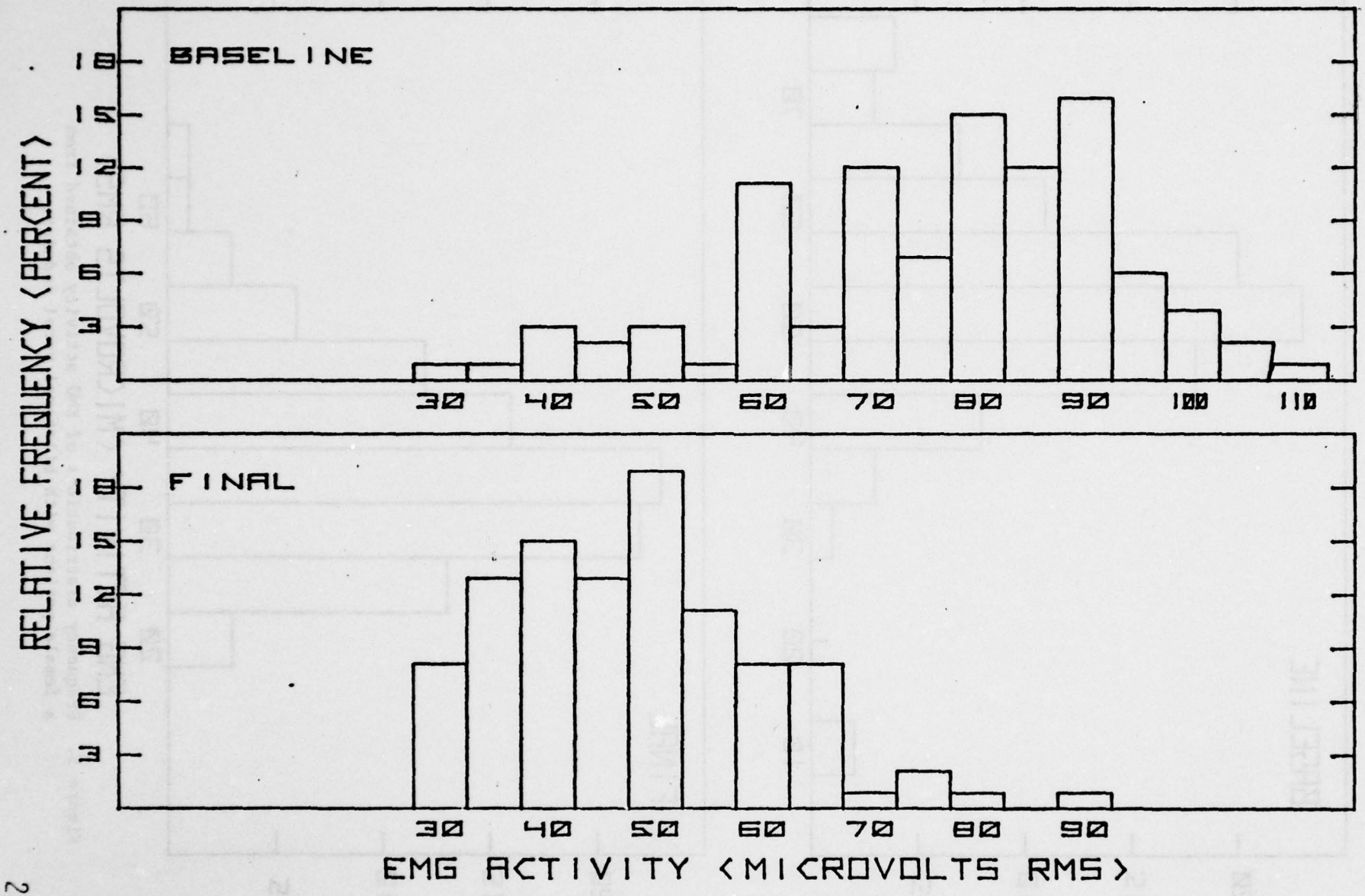


Figure 4. .Frequency distributions of EMG levels obtained from a male patient with traumatic laryngitis.

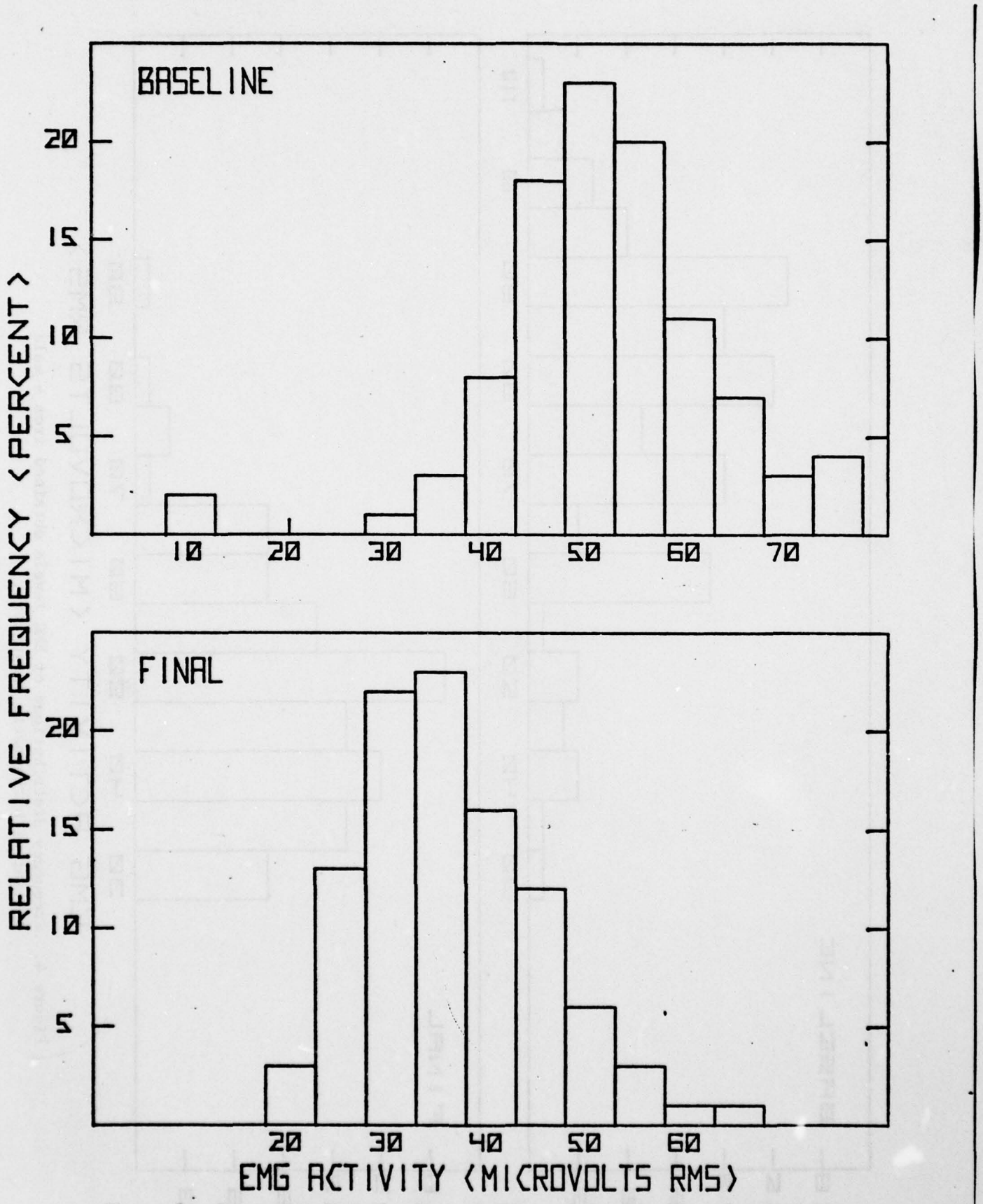


Figure 5. Frequency distributions of EMG activity obtained from a female patient with bilateral vocal nodules.

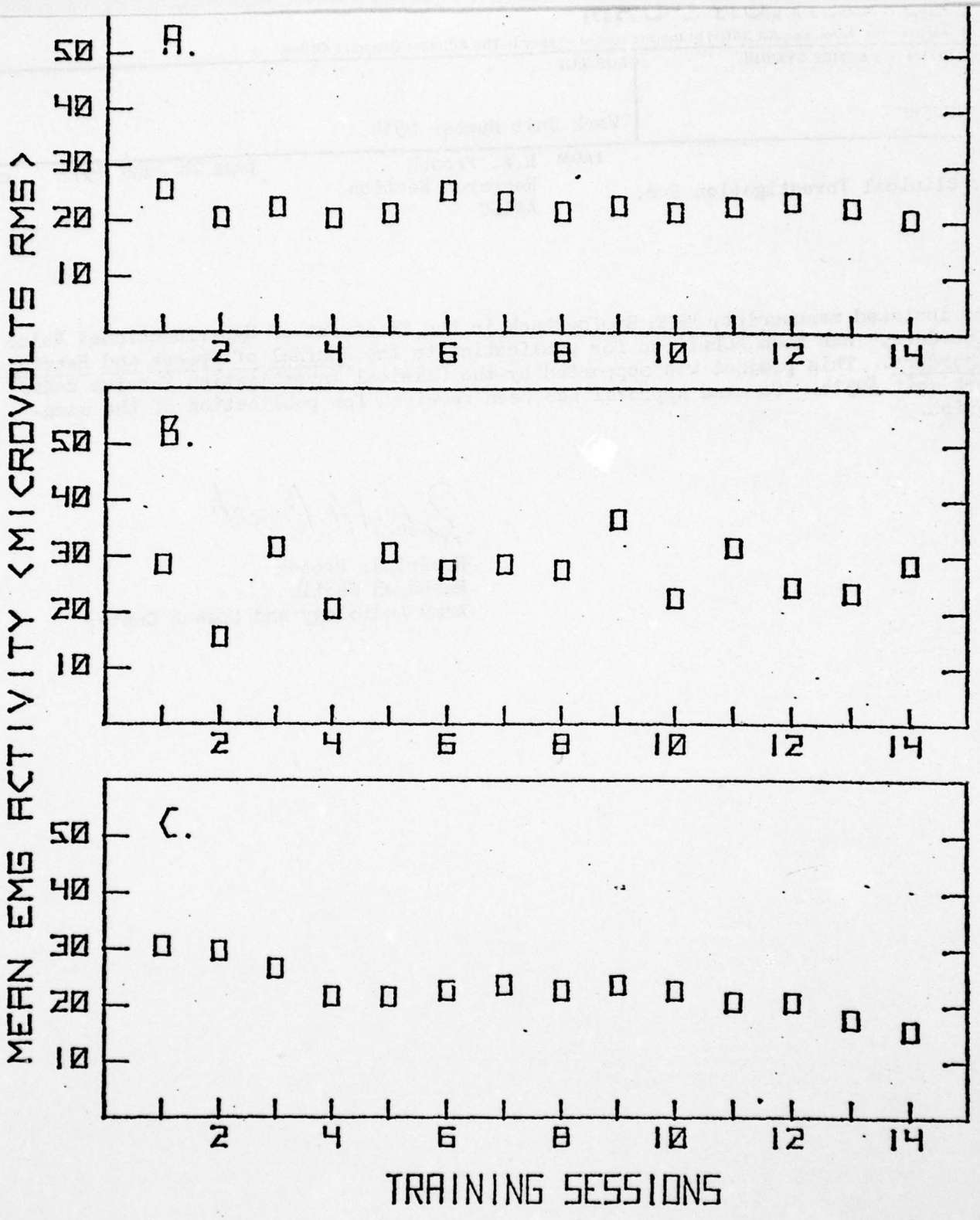


Figure 6. Mean EMG activity displayed as a function of training sessions for A.) a female patient with bilateral vocal nodules, B.) a male spastic dysphonia patient, and C.) a male patient who had had a small carcinoma removed from one vocal fold.

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
SGRP-SMC	Work Unit Number 2514

TO , Clinical Investigation Svc.

FROM R.A. Prosek
Research Section
AA&SC

DATE 28 June 1977

CMT 1

The inclosed manuscript, "EMG Biofeedback in the Treatment of Hyperfunctional Voice Disorders," has been submitted for publication to the Journal of Speech and Hearing Disorders. This project was supported by the Clinical Investigation Service under work unit #2514. Command approval has been received for publication of the manuscript.

Robert A. Prosek

Robert A. Prosek
Research Section
Army Audiology and Speech Center

DA FORM 1 FEB 62 2496 REPLACES DD FORM 96, EXISTING SUPPLIES OF WHICH WILL BE ISSUED AND USED UNTIL 1 FEB 63 UNLESS SOONER EXHAUSTED.

☆ U.S. GPO: 1974—553-130, 3339

WORK UNIT NO.: 2515

TITLE: Development of a Test to Evaluate Binaural versus Monaural Applicability in Hearing Aid Selection.

INVESTIGATORS:

Principal: CPT Donald R. Bender, M.A.

Associate: G. Donald Causey, Ph.D.

OBJECTIVE: To evaluate a test procedure that was developed to gauge whether a patient can demonstrate impairment when utilizing two hearing aids as apposed to one amplifying system.

TECHNICAL APPROACH: The subjects in this study were fourteen adult males with bilateral sloping high frequency sensorineural hearing loss of moderate to severe degree. All subjects were considered appropriate candidates for binaural amplification as determined by prior pure tone and speech tests. The University of Maryland recording of CNC word discrimination lists was the stimulus of interest. Ten, CNC lists of 50 words each comprise this particular speech discrimination test. The competition material was uncorrelated speech babble that was presented simultaneously from five speaker locations (see Figure 1 attached). The speech babble was comprised of three talkers, (2 male and 1 female). When presented simultaneously through five loudspeakers, such that at any given moment spectra are all different from each other, it has the psychoacoustic effect of fifteen talkers which minimized any perceptual masking effects. Based upon the results of a pilot study, a 0 dB signal-to-noise ratio (re: 60 dB SPL stimulus presentation level) was utilized during the actual investigation.

The subjects were equally divided into two groups. The even numbered subjects experienced the binaural condition first, then the monaural. The order was then reversed for the odd numbered subjects. The word discrimination list presentation was counterbalanced within subjects to reduce order effects. Overall, each subject received at least one list in each mode, (monaural, binaural) from each loudspeaker. Subjects were instructed to repeat the stimulus word. They were also asked to identify the loudspeaker from which the stimulus was emanating and the time required to make this localization judgment was determined.

PROGRESS AND RESULTS: All phases of this experiment have been completed with the exception of the preparation of the final manuscript for publication. In data analysis a two factor analysis of variance indicated binaural performance was significantly improved over the monaural condition at the .01 confidence level. The subjects obtained an overall average score of 80.7% in the binaural mode versus 68.6% in the monaurally aided condition. Speaker angle from the subject averaged across the two test conditions was not statistically significant at the .05 level of confidence. The range of mean scores from the five different speaker positions was from 73.4% to 75.6%. An analysis of variance

of localization time yielded no significant main effects or interactions. The difference between the monaural and binaural mean localization time did not reach significance, and no speaker angle, or combination of mode and angle, was significantly different from any other.

There were no significant order effects between presentation modes (monaural, binaural). The presentation order of discrimination lists was also evaluated. Results indicated that none of the ten orders utilized differed significantly from the others. It appears that the results of the study were not influenced by learning effects or fatigue. The results indicate consistent performance throughout the duration of the experiment. Finally, an analysis of variance indicated excellent interlist equivalency between lists for this particular investigation.

CONCLUSIONS: The following statements may be concluded from the data obtained:

1. Word discrimination ability is significantly enhanced, both statistically and clinically, with binaural aids as compared with monaural aids.

2. Localization ability, as measured with this particular method and subject population, was not significantly enhanced when using binaural as opposed to monaural amplification.

3. The test presentation format is a readily adaptable clinical technique for gathering information on applicability of binaural amplification.

FUNDS UTILIZED FY-77: None

FUNDS REQUIRED FY-78: None

PUBLICATIONS: A paper describing this research has been submitted for presentation at the Annual Convention of the American Speech and Hearing Association, Chicago, Illinois, November, 1977. A manuscript is being prepared for submission to the Journal of Speech and Hearing Research.

TYPE OF REPORT: Completed.

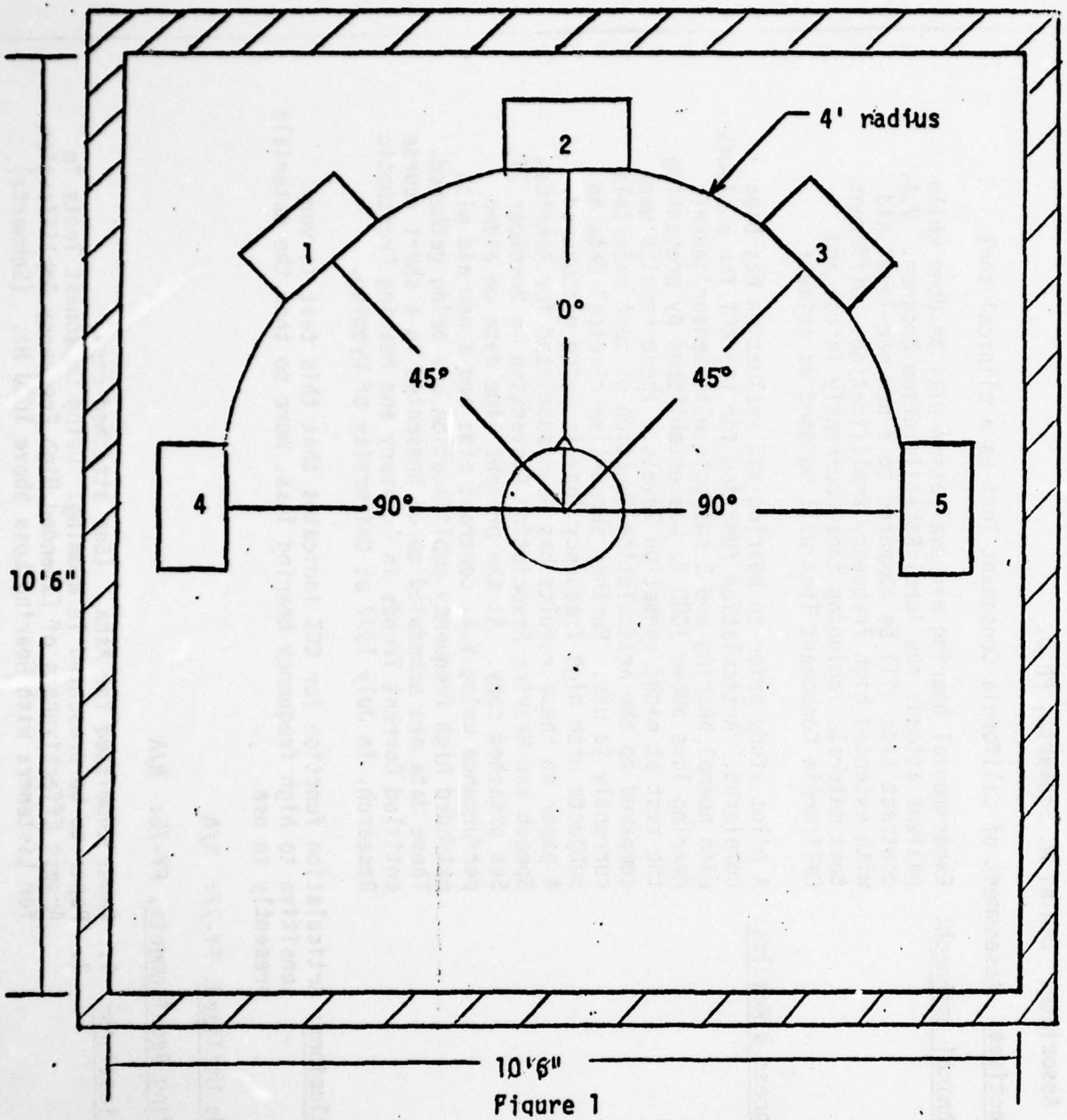


Figure 1

LOUDSPEAKER POSITIONS. Depicted in this illustration is the physical location of the speakers as well as their angle of incidence relative to the subjects position.

Work Unit No.: 2516

Title of Project: The Effect of Amplification on Limited High-Frequency Hearing Loss

Investigators:

Principal: Rauna K. Surr, M.S.

Associate: Daniel M. Schwartz, Ph.D.

Objectives: Assessment of California Consonant Test as a clinical tool.

Technical Approach: Experimental hearing aid evaluation will be done while patient attends the Aural Rehabilitation Program. V.A. contract aids will be compared to a new ear-level aid with extended high frequency amplification. Different test materals including those currently in use and California Consonant Test will be used as stimuli.

Progress & Results: A pilot study prior to hearing aid evaluation has been completed. Articulation function for the CCT for subjects with normal hearing and 2 subjects with sensorineural hearing loss above 1000 Hz was established by presenting the test at eight sensation levels. These results were compared to the articulation function of test materials currently in use. Further supportive clinical data on subjects with high frequency loss is being gathered. A paper on these results has been submitted for American Speech and Hearing Association Convention in November 77. See attached copy. At the present time data on aided performance using V.A. contract aids and a new aid with extended high frequency amplification are being gathered. These data are scheduled to be presented in a short course entitled Current Trends in Auditory and Hearing Prosthetic Research, in July 1977 at University of Wyoming.

Conclusions: Articulation function for CCT indicates that this test is very sensitive to high frequency hearing loss, more so than the materials presently in use.

Funds Utilized, FY-77: N/A

Funding Requirements, FY-78: N/A

Publications:
1. Paper submitted for Asha. (See attached copy)
2. Paper to be presented in Wyoming: Using Consonant Tests To Assess Effectiveness of Extended High Frequency Amplification for Listeners with Hearing Loss above 1000 Hz. (Schwartz)

Type of Report: Interim

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ANNUAL PROGRESS REPORT (FISCAL YEAR 1977) OF THE CLINICAL INVES--ETC(U).
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WORK UNIT NO: 2601

TITLE: In vitro and in vivo properties of sensitized lymphocytes

INVESTIGATORS:

Principal: Everett K. Spees, MD, COL, MC

Associates: Charles R. Annable, MD, COL, MC
M. Wayne Flye, MD, LTC, MC
David D. Oakes, MD, MAJ, MC

OBJECTIVES: To define the kinetics and mechanisms of lymphocyte immune responsiveness to antigens, including allogeneic cells and a variety of other antigens in vitro and in vivo. To develop improved methods of ex vivo organ preservation, transplantation, and immunosuppression.

TECHNICAL APPROACH: The majority of the subprojects of this work unit are concerned with developing improved methods for identifying and quantitating cellular and humoral immune response abnormalities. The assays clearly provide an objective data base for clinical decisions in managing patients with endstage renal disease undergoing renal transplantation; individuals with immune deviations due to immunosuppressive drug therapy, neoplastic diseases, and bone marrow failure; and diabetic subjects who may be candidates for pancreatic islet cell transplants in the near future. Ideally, the integration of the clinical and in vitro data base will improve donor-recipient selection, clarify the causes of transplant dysfunction and thereby, guide rational immunosuppressant therapy.

a. Immunogenetic studies: These include donor-recipient matching by blood group, HLA, leukocyte crossmatch, mixed lymphocyte culture, and Killer-cell assays. While not infallible, favorable results of these assays for a given donor-recipient pair usually indicate a good immunological outcome of the transplant because the recipient will see less "foreignness" in the donor tissues. This information may mislead if the recipient has an unusually vigorous innate immune capacity. Porcine cell-mediated immunity assay methods were also developed in collaboration with an ongoing NIH transplantation project in liver and kidney transplantation miniature inbred swine.

b. Skin testing: Responsiveness to cutaneously applied recall antigens and simple chemicals is a simple but important procedure in the assessment of immunocompetence. Since about 50% of patients with end stage renal disease and malignant neoplasms are anergic to skin tests, the test results allow classification of these individuals. It has recently been shown that patients with end stage renal disease (ESRD) who respond to 2,4 dinitrochlorobenzene (DNCB) skin testing generally reject their renal allografts. In the past many DNCB skin tests were equivocal. Recently we

have developed and applied an excellent in vitro test to quantitate this response.

c. The influence of plasticisers on immune response: Plasticisers are ubiquitous chemicals in our modern industrial society. They have generally seen shown to have a low degree of toxicity. We are assaying the quantities of plasticiser during hemodialysis because recent articles in the literature have pointed out the fact that large amounts of plasticiser are leached out of polyvinyl chloride dialysis tubing and into the patient's bloodstream during exposure to prolonged dialysis. In addition, assays of mixed leukocyte culture and mitogen responsiveness are monitored to determine whether a given patient is being immunosuppressed by the absorption of plasticiser released during hemodialysis.

d. Postoperative immunological monitoring: A panel of ten different in vitro assays of cellular and humoral immune responsiveness is performed on each renal transplant recipient in order to simultaneously evaluate the key immune functions. These tests are further described under Progress and Results.

e. Pancreatic islet cell transplantation: In this project inbred diabetic rats received intraportal transplants of purified pancreatic islet cells from collagenase-digested pancreata. The fact that rejection of the allografts was signalled by elevated blood glucose levels, provided a simple and dependable end-point for the experiments. Various methods of prolonging allograft acceptance were evaluated. The cause of liver enzyme alterations after islet cell transplantation was investigated by injecting glass beads the same size as pancreatic islets into the portal vein to determine whether simple portal capillary obstruction was causing the transient enzyme changes. Also attempts were made to transplant pancreatic islets intraperitoneally in small biologically inert sponges as an alternative to intraportal transplantation.

f. Improved methods of ex vivo preservation: A study was conducted to develop an improved method for sterile organ cassette draping to prevent contamination when the plastic lid was opened for access to the interior of the cassette. Because of the potential danger of damaging renal arteries when the vessels are cannulated for pulsatile perfusion during preservation, several alternate methods of adapting the kidneys to perfusion were explored using pig kidneys donated by the NIH.

PROGRESS AND RESULTS: Parenthetized numbers refer to publications under this Work Unit.

a. Immunogenetic studies: HLA typing, leukocyte crossmatch, and blood group matching have been utilized on all renal transplant patients. The success of this methodology is partially reflected in the absence of any instances of hyperacute rejection during FY 77. The mixed lymphocyte cultures have been useful particularly when they were negative, giving confirmation that donor and recipient were HLA-identical, and that the

recipient could be generally managed on reduced doses of immunosuppressant drugs.

b. Skin testing: Skin testing for recall antigens and DNCB was conducted in collaboration with Dr. Charlotte Casterline of the Allergy-Immunology Service. Most DNCB skin tests were complemented by the 2-stage DNCB in vitro assay developed under this Work Unit. The results were useful in predicting and confirming the presence of immunocompetence to DNCB. The in vitro method proved to be quite sensitive, and detected lymphocyte transformation responses to DNCB for up to 9 months. Examples are shown in Figs. 1 and 2. Several abstracts and papers have been submitted or are in advanced stages of preparation on this topic (1-5).

