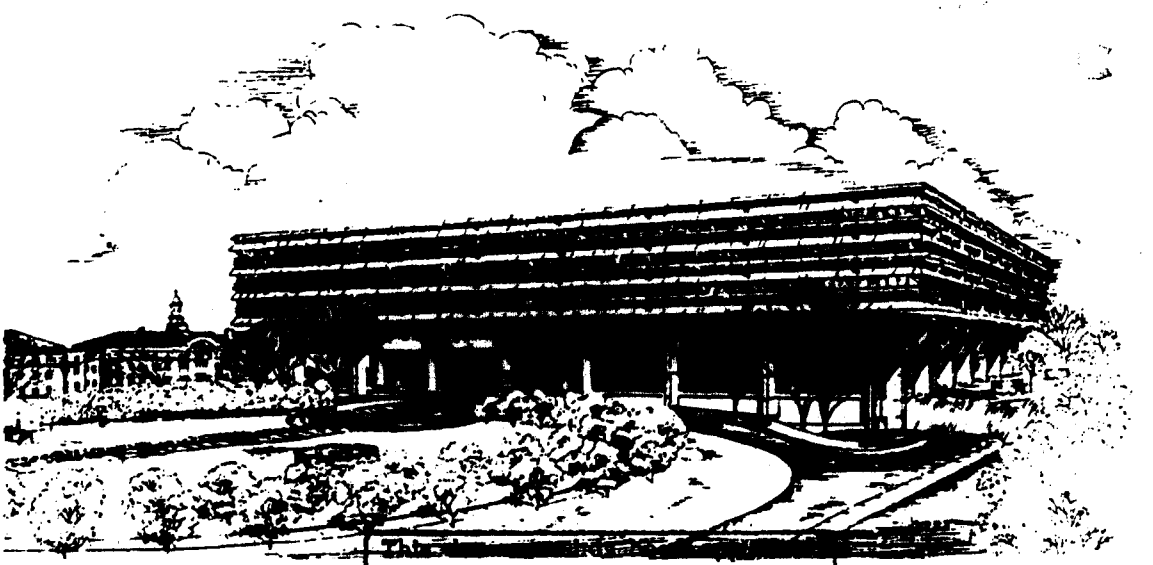
LEVEL II

ANNUAL PROGRESS REPORT

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WALTER REED ARMY MEDICAL CENTER
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This report covers the period 1 Oct 78 thru 30 Sep 79.

(10) Timothy M. Boehm

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FOREWORD

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

The investigations described in this report were conducted under the provisions of AR 40-38, Clinical Investigation Program; AR 40-7, Use of Investigational Drugs in Humans; and WR 70-1, Clinical Investigation Program, WRAMC, to insure that the rights, well being, and dignity of human subjects were maintained.

Research involving animals was performed in accordance with the "Guide for Laboratory Animal Facilities and Care", as promulgated by the Committee on the Guide for Laboratory Animal Facilities and Care of the Institute of Laboratory Animal Resources, National Academy of Sciences, National Research Council.

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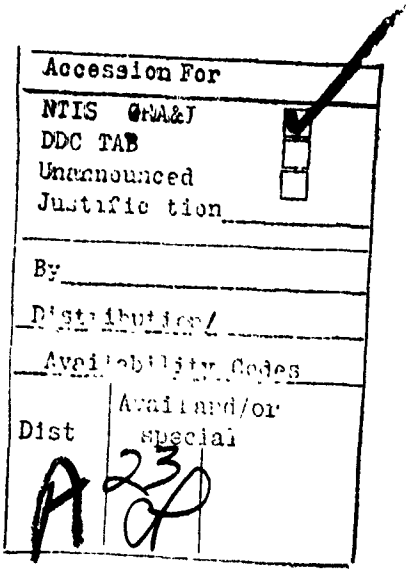


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Clinical Investigation Service

Walter Reed Army Medical Center

This Annual Progress Report is for the Fiscal Year 1980.

1. Mission Changes

a. Expansion. During FY-79, the Clinical Investigation Service implemented a new peripheral vascular research laboratory designed to supplement rather than duplicate, the coagulation research effort of WRAIR. The laboratory located on the sixth floor of the New Medical Treatment Facility is well equipped to include a thromboelastograph to study the clotting mechanism from clot formation to lipis.

b. During FY-79, laboratories under the control of Clinical Investigation Service moved from the old hospital to the NMTF. Currently there are ten (10) Clinical Investigation laboratories at WRAMC with all but two (2) located in the new hospital.

c. An animal procedures laboratory, formerly part of the Organ Transplant Service located at Forest Glen, was moved to Bldg #1 on main post and is now available on a service wide basis for all Clinical Investigation Service research involving animals. Surgical procedures and radioisotope injections are now carried out in this area. Unfortunately, there still is no animal care facility available within the Service. We continue to depend on WRAIR for kenneling and care of animals.