We are now dissecting out the mechanism of the DNCB in vitro assay by sequential dilution of antigen and responder cell numbers. In addition we are removing T cell or B cell subpopulations by ox cell and sheep cell rosetting techniques and anti B cell antiserum. This is being done in order to try to identify which essential cell types could be missing or impaired in patients with cutaneous anergy to DNCB in end stage renal diseases, neoplasm, and other immunodepressed states.

c. The influence of plasticiser on immune responses: Recent evidence has been accumulated that shows a rapid rise in plasticiser compound concentration in the blood of humans exposed to hemodialysis tubing. There is also a large body of evidence confirming the fact that patients on hemodialysis have impaired immune responses. During the course of in vitro immunological evaluations over the past year at WRAMC, we have found consistent alterations in immune responsiveness in mixed lymphocyte cultures with allogeneic cells, and in vitro lymphocyte transformation to mitogens by peripheral lymphocytes from patients who have been recently hemodialyzed. We found that these alterations could be reproduced in vitro if we added pure plasticiser, dioctylpthalate, to the cell cultures in an amount half as large as that found in banked blood (6,7). The amounts of plasticiser received from blood transfusions and hemodialysis appear to be immunologically significant, at least in vitro. We do not know yet whether there is any clinical harm from this immunosuppression, but the results suggest that an alternative to polyvinyl tubing containing plasticiser would be desirable for hemodialysis. It is conceivable that low-grade immunosuppression from plasticisers may be a hitherto unappreciated benefit in the treatment of patients about to undergo renal transplantation. A mass spectroscopy assay for serum plasticiser levels is being developed in collaboration with Dr. B.P. Doctor and Mr. L. Kazyak in the Department of Biochemistry at WRAIR. We plan to follow the levels of plasticiser in our dialysis patients as part of good patient management.

Another point of great interest that we have observed and are preparing for publication is that the in vitro and in vivo DNCB skin test seems to be altered by hemodialysis in some patients. This may be a key observation in explaining the phenomenon previously mentioned that many end stage renal disease patients being treated with hemodialysis have negative delayed hypersensitivity skin tests.

d. Postoperative immunological monitoring of the transplant patient: In December of 1976 we began a pilot program of immunological monitoring of renal transplant recipients. Because alterations of a patient's immunological status can best be discerned, and probably only be studied realistically, by simultaneous assays in several test systems, this project has entailed the setting up of the following assays:

1. Lymphocyte phytohemagglutin mitogen response,
2. Lymphocyte pokeweed mitogen response,
3. Lymphocyte concanavalin-A mitogen response,
4. Determination of the percentage of sheep red blood cell rosetting lymphocytes in the peripheral blood lymphocyte population,
5. Determination of the percentage of membrane immunoglobulin bearing lymphocytes,
6. Mixed lymphocyte culture (mixed leukocyte reaction) response,
7. Lymphocyte mediated cytotoxicity (spontaneous cell mediated lympholysis) activity,
8. Suppressor cell activity in a standardized two way mixed lymphocyte culture,
9. Spontaneous blastogenesis of circulating lymphocytes, and
10. Antibody dependent cellular cytotoxicity activity.

It is anticipated that in the course of the next year we can also develop the use of a leukocyte migration inhibitory factor assay, and the enumeration of active sheep red blood cell rosetting lymphocytes, in a continuing monitoring program.

Initial studies with an immunological status evaluation of 10 patients, including 5 who have received kidney transplants, indicate that the following objectives can probably be achieved: (1) Data obtained from a multiple test monitoring system should provide a measure of the effectiveness and the extent of immunosuppressive therapies and accordingly could be used to regulate such therapy. (2) These tests should provide early indicators of an impending graft rejection reaction and also herald the onset of any serious infections.

A much more tenuous proposition is that immunological status assays would provide indicators of the probable success or failure of a proposed transplantation procedure. Monitoring effects of immunosuppressive therapy and assessing the prodromal period of a rejection reaction are attempts to measure what is happening and our early data indicate that this will be achievable. However, providing indicators of the probable outcome of a grafting operation is an attempt to forecast what will happen, and we have no findings to date that would support this hoped for objective of an immunological monitoring program.

e. Pancreatic islet cell transplantation: Experimental studies already completed have demonstrated that diabetic rats can be functionally cured, as determined by assaying blood glucose levels, with intraportally transplanted isolated pancreatic islet cell isografts (Reckard). Further work

has shown that untreated allografts are quickly rejected. Because of this early rejection (typically less than 5 days) and because of the repeated failure to achieve passive immunologically enhancement of islet allografts with sera that will enhance kidney and heart allografts, it has been hypothesized that isolated islet cell allografts may be readily rejected through primary antibody response mechanisms as well as by the thymus derived lymphocyte cellular immune responses that are normally responsible for the failure and destruction of allografts.

Antilymphocyte serum therapy will readily diminish cellular immune responses even after the establishment of such a response; but, such therapy will not appreciably affect humoral antibody production in response to a given antigen unless the antiserum is given over a time course of several days before the introduction of that antigen. Antilymphocyte serum treatment started at the same time that allografting is carried out can then be expected to importantly interfereonly with the development of host cellular immune responses to the allografted tissues.

The effect of antilymphocyte serum given on two differing schedules was studied during this past year in an attempt to prolong the survival of isolated pancreatic islet cell allografts and to discern the relative importance of antibody responses as a primary mechanism in the rejection of this transplanted tissue. A 10 day course of antiserum treatments started 8 days before carrying out the transfer of allogeneic pancreatic islets to diabetic rats resulted in a mean functional survival of the transplanted islets of 27 days. This was 25 days beyond the last day of giving antilymphocyte serum. Untreated control allografts remained viable for only 4 days. When a 10 day course of therapy was started on the same day that the transplantation procedure was performed, the islet tissue remained productive for 35 days. Again this was 25 days after immunosuppressive treatment had been stopped. This initial set of experiments shows that heterologous antilymphocyte serum will prolong the survival of isolated pancreatic islet allografts and that blocking humoral immune responses does not materially affect the survival of this transplanted tissue. Further, abrogating the cellular immune response is a sufficient maneuver for assuring a prolongation of function of islet grafts.

The results of injection of intraportal microspheres were compared to the injection of intraportal pancreatic islets in streptozotocin-induced diabetic rats. Both islets and microspheres averaged 300 micra in diameter. The results were that microspheres islet allografts, and islet isografts all caused a similar elevation of SGOT, SGPT, and LDH. Enzyme levels returned to normal by the fourth post operative day. These studies suggested that if future islet cell transplants were to be carried out in humans who were receiving the potentially hepatotoxic drug, Imuran, then dosage schedules might have to be modified in order to prevent compounding of hepatic malfunction (8.9).

The experiments with vilscose cellulose sponges as a matrix for pancreatic intraperitoneal islet cell transplantation were unsuccessful since the islets survived poorly within the new environment, and the number of islet cells needed greatly excelled the requirements of intraportal transplantation.

f. Improved methods of ex vivo organ preservation: A new method of organ cassette draping was developed, using a disposable sterile plastic wound drape (10).

In order to prevent cannulation damage to renal arteries during ex vivo perfusion, we developed several new approaches to renal perfusion by cannulating the aorta or a segment of arterial graft attached to the renal artery, as shown in Fig. 3. In paired experiments with pig kidneys donated by the NIH, flow rates were equivalent when one renal artery was cannulated directly, as compared to an indirectly cannulated arterial inflow (11). As a result of these findings we are now perfusing all human cadaver kidneys through indirect arterial perfusion in order to minimize renal artery damage and also to better handle perfusion when multiple renal arteries are present in one kidney. This will undoubtedly reduce the incidence of late renal artery stenosis in some cases, and in other instances will avoid segmental renal infarction due to ligation of polar or accessory arteries. We have used similar prosthetic vascular surgery techniques to repair the renal vein when it is damaged during transplant surgery (12), and to facilitate vascular access for hemodialysis when there is a missing or damaged segment of the upper extremity venous system (13). We have recently published a summary of our experiences in kidney preservation ex vivo (14).

CONCLUSIONS: The clinical research projects covered under this Work Unit have been especially productive during FY 77, and have resulted in several important publications in press, accepted for publication, or in advanced stages of preparation. The most promising projects for emphasis in FY 78 include:

1. Postoperative transplant patient monitoring by the 10-assay profile described
2. Skin testing with in vitro correlation of lymphocyte transformation
3. Pancreatic islet cell transplantation, methods for enhanced adaptation of the graft
4. Studies on the immunological effects of plasticisers
5. Animal studies on a new immunosuppressant, Tilerone, by MAJ A. Wildstein, who will be joining our service in August, 1977, and has published extensively on this subject using a rodent model.
6. Additional studies in the porcine in vitro lymphocyte responses from inbred miniature swine undergoing hepatic or renal transplantation at NIH.

FUNDS UTILIZED FY 77: $39,500

FUNDING REQUESTED FY 78: $98,150

PUBLICATIONS: See list attached

TYPE OF REPORT: Interim

EXPERIMENTAL DRUGS: None used

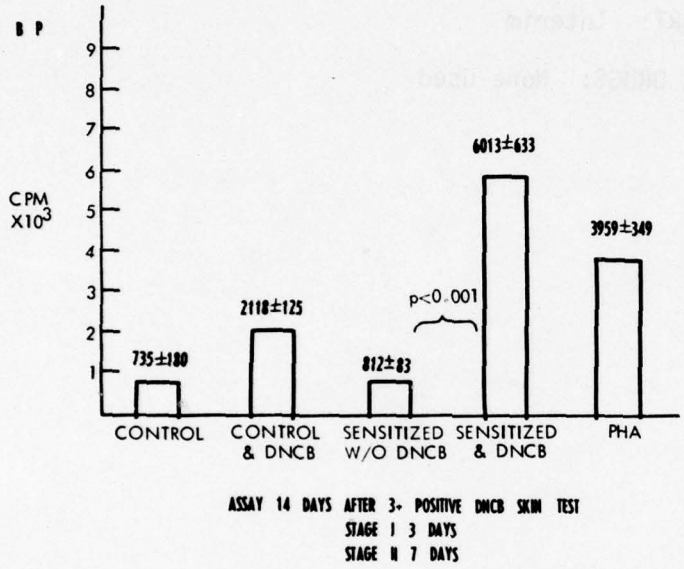


Fig. 1 - Lymphocyte transformation assay for DNCB responsiveness 2 weeks after DNCB skin sensitization. The column "sensitized & DNCB" represents the complete 2 stage test, and the results are highly significant.

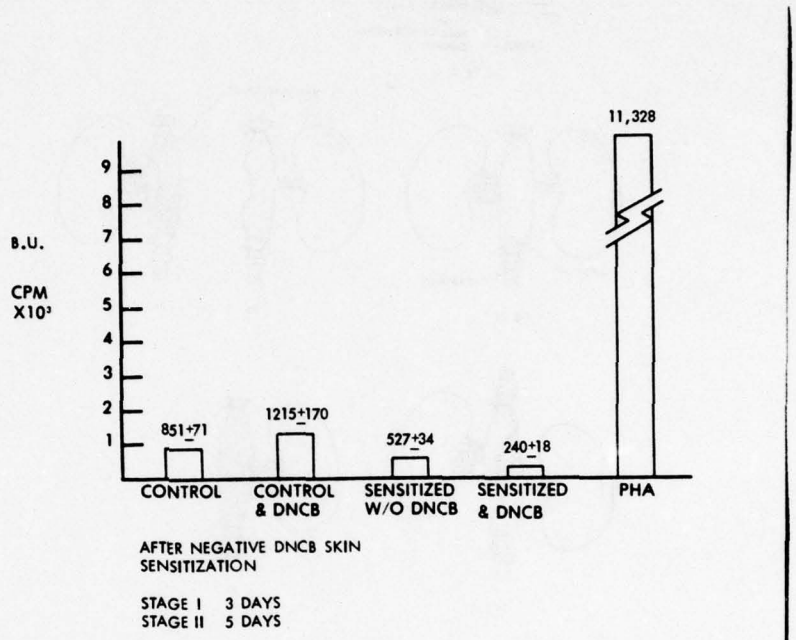


Fig. 2 - An example of a negative in vivo and in vitro DNCB response.

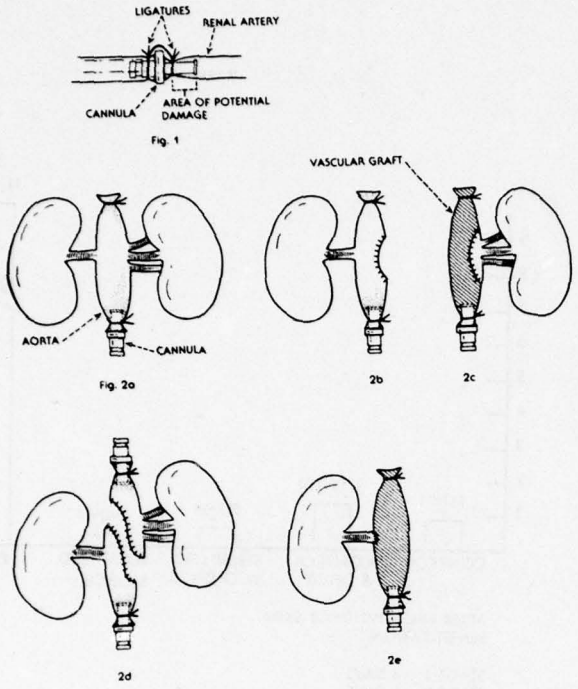


Fig. 3 - Schematic illustration showing several methods developed for perfusion of the kidney ex vivo without renal artery cannulation

PUBLICATIONS

1. Spees, EK, Davis, M, Casterline, C, Oakes, DD, et al. A 2-stage in vitro assay for cell-mediated immunity to dinitrochlorobenzene. Manuscript in preparation.

2. Spees, EK, Davis, M, Casterline, C, Oakes, DD. Assessing DNCB immune response potential without skin testing. Manuscript in preparation.

3. Spees, EK, Davis, M, Casterline, C, Oakes, DD, et al. A 2-stage in vitro assay for DNCB sensitization. Abstract submitted 1977.

4. Spees, EK, Casterline, C, Davis, M, Oakes, DD, et al. A study of DNCB reactivity in patients with head and neck malignancies. Manuscript in preparation.

5. Spees, EK, Casterline, C, Davis, M, Oakes, DD, et al. Studies of DNCB reactivity in patients with end-stage renal disease. Manuscript in preparation.

6. Spees, EK, Davis, M, Gibson, TP, et al. Impairment of in vitro lymphocyte function by a plasticiser, DEHP. Abstract submitted, 1976.

7. Spees, EK, Davis, M, Gibson, TP, et al. In vitro impairment of lymphocyte function by a plasticiser. Abstract submitted, 1977.

8. Oakes, DD, Reckard, CR, Annable, CA, Spees, EK. Acute hepatocullular damage following intraportal transplantation of pancreas. Manuscript in preparation.

9. Oakes, DD, Reckard, CR, Annable, CA, Spees, EK, et al. Acute hepatocellular damage following intraportal transplantation of pancreatic islets in rats. Abstract submitted, 1977.

10. Spees, EK, Oakes, DD, Light, JA. Simplified sterile draping of organ perfusion cassettes, Dialysis and Transplantation, 1977.

11. Oakes, DD, Spees, EK, Flye, MW, Light, JA. Renal perfusion without cannulation: Prevention of post-transplantation renal artery stenosis. Manuscript in preparation.

12. Spees, EK, Oakes, DD, Light, JA, Perloff, LJ, Reckard, CR. Successful renal vein reconstruction with bovine arterial heterografts. Annals of Surgery, 1977.

13. Oakes, DD, Spees, EK, Light, JA, Flye, MW. A three year experience using modified bovine arterial heterografts for vascular access in patients requiring hemodialysis. Abstract submitted, 1977.

14. Light, JA, Annable, CA, Spees, EK, Oakes, DD, Reinmuth, B. Comparison of long term kidney survival following cold storage or pulsatile preservation, Transpl Proc, 1977.

WORK UNIT No. 2610

Title of Project: Antilymphocyte Globulin and Kidney Transplantation: A Controlled Double Blind Study

Investigator: Jimmy A. Light, LTC, MC

Objectives: To define the value of antilymphocyte globulin in clinical transplantation.

Technical Approach: Not applicable.

Progress and Results: This protocol, approved in 1973, has never been implemented. It has been carried in an inactive status pending availability of a suitable ALG for use in the program. This study, although original in design at the time of its adoption is now in progress or has been already completed at a number of other transplant centers. In its present form it no longer is a useful protocol, although it continues to serve a useful purpose in providing background information for the clinical use of Antilymphocyte Globulin. With the proposed amalgamation of the Army, Navy, NIH and Washington VA Hospital transplantation units and the source of antilymphocyte globulin from the Navy Research Laboratory becoming available, there is a good possibility that this protocol or a modification of it may be implemented within this fiscal year. I recommend the protocol continue to be carried in an inactive status pending the development of programs as mentioned above.

Conclusions: Not applicable.

Funds Utilized FY-77: None

Funding Requirements (FY-78): None

Publications: None

Type of Report: Interim

Work Unit No: 2611

Title: Survey of Multiparous Patients for Anti HL-A Antibodies

Investigators: Everett K. Spees, COL, MC

Objective: To survey multiparous females for HLA antibodies suitable for reagent use.

Technical Approach:

Progress & Results: No work was completed on this project due to lack of personnel.

Conclusions: N/A

Funds Utilized, FY-77: None

Funding Requirements, FY 78:

Personnel: None
Equipment: None
Supplies: None
Travel: None
Other: None

Publications: None

Type of Report: Interim

Work Unit No.: 2613

Title of Project: Long Term Pulmonary Function Following Recovery from Pneumocystis Carinii Pneumonia

Investigator:

Principal Investigator: Departed

Objective: This study is designed to determine whether or nor patients who have survived Pneumocystis carinii pneumonia have measurable abnormalities in their subsequent pulmonary function, and, if so, to define the nature of such abnormalities.

Progress and Results: Insufficient patients were entered into the study to obtain meaningful conclusions.

Type of Report: Terminated

Work Unit No: 2703

Title of Project: Exclusive use of autologous blood transfusions (autotransfusions) in elective thoracic and open heart surgical procedures.

Investigators:
Principal: Arthur W. Fleming, MD, LTC, MC
Associates: David C. Green, MD, COL, MC
John H. Radcliffe, MAJ, MSC

Objective: To develop a systematic approach for obtaining a sufficient volume of autologous blood for use during and after all elective thoracic and open heart surgical procedures, thus eliminating the need for homologous blood transfusions.

Technical Approach: Each unit of blood was collected in CPD preservative by AABB standards. Blood collected from donors for open heart surgery was separated into packed cells and plasma. The packed cells were then frozen if the period between donation and surgery was greater than 3 weeks; or stored at 4°C if the interval between donation and surgery was less than 3 weeks. The plasma was frozen regardless of the time interval for open heart surgical procedures. The blood from donors not requiring extracorporeal circulation was maintained as whole blood if the interval between donation and surgery was less than 3 weeks. If the interval between donation and surgery was greater than 3 weeks, the blood was treated in the same manner as for open heart surgery, i.e., the unit of blood was separated into packed cells and plasma, and then both components were frozen. Frozen packed cells were thawed on the afternoon prior to surgery, and the plasma was thawed on the day of surgery. One to two additional units were drawn intraoperatively on open heart surgical cases and the units maintained at room temperature until the completion of cardiopulmonary bypass. These units were then transfused back to the patient in the immediate post-pump period.

Progress and Results: See enclosed manuscript and abstracts.

Conclusions: Utilizing the techniques outlined above, we were able to accomplish the following: The risk of creating a significant hypovolemia was virtually eliminated by extending the interval between phlebotomies; the total volume of homologous blood transfused was reduced by the use of autologous fresh frozen plasma, fresh whole blood and fresh frozen red blood cells; the incidence of hepatitis was reduced; some of the logistical problems in obtaining certain blood types were diminished; and the drain on blood bank stores was decreased.

Funds Utilized FY-77: A paper entitled "Development of a Practical Autologous Blood Transfusion Program" was presented to the Southeastern Surgical Congress in Bal Harbour, Florida on 5 April 1977 (This paper won a gold medal). An exhibit bearing the same title as the paper was also presented to the same surgical congress (TDY- 5 days).

Funding Requested FY-78: Travel: $500.00.

Paper Submitted for Publication (FY-77): Fleming, A.W., Green, D.C., Radcliffe, J.H., et al. Development of a Practical Autologous Blood Transfusion Program. Amer. Surgeon. Manuscript enclosed.

Abstracts Submitted to the American Association of Blood Banks for Consideration of Presentation: (1) Implementation of a Predeposit Autologous Blood Transfusion Program: A Surgeon's Viewpoint (Same authors as above) and (2) Tolerance of Cardiac Patients to Donating Blood for Their Own Elective Operations (Same authors as above). If accepted, the paper(s) will be presented November 11-16, 1977 in Atlanta, GA.

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
HSW-S	Work Unit #2804, An Evaluation of the Efficacy of Tadenan in the Treatment of Benign Prostatic Hyperplasia

TO	FROM	DATE	CMT 1
C, Clin Invest Svc	C, Department of Surgery	9 May 1977	

1. In reply to your correspondence reference the annual progress report on the clinical investigation program work unit #2804, An Evaluation of the Efficacy of Tadenam in the Treatment of Benign Prostatic Hyperplasia, the following comments are in order.

a. This study has not been initiated at Walter Reed Army Medical Center in view of FDA regulations and criteria which we cannot at this time meet.

b. The overall director of this project, Anthony A. Borski, MD, COL, US Army Medical Corps Retired, has advised me that progress is being made in civilian research centers in reference to tests which must be performed prior to initiation of the study.

c. It is requested that this project be continued on a "hold" basis until further information is obtained which will assist us in determining whether or not the project is in fact a feasible study.

2. I hereby request that I be deleted as the primary investigator and that my replacement be R. E. Stutzman, COL, Medical Corps, US Army, the incoming chief of the Urological Surgery Service, WRAMC. His appointment will be effective 1 July 1977.

BERNHARD T. MITTEMEYER, MD
COL, MC, USA
C, Department of Surgery

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Work Unit No.: 2805

Title of Project: Biochemical Studies of Urinary Polyamines in Human Genitourinary Carcinoma

Investigators: Nesbitt D. Brown, DAC, L. DeBarre, M.D., B. P. Doctor, Ph.D., S. Koetitz, DAC, David G. McLeod, M.D., LTC, MC, Luis R. Rivera, M.D., MAJ, MC

Objectives: To determine new methodology in the study of urinary polyamines in urine and serum.

Technical Approach: Urine is taken from patients having genitourinary carcinoma prior to any definitive therapy. The patients are then treated in a routine fashion for their particular disease and at specific points in time follow-up urines are obtained. The purpose of the investigation is to specifically identify increases or decreases of urinary polyamines and compare these changes to changes in their clinical course, i.e., remission and/or exacerbation of disease.

Progress and Results: The methodological approach in assaying diamines and polyamines in urine and serum specimens has been found to be applicable for characterizing various types of metabolic abnormalities. The occurrence of various polyamines in the analyzed sample is indicative of the physiologic changes existing, at that time, within the patient. Tentatively, we have observed levels of "1,2 diamino-ethane," 1, 3 diamino propane, and cadaverine to be biological markers for cellular change during the abnormal growth of tumors and during the rejection process of transplanted kidneys. The preparatory technique of the sample is simple, along with the analysis of the sample being relatively specific and sensitive. At the present time, we can not see any reason, other than a shortage of trained personnel, for the project to be discontinued. Further proof of our finding in verifying this early data will be of great importance in better understanding the mechanics of the body in classifying cellular changes by cancer and the rejection process.

Conclusions: We have developed a new methodology of extraction and measurement of urinary polyamines by an amino analyzer which allows lower operating pressures, reduced buffer flow and ease of operation. We have identified for the first time, two compounds in the urine of patients with carcinoma of the genitourinary system. Both of these compounds in addition to spermine, speridine and putrescine have been found to be elevated in our measurements of some patients with genitourinary carcinoma. We continue to have every reason to believe that these compounds may be utilized as tumor markers in the diagnosis, staging and prognosis of patients with genitourinary carcinoma.

Work Unit No. 2805 (continued)

Funds Utilized: FY-77: Less than $2,000. Funding requested for FY-78: Chemicals, reagents, enzymes, and radioisotopes - $3,500; columns and analytical small equipment - $500; freezer with containers - $2,800; secretarial assistance and attendance at meeting - $2,000.

Publications: A publication to the Journal of Chromotography is being prepared.

Type of report: Interim

Work Unit No.: 2807

Title of Project: Determination of Human Prostatic Acid Phosphatase in Both Benign and Malignant Condition by Radioimmunoassay

Principle Investigators: W.D. Belville, M.D., MAJ, MC, D.E. Mahan, Ph.D., H.D. Cox, M.D., J.C. Clements, LT, MC, USNR, B.T. Mittemeyer, M.D., COL, MC, R.E. Stutzman, M.D., COL, MC, A.S. Buck, M.D., LTC, MC, D.G. McLeod, M.D., LTC, MC, B.P. Doctor, Ph.D.

Co-Investigators: W.R. Greene, M.D., MAJ, MC, L.R. Rivera, M.D., MAJ, MC, R.B. Sweet, M.D., MAJ, MC, W. Babcock, M.D., MAJ, MC, C.F. Miller, M.D., MAJ, MC, J.P. Olmert, M.D., MAJ, MC

Objectives:

1. To establish the normal range of prostatic acid phosphatase in serum and bone marrow using RIA methodology.

2. To establish using radioimmune and enzymatic analysis the duration and magnitude of serum elevations of prostatic acid phosphatase following transurethral prostatectomy and prostatic massage.

3. To assess the diagnostic usefulness of bone marrow acid phosphatase measurement by enzymatic and immunological procedures for confirmation of occult metastatic carcinoma of the prostate.

Technical Approach: Serum and bone marrow aspirates from patients with and without prostatic carcinoma are evaluated for prostatic acid phosphatase content using a quantitative immunochemical procedure. The levels of prostatic acid phosphatase found in the bone marrow of patients with prostatic carcinoma are correlated with the presence of bony metastasis.

Progress and Results:

1. Normal range. Normal range of prostatic acid phosphatase have been established in the serum and bone marrow of 75 patients without prostatic

carcinoma. In these fluids prostatic acid phosphatase was found to be distributed in a non-gaussian manner with an average of 4.7 for serum and 6.4 for bone marrow. An upper limit of 12 ng/ml has been established by non-parametric analysis for the content of prostatic acid phosphatase in both serum and bone marrow.

2. TURP Studies. By studing the serum of 20 patients who had undergone transurethral prostatectomy, it is now clear that all do experience a significant rise during the first twenty-four hours in their serum prostatic acid phosphatase by radioimmune assay. The same serum analyzed by conventional enzymatic approaches did not demonstrate the same consistency. The magnitude and duration of the elevation was proportional to the amount of tissue resected. The evaluation of serum levels of prostatic acid phosphatase following prostatic massage is currently under investigation.