2. Personnel Actions, Current Strength

a. Personnel hired on permanent appointments to provide support for investigative projects.

Rice, Mary K	GS-09	1320	(Vice: Smith)
Ferrigan Marya K	GS-09	0644	(Vice: Davis)

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

Bowers, Mary W	GS-05	0675	
Edwards, Sondra D	GS-04	0675	
Brathwaite, Brenda L	GS-04	0645	
Jackson, Darlene	GS-07	0645	(Temp appoint extended)
Young, Toni M	GS-04	0675	

c. Current Manpower

Description	Grade	MOS	Br	Actual	Name
C, Clin Invest Svc	04	61F9C	MC	1	Boehm
Asst C, Clin Inves Svc	04	61F9B	MC	1	Schuster
Lab Officer (Admin)	04	68F9D	MSC	1	Reed
Biochemist	03	68C00	MSC	1	Bongiovanni
Dietitian	02	3420	AMS	1	Walker-Ramos
Med Lab NCO	E7	92B	AMED	1	Moody
Med Lab NCO	E6	92B	AMED	1	Price
Med Lab SP	E5	92B	AMED	1	Dutton
Med Lab SP	E4	92B	AMED	2	Dickinson Shaker
Science & Eng	E4	01H20	AMED	1	Byrne
Med Lab SP	E3	92B	AMED	1	Lambert
Supv Rsch Chemist	14	1320	GS	1	Bruton
Microbiologist	12	0403	GS	1	Dobek
Microbiologist	12	0403	GS	1	Ciak
Admin Officer	11	0341	GS	1	Young
Physiologist	11	0413	GS	1	Wright
Physiologist	11	0413	GS	1	Lukes
Bio Lab Tech	09	0404	GS	2	Dickson Butler
Med Tech	09	0644	GS	3	Armstrong Burgess Ferrigan
Chemist	09	1320	GS	3	Dawson Maydonovitch Rice
Med Tech	09	0645	GS	1	Barnes
Bio Lab Tech	08	0404	GS	1	Coleman
Med Tech	07	0644	GS	2	Bongiovanni Londono
Secy Steno	07	0318	GS	1	Ervin
Edit Asst	07	1087	GS	1	Hepburn
Clk, DMT	05	0316	GS	2	Laster Legere
Clk, DMT	04	0316	GS	2	McAnally
Med Records Tech	04	0675	GS	1	Kendall
Med Tech (Chemist)	04	0645	GS	1	Martin

3. Investigation Program Summary

Number of Active Protocols	232
Number of Completed Protocols	28
Number of Terminated Protocols	27

4. Incentive

The Bailey K. Ashford Award medallion presented annually to the staff member at Walter Reed Army Medical Center whose research project was voted the most outstanding contribution to the WRAMC investigative program was Major Daniel A. Ramirez, MC, for his paper entitled, "Insect Sting Allergy".

5. Funding, FY-79:

Civilian Personnel	$451,867
Military Personnel	280,600
Travel	21,672
Contracts	106,300
Supplies	426,793
Total	$1,287,232

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Georgoulakis JM. Social Factors and Perceived Problems as Indicators of Success in Basic Combat Training, Part I and II. Military Medicine, Sept 1979.

Work Unit: 1004

Title: Stress Ulceration in the Medical ICU: Incidence and Possible Prevention with Cimetidine.

Investigators:

Principal investigator: David A. Peura, M.D.

Co-investigator: Lawrence F. Johnson, M.D.

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

Technical Approach: See protocol.

Progress and Results: Since the last report, an additional eight (8) patients have been studied under the Protocol for a total of 38 patients. The double blind randomized control code has not been broken by the investigators, so it is impossible to determine at this time the effacacy of Cimetidine vs. placebo. Interim evaluation of the submitted data on approximately 25 patients was superfically examined by the statisticians at Smith, Kline and French Laboratories, and their verbal report to the investigators was that at that time in the study there appeared to be no difference between Cimetidine and placebo in preventing gross bleeding. Because the numbers were still small, it was recommended that the study be continued to increase the statistical pool. In the patients so far studied, there has been no untoward side effects noted that could be related to the study drug or the protocol.

Conclusions: Thirty-eight (38) patients have been studied under the protocol, but because of the double blind randomized nature of the study, the effacacy of Cimetidine vs. placebo can not be determined at this time. Early evaluation of the data on 25 patients appeared to indicate that there was no statistical difference between the two, but the statistical pool was small; and it was recommended by the statisticians that the study be continued to increase the number of patients. It is anticipated that adequate data can be obtained with a total patient pool of 50, so the study will be continued until another 12 patients are assessed.

Funds Utilized, FY 79: None.

Funds Requested, FY 80: Same as initial protocol.

Publications: None to date.

Type of Report: Interim.

Investigational Drug Progress Report

Program Work Unit: 1004

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

Investigators:

Principal investigator: David A. Peura, M.D.

Co-investigator: Lawrence F. Johnson, M.D.

Study is conducted in the Medicine Service, Walter Reed Army Medical Center.

Thirty-eight subjects have been studied to date with no evidence of adverse reaction. Because the study is a double blind randomized study, the code has not been broken, and the effectiveness of Cimetidine over that of placebo is not available at this time. It is anticipated that 12 more patients will be evaluated.

As per requirements by FDA, on site inspection has been carried out by Smith, Kline and French Laboratory, sponsors of the clinical investigation project, and inventory of medication has been kept in the Walter Reed AMC Pharmacy, and interim collaboration of inventory has been performed by representatives of Smith, Kline and French.

1. Work Unit Number: 1121

2. Project Title: Combined Prednisone and Cytoxan Therapy Coupled With Plasmaphoresis in the Treatment of Antiglomerular Basement Membrane Mediated Renal Disease.

3. Investigators: Principal - John P. Johnson, LTC, MC
Associates - Daniel A. Nash, Jr., LTC, MC
Jack Moore, Jr., CPT, MC
Michael Siedlecki, CPT, MC

4. 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.

5. Technical Approach: Patients with confirmed anti-GMB 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.

6. Progress and Results: Twelve patients have been entered into the study. Four have received plasmaphoresis in addition to Cytoxan and Prednisone. Disappearance rates of antibody have been observed. Initial and continuing observation suggest the rate of disappearance may be similar between the two groups. However, the patient experience remains too small at this time for meaningful comparison. The protocol was approved for an additional three year study period in February, 1979. 6a. No unexpected side-effects or complications have occurred.

7. 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 parimeters and outcome to be made.

8. Funds Utilized, FY-79: None

9. Fund Requirements, FY-80: Personnel - None
Equipment - None
Supplies - None
Travel - $600.00
Other - None

10. Publications: Anti-GBM Antibody Mediated Glomerulonephritis. GN and Good Pasture's Syndrome. Briggs, et al. Medicine, 58: 348, 1979.

Johnson, J.P., Briggs, W.A., Bohan L. et al: The role of plasmaphoresis in anti-glomerular basement membrane antibody mediated renal disease. Controversies in Nephrology - 1979 (J. Winchester and G. Schriener eds), In Press.

11. Type of Report: Interim

1. Work Unit Number: 1122

2. Project Title: Evaluation of Urinary Creatinine Excretion as a Reference Point for Comparing Total Body Potassium Determinations.

3. Investigators: Principal - Donald E. Butkus, COL, MC
Associate - Daniel A. Nash, Jr., LTC, MC

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

5. Technical Approach: Ambulatory patients who are receiving no medications and who have normal plasma potassium concentrations will have total body potassium measurements performed in a total body counter measuring naturally occurring K^{40} and no isotopes 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 gram of creatinine excreted, and results will be compared with standard references including height, weight, body surface area and standard predictive formuli.

6. Progress and Results: A reasonable number of subjects have been evaluated in accordance with the protocol. The standard range in variation for those tested has been determined. It appears that there is excessive variation with the techniques employed in the measurement of both total body potassium and 24-hour urinary creatinine excretion severe enough to compromise the utility of one as the reference for the other.

7. Conclusions: Use of the urinary creatinine excretion adds no further information with respect to standardizing the total body potassium measurements when compared to using the individual's height, weight or/and body surface areas as standards. Because of this, it has been determined that no further efforts are warranted to consider the use of creatinine as the ideal reference for measuring total body potassium. With more refined techniques, e.g. 1) improved standardizing techniques for K40 measurement, 2) use of true creatinine, reconsideration may be given in the future to the concept of this protocol.

8. Side Effects or Complications: None

9. Funds Utilized, FY-79: None

10. Funds Requested, FY-80: None

11. Publications and Abstracts, FY-79: None

12. Type of Report: Final Report. This project is no longer to be considered active.

1. Work Unit Number: 1124

2. Project Title: The Effect of Hyperuricemia on Chronic Renal Failure

3. Investigators: Principal: Daniel A. Nash, Jr., LTC, MC
Associate: None

4. Objective: To determine if hyperuricemia occurring in chronic renal failure is an aggrevating factor to residual renal function.