3. Bone Marrow Results by Radioimmune Assay. To date we have determined by radioimmune assay the prostatic acid phosphatase content of 101 bone marrow aspirates obtained from patients with various stages of prostatic carcinoma. Ninety percent of those patients with proven bony metastatic (D_2) disease had elevated bone marrow prostatic acid phosphatase values. In patients with stages C and D_1 disease 19 and 36 percent, respectively had elevated bone marrow prostatic acid phosphatase values. Eight percent of the patients with stage A disease and none of the patients with stage B disease were found to have elevations of bone marrow prostatic acid phosphatase.

Approximately 25 percent of the D_2 population had bone marrow prostatic acid phosphatase levels greater than 50 ng/ml. The highest level recorded

in this group (D_2) was 700 ng/ml, and this patient became paraplegic secondary to this metastatic process. In patients with stage B disease, no values were seen above 11.0 ng/ml. The maximum value observed in stage C was 21.5 ng/ml while that of stage D_1 was 35.0 ng/ml.

We feel that the elevations found in those patients with C and D_1 disease represent the detection of occult metastatic disease. A long term follow-up is being carried out to answer this question.

4. Bone Marrow Results by Enzymatic Analysis. Early in the course of this study bone marrow acid phosphatase was analyzed enzymatically using alpha-naphthol phosphate as a substrate. However, because of the high incidence of false positive results (50%) obtained in patients without prostatic carcinoma we have found this method to be of little diagnostic usefulness. We believe that this is due to the release into the bone marrow serum of contaminating acid phosphatases from cellular elements, especially megakaryocytes, ruptured by the negative pressures generated during a bone marrow aspiration. Electrophoretic experiments are underway to establish this hypothesis.

5. Proposed Studies. Carcinoma of the prostate has traditionally been staged by rectal examination, tissue histology, intravenous pyelography, serum acid phosphatase determinations and skeletal survey. The poor correlation between these investigations and actual stage of the disease has been increasingly recognized. The introduction of bone marrow cytology, bone marrow acid phosphatase determinations, bone scanning, pedal lymphangiography, and pelvic lymphadenectomy in investigating the patient with prostatic cancer has improved the staging of the tumor.

Notwithstanding this most thorough work-up gross accuracies still exist between clinical, radiological and laboratory staging of the disease.

We are currently involved in a collaborative effort with the Department of Urology at Queens University in Kingston, Ontario to evaluate the usefulness of prostatic acid phosphatase as a tumor marker for this carcinoma. In this study serum and bone marrow from fully staged carcinoma patients will be assayed for acid phosphatase immunologically and by three standard enzymatic procedures prior to and following treatment. The results from the various laboratory methods will be compared, and conditions made between these test and other procedures for the staging of prostatic carcinoma.

To assist in this study additional personnel support is requested to aid in the collection of clinical information and to run the radioimmune assay on samples collected.

6. Presentations. As of 10 June 1977, this research has been presented to the Washington Urologic Society where it received first prize in the scientific session, to the Society of University Urology Residents Meeting in St. Charles, Illinois, and to the general scientific session of the American Urologic Association's Meeting in Chicago. It is also on the agenda for the annual meeting of the Canadian Urologic Association Meeting in Toronto, Ontario later this month as well as on the agenda of the British Urologic Societies Annual Meeting held in Aberdeen, Scotland. Abstracts have been sent to the South Central Section, South coast section, and the Northeast section meeting of the American Urological Association this fall.

Conclusions:

1. The evaluation of prostatic acid phosphatase by radioimmunoassay appears to be more sensitive and specific than any conventional enzymatic methodology.

2. Though the patient population is relatively small and the amount of follow-up time no greater than one year it appears that bone marrow prostatic acid phosphatase by radioimmunoassay may be the most sensitive marker of unresectable prostatic carcinoma. Further follow-up as well as additional patients are needed to verify this conclusion.

Funds Utilized, FY-77: N/A

Funding Requirements, FY-78:

1.	Personnel - GS 05 Technician	$ 9,303.00
2.	Equipment	
	Electrophoresis equipment	600.00
3.	Supplies:	
	Pipets, disposable	200.00
	Micropipet tips - 20 X 30	600.00
	Micropipets - 3	300.00
	Centrifuge tubes - 27 X 36	540.00
	Test tubes and cords	300.00
	Columns	150.00
	Buffers	120.00
	^{125}Iodine - 55 X 12	660.00
	GARG - 16 X 25	400.00
	Human Serum - 27 X 50	1,350.00
	Fetal Calf Serum - 10 X 15	150.00
4.	Travel: To South Central and Northeast Sections of the American Urological Association	1,000.00
5.	Other: Computer Services	800.00
	TOTAL	$15,473.00

Publications: Enclosed is a rough draft of a paper being submitted for publication in Cancer. Also a combined report with the group at Queen's University, Kingston, Ontario entitled "An Objective Look at Acid Phosphatase Determination: A Comparison of Biochemical and Immunological Methods". This is being submitted to the British Journal of Urology.

Type of Report: Interim

DISPOSITION FORM

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

ERENCE OR OFFICE SYMBOL	SUBJECT
HSWP-SGU	Completion of Project #2808

C, Clinical Investigation FROM Asst C, Urology Svc DATE 29 Jul 77 CMT 1

We have been informed by Margaret P. Clarke, Ph.D. that the project entitled "Factors related to the decision to seek sterilization among married couples" has been completed. We will receive a copy of the paper at a later date and will forward this on to you.

DAVID G. McLEOD, MD
LTC, MC, USA
Asst C, Urology Service

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A FORM 1 FEB 62 2496 REPLACES DD FORM 96, WHICH IS OBSOLETE. ☆GPO—1975—665-422/1063

Work Unit No.: 3102

Title of Project: Therapy of Immunodeficiency Diseases with Transfer Factor

Investigators:

Principal: Arnold I. Levinson, MAJ MC

Associates: Richard Evans, III, COL MC
Donna Schuster, MAJ MC

Objective: Transfer factor, a low molecular weight substance extracted from leukocytes, has been used by us and others to reconstitute T-cell function in patients with a variety of primary and secondary immune deficiencies. These patients are identified by exhaustive immunologic evaluation as described in Protocol 3317 and therapeutic intervention undertaken when evidence of T-cell deficiency is demonstrated.

Technical Approach: Transfer factor has been prepared as outlined in our original protocol with the aid of the hematology group.

Progress and Results: A 13 year old boy with selective T-cell deficiency continues to receive transfer factor prepared from his titer. Skin test conversion as well as in vitro correlated of cell mediated immunity are being maintained. The boy has remained clinically free of infection.

In addition, we are presently considering the use of transfer factor in a 2 year old boy with recurrent laryngeal papilloma.

Conclusions: Transfer factor therapy continues to maintain a boy with immune deficiency free of infection.

Funds Utilized, FY-76: $4,150.00

Funding Requirements:

Personnel: One GS-07 Technician for 20 weeks		
Equipment: Freezer -20 C	$	2,000.00
Supplies: Consumable		5,000.00
Travel: Conference		600.00
Mission		650.00
TOTAL:	$	8,250.00

Type of Report: Interim

Date Prepared: 15 June 1977

Work Unit No.: 3103

Title of Project: Techniques for the Detection of Antinuclear Antibodies. Comparative Study.

Principal Investigators: Oliver J. Lawless, LTC, MC
Bernard H. Berne, M.D., Ph.D

Objectives:

(1) To compare immunological techniques currently available for the detection of antinuclear antibodies (ANA) in patients with rheumatic disease processes.

(2) To assess such techniques as regards:

(a) Sensitivity
(b) Specificity especially as regards differentiation of systemic lupus erythematosus (SLE) from rheumatoid arthritis (RA), scleroderma, polymyositis, juvenile rheumatoid arthritis, mixed connective tissue disease (MCTD), gout and degenerative joint disease.

(3) To ascertain the association between positive tests and clinical activity of disease.

(4) To assess the reproducibility of positive tests and their quantitation.

(5) To ascertain the association, if any, between levels of ANA determined by the radioactive DNA binding test (Farr technique), and other methods, such as counterimmunoelectrophesis (CIEP).

(6) To analyze the cost and usefullness of the various methods of ANA detection.

Technical Approach: Sera from a panel of 200 patients of the Rheumatology and Clinical Immunology out-patient department rapidly frozen and stored are being used. This panel is composed of known sera of patients with active and inactive SLE, RA, other connective tissue diseases, gout and degenerative diseases. Another panel of sera from 1,000 patients with a variety of other (mostly non-rheumatic) diseases is also used. Many of these sera are collected from the same patients at different stages of their illnesses for the purpose of performing longitudinal studies. All sera were obtained for diagnostic purposes.

Sera are randomly assigned a number and tested blindly in duplicate. The major techniques investigated during the past year and in the forthcoming year are the radioactive DNA binding assay and CIEP for DNA. Because of marked variations in lots of antigen (DNA) obtained

from commercial sources, several DNA preparations are being tested for correlations between them when used in the different techniques. Those preparations whose results correlate best with disease activity are used in subsequent assays.

Progress and Results: In past years, we have studied the correlations between the fluorescent antibody test (FANA), the complement fixation test (CF) for DNA and DNP, the DNA binding assay and the latex (LE) test. As described in previous annual reports, although the FANA was found to be the most sensitive of these for diagnosing SLE, it was positive in a significant percentage of patients with other connective tissue diseases. The DNA binding assay is more specific, but it is negative or equivocal in some SLE cases, particularly when the disease is in remission. In last year's report, the results of approximately 485 positive DNA binding assays were reported which documented the above findings.

During the past year, an additional 600 DNA binding assays were performed. In previous years, assays used 14-C labelled DNA preparations. These are no longer commercially available and therefore 125-I labelled DNA preparations were used during the past year. We found that 125-I assays were simpler to perform than those based on 14-C, since they involve a gamma radiation emitter rather than a beta emitter, and thus do not require the use of scintillation fluid and transfer of precipitates from the reaction tubes. However, since 125-I has a relatively short half life (60 days) compared to 14-C, the DNA deteriorates rapidly. Thus, the same 125-I labelled DNA preparation cannot be used over a prolonged period of time. We found that different 125-I DNA preparations obtained from the same manufacturer often precipitated differently from each other when tested under identical conditions with the same patient's serum. Some DNA preparations therefore produced a larger percentage of binding with a given serum than others did. This impeded standardization of the assay. We mimimized this variable by choosing a standard positive serum (from a lyophilized batch obtained from an acute SLE patient) which was used as a standard in all assays. A system of units was developed referable to this standard, and all unknowns were compared to it. By thus eliminating dependence on the actual percentage of DNA bound using different preparations, inter-assay variability was reduced.

Using the 125-I DNA binding assay with DNA from human KB cells during a 12 month period, we found that we could readily differentiate patients with acute SLE from controls and from those with little active disease in most cases in a study of 96 patients with SLE and related diseases. In 27 of these, serial studies were performed on at least three samples taken at different stages of the disease. Invariably, the highest levels occurred when the disease was most active. In several cases, we were able to predict a clinical exacerbation a month before it became evident by the presence of a high or a rising level of DNA binding. In all cases, DNA bindings fell as the disease remitted. However, some cases (60%)

showed decreases to within the normal range when the disease was in relative remission, while others (40%) maintained levels which were lower than their highest ones but were still significantly above the normal range. The patients with persistent elevations had no system involvement such as nephritis which could differentiate them from those whose levels fell to within the normal range. Prolonged follow-up will be necessary to determine whether those patients with persistently high DNA bindings have prognoses that are worse than those whose levels normalized.

A study of synthetic DNA's was begun using tritiated double stranded deoxyadenylic-thymidylic acid (DAT). This antigen has been reported to be more completely double-stranded than DNA isolated from natural sources. It may thus detect a different spectrum of diseases and be more specific for some forms of SLE (especially SLE with nephritis) than natural DNA preparations. A study of 18 sera from 10 SLE patients showed that the tritiated DAT assay differentiated fewer SLE patients from normals than did the DNA binding assay. A large group will need to be studied to determine whether those with DAT binding elevations share a common system involvement that is different from those with normal bindings.

A study was performed to determine whether counterimmunoelectrophesis (CIEP) could be adequately used in the management of SLE. In CIEP, only precipitating antibodies to DNA are detected, while all antibodies are measured in the DNA binding assay. A panel of 102 sera from 38 patients with SLE and related diseases was compared using calf thymus DNA in the CIEP assay and 14-C labelled DNA from KB cells in the DNA binding assay. The results are charted below.

DNA binding	CIEP % Negative	CIEP % Positive
Above 60%	3	32
40-60%	23	26
20-40%	33	21
0-20%	41	21
	100%	100%

(40% is the upper limit of the normal range of DNA bindings)

It will be seen from this chart that a higher percentage of positive results in CIEP are found with high DNA binding sera than with low ones. Conversely a higher percentage of negative CIEP results are found with low DNA binding sera than with high ones. This positive correlation between DNA binding and CIEP was also seen when the CIEP was quantitated by determing the intensity of the observed precipitin bands. It will be noted, however, that the positive correlation is not complete; a few sera have DNA bindings above 60% with negative CIEP, while 21% of the positive CIEP results were found in patients with DNA bindings of 0 - 20%.

There was no apparent association between CIEP positivity and particular clinical manifestations such as nephritis or vasculitis. The presence of precipitating antibodies in some sera with low DNA bindings and their apparent absence in some with high bindings is of considerable interest and will be studied further. We are currently preparing a publication on this data.

Conclusions and Future Plans:

Both the DNA binding assay and CIEP appear to be useful assays in the diagnosis and follow-up of SLE and related diseases. Both are positive in a large percentage of patients with SLE. Since antibodies directed against DNA are detectable in some sera by one assay but not by the other, the tests are complementary. Further studies are necessary to determine as to which is the better assay to be used in the follow-up of SLE and in its diagnosis.

Because of the variability between lots of commercial DNA, the use of a single preparation of this antigen in different assays over a period of years will be desirable. While adequate results can be obtained using different lots of DNA, an improvement can be expected if a single one is used in all tests. Since 125-I labelled preparations deteriorate rapidly, we are now having a large amount of tritiated DNA from E. coli prepared by Dr. B. P. Doctor and his associates at WRAIR. This preparation, if adequate, will be used in all future assays. We plan to repeat the CIEP-DNA binding comparison using the same lot of tritiated DNA in both tests. This may give a higher correlation than the one reported above. Synthetic DNA's will also be used to a greater extent than in the past.

Because of the time and labor involved in performing large numbers of assays involving beta emitters such as tritium, we plan to automate the DNA binding assay. We hope to acquire an automatic sample preparation system to help expedite the assay and bring it to the state of the art now achievable by laboratories with automated radioimmunoassay facilities.

Funds Utilized (FY-77)

Personnel:	One GS-9 Step 8 *Civilian Technician* 2/5 times	$6,206.00
Supplies:		5,460.00

Funding Requirements (FY-78)

We request continued funding of this project as an essential component of the Rheumatology Clinical Immunology fellowship training program. It is also an essential component of Project #3123 which integrates humoral and cellular immunological mechanisms in SLE and related diseases.

The performance of a DNA binding test is mandatory for the diagnosis and treatment of patients with connective tissue disease. We request continued funding of this project to enable us to continue the study and improve the techniques involved in it. We are currently performing DNA binding assays at the continuing requests of several physicians at other military installations, indicating their acceptance of our laboratory's data for the treatment of their patients.

A new freezer will be required in FY-78 as our present units are nearly filled to capacity with sera and other materials. Anticipated expansion of the serum bank and other storage requirements dictate the acquisition of an additional unit at this time.

Personnel:	One GS-9 Step 8 Civilian Technician at $17,387.00 per year, 2/5 times		$6,954.00
Equipment:	Freezer	800.00	
Supplies:		7,500.00	
Travel:		200.00	
Reprints:		150.00	
			8,650.00
			$15,604.00

Publications: None (FY-1977)

Type of Report: Interim

Date Prepared: 5 July 1977

Work Unit No.: 3105

Title of Project: An Evaluation of Immunologic Response in Ragweed-Sensitive Patients by New Techniques.

Principal Investigator: Richard Evans, COL MC
Chief, Allergy-Immunology Service

Objectives: To intensively study the effects of high dose specific immunotherapy on extrinsic asthma. The goal is to document in an objective manner any change in bronchial sensitivity to an offending antigen subsequent to allergy injection therapy.

Technical Approach: All participants entered into this study have allergen induced bronchospasm. Often patients have an extensive in vivo and in vitro evaluation prior to placement on immunotherapy. A detailed history and physical examination is performed. Patients are selected because of relatively severe specific aero-allergen induced asthma. The following tests are done to assess each individual's degree of sensitivity to the offending antigen. The same antigen (i.e., company and lot number) was used for all testing and treatments.

In vivo studies:
a) Serial skin test titration to extinction
b) Antigen bronchial challenge

In vitro studies:
a) Leukocyte histamine release (LHR)
b) Total serum IgE
c) RAST (specific IgE) - when technically possible.

After the above baseline studies, high dose specific immunotherapy is begun. The patients are followed clinically with repeat of all the above studies at six month intervals.

Progress and Results: Thus far nine patients have entered the study. Three have marked Timothy grass pollen sensitivity. Three have rat dander sensitivity, three have ragweed pollen sensitivity and one has wheat flour induced asthma.

Bronchoprovocation testing following a year of allergen injection therapy has demonstrated decreased bronchial sensitivity to the specific allergen in the circumstances of the laboratory workers sensitive to rat dander and the baker sensitive to wheat flour. Bronchial responses to the pollen allergens have been more variable and in the current patient population size no specific statement can

be made regarding immunotherapy. Several of the pollen sensitive patients have moved from the area during the study. These pollen-sensitive patients have a less consistent exposure than do the patients sensitive to occupational allergens. There is one entire year lapse between each relevant season, for example.

In the coming year, we plan to complete the evaluation on the occupational asthma patients. The pollen-sensitive patient population will be greatly enlarged. These patients will also be treated with higher dose immunotherapy in a shorter period of time consistent with accepted medical treatments practice. It is expected that the in vivo and in vitro responses in these patients will become more clearly manifest with the enlarged patient population and somewhat more aggressive treatment program.

Conclusions: In this protocol we have demonstrated for the first time a reduction in bronchial sensitivity to occupational aeroallergens as a consequence of specific immunotherapy. The Investigative Immunology Laboratory has the unique capability of combining in vivo and in vitro measurements which quantitate immediate hypersensitivity states in specific allergic patients with intrinsic asthma. This protocol has been extremely productive since its onset (see publications below). It is extremely valuable in our fellowship teaching program and should be continued. Dr. Robert Sigler replaces Dr. Blair Thrush as co-investigator.

Funding Requirements, FY-78:

Personnel:	One GS-07 Technician 16 wks/yr	
Equipment:	None	
Supplies, Consumable:		$7,000
Travel:	Mission	400
Publications:		250
		$7,650

Work Unit No.: 3109

Title of Project: Complement Deficiencies and their Relationship to Diseases in Man

Investigators:

Principal: Arnold I. Levinson, MAJ MC

Associate: Richard Evans, III, COL MC

Objective: The complement system, a series of interacting proteins, plays an integral role in the inflammatory response. It is clear that an intact complement system is indispensable in the defense against infections. In other instances activation of the complement system, with generation of phlogistic mediators, may have detrimental consequences for the host. This is an ongoing project in which we are investigating not only the integrity of the complement system in patients with recurrent infection but also the active participation of this system in various disease states.

Technical Approach: Our laboratory has the capability of measuring C_3, C_4, and C_3 activators. These complement components are determined by radioimmunodiffusion.

Progress and Results: We have continued to screen a number of patients presenting with recurrent infections. We have identified a boy whose only immunologic abnormality to date is a markedly diminished C_4. Clarification of this defect is important since C_4 deficiency in man and experimental animals is not associated with recurrent infections. We have also identified a 60 year old lady with C_4 deficiency associated with a lupus-like syndrome, (Her C_3 is normal). We do not believe that the C_4 has been consumed as part of a disease related immune process. Rather, we think that absent C_4 in this patient may represent a true congenital deficiency. Studies are planned to determine if this is the case. We are aware of only one other similar patient in the world's literature.

We have also identified a patient with hereditary angiodema. In the past this disease was often attended by a fatal outcome. Danazol, an impeded androgen, has recently been shown to provide prophylaxis against recurrent episodes. On danazol, our patient is doing extremely well.

Conclusions: Our laboratory has continued to provide useful and necessary information in the management of an heterogeneous group of diseases. Also patients identified as having complement abnormalities provide valuable teaching devices for our fellows and housestaff.

Funds Utilized, FY-77: $1,518.00

Funding Requirements, FY-78:

Personnel: One GS-07 Technician, currently employed for 20 weeks/year

Equipment: No new equipment required

Supplies:	Consumable	5,000.00
Travel:	Mission	500.00
	Conference	600.00
	TOTAL:	6,100.00

Type of Report: Interim

Publication: Selective IgA Deficiency and PiZ Deficiency Associated with Recurrent Sinopulmonary Infections, Emphysema, and Bronchiectasis. Casterline, Charlotte. L., and Richard Evans, COL MC, (Has been accepted in CHEST, in press).

Work Unit No.: 3111

Title of Project: Quantitative Serum IgE in Human Infections, Immune Deficiency States and Diseases with Impaired Cellular Immunity

Investigators:

Principal: Richard Evans, COL MC

Associate: Virginia Battista, BA

Objectives: To study the role of IgE responses in atopic and nonatopic states with emphasis on a possible association between elevated or decreased levels of serum IgE and allergic disease states, infections, immune deficiency states, and impaired cellular immune responses.

Technical Approach: Serum samples from a patient population described above are collected. These are then analyzed for IgE content using a radioimmunoassay. During this reporting period a new radioimmunoassay procedure (PRIST, Pharmacia, Inc.) was tested. This direct antibody method was found to be more sensitive when compared to the previously used inhibition assay. The mean IgE levels in normal adult sera with the new assay is 20 I.U./ml with a S.D. of 43 I.U./ml.

Progress and Results: In the past year we have tested 630 sera for total IgE. Patients studied have included hypersensitivity lung diseases, insect sting allergy, immune deficiency (primary and acquired), idiopathic eosinophilia, and occupational asthma. We are also measuring serum IgE for the WRAMC Blood Bank in all instances of transfusion reaction.

The Principal Investigator is chairman of a new committee of the American Academy of Allergy established to evaluate the current status of standardization of in vitro tests in allergy. The first test evaluated was quantitation of total IgE by radioimmunoassay. This laboratory was one of twelve medical center facilities in the U.S. who cooperated in this study. Lyophilized unknown sera were studied in replicate on the same day and on separate days. Variance among the laboratories' results was considered excessive by the committee members who also represented the participating laboratories.

This laboratory is now cooperating in an evaluation of the reasons for the variance. It is expected that a new U.S. standard for common use by all the laboratories will be established.

Conclusions: This protocol warrants continuation for another year. In addition to the forementioned progress, the protocol supports the house staff teaching mission of WRAMC and is a format for an excellent relationship with other academic centers.

Funds Utilized, FY-77: $6,700.00

Funds Required, FY-78:

Personnel:	One GS-07 Technician, 3 mo/yr	
Supplies, consumable:	Radioassay material	$8,900.00
Travel, mission:		400.00
	Total:	$9,300.00

Publication: Quantitative Immunoglobulin Levels in Tuberculosis. Charlotte L. Casterline, MD, Richard Evans, COL MC, and George W. Ward, Jr., MD. CHEST, (in press).

Presentation: Standardization of the Quantitation of Total Serum IgE Presented to the Research Council, Amer Acad Allergy, NYC, Mar 1977.

Work Unit No.: 3113

Title of Project: Synovial Fluid in Rheumatic Disease

Investigators:

Principal: Oliver J. Lawless, MD, LTC MC

Associate: John A. Boice, CDR, MC, USN

Objective:

Patients with rheumatic diseases often present joint effusions as part of their symptom complex. Classically synovianalysis has differentiated these into four categories:

(1) Noninflammatory fluid characterized by a low white blood cell count and good mucin clot, as exemplified by degenerative joint disease (DJD).

(2) An inflammatory fluid with elevated white blood cell count and poor mucin clot as found in rheumatoid arthritis (RA).

(3) A crystal-associated fluid found with gout and pseudogout.

(4) A turbid fluid with extreme white blood cell count, mucin clot poor, and low glucose, characteristic of infection.

As can be seen by the accompanying tabulated results, these categories are broad and allow considerable overlapping. Nonetheless, the differential diagnosis can be narrowed significantly in most cases, and in trauma, crystal-induced arthritis and infection, it can often be established. This study, therefore will be of aid in the current diagnosis and management of patients seen in the Rheumatology and Clinical Immunology Service and other services in WRAMC.

Technical Approach:

At the time of aspiration, synovial fluid is collected in appropriate containers for the determination of clarity, color, viscosity, mucin clot, total white blood cell count, differential cell count, protein, albumin, gamma globulin, glucose, complement (C3, C4, CH50), inclusions, crystals, culture and gram stain. A portion of the sample is stored for future analysis. As results are obtained, a formal assessment is made of the sample and whether they are consistent with the diagnosis. An appendix shows an example of the work sheet used.

Progress and Results:

Synovial fluid analysis has now been carried out on several hundred samples. Complete clinical and laboratory data were available on 336, which fall into 16 catagories for the diagnosis of "arthritis". These

(4) Serologies and complement levels, while having a low incidence of positivity and while never completely diagnostic, may produce important clues to the consideration of connective tissue diseases that may not be considered pertinent on clinical grounds alone.

(5) Inclusions, as seen in leukocytes by light microscopy, are significantly more abundant in RA than in other conditions.

(6) A larger number of fluid analyses are required in several categories in order to produce statistically relevant comparisons.

Future Directions:

(1) The original protocol will be continued in order to achieve statistically significant data.

(2) Specific diagnostic entities will be scrutinized in detail in order to better correlate the clinical status of patients with their joint fluid analyses.

(3) The correlation of synovial fluid complement (C3, C4, CH 50) to that of serum values and to synovial fluid protein will be analyzed.

(4) Gas-liquid chromatography will be performed on stored samples to further refine the diagnostic usefullness of synovial fluid analysis.

Funds Utilized (FY-77)

Funded: $777.00; Utilized (supplies): $777.00

Funding Requirement (FY-78)

Supplies:	$700.00
Publication Costs:	150.00
Total:	$850.00

Total funding request (FY-78): $850.00

Publications: None

Type of Report: Interim

Date of Report: 5 July 1977

are listed in a table. The data can be interpreted by the following code as used in the appended tables. The number in parentheses in the top right corner of each box represents the total number of fluids tested. In the top left corner, the minimum value is recorded, in the center, the average is found and in the lower right corner the maxium value is noted.

The classification of diagnoses is as follows:

CLASS I: Normals, traumatic, chondromalacia, osteoarthritis.
CLASS II: Systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), juvenile rheumatoid arthritis (JRA), ankylosing spondylitis, Sjogren's colitis.
CLASS III: Gout, pseudogout.
CLASS IV: Septic hemorrhagic arthritis.

There is some overlap among these broad categories.

Of particular interest are the following findings:

(1) Inflammatory-type fluids are present in certain clinically degenerative type joints.

(2) It is important to correlate synovial fluid complement levels with fluid protein levels to reduce the chance of improperly inferring the presence of an immune-mediated arthritis from the occurrence of a low complement level.

(3) Fluids of RA and JRA, as well as SLE, show a significant incidence of positivity for flourescent antinuclear antibodies (FANA).

(4) When related to protein concentration, the lowest complement level observed occurred in Reiter's syndrome.

Conclusions:

(1) No single test, such as the total white blood cell count, can be used to establish a definitive diagnosis of any type of arthritis.

(2) The combination of tests used in this study may likewise not establish the cause of arthritis. However, the combination of tests used enables the number of differential diagnoses to be reduced to a few. The laboratory findings can invariably establish a clinical diagnosis of a definitive nature when they are considered together with the clinical findings.

(3) A total white blood cell count above 50,000, while typical of septic arthritis, can be present in other diseases, e.g., crystal-induced synovitis, JRA, RA and Reiter's Syndrome. This finding mandates the use of a polarizing microscope, appropriate cultures and other tests to avoid inappropriate treatment.

TABLE I Page 1a

SYNOVIAL FLUID

Minimum Average Maximum	Clarity 1+ clear 2+ cloudy 3+ " 4+ turbid	Viscosity 1+ good 2+ 3+ 4+ poor	Color	Mucin clot G good F fair P poor	W.B.C. ($1x10^3$)	Polymorpho Lymphocytes %	Crystals G Gout P Pseudo-gout	Total Proteins gm %
Normal Class I	(57) 1+ 98% 2+ 2% 3+ 0 4+ 0	(33) 1+ 91% 2+ 6% 3+ 0% 4+ 3%	(11) yellow	(36) G 94% F 3% P 3%	(38) 0.013 0.455 6.7	(37) 11/85 88/100	(57) 0% (+)	(19) 1.1 2.4 4.8
Trauma	(16) 1+ 69% 2+ 19% 3+ 0% 4+ 12%	(16) 1+ 12% 2+ 13% 3+ 31% 4+ 44%	(16) yellow 87% red 13%	(17) G 59% F 35% P 6%	(16) 0.001 1.65 5.2	(15) 0/01 48/56 99/100	(17) 0% (+)	(9) 2.5 3.58 5.1
Degenerative Joint Disease	(64) 1+ 67% 2+ 23% 3+ 6%	(53) 1+ 64% 2+ 7.5 3+ 11%	(17) yellow	(67) G 72% F 21% P 7%	(65) 0.007 2.43 22.8	(57) 0/0 30/67 95/100	(55) 0% (+)	(35) 1.5 3.2 5.7
Systemic Lupus Erythematosus	(15) 1+ 26% 2+ 33% 3+ 26%	(16) 1+ 25% 2+ 12% 3+ 12%	(8) yellow	(14) G 28% F 28% P 44%	(17) 0.033 8.88 32.0	(15) 0/0 47/54 99/100	(18) 0% (+)	(9) 2.3 4.1 6.8
Crystal Induced	(14) 1+ 21% 2+ 57% 3+ 14%	(13) 1+ 31% 2+ 31% 3+ 15%	(16) yellow	(14) G 7% F 36% P 57%	(12) 0.255 10.78 42.3	(12) 0/0 70/30 98/100	(16) G 100% P 0%	(8) 3.1 4.1 4.9

SYNOVIAL FLUID

Minimum Average Maximum	Albumin (%)	Gamma Globulin (%)	Glucose	Fluorescent antibody (%)	Rheumatoid Factor	C3	C4	CH50	Inclusions (%)
Normal Class I	(6) 45 54 60	(6) 14 20 35	(5) 72 86 98	(50) 0% (+)	(50) 0% (+)	(4) 10 46 70	(0) -	(1) - 70 -	(7) 0% (+)
Trauma	(5) 52 59 63	(5) 12 15 21	(11) 40 95 162	(8) 12.5% (+)	(8) 0% (+)	(5) 20 59 91	(0) -	(3) 30 150 153	(12) 0% (+)
Degenerative Joint Disease	(7) 41 58 64	(4) 9.9 21 33	(37) 63 96 163	(44) 0% (+)	(44) 2% (+)	(34) 21 73 45	(0) -	(10) 30 79 196	(17) 5.8% (+)
Systemic Lupus Erythematosus	(2) 44 54 66	(2) 13 30 47	(7) 37 84 116	(11) 64% (+)	(12) 25% (+)	(11) 03 57 104	(1) - 7.8 -	(3) 30 59 73	0% (+)
Crystal Induced	(3) 60 62 67	(8) 11 17 21	(8) 84 98 118	(7) 0% (+)	(9) 0% (+)	(6) 56 80 104	(0) -	(2) 60 90 120	0% (+)

TABLE I Page 2a SYNOVIAL FLUID

Minimum Average Maximum	Clarity 1+ clear 2+ cloudy 3+ " 4+ turbid	Viscosity 1+ good 2+ 3+ ↓ 4+ poor	Color	Mucin clot G good F fair P poor	W.B.C. ($1x10^3$)	Polymorpho Lymphocytes %	Crystals G Gout P Pseudo-gout	Total Proteins gm %
Rheumatic Fever	0	0	0	0	0	0	0	0
Rheumatoid Arthritis	(79) 1+ 10% 2+ 40% 3+ 25% 4+ 25%	(77) 1+ 7% 2+ 10% 3+ 18% 4+ 61%	(28) yellow	(75) G 16% F 17% P 67%	(79) 0.05 11.52 36.0	(74) 0/0 69/31 100/100	(77) 0% (+)	(47) 2.9 5.05 7.6
Juvenile Rheumatoid Arthritis	(23) 1+ 9% 2+ 39% 3+ 30% 4+ 22%	(20) 1+ 10% 2+ 0 3+ 15% 4+ 75%	(7) yellow	(18) G 11% F 33% P 56%	(28) 4.6 26.8 74.6	(28) 0/0 73/30 95/100	0% (+)	(19) 3.4 4.6 6.0
Ankylosing Spondylitis	(1) 1+ 0 2+ 100% 3+ 0 4+ 0	(1) 1+ 0 2+ 100% 3+ 0 4+ 0	(1) yellow	(1) G 0 F 0 P 100%	(1) - 4.7 -	(1) 1 68/21 1	(1) 0% (+)	(1) - 3.6 -
Sjögrens	(2) 1+ 0 2+ 100% 3+ 0 4+ 0	(4) 1+ 75% 2+ 25% 3+ 0 4+ 0	(0)	(3) P 100%	(6) 1.45 5.36 13.2	(6) 14/10 48/44 90/86	(5) 25% (+)	(4) 4.2 5.0 6.6
Colitic Arthritis	(2) 1+ 0 2+ 0 3+ 0 4+ 100%	(2) 1+ 50% 2+ 50% 3+ 0 4+ 0	(0) -	(2) P 100%	(2) 4.45 13.27 22.0	(1) 1 90/0 1	(2) 0% (+)	(1) - 9.4 -

SYNOVIAL FLUID

Minimum Average Maximum	Albumin (%)	Gamma Globulin (%)	Glucose	Fluorescent antibody (%)	Rheumatoid Factor	C3	C4	CH50	Inclusions (%)
Rheumatic Fever	0	0	0	0	0	0	0	0	0
Rheumatoid Arthritis	(13) 41 51 57	(13) 18 22 35	(46) 36 87.7 132	(58) 14% (+)	(58) 43% (+)	(52) 10 58.8 148	(1) - 28 -	(4) 30 30 30	(26) 36% (+)
Juvenile Rheumatoid Arthritis	(3) 49 66 93	(1) - 20 -	(16) 51 87 110	(19) 16% (+)	(20) 15% (+)	(20) 50 97 150	(0) -	(3) 40 100 140	0% (+)
Ankylosing Spondylitis	(1) - 54 -	(1) - 16 -	(1) - 77 -	(1) 0% (+)	(1) 0% (+)	(1) - 115 -	(0) -	(0) -	(1) 0% (+)
Sjögrens	(0) -	(0) -	(2) 66 84 102	(5) 20% (+)	(4) 0% (+)	(4) 47 64 87	-	-	-
Colitic ARthritis	(0) -	(0) -	(1) - 114 -	(2) 0% (+)	(2) 0% (+)	(1) - 37 -	(0) - - -	(0) -	(2) 0% (+)

TABLE I Page 3a SYNOVIAL FLUID

Minimum Average Maximum	Clarity 1+ clear 2+ cloudy 3+ " 4+ turbid	Viscosity 1+ good 2+ 3+ ↓ 4+ poor	Color	Mucin Clot G good F fair P poor	W.B.C. ($1x10^3$)	Polymorpho- Lymphocytes %	Crystals G Gout P Pseudo-gout	Total Proteins gm%
Reiter's Syndrome	(14) 1+ 7% 2+ 29% 3+ 43% 4+ 21%	(14) 1+ 64% 2+ 14% 3+ 0 4+ 22%	yellow	(15) G 20% F 20% P 60%	(14) 10.57 35.7 0.2	(13) 01/0 70/60 91/99	(14) 0% (+)	(14) 3.4 5.9 145
Infectious Arthritis	(6) 1+ 0 2+ 33% 3+ 0 4+ 66%	(4) 1+ 0 2+ 50% 3+ 0 4+ 50%	yellow	(6) G 0 F 16% P 83%	(7) 17.7 83.3 260	(6) 30/1 82/18 99/70	(6) o% (+)	(3) 3.4 4.4 5.4
Chondromalacia	(5) 1+ 40% 2+ 40% 3+ 20% 4+ 0	(5) 1+ 0 2+ 20% 3+ 0 4+ 80%	yellow	(5) G 100%	(7) 0.25 1.58 4	(4) 27/01 65/35 99/78	(5) 0% (+)	(2) 3.2 3.25 3.3
Tuberculosis Arthritis	0	0	0	0	0	0	0	0
Gonococcal Arthritis	(4) 1 + 0 2 + 0 3 + 0 4 + 100%	(4) 1+ 100% 2+ 0 3+ 0 4+ 0	(4) yellow	(4) G 0 F 50% P 50%	(4) 1.45 22.61 43.0	(4) 50/0 83/18 100/50	(4) 0% (+)	(4) 3.3 4.6 5.0

TABLE I Page 3b SYNOVIAL FLUID

Minimum Average Maximum	Albumin (%)	Gamma Globulin (%)	Glucose	Fluorescent antibody (%)	Rheumatoid Factor	C3	C4	CH50	Inclusions (%)
Reiter's Syndrome	(4) 51 53 62	(4) 18 21 25	(12) 60 88 106	(13) 0% (+)	(14) 0% (+)	(12) 83 110 193	(6) - - -	(6) 120 132 150	0% (+)
Infectious Arthritis	(1) 46%	(1) 21%	(3) 6 76 125	(3) 0% (+)	(3) 0% (+)	(2) 74 82.5 91	(0) - - -	(0) - - -	(1) 0% (+)
Chondromalacia	(0) -	(0) -	(2) 83 89 96	(4) 0% (+)	(5) 0% (+)	(1) - 62 -	0	(1) - 120 -	(3) 0% (+)
Tuberculosis Arthritis	-	-	-	-	-	-	-	-	-
Gonococcal Arthritis	(0) -	(0) -	(4) 6 11 40	0% (+)	0% (+)	(0) -	(0) -	(0) -	(4) 0% (+)

TABLE 2

SYNOVIANALYSIS CHART

DATE:	DIAGNOSIS:

FLUID FILED ☐ yes ☐ no

FASTING ☐ yes ☐ no

BIOPSY ☐ yes ☐ no

JOINT ASPIRATED:
VOLUME ASPIRATED:

APPEARANCE
COLOR:
TURBIDITY:
CLOT:
VISCOSITY:

MUCIN TEST

SUGAR
BLOOD:
S. FLUID:

CELLS: WCC POLYS LYMPHS MONOS

INCLUSIONS
Cells With _____
Inclusions per Cell _____

RCC: Few
Many
TNTC

CULTURE BACTERIAL Aerobic
Anaerobic

GRAM STAIN

COMPLEMENT: BIC
CH50

FUNGAL

VIRAL

OTHER

CRYSTALS ☐ yes Bire
☐ no Bire

RHEUMATOID FACTOR
FAT

LIPIDS
ENZYMES
PROTEIN

_____ M.
(Signature)

COMMENT AND CLINICAL INTERPRETATION:

_____ M
(Signature)

PATIENT'S NAME (Last, First, Middle):	SSAN:	STATUS:

313

WRAMC FORM 1611

Work Unit No.: 3117

Title of Project: Evaluation and Study of Patients with Primary and Secondary Immunodeficiencies

Investigators:

Principal: Arnold I. Levinson, MAJ MC

Associate: Donna Schuster, MAJ MC

Objective: The immune system consists of a number of complex cellular and humoral components acting to protect the intact organism. When the integrity of this system is breached, either due to genetic aberrations or to acquired disease, individuals suffer dire consequences. The present protocol has been developed to identify and further the understanding of such breaches of host defenses. The elucidation of pathogenic mechanism in immune deficiencies is requisite for therapeutic intervention In addition, study of these so-called experiments of nature often leads to new insights into the immune response itself.

Technical Approach: The Clinical Immunology Investigative Laboratory is able to study a broad range of immune functions, relevant to both major arms of the immune response, i.e., T and B cell systems. It is becoming increasingly apparent that this kind of capability is necessary in a major teaching and referral center. We continue to employ all of the techniques mentioned in last year's annual report. In addition, it should be mentioned that we have modified our basic cell culture technique so that smaller samples of blood are obtained from our patients. The development of assays for chemiluminescence and chemotaxis in the past year provides us with the capacity to test phagocytic and chemotactic function, respectively.

Progress and Results: Within the past year we have examined the cellular and humoral function of over 60 individuals. The patients have been referred by various departments within Walter Reed Army Medical Center as well as armed forces facilities through the world. For the most part such individuals have presented with recurrent infections. In addition, we have established an in vitro assay to identify suppressor cells in man. This assay will provide insight into the pathogenesis of a number of clinical disorders. To date our studies have provided not only the diagnosis but also the most appropriate therapeutic strategies in a number of these individuals.

Listed below are some of these patients:

1. A 6 month old boy with hypogammaglobulinemia. Differential Dx. Bruton's agammaglobulinemia versus transient hypogammaglobulinemia of infancy. We are now following his course, looking for evidence of immunoglobulin production.

2. A 2-1/2 year old girl with IgA deficiency with probable chemotactic defect. She is presently undergoing intensive evaluation of granulocyte function. This may represent the first report of selective IgA deficiency and associated chemotactic dysfunction.

3. A 3 year old boy with recurrent infections due to hypogammaglobulinemia with intact T-cell system.

4. A 60 year old woman with hypogammaglobulinemia secondary to Menitrieve's disease, a previously poorly documented association.

5. A 6 month old child who presented with pneumocystis carcinii pneumonia as an initial manifestation of immune deficiency. Extensive workup revealed the patient to have Bruton's agammaglobulinemia. The patient also had a C-group chromosome abnormality, the first instance of chromosome defect associated with agammaglobulinemia.

6. A 4-1/2 year old girl who presented with recurrent pyogenic infections, mucocutaneous candidiasis and hyper IgE. Workup of her leukocyte function revealed sluggish intracellular killing of bacteria. We are continuing to investigate this child's function with the thought she may be a candidate for levamisole therapy?

7. The child with Pseudo-DiGeorge Syndrome described in Annual Progress Report, FY-76, continues to do well from an immunologic sense. Unfortunately, his father's abrupt termination from active duty precluded further laboratory assessment.

8. We have continued to follow the 28 year old lady with common variable hypogammaglobulinemia (described in Annual Progress Report, FY-76), associated with interstitial lung disease. Despite maintenance gammaglobulin therapy, the patient has suffered repeated

upper respiratory infections. She is presently being considered for plasma infusion therapy.

Conclusions: Our immunodeficiency protocol plays a vital role in the delineation of aberrant immune mechanisms in a diverse array of disease states. Not only have our studies provided the means for diagnosis but also intelligent selection of therapy.

Funds Utilized, FY-77: $2,096.00

Funding Requirements, FY-78:

Personnel: One GS-07 Technician for 52 weeks.

Equipment: No new equipment needed.

Supplies: Consumable		$ 12,000.00
Travel: Conference		600.00
Mission		650.00
	TOTAL:	$ 13,250.00

Type of Report: Interim

Date Prepared: 15 June 1977

Publications:

1. Milluncheck, E., deShazo, R., Levinson, A.I., Ruymann, F., Grogan, T.: Pneumocystis pneumonia hypogammaglobulinemia and C-Chromosomes aberration. Submitted for publication.

2. Levinson, A.I.: Pseudo-DiGeorge Syndrome. Amer Acad of Allergy, 1977.

3. Levinson, A.I., Marcks, C., deShazo, R.: Concanavallin A induced suppressor cells in healthy man. Presented at Federation of Experimental Biology, Chicago, 1977.

4. Levinson, A.I., Marcks, C., deShazo, R.: Concanavallin A induced suppressor cells in healthy man. Submitted for publication.

Work Unit No.: 3119

Title of Project: The Role of Sensitized Leukocytes in Antigen Induced Serotonin Release from Human Platelets

Investigators:

Principal: Richard Evans, COL MC

Associate: George J. Gibiely

Objectives: To demonstrate the presence (or absence) of a platelet activating factor released by IgE mediated, immediate hypersensitivity reactions of humans.

Technical Approach: To combine, using human blood cells, the in vitro assays of antigen-induced leukocyte mediator release with the immunologic mediation in vitro of platelet serotonin release. The goal has been to demonstrate in vitro antigen induced liberation of a platelet activating factor from sensitized human leukocytes.

Progress and Results: In hopes of reaching this project's goals, we have been required to develop a number of important new techniques in the past year. These include white blood cell separation techniques such as Hypaque Ficoll Differential Centrifugation and Glass Bead Column Chromatography for basophil separation. As a result, high percentage Basophil preparations have been derived for a better controlled mediator release assay. In addition, the previously described C^{14} Serotonin platelet labelling system is still in use.

Several experiments have been attempted to demonstrate the existence of platelet activating factor in an in vitro human assay. Platelet release of C^{14} Serotonin was induced using 1 ml supernatant fractions of ragweed, antigen E challenged basophils, dose-response experiments, kinetic studies of platelet serotonin release, studied quantitating the amount of cell bound and supernatant bound PAF, and studies using passively sensitized basophils were among the experiments performed.

Although platelet serotonin release has been demonstrated using basophil supernatants, the results are ambiguous since supernatants of both control and antigen challenged basophils induce high release. If this high serotonin release is caused by spontaneous PAF release from control basophils, then our current task is to minimize the spontaneous release. All recent attempts to do this, however, have been unsuccessful.

Conclusions: This protocol has provided our laboratory with a number of new and extremely useful techniques. Furthermore, it has been a very instructive experience for one of our premedical summer students. The protocol does not warrant continuation, however. The techniques available are sensitive enough to quantitate human platelet responses in the described system.

Type of Report: Termination

WORK UNIT NO. 3123

TITLE OF PROJECT: Study Immune Mechanisms in Systemic Lupus Erythematosus

Principal Investigators: Oliver J. Lawless, MD, LTC

Bernard Berne, PhD, MD

Objective: To simultaneously assess the function of the phagocytic T & B Components of the immune system in the production of the symptoms of acute Lupus, and to compare these findings with those found during inactivity or remission of the disease.

Technical Approach: Lupus is an antigen induced disease, the major responsible antigen being double stranded DNA. The modulation of phagocytic, T & B cell function by antigen, antibody, and antigen antibody complex has pertinence not only to Lupus but to all infectious diseases where antigen persistence plays a role, but also to the mechanisms of transplantation, and tumour rejection. Lupus patients are unique in that the DNA antigen, and antibody systems can be isolated, purified, and tested in an in vitro system on the cells of the patient without potential injury to him. Identification of the modulation mechanism in Lupus would have direct importance to host resistance to infection, and to transplant and tumour rejection, all of which are major thrusts of military research.

Inflammation in Systemic Lupus is caused by immune complexes. Patients with acute disease frequently have local deposition of complexes, high levels of free DNA, anti DNA, and elevated anti DNA levels after treatment of serum with anti DNAse. They also have elevated levels of proteins and immunoglobulins, reduced levels of complement C3, C4, and CH50 and depressed T cell function. Rheumatoid factors are frequently found also. It is our hypothesis that complexes are deposited because of ineffective clearance by the phagocytic system. The mechanism for clearance of these complexes has not been directly defined in Systemic Lupus Erythematosus. It is our proposal to study the role of DNA ag, anti DNA antibody, and DNA-anti DNA complexes and rheumatoid factor on phagocytic, T & B cell function in acute active, and inactive Systemic Lupus Erythematosus (SLE). Immune complexes incite an inflammatory reaction at the site of their depostion eg. kidney, skin, lung, etc. Clearance of complexes from the circulation is by the RE system - monocytes and polys, of peripheral blood, and by fixed and wandering RE cells of parenchymal organs eg. liver, kidney, etc.

Phagocytic clearance has not been measured in SLE. All assays for functional activity of phagocytes depend upon indirect assays such as NBT test, iodine incorporation into protein and clearance studies

using radio labelled macro-aggregated proteins. Clearance of DNA anti DNA complexes with radioactively labelled DNA would provide us with information more specifically relatable to phagocytic function in this disease.

T lymphocyte number and function have been shown to be reduced in acute untreated SLE. The mechanism responsible for this has not been defined. Three potential explanations for this phenomenon can be proposed (1) the presence of lymphocytotoxic factors, (2) the presence of blocking factors that are not cytotoxic, (3) the presence of immune complexes that "alter" lymphocyte re-activity, (4) the presence of antibody against T cell receptors in SLE sera. Fundamental to the understanding of blocking or enhancing factors on the T lymphocyte is definition of the role of complexes of DNA anti-DNA made up in antigen excess, equivalence and antibody excess, on these cells as we have shown that depending upon the Ag-Ab ratio of these complexes serum containing these complexes can be either enhancing or blocking to Ag and PHA induced T cell responses.

HLA profiles have been recently linked with a high statistical significance to certain diseases considered to be immunologically induced. HLA profiles in SLE have been reported to yield variable results. It is to be noted however that SLE serum can display blocking factor activity, in relation to lymphocyte function and HLA expression. Culture and washing of peripheral blood lymphocytes of SLE patients for twenty-four hours may yield additional HLA antigens not detectable at time zero. The relationship of this finding to the presence of DNA-anti DNA complexes needs further definition and confirmation. Antigen, and mitogen induced T cell responses result in lymphocytic blast transformation and lymphokine production in tissue culture. Lymphokines have shown to have specific effects on polys, and monocytes as well as other lymphocytes. If T cell responses are diminished by reason of cytotoxic factors or blocking factors then theoretically mediator release from T cells would be suppressed, and accordingly loss of T effect on poly and monocyte would be expected, a phenomenon that could contribute to decrease in phagocytic function and clearance of complexes.

The practical application of this project is as follows. If one can show that complexes present in serum are responsible for suppression of T cell directly and poly and monocyte indirectly then two potential treatment approaches are virtually free of toxicity. (1) Plasmaphoresis for removal of complexes, (2) transfer factor therapy, made from the patient himself during the non-acute man "suppressed" phase of this disease with a view to (a) removing the blocker, (b) boosting the deficient cell system responsible for defective clearance of complexes.

B2 microglobulin has been shown to be (1) produced by cells including T cells and monocytes in tissue culture, (2) to be metabolized by tubular epithelium cells of the kidney, (3) to be high in the serum of patients with severe renal disease, and (4) anephric patients, and to be (5) high in the urine of patients following transplantation. It has furthermore been shown to be similar to the C_3 domain on the H chain of IgG molecule and to be closely linked to the HLA antigen bound on the surface membrane of T lymphocytes.

It is theoretically possible therefore that serum levels of B_2M will be altered in SLE, and urinary levels may be altered prior to evidence of clinical activity of the disease. Epstein has shown that free light chains in an effect to identify if these measurements afford earlier recognition of exacerbation of SLE. Within this overall project the following individual projects and protocols are proposed:

Phagocytic Function

(1) Development of in vitro phagocytic assay using C^{14} labelled DNA anti DNA complexes of fixed molar ratios and peripheral blood monocytes and polys,

(2) Measurement of effect of Ag (DNA) Ab (anti DNA) C^1, and Rheumatoid Factor on this assay system,

(3) Measurement of effect of lymphokines on this assay, from normal, and active and inactive SLE patients lymphocytes,

(4) Measurement of effect of lymphotoxic serum on this assay.

Lymphocyte T Function

(1) DH to battery of Ags,

(2) Enumeration of T & B cell numbers by Rosette and surface staining techniaue,

(3) Measurement of T cell response to Ag, MLC, PHA, PWM, DNA and DNA anti DNA complexes, in different molar ratios,

(4) Measurement of the effect of Ag - Ab complexes in different molar ratios on the kinetics of T cell responses in normal and SLE patients in response to Ag and PHA and PWM,

(5) Measurement HLA profile of SLE patients and the influence of time, Ag and Ab complex on this profile,

(6) Measurement of lymphokine production in SLE lymphocytes and the effect on macrophage migration inhibition and leukocyte migration inhibition.

B Cell Function

(1) Measurement of IgG, A, M, D and E levels,

(2) Measurement of antinuclear antibodies by FANA, and DNA binding technique,

(3) Measurement of C^3 and CH50 complement levels.

Immune Complexes (IC) Detection

Immune complexes will be detected by a solid phase sandwich radioassay using labelled C1q, a part of the first component of complement. C1q, a protein with a molecular weight of 600,000 can bind and precipitate with IC, although existing tests utilizing this reaction are generally either cumbersome or insensitive, they have been shown to be useful in documenting the rise in IC during exacerbations of SLE.

While several polyanions (DNA, Heparin, Endotoxin, etc.) are known to also bind to C1q, the specificity of the reaction with IC appears sufficient to enable this to form a sensitive assay for IC, as increased binding correlates with disease activity in SLE. Improvements in methodology such as the radioassay proposed here will allow an assessment of the actual effects of non-specific binding on the assay for IC.

Urine Proteins

Measurement of urinary light chain excretion, and B_2 microglobulin excretion in the urines of quiescent and active Lupus patients.

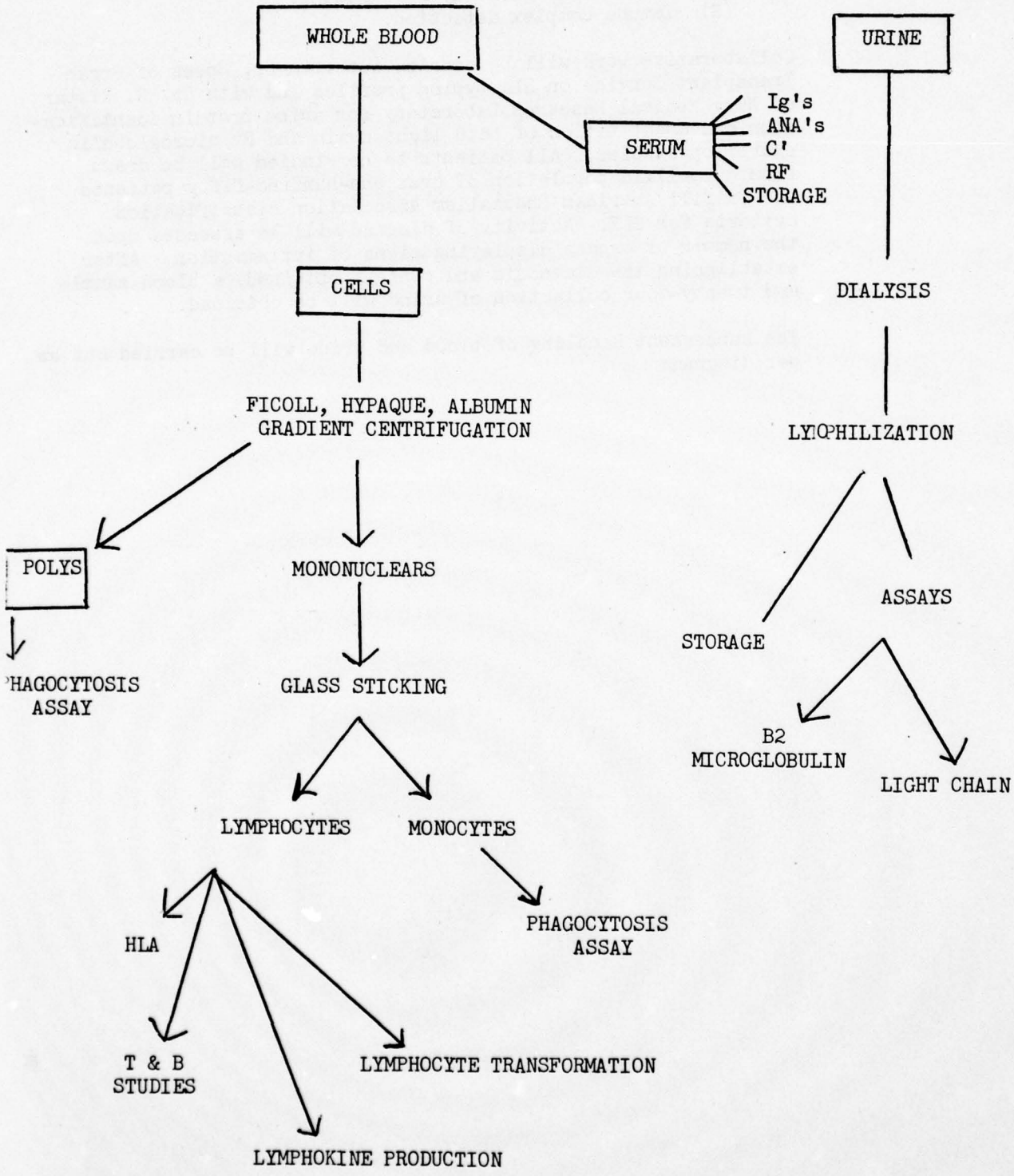
Plan: The technique essential for completion of these studies are all currently in use in our laboratory, having been developed during the past three years as follows:

(1) Leukocyte, poly, monocyte, and lymphocyte separation.
(2) Phagocytic function using C^{14} labelled immune complexes.
(3) Lymphocyte transformation.
(4) Lymphokine production and characterization.
(5) Immunoglobulin levels.
(6) T and B cell enumeration.

(7) Antinuclear antibody measurement.
(8) Immune complex detection.

Collaborative work will be carried out with Dr. Spees of Organ Transplant Service on HLA typing profiles and with Dr. R. Wistar of Navy Medical Research Laboratory for urine protein identification and quantitation of both light chain and B^2 microglobulin excretion studies. All patients to be studied will be drawn from our clinic population of over one-hundred-fifty patients who fulfill American Rheumatism Association classification criteria for SLE. Activity of disease will be assessed upon the number of organs displaying signs of inflammation. After establishing the diagnosis and consent obtained, a blood sample and twenty-hour collection of urine will be obtained.

The subsequent handling of blood and urine will be carried out as per diagram:


WHOLE BLOOD
URINE
SERUM
Ig's
ANA's
C'
RF
STORAGE
CELLS
DIALYSIS
FICOLL, HYPAQUE, ALBUMIN
GRADIENT CENTRIFUGATION
LYOPHILIZATION
POLYS
MONONUCLEARS
ASSAYS
STORAGE
PHAGOCYTOSIS
ASSAY
GLASS STICKING
B2
MICROGLOBULIN
LIGHT CHAIN
LYMPHOCYTES
MONOCYTES
PHAGOCYTOSIS
ASSAY
HLA
T & B
STUDIES
LYMPHOCYTE TRANSFORMATION
LYMPHOKINE PRODUCTION

Progress and Results:

Lymphocyte Function - The series has been expended to include 30 SLE patients and 30 controls. All were untreated at time of study. Six had active disease including active nephritis. Data has been analysed on 25 patients and is seen in Tables I and II below.

COMPARISON OF LYMPHOCYTE FUNCTION IN 25 SLE PATIENTS VERSUS CONTROLS IN NORMAL AND SLE PLASMA, IN THE PRESENCE OF ANTIGEN, MITOGENS, ALONE AND IN THE PRESENCE OF ADDED DNA

TABLE I

	NORMAL CONTROL CELLS		SLE CELLS	
PLASMA	NORMAL	SLE	NORMAL	SLE
Background	374	469	266	302
Background with DNA	1,001	1,300	548	665
SKSD	9,075	11,371	2,735	3,729
SKSD with DNA	8,709	10,482	3,450	4,027
PHA	25,777	25,333	17,377	17,333
PHA with DNA	23,000	18,314	13,680	11,153
PWM	7,262	6,247	5,274	5,304
PWM with DNA	4,384	4,072	5,511	4,663

COMPARISON OF LYMPHOCYTE FUNCTION MEASURED IN MEAN CPM IN 6 ACTIVE SLE PATIENTS IN NORMAL AND SLE PLASMA, IN THE PRESENCE OF ANTIGEN, AND MITOGENS

TABLE II

	PLASMA	
	NORMAL	SLE
Background	169	174
SKSD	2,056	468
PHA	19,104	9,870
PWM	6,614	3,047

Interpretation of this data will be based on accurate statistical analysis which is currently being performed. It appears however that cell responses are reduced in SLE patients in response SKSD, and PHA with nominal differences to PWM. When cases with active disease (including nephritis) are analysed from the entire group there is a more marked reduction in responses to SKSD, PHA, and this reduction is further enhanced by acute plasma.

In an effort to assess the effect of acute SLE plasma on control lymphocytes, lymphocyte transformation was tested on 6 control patients (to insure absence of HLA specificity in the response). The acute plasma did not exhibit lymphocyte cytotoxicity. All six controls were suppressed significantly below that of control plasma. Furthermore, suppression could be significantly enhanced by addition of full DNA at .1, 1, 10, and 50 Ug doses. These data (DNA anti DNA) imply that immune complexes modulate lymphocyte responses to T cell mitogens and antigen. As this is a significant new finding, it has been repeated several times. When fractions of acute serum were obtained from Sephadex G-200 the dominant suppressing fraction was found to be fraction III (approximately 60,000 m.w.). This latter material from acute SLE plasma (not found in non acute or control plasma) was found to (1) suppress lymphocyte transformation (LT) to SKSD and PHA on control as well as SLE lymphocytes in the presence of 20% plasma (normal), (2) promote and potentiate LT of normal lymphocytes in response to PHA in the absence of plasma, at lower doses, (3) inhibit LT to PHA at high doses.

Thus a serum factor approximately 60,000 m.w. in acute SLE plasma has been shown to augment or inhibit normal LT and to promote LT in the absence of serum. As both MIF and SIRS have molecular weights in this range, current studies are in progress to compare this factor with both SIRS and MIF generated from SLE spleen cells.

Papers are currently in preparation on the above results as follows:

1. Lymphocyte Transformation in SLE.

2. Effect of DNA anti DNA complexes on Lymphocyte Transformation in SLE.

3. Detection of serum potentiating, and suppressing factor in acute SLE plasma.

Phagocytosis - An assay for phagocytosis has been set up using C14 labelled Staphylococcus albus as the indicator system. The assay is performed by a tube method and currently attempts to automate it using either a MASH harvester system, or a millipore filter system are in progress. Once the above system has been standardized, it will be applied to the assessment of phagocytosis in acute SLE patients and controls.

Urine Proteins:

Proteins in urine were quantitated by reacting dilutions of urine with antisera to IgG transferrin and kappa and lambda immunoglobulin light chains. Urines from 110 patients with various rheumatic diseases were tested; in 30 SLE patients serial studies were performed. The proteins measured ranged from molecular weights of 20,000 for the light chains to 150,000 for IgG. All of the proteins were detected in urines with proteinuria of 2+ on dipsticks (which detect albumin). The smaller proteins were detectable in some unconcentrated urines from SLE patients with no dipstick proteinuria. Presence and levels of the proteins usually correlated with disease activity. Some patients with nephritis continued to excrete even the larger proteins while in remission; however, while their disease was active, greater concentrations were spilled.

In patients without nephritis, some of whom excreted only the smallest proteins measured, urinary proteins were detectable at low levels during exacerbations and were undetectable while the disease was under control. Since the presence of the small proteins in the urine can reflect renal tubular damage of a mild degree, measurement of these provides a useful test for the detection and diagnosis of SLE exacerbations even the absence of documented nephritis or proteinuria measurable by traditional methods. The studies on the urinary proteins is continuing and a publication is planned in the near future that will document the above findings.

Immune Complex Detection:

An assay for the measurement of immune complexes is being developed using the C1q precipitation test. In this assay, C1q is labelled with 125-I. The labelled C1q binds to immune complexes, and when bound, is precipitable and quantifiable with polyethylene glycol. We have isolated pure C1q on several occasions and have produced large quantities of a monospecific antiserum to it in a sheep. We are in the process of preparing sufficient C1q to perform the assay. In addition, we have observed that immune complexes can be precipitated in polyethylene glycol without the need for adding radioactively labelled material, and are developing methods of quantitating these by measuring their protein, immunoglobulin and C1q contents by immunodiffusion and quantitative immunofluorometry.

Funds Utilized in FY 77: Funded (Supplies), $13,440.00. Utilized (Supplies $13,440.00.

Funding Requirement in FY 78:

We will require continuing funding of this project as an essential component of the Rheumatology and Clinical Immunology Service fellowship program as it integrates cellular and humoral immune mechanisms in the pathogenesis of disease. Techniques are being developed for cellular assays

and for such protein isolation and identification techniques as Sephadex and ion exchange chromotography, isoelectric focusing, and polyacrylamide gel electrophoresis. Some of the equipment for this is now on hand; expendable supplies and chemicals need to be purchased on a continuing basis. As there is now an increased TDA to provide 4 staff, including a Ph.D., there is an increasing emphasis on research in our service.

Several new pieces of equipment are needed to support this protocol and its companion # 3103.

1) An automatic sample preparation unit is required to enable the laboratory to keep pace with an increasing number of specimens used in radioimmunoassays, including DNA binding assays and in the near future, immune complex assays with C1Q. At present, we are performing 100 such tests each week. This requires three full days of a technician's time each week. The unit requested (Packard PRIAS system) will automatically dilute, deliver and transfer the samples and will reduce the technician time to less than one day per week for an even larger number of samples. Thus the unit will not only allow an increase volume of samples to be processed but will free the technician for other tasks. As we are performing some of these assays at the requests of physicians at WRAMC and other military hospitals, the unit will allow the laboratory to answer these requests in a more timely manner than has been possible during the past year, and to send results to the physicians without undue delay.

2) An LKB Multiphor Electrophoresis unit is needed to allow the performance of isoelectric focusing and other techniques in a horizontal plane. Some protein isolation procedures enumerated in this protocol will be enhanced by the use of this newly available piece of equipment.

3) A 2000 volt Power Supply is required for the performance of isoelectric focusing and high voltage electrophoresis for protein purification. Our present power supply (500V) is inadequate for these methods.

4) A refrigerated constant temperature circulator is required for the operation of our existing electrophoresis apparatus and the Multiphor referred to above.

Personnel:	One GS-9, Step 8, Civilian Technician, 3/5 Time at $17,387.00 per year	$10,432.00	$10,432.00
Equipment:	Packard PRIAS Automatic Sample Preparation Unit	$11,000.00	
	LKB Multiphor Basic Unit and Electrophoresis Kit	620.00	
	LKB 2000 Volt D.C. Power Supply	1,750.00	
	Lauda Refrigerated Constant Temperature Circulator	800.00	
	Total Equipment	$14,170.00	14,170.00
Supplies:	Cellular Immune Testing		
	Radioisotopes	$3,500.00	
	Culture Media	500.00	
	Scintillation Fluid	450.00	
	Scintillation Vials	4,500.00	
	Glassware and Disposables	3,000.00	
	Total	$11,950.00	
	Humoral Immune Testing		
	Radioisotopes	$2,500.00	
	Chemicals	3,000.00	
	Antisera	2,500.00	
	Glassware and Disposables	2,000.00	
	Total	$10,000.00	
	Total Supplies	$21,950.00	21,950.00
Equipment Rental:	Water Deionizer	$200.00	200.00
Total Funding Requirement FY 78:			$46,752.00

Publications: None.

Type of Report: Interim

Date of Report: 5 July 1977.

Work Unit No.: 3125

Title of Project: Histocompatibility Antigens in Patients with Anterior Uveitis Spondyloarthropathies

Investigator:

Principal Investigator: LTC Oliver J. Lawless, MD, MC

Objective: Histocompatibility antigens have been linked with various disease processes including Ankylosing Spondylitis, Reiter's Disease, and Psoriatic Arthritis when accompanied by Spondylitis. In all these entities Anterior Uveitis may occur suggesting that the host response may be modified by genetic factors. A study of patients with Anterior Uveitis for presence of HL-A 27 will be undertaken.

Technical Approach: A HLA panel will be performed on all patients by the transplant laboratory using the Terasaki Technique.

Progress and Results: This project was commended and tests have been performed for us by COL Everett Spees Transplant Laboratory. The numbers to date are small and inadequate for statistical analysis.

Conclusions: The results to date despite low numbers, however, conform to those reported by others that HLA B27 is present in greater than 90% of those tested with Ankylosing Spondylitis and Reiter's Syndrome.

Funds Utilized, FY-76: None

Funding Requested, FY-77: None

Publications: None

Type of Report: Terminated - Insufficient patients with anterior uveitis were accrued to justify continuation of the protocol.

Work Unit No.: 3136

Title of Project: An Evaluation of An Oral Xanthone in an Inhibition of Allergen, Histamine and Exercise-Induced Bronchospasm

Investigators:

Principal: Paul M. Ehrlich, LCDR, MC, USNR

Associates: Richard Evans, COL MC
Laura Smith, MD

Objectives: To evaluate new bronchodilation manufactured by Syntex Corporation.

Progress and Results: Twenty adults asthmatic ages 17 to 50 years were studied by the Allergy-Clinical Immunology Service of Walter Reed Army Medical Center for the effects of an oral xanthone as prophylaxis of allergen and histamine-induced bronchospasm. During the course of the study it was decided to eliminate this evaluation of the drug in terms of its effect on exercise-induced bronchospasm.

While the clinical study was completed by 31 January 1977, the data, which was submitted to Syntex Corporation within 30 days of the completion, has not been statistically evaluated as of this date.

Because of the absence of any statistical analysis of the data, no decision as to the future of the drug has been made. No side effects were noted by the investigators and no apparent positive results with the drug were noted in "eyeballing" the data.

All unused drugs were accounted for and returned to the Syntex Corporation.

Conclusions: While the results of the drug study are not complete, the purpose served by doing this was and that is that the above investigators gained expertise in performing bronchial challenges.

Funds Utilized, FY-77: None

Funding Requirements, FY-78: None

Publications: None

Type of Report: Interim

Work Unit No.: 3137

Title of Project: *In Vivo* Effect of Heparin on Cell-Mediated Immunity

Investigators:

Principal: Arnold I. Levinson, MAJ MC

Associate: Richard Evans, III, COL MC

Objective: To determine if pharmacologic doses of heparin interfere with *in vitro* correlates of cell-mediated immunity.

Technical Approach: The assays described in the original protocol were to be employed in patients prior to and after receiving therapeutic doses of heparin.

Progress and Results: The protocol was approved by the local committees in January 1976, approved at the Surgeon General's Office, seven months later, but not funded until FY-77, 10 months after its approval locally. By this time, the priority of this project was downgraded. It also became apparent that processing of blood samples would become a logistic problem and the project was not started.

Type of Report: Terminated

Work Unit No.: 3138

Title of Project: Immunologic Mechanisms of Cutaneous Reactions to Inhalant Allergens

Investigators:

Principal: Richard deShazo, M.D. MAJ MC

Associates: Arnold I. Levinson, M.D. MAJ MC
Richard E. Evans, III, M.D. COL MC
Harold Dvorak, M.D.

Objective: The purpose of this study is to define the immunologic mechanisms responsible for untoward cutaneous reactions seen with the injection of inhalant allergens.

Technical Approach: The technical approach has previously been described in detail in the original protocol.

Progress and Results: Considerable progress has been made on this protocol during the last year. Approximately 40 patients have been studied and a total of 50 skin biopsies have been obtained. All of these biopsies have been studied by immunofluorescence and are presently being studied under thin section microscopy by Dr. Harold Dvorak, in Boston, Mass. Serum IgE levels and Ragweed RAST determinations have been done on the study group as well as several control groups. Skin testing as outlined in the original protocol has been performed in approximately 40 patients.

The study to date has determined that the immediate cutaneous reaction is indeed determinant on the presence of antigen specific IgE antibody in the patient's serum. Preliminary histological results suggest that the path ology seen is characteristic neither of a delayed hypersensitivity reaction or an Arthus Reaction. The present data suggests the possibility that the reaction represents an exaggerated form of the immediate wheal and flare reaction rather then a different reaction altogether. However, our inability to reproduce untoward reactions with intradermal injection of histamine suggests that some other, perhaps new mediator may be involved.

The presence of fibrinogen in numerous biopsy specimens necessitates evaluation of the part the coagulation system plays in these responses.

At the present time the large amount of data obtained during preliminary phases of this protocol is being analyzed. We feel sure that this data will be of great assistence in directing future study to further define the immunologic mechanisms operable in this reaction.

Conclusions: Preliminary data suggests that the late phase of the immediate cutaneous response seen on intradermal injection of inhalant allergens is dependant on the presence of antigen specific IgE in the serum of the patient. Histological studies suggest that the reaction may be an exaggerated form of the immediate cutaneous response. IgE and RAST determinations suggest that patients with late cutaneous allergic reactions have high antigen specific IgE.

Funds Utilized, FY-77: None

Funding Requirements:

Personnal:	No additional requirements	
Equipment:	No additional requirements	
Supplies:	Consumable	$2,000.00
Travel:		
Mission:		600.00
Consultant:	Dr. Dvorak	1,200.00
		$3,800.00

Publications: Presently being drafted

Type of Report: Interim-Renewal.

Date Prepared: 1 May 1976

Note: Major A. I. Levinson, MC, will be the new Principal Investigator for FY-78 to replace Major deShazo.

Work Unit No.: 3139

Title of Project: Immunologic Function of Human Tonsil and Adenoid Cells

Investigators:

Principal: Arnold I. Levinson, MAJ MC

Associates: Michael Johns, MAJ MC
Carol Marcks, MS

Objective: This study was designed to investigate, in comparative fashion, immunologic function of human tonsil, adenoid, and blood lymphocytes.

Technical Approach: The technical approach has previously been described in detail in our original protocol.

Progress and Results: In the first phase of this study, lymphoid populations in the tonsil and adenoids were determined. In contrast to the blood, tonsils and adenoids are primarily B-cell organs. We next examined the proliferative responses of tonsil, adenoid and blood lymphocytes. In general, all three tissues responded to the same peak doses of the mitogens Concanacallin A (Con A) and Phytohemagglutinia (PHA). Similar responses were noted to the antigen, Candida. In contrast, the peak response to the antigen, SKSD, occurred at a lower concentration in both tonsil and adenoid tissue than the peripheral blood lymphocytes.

Kinetic studies indicate that the peak response to PHA occurs later in tonsil and adenoid cells than in blood (5 days versus 3 days). The peak response to Con A occurs at the same time in all three tissues (3 days).

Conclusions: These preliminary studies have provided information on the lymphoid constitutents of tonsils and adenoid tissue. Functional assessment indicates that mitogen and antigen reactive cells are present, although the kinetics of their response differ from that of blood lymphocytes. It is likely that this difference is due to the smaller

number of T-cells in the tonsils and adenoids. Future studies on purified populations of T-cells from tonsil, adenoid and blood will investigate this possibility. Lymphocytes reactive to SKSD, an antigenic determinant of the streptococcal organism, were found in tonsil and adenoid tissue. Thus, patients with recurrent tonsillitis have cells reactive to the specific infecting organism at the focus of infection as well as in their peripheral blood.

Funds Utilized: $529.00

Funding Requirements:

Personnel: One GS-07 Technician for 30 weeks

Equipment: No new equipment needed

Supplies: Consumable		$ 5,000.00
Travel: Conference		600.00
Mission		650.00
	TOTAL:	$ 6,250.00

Type of Report: Interim

Work Unit No.: 3140

Title of Project: Hyposensitization: Long Term Sequelae

Investigators:

Principal: Arnold I. Levinson, MAJ MC

Associates: Richard Summers, LTC MC
Marc Stein, MAJ MC
Richard Evans, COL MC

Objective: The purpose of this study was to determine if chronic allergen hyposensitization therapy is associated with late sequelae.

Technical Approach: Details of the technical approach were outlined in the original protocol.

Progress and Results: To date we have examined 45 patients on long term immunotherapy and 25 control subjects. The groups are compatible from the standpoints of age, race, sex, and disease durations. Based on a complete history and physical examination, as well as extensive laboratory evaluation, we can say that chronic hyposensitization is not attended by adverse clinical or laboratory sequelae. These results were recently presented at the American Academy of Allergy (March 1977).

Conclusion: Chronic hyposensitization does not appear to be attended by long term adverse clinical sequelae. We would like to extend the study to include more patients.

Funds Utilized, FY-77: $957.00

Funding Requirements (FY-78):

Personnel 20 hours of GS-07 Technician time/week for 52 weeks

Funding Requirements (FY-78) Cont.

Supplies (Consumable)		$ 3,500.00
Travel : Presentation of paper		650.00
Mission		600.00
	TOTAL:	$ 4,750.00

Publications: Levinson, A.I., Summers, R., Evans, R., III, et al. Late Sequelae to Long-Term Hyposensitization. Am Acad of Allergy, March 1977.

Type of Report: Interim

Work Unit No: 3141

Title: A Multiclinic Long Term Comparative Efficacy and Safety Study of Albuterol Versus Isoproterenol Nebulizer Solution(by Hand-Bulb Nebulization) in the Treatment of Reversible Obstructive Airway Disease in Adults.

Investigators:
Principal: Richard W. Huss M.D. MAJ MC
Associate: Richard Evans M.D. COL MC
Richard Summers M.D. LTC MC

Objectives: 1. To determine the efficacy, safety and tolerance of albuterol nebulizer solution when administered by hand-bulb nebulization for six months in patients with reversible airway disease. Clinical efficacy and safety will be monitored.
2. To determine the spectrum and frequency of side effects which may be associated with chronic treatment with albuterol nebulizer solution delivered by hand-bulb nebulization.
3. To determine whether the magnitude and duration of bronchodilation is maintained when albuterol nebulizer solution delivered by hand-bulb nebulization is used regularly for six months.
4. To compare the effects of albuterol with those of isoproterenol nebulizer solution.

Technical Approach: the patient comes to the clinic in the morning having taken none of his medications. He then administers ten inhalations of the drug(either albuterol or isoproterenol). Observations are made over the next six hours to include heart rate and blood pressure and pulmonary function tests. A lead II rhythym strip is obtained and chest auscultation is periodically done.

Progress and Results:

Fifteen patients between the ages of 18 and 60 were enlisted for this study.. The study got underway in May 1977 and the first patients thus are planned to complete the study in November 1977. It is expected that all patients will have finished by March 1978. Two patients had to be dropped from the study after four months because they have moved from this area.

The study drug is maintained and dispensed by the pharmacy.. Thus far no one has had any significant drug intolerances. All patients remain on the full dose of ten inhalations four times daily.

Since this is a double-blind study no results have yet been analyzed. Thus far as a group all patients seem to be doing as well as or better than when they started the study with regard to their asthma.

Conclusions: 1. All patients seem to be tolerating their study drug well.
2. We expect all fifteen patients to complete this study by March 1978.

Funds Utilized FY-77: there has been no costs to Clinical Investigation Service WRAMC.

Funding Requirements FY-78
Personnel: No additional personnel will be required
Equipment: No additional equipment will be necessary
Supplies: Consumable: none
Travel: Mission $1000

Publications FY-77: None

Type of Report: Interim

Work Unit No.: 3143

Title of Project: Biologic (Skin Testing) Potency of Allergenic Extract Reference Preparations.

Investigators: Richard Evans, COL MC
Harold Baer, Ph.D.

Objectives: To establish a biologic potency for comparison with *in vitro* potency testing of four different allergenic extracts, prepared by the FDA, Bureau of Biologics, and intended for use as US reference standards.

Technical Approach: Allergenic extracts of short ragweed, Timothy grass, white oak tree and birch tree, prepared and lyophilized by FDA, are resuspended in buffer diluted and used for serial titration skin testing in allergic volunteers. In addition, whole blood is drawn from the volunteers and tested for *in vitro* antigen induced leukocyte histamine release and serum specific IgE antibody by the RAST procedure.

Progress and Results: To date serial titration skin testing has been completed in four oak pollen sensitive patients, 13 Timothy, six ragweed and three birch tree sensitive patients. Variation in endpoint titration has not been more than 100 fold with the exception of ragweed where one patient was a 1000 fold more skin sensitive than was the least reactive patient. Leukocyte histamine release and RAST assays are in progress on these patients.

Conclusions: This protocol is progressing well. It should be continued until the goal of at least ten patients in each category is reached.

Funding Requirements, FY-78:

Personnel: One GS-07 Technician for 20hrs/week for 20 weeks

Supplies: Radioisotopes and other consumable supplies $6,000

Type of Report: Interim

Work Unit No.: 3144

Title of Project: Neurophysiologic, Immunologic and Biochemical Aspects of Bronchial Asthma

Investigators:

Principal: Richard Evans, COL MC

Associates: Laurie Smith, MD
Richard Summers, LTC MC

Objectives: 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 brnochial challenge. The following tests will be performed at NIH:

1) *Oral aspirin challenge*

2) Eccrine sweat responses to saline mecholyl and propranolol

3) Cutaneous blood flow by means of Xenon disappearance from an injected site

4) Pupillometry to measure pupil responses to Carbachol and Phenylephrine

5) 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/O_2

2) Histamine bronchial challenge with air and He/O_2

Note: Certain equipment must be expanded and modified.

Progress and Results: Currently we have been in the process of acquiring critical equipment for the study. Patients have been interviewed and two patients have been scheduled for study in late July. (The studies had to be postponed until then because of grass pollen season. At NIH six normal volunteers have been interviewed, and have gone through one or more of the tests to be done at NIH.

Conclusions: This protocol warrants continuation for another year. It will provide important information about asthma and good training experience for allergy fellows.

Funds Utilized, FY-77: None

Funding Requested, FY-78:

Personnel: Part-time 1-2 day/week technical support in performing bronchial challenges

Supplies, Consumable: 750.00

Modification of Equipment: Addition of spirometry print out with interpretation capacity to current equipment. $ 11,135.00

Total: $ 11,885.00

Publications: None

Type of Report: Interim

Work Unit No.: 3145

Title of Project: A Fluorescent Test for Extractable Nuclear Antigen.

Investigators:

Principal: John A. Boice, MD, CDR, MC, USN.

Associate: Oliver J. Lawless, MD, LTC, MC

Objective: To establish a rapid reliable fluorescent assay for the diagnosis of mixed connective tissue disease.

Medical Application: At present the diagnosis of mixed connective tissue disease (MCTD) necessitates serologic confirmation by a hemagglutination test for extractable nuclear antigen (ENA). This test is difficult to perform due to the need to extract pure ENA from crude calf thymus tissue. A fluorescent test will avoid the need for calf thymus tissue. KB cells, another source of ENA, moreover, can be purchased commercially and stored frozen until needed. The availability of a fluorescent assay would make this diagnostic test readily available to all facilities instead of only the few centers which now perform the hemagglutination test.

Methods: Sera from 24 MCTD patients, 14 SLE patients, 3 PSS patients, and one rheumatoid arthritis patient were randomly arranged by double blind technique. Utilizing test Sera known to contain only RNP (kindly supplied by Dr. Gordon Sharp), it was determined that a RNase concentration of 30 mg % was the most appropriate strength. The samples were then run both prior to and after digestion with RNase utilizing the Virgo Slide kit from Electronucleonics, Inc. Several of the Sera were also sent to Dr. G. Sharp for determination of ENA titers by hemagglutination assay.

Preliminary results indicate that digestion with 30 mg% RNase eliminates that percentage of FANA which is attributable to RNP. Final statistical correlations awaits the results from Dr. Sharp.

Conclusions:

1) The fluorescent antibody test can be modified to give meaningful data on the specific antibodies which react with the nuclear constituants by pre-digesting the slides with RNase.

2) Preliminary data indicate that these results correlate with those utilizing hemagglutination assay.

3) Further samples need to be tested to achieve greater statistical significance.

Funds Utilized FY 77: None

Funding Requirements FY 78:

Personnel:	None	
Equipment:	None	
Supplies:	Virgo FANA Kits	$1,000.00
	RNase	100.00
	Total:	$1,100.00

Type Report: Interim.

Date of Report: 1 July 1977.

Work Unit No.: 4102

Title of Project: Study of the Relationship Between Growth Pattern and Lymphangetic and Vascular Involvement in Women with Stage IA Cervical Cancer.

Investigator:

Principal: Robert C. Park, COL, MC

Associate: Samuel Goodloe, LTC, MC

Objectives: The objective of this study is to determine the motive spread of squamous cell carcinoma of the cervix.

Technical Approach: Patients are receiving surgery and histologic examination of tissues removed in a defined manner in order to gain maximum information from studying of the growth of this tumor.

Progress & Results: This study has been closed. Thirty-two patients were entered by Walter Reed and 367 from the entire GOG. Final results are being tabulated and a GOG paper will be forthcoming.

Conclusions: Patients with stage IA cervical cancer whose diagnostic conization has margins free of tumor can be safely treated with simple hysterectomy.

Funding Requirements: No local funds were necessary as this is a Gynecologic Oncology Group funded protocol.

Publications: Microinvasive Carcinoma of the Cervix, Obstetrics and Gynecology Vol. 48, No. 5, November 1976

Type of Report: Completed

Work Unit No.: 4104

Title of Project: Post-Operative Treatment of Women with Stage III Ovarian Cancer by Radiotherapy or Chemotherapy Either Alone or in Both Sequences.

Investigators:

Principal: Robert C. Park, COL, MC

Associate: Bernard Percarpio, MAJ, MC and Johannes Blom, MD

Objectives: The objective of this study is to determine whether radiotherapy or chemotherapy is better in treating patients with advanced carcinoma of the ovary.

Technical Approach: Patients will be randomized between radiotherapy or Alkeran either alone or in sequence of one following the other.

Progress & Results: This study has terminated. Walter Reed has 11 patients entered, and 340 from the entire GOG. The data is being reviewed, and will lead to a GOG publication.

Conclusions: Radiation therapy alone is less effective in patients with stage III ovarian carcinoma than chemotherapy alone or chemotherapy and radiation combinations.

Funding Requirements: No local funds are required since this is funded thru the Gynecologic Oncology Group.

Type of Report: Completed

Work Unit No.: 4106

Title of Project: Post-operative Treatment of Women with Resectable Ovarian Cancer with Radiotherapy Alkeran or No Further Treatment.

Investigators:

Principal: Robert C. Park, COL, MC

Associate: Johannes Blom, MD and Bernard Percarpio, MAJ, MC

Objectives: To determine the best approach to possible treatment of patients with Stage IA and IB ovarian cancer.

Technical Approach: Post-operative patients with ovarian cancer Stage IA and IB which is totally removed will be treated with either radiotherapy, chemotherapy or no further treatment.

Progress & Results: Sixteen patients have been entered from Walter Reed, and 136 from the entire GOG. This protocol is still active, but will conclude within the next year.

Conclusions: At the present time there seems to be no differences in the three treatment arms.

Funding requirements: No local funds are required in this protocol since it is funded thru the Gynecologic Oncology Group.

Type of Report: Interim

Work Unit No.: 4112

Title of Project: Diagnosis and Pretreatment Evaluation of Benign and Malignant Uterine Abnormalities Using the Operating Hysteroscope.

Investigators:

Principal: Donald A. Simsen, COL, MC

Associate: Robert C. Park, COL, MC and Warren E. Patow, COL, MC

Objectives: To determine the usefulness or lack of same of the hysteroscope in detecting uterine abnormalities.

Technical Approach: A hysteroscope utilizing dextran solution will be used to visualize the inside of the uterus, by a trans-cervical approach.

Progress & Results: Initiation of the project was originally delayed because the dextran solution which is used to distend the uterus for visualization was not released by the F.D.A. Subsequently, it became generally accepted that in the presence of known or strongly suspected intrauterine cancer, hysteroscopy may be hazardous because of the possibility that malignant cells could be disseminated during the procedure. Although such an occurrence has never been reported the theoretical chance of its happening constitutes a relative contraindication for hysteroscopy when intrauterine malignancy is suspected.

Conclusions: The present project, which was never initiated, should be modified. The most convenient format is termination, with future submission of a revised application for Clinical Investigation project.

Funds Utilized: FY 77- None

Funding Requirements: FY-78 - None

Publications: None

Type of Report: Terminated

Work Unit No.: 4113

Title of Project: Cooperative Gynecologic-Oncology Group

Investigators:

Principal: Robert C. Park, COL, MC

Associate: Warren E. Patow, COL, MC, Michael K. Kowalski, MAJ, MC, Samuel Goodloe, LTC, MC, Bernard Percarpio, MAJ, MC, and Johannes Blom, MD

Objectives: The Walter Reed section of Gynecologic Oncology is involved with the nationally organized Gynecologic Oncology Group, which contains 40 of the major medical centers in the country who are interested in the area of Gynecologic tumor treatment.

Progress & Results: WRAMC is active in 16 protocols involving treatment of ovarian carcinoma, cervical carcinoma, adenocarcinoma of the endometrium, and uterine sarcoma. To date over 600 patients have been registered in this group from WRAMC, and 115 have been placed in specific protocol studies.

Funding Requirements: No local funding is requested as this group is supported by the NCI thru Jefferson University of Philadelphia.

Type of Report: Interim.

Work Unit No.: 4116

Title of Project: 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.

Investigator: Henry Klapholz, MAJ, MC

Associate: Frank C. Miller, LTC, MC and Helen Skiba, RN

Objectives: To determine how the systolic time intervals of the fetus may be predictive of early fetal distress in the antepartum and intrapartum period. The establishment of normal values of pre-ejection period and the manner in which it varies with rate, gestational age and conditions of asphyxia will be determined.

Technical Approach: This will be done by external heart monitoring and doing fetal heart ultrasonography to intergrate these factors on a multiple channel recorder along with maternal heart beat and maternal blood pressure to evaluate the impact of these various factors.

Progress & Results: Twenty patients have been studied in the intrapartum period using the described technique. Pre-ejection period has been computed for from 5 to 20 cardiac cycles per patient. This work has been done on patients who exhibited no evidence of fetal distress in order to determine the range of normals that might be encountered at all gestational ages. The study has focused on term infants 36 to 43 weeks so far.

Conclusions: The interim conclusions based on the twenty studied patients is that the pre-ejection period (PEP) does not correlate well with rate (R-R interval of the preceding cardiac cycle). It is likewise not statistically different among fetuses of different weights and gestational ages. In fetuses that exhibit normal fetal heart rate patterns in labor with no evidence of periodic decelerations and normal amounts of baseline variability of heart rate, a PEP of from 60 to 80 may be within normal and cannot be used as a measure of response to hypoxia.

Funding Requirements: In order to continue the present work and extend it to the asphyxiated fetus (i.e. the ones that show fetal distress patterns in labor) it is expected that Ms. Christine Grapsas will be required to continue handling the large amounts of data that are collected and then fed into the computer for analysis.

Type of Report: Interim

This data will be presented to the Armed Forces District Meeting in New Orleans in October 1977 as per the enclosed abstract that has been accepted.

Work Unit No.: 4124

Title of Project: Fetal Intensive Care Monitoring in a Long-Range Continuing Project

Investigators:

Principal: Henry Klapholz, MAJ MC

Associates: James Haddock, MAJ MC
Norman Neches, MAJ MC

Objectives: The objective of this research is to evaluate the usefulness of fetal monitoring and labor in detecting early fetal distress and abnormal fetal heart rate patterns. Beginning 1 July 1974 an increased effort was made to monitor all labor (where feasible) utilizing electronic clinical fetal monitoring equipment. A work sheet is completed on each patient and all the FHR tracing are being reviewed. To date the clinical correlations between normal FHR and good 1 & 5 minute Apgar scores has been excellent. Currently work is being done to develop and test a standard code sheet which may be utilized with a computer.

Progress and Results: A form has been developed that enables us to record and summarize the fetal monitor data for each patient. This has shown to be an inefficient, error prone method of permanently recording fetal heart rate data. It will be the continued objective of this study to develop an automated system using high speed digital computer and analogue to digital conversion techniques that will summarize the results of many hours of fetal monitor data and produce a document containing this data for the chart. In addition, such data will be easily retrievable for study purposes. The criteria for what constitutes fetal distress and the algorithm that will determine how best to summarize such large quantities of data to give an accurate picture of the labor will be developed. The new hospital is being equipped with a computer for the OB-GYN Service and this will form the basis for our research effort. Data from all bedside fetal monitors will be analyzed on line and techniques for summary will be optimized.

Funding Requirements: It is expected that as this project advances a clinical research secretary will be required to collect and process the accumulated data. The services of a computer programmer (FORTRAN) will be required on a half time basis to augment the programming talent in the Department of OB-GYN (Drs. Klapholz and Neches)

Type of Report: Interim

Work Unit No.: 4126

Title of Project: The Clinical Evaluation of a Rapid Method for Presurgical Cleansing of the Hands.

Investigators:

Principal: Frank C. Miller, LTC, MC

Associates: Lawrence Decker, MAJ, MC, John Read, MAJ, MC
Arthur Gross, COL, DC and Duane Cutright, COL, DC

Objectives: To compare the effectiveness of a 90 second pulsed jet hand and forearm wash with a standard 10 minute presurgical scrub.

Progress & Results: The evaluation of a new rapid method of presurgical cleansing of hands has been done at the United States Army Institute of Dental Research. The purpose of this exhibit is to compare the effectiveness of a 90 second jet wash method to the standard 10 minute presurgical scrub in a clinical setting.

Interns, residents, and staff of the Department of OB-GYN of the Walter Reed Army Medical Center submitted fingertip cultures before and after five 90 second jet washings and five 10 minute traditional scrubs. Each jet wash and each traditional scrub was the first hand wash procedure of that day. Each participant served as his or her own control. The results revealed the 90 second jet wash more effective in cleansing the hands of bacteria than the 10 minute standard scrub. The jet wash offers distinct advantages in the amount of time saved, the standardization of cleansing, and reduced skin irritation.

Conclusions: The study has been completed. The results have been submitted for publication in the American Journal of Obstetrics and Gynecology. A copy of the paper is enclosed. In addition,a documentary film has been made of the procedure. The film has been shown in a scientific exhibit at the Armed Forces Obstetric and Gynecology Meeting in Los Vegas in September 1976. The association of Military Surgeons Meeting in San Antanio. The Annual Clinical Meeting of the American College of OB-GYN in Chicago in May and at the Annual Clinical Meeting of the AMA in June in San Francisco.

Type of Report: Interim

Work Unit No.: 4129

Title of Project: Antepartum Fetal Evaluation of Noise Evoked Fetal Heart Rate Response as an Indicator of Fetal Well Being

Investigators:

Principal: James Haddock, MAJ MC

Associates: Warren E. Patow, COL MC
Henry Klapholz, MAJ MC

Objectives: To study the evoked heart rate patterns after the fetus is subjected to intrauterine sound stimulation at various intensities and relate the heart rate pattern response to fetal outcome.

Progress and Results: Fetuses were subjected to intrauterine sound stimulation at various intensities to pulsed sine-wave sound. Fetal heart rate reactivity as indicated by acceleration in fetal heart rate after exposure to sound was correlated to eventual fetal outcome. These fetuses were also subjected to the standard oxytocin challenge test and the results of these tests were compared to the fetal sound reaction pattern.

It was found that all fetuses that exhibited reactive sound stimulation patterns has negative oxytocin challenge tests. All these fetuses delivered in good condition. Those fetuses that did not appear to react to sound did well in general but a few had positive oxytocin challenge tests. It was concluded that a positive sound stimulation test may obviate the need for a formal oxytocin challenge test although more patients would have to be studied to assure this with greater certainty.

This study will continue in an attempt to build up a larger volume of patients since the importance of a negative oxytocin challenge test is still primary in the management of high risk patients.

Type of Report: Interim

Presentations: Armed Forces District Meeting of the American College of OB-GYN, Las Vegas, Nevada, September 1976.

Work Unit No.: 4131

Title of Project: Evaluation of Gonorrhea Screening in a Prenatal Population of Military Dependents

Investigators:

Principal: Patrick Duff, M.C. MAJ MC

Associate: Kenneth Kacenga, D.O., CPT MC

Objective: The purpose of the study is to evaluate the usefulness of routine screening for gonorrhea among prenatal patients from a cost-benefit perspective.

Progress and Results: The study was conducted from July 1, 1976 through October 31, 1976. 483 consecutive prenatal patients were entered into the study. Only one cervical culture was positive for gonorrhea. A detected incidence of 0.21%.

Conclusions: Based on a careful survey of the literature and the results of the present study, it is concluded that routine screening for gonorrhea is not a sound economic or medical decision for all populations of patients. A profile is developed that highlights the patient at high-risk for harboring asymptomatic gonorrhea. Recommendations are made for the judicious application of this profile to a selective screening program.

Funding Requirements: Travel expenses for the authors to present the paper at the Military District Meeting - ACOG in New Orleans, October 1977.

Personnel: None

Type of Report: Complete

Publications: (1) To be presented at the Military District Meeting in New Orleans in October 1977.

(2) To be submitted for publication of Obstetrics and Gynecology.

Work Unit No.: 4132

Title of Project: Prophylactic Antibiotics for Cesarean Section

Investigator:

Principal: Patrick Duff, M.D., MAJ MC

Associate: Kenneth Kacenga, D.O., CPT MC

Objective: The purpose of the study is to determine if prophylactic antibiotics are effective in decreasing the morbidity associated with Cesarean Section.

Progress: The study now is complete. Seventy patients were entered into the protocol. The data presently is being analyzed.

Conclusions: Awaiting analysis of data

Funding Requirements: Travel expenses for authors to present paper at Scientific Meeting.

Personnel: None

Type of Report: Interim

Work Unit No.: 4134

Title of Project: Treatment of Women With Cervical Cancer Stage II B, III B, IV A, and or Periaortic Nodes with Radiotherapy Alone Versus Radiotherapy Plus Immunotherapy (Intravenous C-Parvum) Phase II

Investigators:

Principal: Robert C. Park, COL, MC

Associates: Michael K. Kowalski, MAJ, MC and Bernard Percarpio, MAJ, MC

Objectives: Radiotherapy is the standard treatment for patients with advanced cervical carcinoma. The goal of this project is to determine if the addition of immunotherapy will enhance the radiation response rate.

Technical Approach: Patients are randomized by the closed envelope technique to one of two treatment regimens.

Progress & Results: This is a newly activated GOG Protocol. To date Walter Reed has no patient entries.

Conclusions: None at present.

Funding Requirements: No local funds are necessary as this is a Gynecologic Oncology Group funded protocol.

Type of Report: Interim

Work Unit No.: 4135

Title of Project: A Randomized Comparision of Melphalan Alone Versus Adriamycin and Cyclophosphamide Versus Hexamethylenamine and Melphalan in Patients With Ovarian Adenocarcinoma Suboptimal Stage III, Stage IV, and Recurrent Equivalent to Stage III and IV (Phase 3)

Investigators:

Principal: Robert C. Park, COL, MC

Associate: Michael K. Kowalski, MAJ, MC and Johannes Blom, MD

Objectives: Single alkalating chemotherapy agents produce a 50% response rate in patients with epithelial ovarian cancer. The objective of this study is to determine if adding Adriamycin or Hexamethylenamine will enhance the response rate.

Technical Approach: Patients are randomized by the envelope technique to 3 treatment arms.

Progress & Results: This is a newly activated GOG Protocol, to date Walter Reed has 6 patients entered. It is tooearly for statistical analysis. Hexamethylenamine is an investigational drug. To date there have been no adverse reactions observed in any of the GOG or Walter Reed patients.

Conclusions: None

Funding Requirements: No local funds are required in this protocol since it is funded thru Gynecologic Oncology Group.

Type of Report: Interim

Work Unit No.: 4136

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

Investigators:

Principal: Robert C. Park, COL, MC

Associate: Johannes Blom, MD

Objectives: Melphalan alone produces a 50% response rate in patients with epithelial cancer. The objective of this study is to determine if the addition of immunotherapy will enhance the response rate.

Technical Approach: Patients with optimal stage III epithelial ovarian carcinoma are randomized by the envelope technique to one of two treatment regimens.

Progress & Results: This is a newly activated GOG Protocol, to date Walter Reed has had no patient entries, and there is no statistical data at present.

Conclusions: None

Funding Requirements: No local funds are required in this protocol since it is funded thru the Gynecologic Oncology Group.

Type of Report: Interim

Work Unit No.: 4137

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)

Investigators:

Principal: Robert C. Park, COL, MC

Associate: Michael K. Kowalski, MAJ, MC, Bernard Percarpio, MAJ, MC and Johannes Blom, MD

Objectives: The standard treatment for patients with stage II ovarian carcinoma has been postoperative irradiation. Recent data supports that single alkylating chemotherapy is equally effective. The objective of this study is to determine if radiation alone, chemotherapy alone, or combinations of the two are the best treatment methods for this disease.

Technical Approach: Patients are randomized by the closed envelope technique to one of three treatment arms.

Progress & Results: This is a newly activated GOG - RTOG - RTOG - EECOG Protocol. To date Walter Reed has one patient entered, and there is no statistical data.

Conclusions: None at present.

Funding Requirements: No local funds are necessary as this is a Gynecologic Oncology Group funded protocol.

Type of Report: Interim

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WORK UNIT NO: 4501

Title: CLINICAL EVALUATION OF FLUORESCENCE SCANNING OF THE THYROID WITH AMERICIUM 241 SOURCE.

Investigators: Principal: M. C. Johnson, COL, MC
Associate: Robert J. Corcoran, MAJ, MC

PROGRESS & RESULTS:

Hyperthyroninemia may accompany subacute thyroiditis (SAT) in 10-30% of patients. When SAT is painless, the diagnosis may be erroneously ascribed to Graves' disease unless a radioiodine uptake (RAIU) is performed. In contrast to Graves' disease, the clinical course of the thyrotoxicosis of SAT is predictably self-limited. Serial Fluorescent thyroid scanning as a means of quantitating thyroidal content of stable iodine was performed in six patients with thyrotoxic SAT in an attempt to differentiate this disorder from Graves' disease and to gain further insight into the temporal relationship between serum T4, RAIU, and depletion and repletion of thyroidal iodine. Six previously untreated patients (4F, 2M; age range 35-61) presented with signs and symptoms of thyrotoxicosis. The syndrome was painless in four of the six patients. Initially, mean ($\pm$ SE) T4 averaged 18.9 $\pm$ 1.8 ug% and RAIU 0.7 $\pm$ 0.4%. All were treated symptomatically with propranolol but no thiourea compounds.

In clinical studies, normal subjects (n = 30) had an average thyroidal content (TI) of 10.1 $\pm$ 3.9 mg, while patients with untreated Graves' disease and elevated RAIU (N = 28) had mean TI of 24.4 $\pm$ 9.9 mg. In contrast, six patients with thyrotoxic SAT had a markedly decreased TI of 5.0 $\pm$ 1.8 mg, suggesting early depletion of hormonal iodine. During resolution of the thyroiditis (follow-up one to six months), serial measurements of TI remained low until after serum T4 fell to below normal, with subsequent increases in TSH and RAIU.

CONCLUSIONS: 1. The fluorescent scan and RAIU allow discrimination between thyrotoxic painless SAT and thyrotoxic Graves' disease. 2. TI is depleted early in SAT and repletion of glandular stores depends upon return of iodine trapping functions. 3. Fluorescent scanning permits accurate <u>in vivo</u> measurement of TI.

Funds utilized (FY 77) =

Funding requested (FY 78) = $1,500.00

Publications (FY 77)

EVALUATION OF A THYROID FLUORESCENT SCANNING SYSTEM OF CONCENTRIC SOURCE DETECTOR DESIGN, J Nuc Med 18:163-7 (77).

Work Unit No: 4502

Title of Project: Plasma Angiotensin Levels and Response to Antihypertensive Therapy in Essential Hypertension

Investigators:

Principal: Robert J Corcoran MD Maj MC

Associate: Jules Bedynek MD Col MC
Robert J Kaminski MD Maj MC

Objectives: To investigate the effect of various antihypertensives as thay may be related to angiotensin levels determined during the original evaluation of hypertensive patients.

Technical Approach: Patients referred to cardiology for evaluation of a hypertensive state will be placed on antihypertensive medications thought to be effective in "high" and "low" renin hypertension; their blood pressure response measured in this related to initial angiotensin levels

Progress and Results: During the past year seventeen patients were entered into the study This patient population was considered too small to make valid conclusions . It is encouraging to note that the test kits with modifications gave results that were in good agreement of those of Wallach and Dawson .It is anticipated that in the following year with vigorous followup that the study should be completed.

Conclusions: None to DATE.

Funding Requirements: $1,100 for supplies and medication

Publications : none

Work Unit No.: 4514

Title of Project: Clinical Evaluation of 111 Indium-DTPA

Investigators: M Merrill C. Johnson, MD COL MC
Robert J. Corcoran, MD COL MC

Progress and Results: A total of 25 radiocisternograms were performed on 18 patients during the past year. After review and correlation with clinical, pathological and radiographic findings, there were 15 positive results; 7 normal and 1 suspicious. 1 study was unsatisfactory. Since the inception of this study, a total of 36 patients have been studied with 27 positives; 11 negatives, 3 unsatisfactory and 1 suspicious. There were no false positives and no false negatives. The one suspicious study was also suspicious on computerized axial tomography. There were no cases of adverse reactions.

Conclusions: While it was expected that computerized axial tomography would supplant this methodology, such has not been the case. While CT scanning is particularly accurate in defining CSF spaces, it does not provide an answer to the question of what to do with the patient, once the answer is known. It is in estimating the CSF clearance capacity that the radiocisternogram is of most value. This has been clearly indicated in our small series where shunt patency has been correctly predicted and the value of shunts correctly ascertained.

Type of Report: Interim

Work Unit No: 4515

Title of Project: Clinical Evaluation of 99m Technetium Labeled Stannous Glucoheptonate as a Diagnostic Agent for Studying the Kidneys.

Investigator: Merrill C. Johnson, MD COL MC

Objective: To evaluate 99m Technetium Stannous Glucoheptonate as a diagnostic aid in study of renal blood flow dynamics.

Technical Approach: See approved protocol.

Progress and Results: During the past year nine patients has a total of eleven renal studies with 99m Tc Stannous Glucoheptonate as the imaging agent. The indications for examination were varied but included the evaluation of renal failure, abdominal mass lesions and transplant function This agent was found to be adequate for studying the dynamics of renal blood flow, however, it was particularly well suited for the detection of parenchymal abnormalities.

Conclusions: The series is too small to make any conclusions at this time.

Status: Interim Report

Work Unit No: 4516

Title of Project: Clinical Evaluation of 123 Iodine

Investigator: Robert J Corcoran MD Maj Mc

Objective : See original Protocol

Technical Approach: See Original Protocol

Progress and results: The clinical usefulness of 123 Iodine has been well established amd is no longef a Phase III Investigational Drug.

Type of Report: Terminated

Work Unit No: 4518

Title of Project: Clinical Evaluation of 99m Tc Electrolytically Labeled Human Serum Albumin

Investigator: Merrill C Johnson MD Col MC

Associate: Robert J Corcoran MD Maj MC

Progress and Reports: A total of 14 patients were evaluated with this radiopharmaceutical without adverse effects. All 14 patients were referred for shunt analysis. Shunts were correctly predicted in all patients when compared by angiocardiography. Shunt sizes were within ± 2% of those shown by other modalities. It is too early to make conclusions on the overall effectiveness of this method.

Conclusions: The total population studied thus far, prec des any definite conclusion. It is anticipated that in the next year, sufficent data will have been accumulated, allowing for a more precise analysis and corr lation with angiocardiography.

Type of Report; Interim

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.

Associate Investigator: Hans Blom, M.D. and Bernard Percarpio, M.D.

Objectives: To study the effects of differing irradiation volumes on the survival of patients with early staged Hodgkin's Disease.

Technical Approach: This clinical study was randomized comparing localized irradiation to clinically involved region to extended-field radiotherapy.

Progress & Results: An interim report was presented at the last meeting of all the participating institutions held in Chicago, July, 1976. While there were many more local recurrences in the patients receiving localized treatment, there were a few more deaths in the extended-field treatment group.

Entry of patients into this study was terminated in 1971. At the meeting mentioned above 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 at the outset.

Conclusions: To date, comparison of localized fields to extended-field therapy of early Hodgkin's Disease has not shown a clear superiority of either technique within the follow-up period so far achieved. The study suggests that extensions following extended field therapy may routinely carry a poor prognosis but that local extensions following local field therapy may not have this grave significance.

Funding Requirements:

a. Personnel: None
b. Equipment: None
c. Supply: None
d. Travel: $4,800

Publications:

1. Hutchison, George B., Progress Report. Hodgkin's Clinical Trial, 1972, National Cancer Institute Monograph, No. 36, International Symposium on Hodgkin's Disease, Pgs. 387-393.

2. Nichson, James J., Hutchison, G. B., Hodgkin's Disease Clinical Trial. Sixth National Cancer Conference Proceedings, 1968., pgs. 77-81.

3. Nickson, James J., Hutchison, G.B., Extensions of Disease, Complications of Therapy, and Deaths in Localized Hodgkin's Disease; Preliminary Report of a Clinical Trial. The American Journal of Roentgenology, Radium Therapy and Nuclear Medicine, Vol. CSIV, No. 3, March, 1972, pgs. 564-573.

Funding Requirements:

Authorized FY 77: $4,800

FY 78:

Travel: $4,800

Work Unit No: 5501

Title of Project: Incidence of Hemolytic Disease of the Newborn due to ABO Incompatibility (ABO/HDN) at Walter Reed Army Medical Center.

Investigators: Bobby F. Chaney, CPT, MSC
Ronald C. Vura, CPT, USAF, BSC

Objectives: To determine retrospectively, through the investigation of patient statistics, medical records and laboratory data, the incidence of ABO/HDN at WRAMC. Further, to compare this incidence with that reported in the literature.

Technical approach: The pediatric log book of births for the period 1 Sep 72 - 31 Dec 76 was correlated with the Blood Banks serology results for the same period.

Progress and Results: Clinical and Serological results for 2500 births have been recorded. Detailed analysis and correlation of results has not yet been concluded.

Conclusions: Pending completion of analysis of results.

Funds utilized FY 77: None

Funding requirements FY 78: None

Publications: None

Type of Report: Interim, Final Report to follow by 26 August 1977.

Work Unit No.: 6009

Title of Project: Clinical and Laboratory Investigation of Meningeal Leukemia

Investigators:

Principal: Frederick B. Ruymann, M.D., LTC, MC

Associates: Alan Mease, M.D., MAJ, MC
Askold Mosijczuk, MD, MAJ, MC

Objectives: Comparison of biochemical and immunological variables in the cerebrospinal fluid of patients with Acute Lymphocytic Leukemia under treatment with intrathecal methotrexate vs. intrathecal methotrexate and CNS irradiation

Technical Approach: Patients with leukemia under the direct and consultative care of the Pediatric Hematology/Oncology Section will be used as the primary source. Additional patients will be studied. Clinical histories, flow sheets, and summaries are already maintained by child and adult oncologists at present. Particular note will be made of the time of diagnosis, length of remission, past history of CNSL, and therapy for CNSL and type of prophylactic CNSL treatment. As new patients are acquired on #7411 they will be followed along. Spinal fluid and blood specimens will be obtained. Patients in clinical remission will have confirmatory bone marrow aspirated and spinal fluid analysis every two months. This consent will be obtained on all procedures. This protocol involves no procedures beyond those already recommended by ALGB.

Progress and Results: Use of the cytocentrifuge continues to be an extremely valuable diagnostic procedure in detecting the spread of malignancy into the subarachnoid space. Recently the main laboratory has acquired a cytocentrifuge and is also checking specimens done by our laboratory. The correlation has been good and this concomitant evaluation needs to be continued for only one year.

Conclusion:

(1) The value of cytocentrifuge prepared specimens has become well established and is approaching a routine laboratory capability

(2) Continue this project for one year until full histological interpretation is available in the Department of Pathology, WRAMC.

Funds Utilized FY-77: $550

Funding Requirements, FY-77:

Personnel: Doris Burgess, GS-9 technician

Equipment: None

Supplies: $450 reagents, histochemical stains, LDH, isoenzyme reagents

Travel: None

Publications: None applicable to this project

Type of Report: Interim

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
WRAMC-SWP-CCR	Work Unit # 6013, Evaluation of Four Modes of Therapy of Reyes Syndrome, Acute Encephalopathy with Fatty Infiltration of the Viscera: A Multi-Hospital Study.

TO THRU: C, Dept of Peds FROM C, Clin Invest Svc DATE 8 Mar 77 CMT 1

Dr. Boehm/jr/63266

TO: William J. Oetgen, MAJ MC

1. Information has been received in this office that the Principal Investigator of the above project is being reassigned.

2. Request that a new Principal Investigator be designated for the above project, or if the project will not be continued, this office be so informed.

3. Also request that the departing Principal Investigator furnish this office with an annual or final progress report prior to departing.

Richard Evans

RICHARD EVANS
COL MC
Chief, Clinical Investigation Service

10 April 1977

1. Information cited above is correct.

2. The new principle investigator will be Dr. Richard Gardner, Department of Pediatrics, WRAMC.

3. Progress Report: Since the activation of this protocol, there have been no new cases of Reye's Syndrome admitted to this study.

William J. Oetgen, M.D.

William J. Oetgen, M.D.
MAJ, MC
Department of Medicine

DA FORM 1 FEB 82 2496 REPLACES DD FORM 96, EXISTING SUPPLIES OF WHICH WILL BE ISSUED AND USED UNTIL 1 FEB 83 UNLESS SOONER EXHAUSTED.

☆ U.S. GPO: 1974—653-130/8858

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Work Unit No.: 6014

Title of Project: Granulocyte Transfusion in Children: A comparison of continuous flow centrifugation and filtration leukophoresis

Investigators:

Principal: Frederick B. Ruymann, M.D., LTC, MC

Associates: Alan Mease, M.D., MAJ, MC
Askold Mosijczuk, M.D., MAJ, MC
Mark Simpson, M.D , MAJ, MC

Objectives: The goal of this research is to compare two methods of granulocyte collection and subsequent transfusion in children. Comparisons of effects on donor and recipient are planned with specific investigations of granulocyte chemotaxis and other basic function studies.

Technical Approach: The basic method for granulocyte collection by continuous centrifugation are outlined in the attached publication. The method for filtration leukophoresis is outlined by the protocol and follows standard published methods. The experimental design involves sequential daily transfusions to an eligible patient using alternating collection methods from the same donor. Comparisons will then be made of donor reaction, recipient reaction, and granulocyte parameters as outlined by the protocol.

Progress & Results: Implementation of the filtration leukophoresis arm of the protocol was prevented by delays in civilian personnel branch, WRAMC. These administrative delays prevented adequate staffing of the WRAMC donor center. Using our IBM/NCI cell separator granulocytes were collected by continuous flow centrifugation and administered to approximately 15 eligible pediatric patients during the past year. In two-thirds of the patients infection was documented by a positive culture or chest x-ray. All patients survived three or more serial granulocyte transfusions. Although a non-random experience, these results support our earlier impressions, see attached article and recent articles in the NEJMED that granulocyte transfusion is highly efficacious in the neutropenic, immunosuppressed, febrile child who has persistent fever and/or documented infection despite several days of appropriate antibiotic therapy. Patients early in induction chemotherapy in whom marrow aplasia is present, are more likely to recover than those with resistent malignancy.

Conclusions: (1) Continued effort at solving personnel problems of the donor center will be made.

(2) Efficacy of granulocyte transfusion in the neutropenic, febrile child is apparent.

(3) Granulocyte transfusion utilizing the continuous centrifugation collection method will be continued until the filtration leukophoresis method can be implemented in the WRAMC donor center.

Funds Utilized, FY-77: $5,000

Funding Requirements, FY-78:

Personnel: Doris Burgess, GS-9

Equipment:

(1) Shaker water bath - $800

(2) Consummable supplies - $1,000

Travel: Training - $500

Publications: Granulocyte Transfusion therapy in children, Maybee DA, Milan, AP, Ruymann, FB. Southern Med Journal 70:320-324, 1977

Type of Report: Interim

WORK UNIT NO.: 6015

TITLE OF PROJECT: Assessment of Infant Immunity

INVESTIGATORS:

Principal: Edward W. Millunchick, MC

Associate: George Lowell, M.D.

OBJECTIVES: To determine the effect of infant lymphocytes on normal lymphocyte function.

TECHNICAL APPROACH: Laboratory methods including In-vitro lymphocyte cultures, solid phase radio immuno assay

PROGRESS: Techniques for obtaining, culturing and assaying cells have been developed. No co-culturing has been performed.

FUNDS UTILIZED, FY 77: $1320.79

FUNDING REQUIREMENTS, FY 78: None

PUBLICATIONS: None

TYPE OF REPORT: Terminated due to completion of fellowship. Dr. Lowell (WRAIR) will further research using the techniques developed and funds from WRAIR.

Work Unit No.: 6017

Title of Project: Clinical Studies in Thermometry

Investigators:

Principal: Lewis B. Harden, LTC MC

Associates: Robert Mesrobian, CPT MC
Doreen Roberts, R.N.
Virginia Leaper, LPN

Objective: To obtain data for the evaluation of routine procedures used in thermometry as presently practiced on pediatric outpatients. Specifically we are asking, "Can axillary temperatures be used in patients up to age 4 without loss of accuracy when compared to the rectal temperature?" A single use chemical thermometer is also being tested for accuracy at both axillary and rectal sites.

Technical Approach: A crossover design allows each patient to act as their own control while comparing axillary and rectal measurements. A rectal temperature taken at 3 minutes with a glass reference thermometer serves as the standard for comparison of values. Axillary temperatures with a glass reference thermometer and both axillary and rectal measurements with the single use thermometer are then analyzed for variation from the standard.

Progress and Results: Such wide variation in results at the axillary site led to extension of the axillary time to 5 minutes. Approximately 100 observations are complete and a wait statistical analysis.

Conclusions: Until the statistical analysis is available conclusions are uncertain. The axillary site in this age group appears to be unreliable when compared to the rectal site. The single use thermometer duplicated the glass reference thermometer values at all sites.

Funds Utilized, FY-77: None

Funding Requirement, FY-78: None

Personnel: $200.00 Secretarial Expenses

Equipment and Supplies: None

Travel: $500.00 Anticipated travel for presentation of results as nursing scientific meeting by Doreen Roberts, RN

Other: $250.00 for independent Statisfocal Analysis

Total: $950.00

Publications: None to Date

Type of Report: Annual

Work Unit No: 7105

Title of Project: Study of CEP Responses in Pediatric Epileptic Patients Before and After Withdrawal of Anticonvulsants

Investigator:

Principal: Archer D. Huott, COL MC

Objectives: To develop technique for prediction of favorable prognosis regarding pediatric epiletic patients after anticonvulsant drug withdrawal.

Technical Approach: This study is essentially a comparison of a child's prior CEP's before and after withdrawal of anticonvulsant drugs in those epileptic patients meeting the following criteria:

(a) Onset of idiopathic epilepsy afebrile seizures below the age of 12.

(b) Freedom of minor or major seizures for a period of two years.

(c) Normal awake EEG with sleep, hyperventilation, auditory and stroboscopic activation.

It is felt that by such a study those patients who will eventually relapse will be detected early enough to reinstitute therapy and prevent the resumption of clinical seizures.

Progress and Results: The past year has been spent debugging currently present equipment. Data acquisition on our equipment is unsatisfactory for compilation at A.F. F. R.I., is currently being installed to use in this project.

Digital computer on loan from A.F.F. R.I. was incompatible with our soft ware, therefore study was abandoned during this year. Our on Line Computer arrives June 1977.

Funding Requested, FY-78: None

Publication - FY-77: None

Type of Report: Interim

Work Unit No. 7108

Title of Project: Visual Evoked Responses in the Diagnosis of Multiple Sclerosis.

Investigators:

Principal: Archer D. Huott, COL, MC

Objectives: To arrive at an objective criterion for retrobulbar neuritis.

Technical Approach: Flashes of light are presented to each eye independently and patient's CEP from recording electrodes over the occiput are analyzed by computer technology.

Progress and Results: None. Past year spent acquiring additional apparatus and equipment necessary to insure an artefact-free recording. Newly arrived equipment should eliminate these problems.

Conclusions: None.

Funds Utilized: None.

Publications: None.

Type of Report: Final. This "research project" is now considered a clinical test and therefore request termination of study.

Work Unit No. 7109

Title of Project: The Application of Somatosensory Spinal Evoked Response in Spinal Cord Pathology.

Investigator: Archer D. Huott, COL, MC

Objectives: To correlate clinical and evoked level of lesion with finding at operation. Also to obtain normative data.

Technical Approach: Somatosensory input in the form of electrical shocks to the nerves of the leg and pickup of these potentials over the spinal cord at various levels and also over the samatosensory cortex. This analysis utilizes computer technology.

Progress and Results: Digital computer on loan from A.F.F.R.I. was incompatible with our soft ware, therefore study was abandoned during this year. Our on Line Computer arrives June 1977.

Funding Requirements: FY-78: None.

Publications: None.

Type of Report: Interim.

WORK UNIT NO: 7110

TITLE OF PROJECT: System Analysis Applied to Clinical Neurology

PRINICPAL INVESTIGATOR: Darrell S. Buchanan, MD, COL, MC

PROGRESS AND RESULTS: This project is terminated. NIH funding could not be obtained for basic project which was to be performed at civilian facilities.

FUNDS UTILIZED (FY-77): None.

FUNDS REQUESTED (FY-78): None.

PUBLICATIONS (FY-77): None.

TYPE OF REPORT: Terminated, due to lack of funding.

WRAIR UNIT NO: 7150

TITLE OF PROJECT: Systematic Relaxation Training and Its Use as a Self-Control Skill

PRINCIPAL INVESTIGATOR: E. Thatcher Beaty, 1LT, MSC
ASSOCIATE: James Siebold, CPT, MSC

OBJECTIVES: To compare the relative efficacy and long-term benefits of systematic relaxation training and EMG biofeedback.

TECHNICAL APPROACH: Individual instruction in relaxation or biofeedback. Assessment will be made with both self-report and physiological measures.

PROGRESS AND RESULTS: This research protocol was approved by my doctoral dissertation committee on 20 June 1977. I am being reassigned to a new duty station in August 1977. There was not sufficient time remaining between the date of committee approval and my date of departure to complete this study. Therefore, this study is being terminated at WRAMC, and will be completed at my next duty station.

CONCLUSIONS: Pilot work suggests that systematic relaxation and EMG biofeedback training are equally useful in the control of tension and anxiety, as assessed by both subjective and physiological measures.

FUNDS UTILIZED (FY-77): None.

FUNDS REQUESTED (FY-78): None.

PUBLICATIONS (FY-77): None.

TYPE OF REPORT: Terminated.

WORK UNIT NO: 7151

TITLE OF PROJECT: Cognitive Components of Interpersonal Functioning in Brain Damaged Adults

PRINCIPAL INVESTIGATOR: David H. Edwin, Graduate Student
Psychology Department, University of Maryland

OBJECTIVES: The purpose of this study is to develop a psychometric tool for assessing the cognitive components of interpersonal functioning which may be impaired in brain damaged adults. Specifically, the aims of the research are threefold:

1. To develop an alternative scoring system for the Picture Arrangement subtest of the Wechsler Adult Intelligence Scale (a standardized test of intelligence) that will identify and differentiate cognitive processes believed to be basic to interpersonal functioning.
2. To understand the nature of impairment in social cognition by comparing brain damaged and non brain damaged populations.
3. To compare and discriminate between different kinds of difficulties in social cognition evidenced by stroke patients with right hemisphere brain damage as contrasted with patients with left hemisphere brain damage.

TECHNICAL APPROACH: Individuals participating in the study will include three groups of hospitalized patients:

1. left hemisphere acute CVA patients,
2. right hemisphere acute CVA patients,
3. non brain damaged medical patients matched for age and socio-economic status with the two brain damaged groups.

The criteria for localization of lesions are worked out with the neurologic co-investigator. A minimum level of performance across the Wechsler Scales is necessary for inclusion in the research sample. Further, it is necessary that subjects show no evidence of cortical damage other than that related to their inclusion in the sample. Finally, subjects must have no history of severe psychiatric disability or alcohol abuse.

Participants are administered the Wechsler Adult Intelligence Scales, which are commonly used with patients where intellectual functioning or rehabilitation are at issue. The Picture Arrangement subtest is extended in a standardized manner, so that subjects may describe how they arrived at their responses. Then, each subject is asked to match a series of five "situations" with appropriate behavioral responses and feelings. Finally each is interviewed briefly (about fifteen minutes) about their views of the present situations and their plans for the future.

The above procedures are aimed at demonstrating the construct and discriminative validity of the scoring system that has been developed for the extended administration of the Picture Arrangements subtest. Results of the testing, demographic data, and the neurologic diagnosis will be correlated when the data has been gathered. Multivariate procedures will then be used to identify the cognitive components of interpersonal functioning that are impaired in cerebral vascular lesions in the left and right hemispheres.

PROGRESS AND RESULTS: At this point, we have completed assessments on eleven suitable control subjects, seven suitable left hemisphere stroke patients, and one suitable right hemisphere stroke patient. A major difficulty has been the relative infrequency of "straightforward" stroke patients at Walter Reed General Hospital. About eight patients have been assessed who are not suitable for inclusion in this study.

CONCLUSIONS: No conclusions have been drawn at this point.

FUNDS UTILIZED (FY-77): None.

FUNDS REQUESTED (FY-78): None.

PUBLICATIONS (FY-77): None.

TYPE OF REPORT: Interim.

WORK UNIT NO: 7211

TITLE OF PROJECT: Discharge Recommendations and Morbidity in Psychotic Servicemen

PRINCIPAL INVESTIGATOR: Donald W. Morgan, MD, COL, MC

PROGRESS AND RESULTS: This project is terminated. Criteria for inclusion in the study were found to be too restrictive. Revised criteria and a new project (Work Unit No.7214) are currently in progress.

FUNDS UTILIZED (FY-77): None.

FUNDS REQUESTED (FY-78): None.

PUBLICATIONS (FY-77): None.

TYPE OF REPORT: Terminated; superseded by Work Unit No. 7214.

WRAIR UNIT NO: 7212

TITLE OF PROJECT: RBC Lithium Concentration and Clinical Correlates

PRINCIPAL INVESTIGATOR: R. Harlan Bridenbaugh, MD, LTC, MC
ASSOCIATES: James G. Hunter, MD, CPT, MC
John L. Wamble, MD, MAJ, MC

OBJECTIVES: 1. To establish WRAMC norms for RBC lithium concentration,
2. To determine clinical correlates (treatment response, side effects) of RBC lithium concentration and RBC to plasma ratios.

TECHNICAL APPROACH: Beginning on 27 September 1976, all blood for lithium testing at WRAMC has been collected in a heparinized (10cc green top) tube to allow for both plasma and RBC determination. The principal investigator, shortly after the project began, made contact with Drs. Joseph Mendels and Alan Frazier from the Department of Psychiatry, University of Pennsylvania for advice on the technical aspects of RBC lithium determination. In spite of this consultation, we experienced much technical difficulty, and noted intermittent, marked disparities in lithium values run at different dilutions (1:10, 1:25, 1:50). Finally, in early March 1977, we empirically developed a technical procedure which yielded consistent, apparently valid determinations.

PROGRESS AND RESULTS: We have developed a reliable, valid method for determination of RBC lithium levels utilizing the existing equipment in the WRAMC laboratory. Data analysis is not possible at the present time since the total number of samples run since March 1977 is too small. However, inspection of values obtained on the few patients being evaluated through the duration of the project does not show the RBC level to have any exceptional clinical correlation. Moreover, papers recently presented (American Psychiatric Association - annual meeting - May 1977) have shown generally negative results as far as clinical correlations are concerned. Factors such as sex, race, heredity, and plasma levels appear to markedly influence the RBC lithium level. Psychiatric diagnosis, clinical response, and side effects do not consistently correlate with RBC lithium levels. However, it is felt that the RBC:plasma ratio has some clinical utility (to assess patient compliance), that is, the ratio should be stable once steady state conditions are reached. A patient with a fluctuating RBC:plasma ratio should be evaluated for erractic compliance.

CONCLUSIONS: The measurement of the RBC lithium level appears to offer no particular advantage to the clinician except to help assess the compliance of patients on maintenance lithium therapy. We plan to continue

the routine analysis of RBC lithium, on a once a week availability, so that a further data base concerning the stability of the RBC:plasma ratio will be generated for the clinicain. We will discontinue any organized attempt to pursue clinical correlates of RBC lithium levels and will therefore discontinue the portion of the project requiring formal project entry and volunteer consent.

FUNDS UTILIZED (FY-77): None.

FUNDS REQUESTED (FY-78): None.

PUBLICATIONS (FY-77): None.

TYPE OF REPORT: Interim.

WORK UNIT NO: 7213

TITLE OF PROJECT: The Effects of Patient Attire on Ward Atmosphere and Recovery from Psychosis

PRINCIPAL INVESTIGATOR: John F. Rogers, MD, CPT, MC

OBJECTIVES: To observe the effects of particular changes in clothing policy on a psychiatric ward environment. The policy change related to these observations was to no longer require patients to wear a particular type or style of clothing or pajamas while on a psychiatric ward. The observations to be made were: (1) a series of ward atmosphere scales, as measured by the Moos Ward Atmosphere Scale (WAS), a standardized, copyrighted instrument for the evaluation of psychiatric wards, (2) the number of days patients spent on a closed ward status, and (3) the amount of medication administered to patients with a psychotic diagnosis.

TECHNICAL APPROACH: The Moos WAS was administered by nursing personnel on the wards involved on three occasions to patients and staff on all psychiatric wards at Walter Reed Army Medical Center on a voluntary basis using the Consent Forms approved at the WRAMC Clinical Investigation Service and at the OTSG level. Administration of the examination consists of explaining how to fill out an Answer Sheet of 100 "Yes" or "No" type questions relating to life on a psychiatric ward. The dates were September and November 1976 and February 1977. The number of days spent on closed ward and the amount of medication used was taken from copies of doctors' orders collected for research purposes from the psychiatry wards at WRAMC.

PROGRESS AND RESULTS: The Moos WAS test forms have been administered, collected, and scored. Statistical analysis of the results has revealed the following: (1) a stable profile on all 10 scales of the Moos WAS from September to November 1976--the period of baseline data collection, and (2) an increase in patient and staff perception of the patient's autonomy, as measured by the Moos WAS Automony Scale, statistically significant at the $p < .05$ level, using a two-tailed t test. The inpatient closed ward days and medication data has been collected and analyzed. The medication levels have not changed to a statistically significant amount. The closed ward average number of days prior to going on open ward status for the first time increased significantly ($p < .001$).

CONCLUSIONS: Distinct observations about ward life and patient progress can be made using these methods. The increase inclosed ward days is significant and may be related to increased need for staff control of patients who are less readily identified or to decreased patient desire to move off a status (closed ward) which no longer has the disadvantage of being required to wear pajamas.

The results of this project were presented at a Department of Psychiatry and Neurology conference on 31 May 1977. An outside consultant, Dr. Dean Nielsen of Stanford University Medical Center participated as discussant.

FUNDS UTILIZED (FY-77): Consultant (Dr. Dean Nielsen):

FEE:	$100.00
AIR FARE:	392.00
PER DIEM:	50.00
TOTAL:	$542.00

FUNDS REQUESTED (FY-78): None.

PUBLICATIONS (FY-77): None.

TYPE OF REPORT: Completed.

WORK UNIT NO: 7214

TITLE OF PROJECT: Pre- and Post-Discharge Assessment of Psychiatric Patients

PRINCIPAL INVESTIGATOR: Donald W. Morgan, MD, COL, MC

OBJECTIVES:

1. To establish, within the Psychiatry Service, WRAMC, a structured method of assessing pre- and post-discharge levels of psychosocial function of psychiatric patients seen by a Medical Evaluation Board (MEB).
2. To compare pre-discharge morbidity with post-discharge function of psychiatric patients seen by an MEB.
3. To systematize the MEB procedure in order that training and education goals can be met.

TECHNICAL APPROACH: At the conclusion of MEB psychiatric interviews, an emphasis is placed on post-discharge treatment and individual patients are asked permission to be followed by correspondence every three months for an initial one-year period, with the possibility of longer follow-up included. Following the interview, the three physicians present at the MEB complete standard rating scales appropriate to the diagnosis. The completion of these standard scales at the time of the MEB serves to structure and systematize the board procedure and at the same time, to allow for staff-resident discussion and comparison of ratings. During the seven to fourteen days following the MEB patients are administered the following: Minnesota Multiphasic Personality Inventory (MMPI), the Shipley-Hartford IQ Test, the Beck Depression Inventory, the Zung Self-Rating Scale, and the Leeds Anxiety-Depression Scale. Social and demographic data are obtained as well by means of a self-completing form previously designed by the Department of Psychiatry and Neurology. Patients are sent a letter and a short questionnaire at three, six, nine, and twelve months post-discharge. The questionnaire is designed so that outcome status can be quantified using the Strauss-Carpenter Outcome Scale.

PROGRESS AND RESULTS: As of 15 June 1977, a total of 118 patients entered in the project have been discharged. Of these, 103 were transferred to V.A. hospitals, and 12 sent directly home. One subject was returned to duty, another retired, and a third air-evacuated to the hospital at Ft. Fort Sam Houston for further medical evaluation. Fifty-one three-month follow-up questionnaires have been mailed and seventeen of these returned (as of 15 June 1977).

We anticipate completion of the entry and initial testing of patients (N=200) within the next month, and plan then to continue on with the established follow-up procedure, with further progress reports at required intervals.

CONCLUSIONS: No conclusions have been drawn at this point.

FUNDS UTILIZED (FY-77): None.

FUNDS REQUIRED (FY-78): None.

PUBLICATIONS (FY-77): None.

TYPE OF REPORT: Interim.

Work Unit No.: 8001

Title of Project: The effect of a diet controlled in lactose, gluten, fat and residue on malabsorption syndrome in oncology patients receiving abdomino-pelvic radiation

Investigators:

Principal: Jane T. Coffin, 1LT,AMSC,R.D.

Associate: Thelma Arnold, Maj,AMSC, PhD.,R.D.

Objectives: To observe the results of the test diet in adult patients when administered as a preventive measure at the onset of radiation therapy against malabsorption syndrome often observed in these patients as an immediate or delayed effect of abdomino-pelvic radiation. Particular emphasis will be placed on the incidence of fat and carbohydrate malabsorption and diarrhea. Changes in energy balance will be determined from daily weights and caloric analyses.

Technical Approach; The study is divided into two parts which run sequentially. Patients are randomly assigned to either the test or control group. A data sheet is completed on each subject to include information e.g. height, weight, age, diagnosis. An analysis for kilocalories, protein, carbohydrate, and fat is made for a 5-day baseline period before radiation is initiated. Serum B-carotene and D-xylose tolerance tests are performed on each subject before irradiation. The test group follows the test diet for the entire abdomino-pelvic radiation period. The control group follows the regular hospital diet. All subjects' intakes are analyzed for kilocalories, protein, carbohdrate and fat for the entire radiation period. Data is recorded for all patients re: daily weight, incidence of vomiting and diarrhea, antidiarrheal agents used. Clinical tests are again performed at the end of radiation to compare with the baseline values.

Progress and Results: At this point in time, results aren't as yet computed. Data arestill being collected. To date, 24 patients have participated; 3 patients revoked consent; 24 patients are required for statistical significance to be obtained; 8 patients are actively participating in the study at present; 13 patients have been completed; 11 patients have (or still are) followed the test diet; 10 patients have followed the regular hospital diet.

Progress & Results (cont.): Diagnoses include: Ca testicle (seminoma, teratoma, and embryonal), Ca prostate, Ca bladder, Ca cervix, Ca vagina, Ca endometrium, and Ca ovary. Radiation dosage (rads) has ranged from 3,000 to 5500 (excluding rads received to other than pelvis or abdomen). Ages of patients have ranged from 25 yrs. to 74yrs.

Conclusions: Pending completion of data collection.

Funds Utilized, FY-77: N/A

Funding Requirements, FY-78:

Personnel: N/A
Equipment: N/A
Supplies: N/A
Travel: Request permission and funding to attend the Annual American Dietetics Association Convention (location to be announced) 1978, to present results and conclusions from research.
Other: N/A

Publications: N/A

Type of Report: Interim

Work Unit No: 8027

Title of Projects: Clinical Evaluation of Freeze-dried Bone Allographs in the Treatment of Severe Periodontal Osseous Defects

Investigators:

Principal: Ronald L. Van Swol, D.D.S.
Chief, Periodontia Service, WRAMC

Associate: All Residents and Staff assigned to the Periodontia Service

Objectives: To evaluate the effectiveness of freeze-dried human bone allographs in the treatment of periodontal osseous defects.

Technical Approach: Consenting patients with large, severe periodontal osseous defects will be treated, using freeze-dried human bone allographs. Full thickness buccal and lingual flaps are developed in the surgical area, all granulation tissue is removed from the defect, the root surface is cleaned, and the osseous defect filled with the allograph material. The flaps are then repositioned and sutured to place. The surgical field is then covered with periodontal dressing and postoperative instructions given. The patient is seen in one week for suture removal and periodontal dressing change. At the two weeks postoperative time frame, the dressing is removed and home care instructions are given. The patient is then seen every 3 months for clinical and radiographic re-evaluation of the grafted area. At one year postoperatively, the area is re-entered for final evaluation and further grafting, if needed.

Progress and Results: During FY-77, 9 severe periodontal osseous defects were grafted. No complications were encountered in any of the cases, and good documentation was acquired in all instances.

Conclusions: During FY-77, we grafted 9 periodontal osseous defects. Our overall response has been of greater than 50% osseous regeneration, which has been very gratifying to the principal investigator.

Funds Utilized, FY-77: None

Funding Requirements, FY-78: None, the personnel, equipment and staff (D.D.S.) of the Periodontia Service, Department of Dentistry, Walter Reed Army Medical Center will be utilized.

Publications: None

Type of Report: Interim.

Work Unit No.: 8028

Title of Project: Development and Evaluation of Dental Materials and Materiel for Army Use.

Investigators:

Principal:	MAJ Frank E. Pulskamp, DC
Associates:	LTC Eugene F. Huget, DC
	COL John P. McCasland, DC
	Mr. Howard E. Cosner, CDT

Objectives:

1. To establish and define the parameters of apparent fit for cast removable partial denture frameworks.

2. To compare the clinical fit of castings made by two conventional techniques utilized presently by U.S. Army Dental Laboratories.

3. To determine, for each technique, the amount of time required to achieve an acceptable clinical fit.

4. To determine, on a comparative basis, the cost effectiveness of each technique.

Technical Approach: The investigation will require approximately 50 patients. All participating subjects will be advised of the intent of the research. A consent form denoting agreement to participate in the study will be executed by each patient prior to commencement of clinical work. The document will stipulate that (1) supporting tissues will be prepared in a conventional manner, (2) restoration of diseased, damaged, poorly contoured or malaligned teeth will be accomplished by means of current and conventional "state-of-the-art" techniques, (3) routine procedures for the making of impressions for diagnostic casts and master casts will be employed, (4) procedures for the clinical evaluation of framework-fit will be noninvasive and (5) participation in the study will require, from each patient, expenditure of chair-time in excess of that associated with routine partial denture service (estimated additional chair-time is one hour).

All clinical procedures to include patient counseling, diagnosis, mouth preparation, impression making, registration of jaw and occlusal relationships, design, fabrication of master casts, selection of artificial teeth, assessment of framework accuracy, framework correction and insertion of completed prostheses will be responsibilities of the Removable Prosthodonti Service, Department of Dentistry, Walter Reed Army Medical Center.

To reduce experimental variables, all impressions for the fabrication of master casts will be made with a single irreversible hydrocolloid.+ All master casts will be poured from a single improved dental stone.++

Two master casts for each clinical case will be transmitted to the Division of Dental Materials, U.S. Army Institute of Dental Research. The casts, after blockout of interfering undercuts, will be duplicated in appropriate refractory materials. From the design and prescription of the responsible clinician, a wax pattern will be fabricated for each refractory model. Framework patterns will include major and minor connectors, occlusal and/or incisal rests, reciprocal arms, and when indicated by the prescription design, direct retaining devices (clasps).

One waxed refractory model for each clinical case will be invested in a "low-heat" gypsum bonded refractory materials (Investic#). The mold will be burned out at 1,350°F and cast in Ticonium 100 with the use of an automatic induction casting machine.* Casting temperature of the alloy will be 2,580°F. The mold will be cooled to room temperature before retrieval of the cast framework is attempted.

A second waxed refractory model for each clinical case will be invested in a high-heat silica-bonded refractory material. ** The model will be burned out at 2,100°F and cast in Vitallium. Casting temperature of the alloy will be 2,850°F. Cast molds will be bench-cooled to room temperature before further handling.

All castings will be liquid honed to remove investment and oxide coatings. Mechanical manipulation of castings within the Division of Dental Materials will include, but will not exceed removal of sprues, vents and reservoirs, removal of fins and casting bubbles, and preliminary (rough) polishing.

The Chief, Division of Dental Materials, will insure explicit compliance with manufacturers' prescribed technics and procedures for model replication, investment, burnout, casting, breakout and preliminary metal-finishing. Also, he will insure prompt transmittal of castings to the responsible clinician for accuracy determination.

Assessment of casting accuracy will be based upon the following criteria: (1) Fit and adaptation of rests to prepared occlusal and incisal seats

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+ Jeltrate, The L.D. Caulk Co., Milford, Del.

++ Silky Rock, Whip-Mix Corp., Louisville, Ky.

CMP Industries, Albany, N.Y.

* Electromatic Casting Machine, Howmedica, Inc., Chicago, Ill.

** VR-Investment, Howmedica, Inc., Chicago, Ill.

and (2) degree of contact between prepared tooth surfaces and elements of the framework such as bracing components, guiding planes, continuous clasps and lingual plates.

Evaluation of the intimacy of metal-tissue contact will employ use of a soft disclosing wax. The technique has been described in great detail by Rudd. Specifically, however, a disclosing wax will be applied to the intended tooth-contacting areas of each casting. With regard to a predetermined path of insertion, the casting will be seated manually on its master cast. After withdrawal, the wax-covered tooth-contacting surface of the casting will be examined. Loci of mechanical interferences will be denoted by bared areas of metal. Insufficient metal-tooth contact will be indicated by the presence of prominent white patches of wax, of varying thickness, in areas in which metal-tooth contact is desired. Desired metal-tissue contact will be revealed by even expression of the disclosing wax. Wax remaining on the casting, in the area of metal-tissue contact, will present a distinguishable grayish hue.

Apparent fit of cast frameworks will be graded as inadequate, minimally acceptable or excellent.

Parameters of fit:

1. Inadequate
    a. Failure of rests to contact prepared seats.
    b. Failure of bracing components to make point contact with appropriate structures.

2. Minimally acceptable
    a. Incomplete contact of rests with prepared seats. Contact may range from "point-origin" to a maximum apparent area of 50 percent.
    b. Incomplete contact of bracing components with designated structures. Contact may range from "point-origin" to a maximum apparent area of 50 percent.

3. Excellent
    a. Contact area of rests greater than 50 percent.
    b. Contact area of bracing components greater than 50 percent.

After initial assessment of fit, the castings will be adjusted by grinding, and reevaluated for quality of fit. A record of the time required for adjustment to achieve satisfactory fit will be kept.

The evaluation procedure will also be followed for determination of apparent clinical-fit. Such methods for evaluation of fit are commonplace. They do not, by any means, reflect an unusual departure from acceptable standards of dental practice.

It is anticipated that accomplishment of the proposed task will lead to the establishment of rational guide-lines for the improvement of prosthetic

dental service within the U.S. Army. Furthermore, the most satisfactory laboratory procedures and materials involved in partial denture fabrication will be identified.

Progress and results: Ticonium-100 and Vitallium^2 were selected equally for our clinical cases. Ticonium-100 took about fifteen minutes less to fit clinically than did Vitallium^2. Most of the study cases were of the Kennedy Class I partially edentulous arch type.

Conclusions: There are no differences clinically between Ticonium-100 and Vitallium^2. Ticonium-100 did require less fitting time than Vitallium^2 for Kennedy Class I partially edentulous arch classifications.

Funds utilized FY 1977: None

Funding requirements FY-78: None

Publications: None

Type of Reported: Project completed.

Work Unit No.: 9009

Title of Project: Abnormalities of B6 metabolism and glycogen metabolism in Hodgkin's disease

Investigators:

Principal: LTC Michael J. Haut, M.D., MC
MAJ John A. Kark, M.D., MC
Associate: Johannes Blom, M.D.
LTC Robert W. Muir, M.D., MC
MAJ William Babcock, M.D., MC
MAJ Salvatore Scialla, M.D., MC
LTC Daniel B. Kimball, M.D., MC

Objectives: To evaluate B6 and glycogen metabolism in tissues of patients with Hodgkin's disease in order to answer two questions: (1) Are the diminished levels of vitamin B6 coenzyme in Hodgkin's disease due to alterations in the enzymes regulating B6 metabolism? If so, in what tissues is B6 metabolism altered? (2) Does the deficiency of coenzyme B6 contribute to muscle weakness by decreasing the activity of muscle glycogen phosphorylase, a B6-containing enzyme?

Technical Approach: Our initial studies showed that some patients with Hodgkin's disease or other malignancies had lower plasma B6 levels than control subjects, but had increased capability for red cell conversion of precursors to pyridoxal-5-phosphate under optimal conditions. To examine this apparently paradoxical phenomenon, we have concentrated our efforts for the past two years on development of methods to examine B6 and glycogen metabolism in detail in isolated subpopulations of both developing and mature blood cells, and in numerous other tissues (particularly lymph nodes, liver, spleen, and muscle).

Progress and Results: Our pilot studies on this protocol, performed in FY 75, indicated that some but not all patients with Hodgkin's disease or other malignancies have lower plasma B6 levels than control subjects, and increased capability for red cell conversion of precursors to pyridoxal-5-phosphate under optimal conditions. Subsequent studies in our laboratory confirm our earlier observations, but indicate that, among hematologic malignancies, there is a spectrum of alterations in B6 metabolism. In our initial studies, we also found that patients with infectious mononucleosis have enzyme and PLP levels intermediate between those of patients with malignancies and controls. PLP levels per cell are not abnormal in either the RBC's or the lymphocytes, and the red cell levels appear to reflect the plasma levels.

Before studying additional patients, we felt that we should perfect methods for study of (1) isolated peripheral blood cells, (2) isolated marrow hematopoietic cells, and (3) nonhematopoietic tissues. Our efforts

on this project during the past two years have focused on establishing workable methods for each of the above. Our progress in each of these areas is detailed below. We feel that we should be able to utilize the more sophisticated methodology by January or February 1978.

1. Isolation of subpopulations of peripheral blood cells.

We have now established normal values in our laboratory for pyridoxal-5-phosphate, pyridoxal kinase, glycogen, and glycogen phosphorylase in isolated erythrocytes, platelets, lymphocytes, and granulocytes. We have made arrangements to examine isolated lymphocyte subpopulations (T, B, and "null" cells) as well.

2. Isolation of bone marrow precursors of each type of hematopoietic cell.

Our progress has been slowest in this area. After unsuccessful attempts at differential centrifugation, we have selected unit gravity sedimentation, using the Staput apparatus, as the most appropriate way to separate bone marrow erythroid precursors by age. If we are not successful at setting this method up by November 1977, we will utilize differential centrifugation to obtain partially purified bone marrow subpopulations for our clinical studies until the other method is perfected. Such crude separation has provided valuable information about marrow erythroid cell metabolism both in our hands (heme synthesis in marrow of patients with sideroblastic anemia and in marrow of dogs with dietary B6 deficiency), and in the hands of other investigators.

3. Study of B6 and glycogen metabolism by specific nonhematopoietic tissues.

Using animal tissues, we have established appropriate conditions for assay of PLP, pyridoxal kinase, glycogen, glycogen synthetase, and glycogen phosphorylase in several nonhematopoietic tissues. Using discarded bits of frozen human muscle tissue obtained from the muscle laboratory at AFIP, we have demonstrated that these methods are applicable to human tissue as well as animal tissue.

In addition, we have set up procedures for chromatographic separation and subsequent fluorometric quantitation of the various B6 vitamers from liver, and are now extending this procedure to other tissues.

Conclusions: None

Funds Utilized, FY 77: None

Funding Requirements, FY 78: None

Publications, FY 77: None

Type of Report: Interim

Work Unit No.: 9010

Title of Project: Vitamin B_6 metabolism in the hematopoietic system of patients with sideroblastic anemias

Investigators: John A. Kark, MD, MAJ, MC
Michael J. Haut, MD, MAJ, MC

Objectives: To apply new information about the metabolism of vitamin B_6 to the diagnosis and management of the sideroblastic anemias.

Technical Approach: As described in previous protocols (#9010), we have measured plasma pyridoxal-P levels and red cell synthesis of pyridoxal-P in untreated or treated cases of sideroblastic anemia. Although accurate measurement of normal fasting red cell pyridoxal-P levels is not yet possible, we found that red cell pyridoxal-P could be measured in patients taking vitamin B_6 because the amounts of pyridoxal-P present are 20 to 50 times higher. This has permitted us to compare the biochemical and hematologic responses to vitamin B_6 treatment in 30 patients with non-drug induced sideroblastic anemias.

Progress and Results: We found that none of the 30 patients had a significant hematologic response to vitamin B_6 treatment. However, in all 30 patients treatment with pyridoxine resulted in an adequate biochemical response in terms of plasma pyridoxal-P and the rates of red cell synthesis of pyridoxal-P. In half our patients quite adequate levels of red cell pyridoxal-P have been demonstrated.

Conclusions: We conclude that defective synthesis of vitamin B_6 or excessive breakdown of pyridoxal-P did not account for the anemia in our 30 cases of sideroblastic anemia. Therefore, the enzyme defects proposed to be important by John Hines must be much less common than reported in his papers.

Funds Utilized: none.

Funding Requirements: none.

Publications: JA Kark, MJ Haut, CT McQuilkin, and CU Hicks. Dissociation of biochemical and hematologic responses to pyridoxine in patients with sideroblastic anemia. Blood 48: 966, 1976.

Type of Report: Interim.

Work Unit No.: 9012

Title of Project: The Effect of Infectious Hepatitis on Erythroid Colony Formation in the Plasma Clot Culture Method.

Investigators:

Prinicpal: August Salvado, MAJ MC

Assoicate: William Babcock, MAJ MC

Objectives: To determine whether the hepatitis virus which can cause abnormalities in all three cell lines in the injury in the stem cell population of the bone marrow.

Technical Approach: The plasma clot tissue culture technique for hematopoietic stem cells is used to determine colony growth of committed erythroid stem cells from the marrow of patients infected with hepatitis. "Normal" control marrow is obtained as an extra aspirate from patients having bone marrow aspirates done as a staging workup for other malignancies & whose marrow ultimately shows no evidence of invasion by malignant cells.

Progress & Results: A long delay was encountered in the process of adapting the plasma clot technique to grow human stem cells. The technique requires that both fetal calf serum and bovine serum albumin are used as part of the medium of the plasma clot. Both of these protein reagents, however, must be screened separately beforehand for "activity" or ability to support stem cell growth for the species of interest. The literature indicates that it is frequently necessary to screen many lots of both fetal calf serum and bovine serum albumin to find those that can support human stem cell growth. We found this to be true. As a matter of fact we had to screen 16 lots of fetal calf serum and 6 lots of bovine serum albumin to meet our needs. This along with the fact that a single culture has to incubate for one week before it can be processed and counted constituted a delay of many months. As a result, our system has just reached a stage where we have reproducably adequate colony growth and are ready to proceed.

Conclusions: Not applicable

Funds Utilized FY-77: None

Funding Requirements FY-78: None

Publications: None

Type of Report: Interim

Work Unit No.: 9077

Title of project: Peripheral Neuropathy and Chronic Obstructive Lung Disease - A Clinical and Electrophysiological Study

Investigators:

Principal: Alan Ira Faden, M.D., MAJ, MC

Associate: W. K. Hunt, M.D., LTC, MC
A. D. Huott, M.D., COL, MC

Objectives: To determine whether there exists clinical or subclinical peripheral nerve impairment in patients with chronic obstructive pulmonary disease (COPD) and if so, what duration and degree of pulmonary dysfunction is required to produce it.

Technical Approach: Patients are selected by the pulmonary section on the basis of a history compatible with COPD, an FEV of less than 50% of predicted, and the absence of conditions known to be associated with neuropathy. These patients are evaluated by standard neurological and electrophysiologic examination. The latter includes sensory and motor conduction velocities as well as sample EMG's when indicated.

Progress and Results: Only 2 patients have been studied to date. Both had normal clinical examinations. One had absent sural sensory evoked potential but normal EMG and motor conduction studies. The other had widespread evidence of chronic partial denervation on EMG examination, as well as absent sural sensory evoked potentials and moderate slowing of peroneal motor conduction velocities.

Conclusions: Obviously too few patients have been studied to draw any meaningful conclusions, but the data do suggest that a subclinical polyneuropathy associated with COPD may exist.

Funds Utilized: None

Funding Requirements: None

Publications: None

Type of Report: Interim

Work Unit No.: 9078

Title of Project: Encephalopathy Following Treatment of Chronic Pulmonary Failure: A Clinical and Electroencephalographic Study

Investigators:

Principal: Alan Ira Faden, M.D., MAJ, MC

Associate: R. W. Enquist, M.D., MAJ, MC

Objectives: To determine the frequency of the encephalopathy which may be seen following the treatment of chronic pulmonary failure and to distinguish the relative importance of the two presumed caused variables - alkalosis and aminophylline administration.

Technical Approach: Patients are to be selected by the ICU staff on the basis of clinical history, a PCO_2 of greater than 50, a pH of less than 7.25 and who are to be placed on respirators. Patients with evidence of other significant metabolic disturbances will be excluded. Clinical neurological and electroencephalographic examinations will be performed as soon as possible after admission and repeated in 6-12 hours. Routine arterial blood gases will be drawn as well as a serum aminophylline level at the time of the second EEG.

Progress and Results:)
Conclusions:) No patients have been found to date which meet the requirements described above.

Funding Utilized: None

Funding Requirements: None

Publications: None

Type of Report: Interim

Work Unit No.: #9092

Title of Project: An Evaluation of the Dental-Medical History

Investigators:

Principal: David M. Lewis, MAJ, DC

Associate: A.M. Krakow, MAJ, DC
Thomas F. Payne, LTC, DC

Objectives: The object of this study was to determine if access to the patient's medical record would significantly enhance the accuracy and completeness of the medical history as reflected in the dental record.

Technical Approach: The dental records of 100 active duty personnel were randomly selected and matched with their medical records. The medical history recorded in each dental record was abstracted and compared to an abstract of the patient's medical record.

Progress and Results: On 24 Aug 76 the protocol was approved by the Clinical Investigation Committee, WRGH. Data collection began on 24 Sep 76 and was completed on 19 Nov 76. Data was analyzed and tabulated on 22 Dec 76 and a 1st draft was completed by 29 Dec 76. Final draft was submitted for approval on 7 Apr 77.

Conclusions: A total of 39 discrepancies were discovered. Significant medical conditions were found in 11 patients that were not recorded in the dental-medical histories. It is recommended that when feasible patients present for dental examination with their medical records.

Funds Utilized, FY-77: N.A.

Funding Requirements, FY-78: None

Publications: Pending

Type of Report: Completed

*WR-70-1

DEPARTMENT OF THE ARMY
HEADQUARTERS WALTER REED ARMY MEDICAL CENTER
Washington, D.C. 20012

WRAMC Regulation 1 April 1973

Clinical Investigation Program

WRAMC RESEARCH ACTIVITIES

	Paragraph
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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.

e. The studies are performed in a considered, coordinated, and professional manner.

*This regulation supersedes HR 70-1, 9 December 1971.

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f. 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.

g. 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).

h. 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.

i. The voluntary consent of the 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 hazards reasonably to be expected; and the effects upon his health or person which may possibly come from his participation in the study. 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.

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.

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 inpatients, outpatients, organ donors, informants, or normal individuals who participate in studies of medical, physiological, sociological, or psychological orientation.

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. Responsibility for this determination resides at all levels of institutional and departmental review.

4. COMMITTEES. The following committees will be appointed:

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 the following:

Director, Professional Services (Chairman)
Chief, Clinical Investigation Service (Secretary)
Chief, Department of Medicine
Chief, Department of Surgery
Chief, Department of Pathology
Chief, Department of Radiology
Chief, Department of Pediatrics
Director, WRAIR
Chief, Health Physics
Chief, Pharmacy Service (ex officio)
Chief, Patient Administration (ex officio)
Chief, Nursing Research Service (ex officio)

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 the following:

Director, Professional Services (Chairman)
Chief, Clinical Investigation Service (Secretary)
A Chaplain
A JAG Officer
Chief, Department of Nursing
Chief, Department of Psychiatry and Neurology
Chief, Department of Obstetrics and Gynecology
Command Sergeant Major
Director, Human Resources Directorate
Chief, Department of Dentistry
Clinical Pharmacist, Hematology-Oncology Service

5. CLINICAL INVESTIGATION COMMITTEE: The Clinical Investigation Committee will meet once monthly, usually on the fourth Tuesday at 1400 hours. The committee will review all new research proposals. 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 major change either in the goals or the procedures or drugs used in human subjects. Adverse reactions to investigational drugs or procedures will be promptly reported to the committee. The committee will make recommendations to the Commander.

6. HUMAN USE COMMITTEE: The Human Use Committee will meet once monthly, usually on the fourth Tuesday at 1500 hours. The committee will review all new research proposals in which human subjects are used. Periodically, 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 major change in the goals or the procedures or drugs used in human subjects. The committee will make recommendations to the Commander.

7. RECORDS AND REPORTS.

a. Initial Report. 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. 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 a written forwarding comment describing the study in relationship to its scientific contribution, military relevance, and contribution to the teaching program; an indorsement that the proposal conforms to the criteria described in paragraph 2 above; and the availability or unavailability of the resources requested in the proposal.

b. 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 May of each year until the investigation is completed. See Appendix B.

c. Interim Reports. Interim reports are discretionary and may be submitted at any time when important development, adversities or other circumstances occur which should be brought to the attention of higher headquarters. Interim reports may also be used to add or remove procedures or methods from the original protocol.

d. 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.

e. 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.

f. 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.

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 clinical investigation program are presented to the Center Command annually during the month of March.

a. Projects requiring refunding in the amount of $1,000.00 or more are submitted each year prior to 1 March in the format of Appendix A for consideration.

b. New proposals which require funds may be submitted at any time. Approval of funding is dependent upon availability of local 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 consent must be based upon his 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.

b. Human Volunteer. Investigative studies in which drugs or procedures are employed that will not benefit the person 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.

HSW-QCCR

FOR THE COMMANDER:

FRED C. BRAND
LTC, MSC
Adjutant

DISTRIBUTION:
I plus 100 cys to
Clinical Research

APPENDIX A

APPLICATION FOR CLINICAL INVESTIGATION PROJECT

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 a project.)

7. BIBLIOGRAPHY: (List source of information.)

8. FACILITIES TO BE USED: (Such as laboratory, ward, clinic.)

9. TIME REQUIRED TO COMPLETE: (Give month and year of expected start and anticipated completion.)

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:

	O&MA	OPA	TOTAL
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

Patients:

Bed Occupancy:

Laboratory:

Radiology:

Pharmacy:

Nursing Service:

Registrar:

Other:

Approvals	Chief of Service	Chief of Dept	For Hosp Comm
Date:			
Sig:			
Name:			
Grade:			
Position:			

R & D Approval Requested ☐ Yes ☐ No Date:

☐ Yes ☐ No Date:

(This is a format. It will not be used as a form.)

APPENDIX A
VOLUNTEER AGREEMENT

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/Division/Institute of

_____, Walter Reed Army Medical Center, Wash., 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 reverse side 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 medicial 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 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.

_____ _____

Signature Date

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

On this side of the Volunteer Agreement, the principal investigator should set forth full details concerning the investigation 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:

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 subject 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?

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 & Results: (organized 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)

Conclusions: (concise statement of goals achieved by current studies)

Funding Requirements: (present and next FY)

Personnel: (name and grade)
Equipment:
Supplies:
Travel:
Other:

Publications: (list only those published during present FY from your service which are related to the research described in this report)

(Report should be typed on 8 x 10-1/2" bond paper with 1" margins on all four sides. Do not number pages. Double space between sections of the report. Single space typing within each section. Do not put a signature block on the report.)

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