5. Technical Approach: Randomized controlled evaluation in which patients do or do not have their serum uric acid concentrations normalized with the drug Allopurinal as they approach end-stage renal disease. The consequential courses of these two groups are compared.

6. Progress and Results: Three patients have received Allopurinal with an expected lowering of their serum uric acid concentrations. In two, there appeared to be a stabilization of the creatinine clearance with a change in the rate of deterioration of renal function. However, the interval of therapy was limited to five months and two months in these cases because of side effects of the drug. In the third patient, there appeared to be no change in the rate of deterioration of renal function.

7. Conclusions: Preliminary considerations suggest that uric acid may contribute to nephrotoxicity in end-stage renal disease. However, Allopurinal toxicity may be a limiting factor in managing this hyperuricemia.

8. There have been no serious or unexpected side-effects/complications in subjects participating. The side effects in the two cases sited were both skin rashes that resolved with discontinuence of the agent.

9. Funds Utilized, FY-79: None

10: Funds Requested, FY 80: None

11. Publications and Abstracts, FY-79: None

12. It is estimated that three years will be needed to obtain sufficient patient data for statistically significant meaning. This should include approximately twelve additional subjects.

Type of Report: Interim

1. Work Unit Number: 1125

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

3. Investigators: Principal - Suzanne M. Bergman, MD
James D. Fitz, MD

Associates - Donald E. Butkus, MD
Daniel A. Nash, Jr., MD
Lee D. Nelson, Chemist

4. Objective: To determine the frequency of total body potassium depletion in patients with untreated leukemia and to access the effects of therapy in the known modulators of potassium homeostasis on renal potassium excretion and potassium distribution.

5. Technical Approach: Fifteen to twenty patients with newly diagnosed acute leukemia will be studied for serum, red blood cell, and whole body potassium (using endogenous K^{40}). A twenty-four hour urine for potassium, sodium, and creatinine will be collected. The above will be repeated prior to each discharge from the hospital and during any hypokalemic period.

6. Progress and Results: One adult female leukemic patient was entered into the protocol. Blood work for initial determination of serum electrolytes, BUN, creatinine and urine collection for creatinine studies, potassium volume were obtained. The patient did have blood work drawn for renin aldosteron and had her total body potassium counted. The patient did not develop hypokalemia subsequently and eventually died during her initial hospitalization.

7. Conclusions: No conclusion can be drawn from the above data.

8. Funds Utilized, FY 79: None

9, Funds Requested, FY 80: Expendable Supplies $1,000.00
Reprints $150.00
Presentation at American
Society of Nephrology Meeting $500.00

10. Publications: None

11. Type of Report: Interim

1. Work Unit Number: 1126 (Same as and replacing Work Unit 1112)

2. Project Title: Minoxidil as an Antihypertensive in Patients Refractory to Available Medication. (Same as and replacing Project Title: Use of Minoxidil in the Treatment of Severe, Uncontrolled or Poorly Controlled Hypertension)

3. Principal Investigator: Daniel A. Nash, Jr., LTC, MC
Associates: Suzanne M. Bergman, MAJ, MC
Khaldoun A. Nsouli, MAJ, MC
Jack Moore, Jr., CPT, MC
Michael Siedlecki, CPT, MC
J. Brian Copley, MAJ, MC
Raymond D. Pratt, CPT, MC

4. Objective: To assess the efficacy and safety of Minoxidil in severe hypertension refractory to currently available potent anti-hypertensive agents.

5. Technical Approach: Patients who are determined to be unresponsive to standard antihypertensive drugs with persistent, severe hypertension are selected for treatment with Minoxidil. The response of their hypertension to the therapy, consequential complications, intercurrent events, etc. are followed very closely. This is an uncontrolled study with results based on data from our unit and from numerous collaborators around the country and reported as clinical experience.

6. Progress and Results: Since initiation of this protocol in March 1974 at the Walter Reed Army Medical Center, nineteen patients have required entry because of hypertension refractory to standard antihypertensive therapy. At this time five patients remain active, one since 1974 and once since 1975. In each case there has been a clearly demonstrable improvement in the control on the antihypertensive medication and in the well-being of the patient. Major untoward complications directly related to the antihypertensive agent have not occurred. As a consequence of the observations and reports given to the Upjohn Manufacturing Company, the agent has been tentatively approved by the Food and Drug Administration for general use.

7. Conclusion: Minoxidil is a potent agent that is effective when other agents in use are not. Side effects and intolerance have not been limiting factors in the use of this agent in our small series. On a broader scale the preliminary results from collateral studies also appear to be favorable toward the effectiveness and tolerance of the agent. This is suggested by the apparent acceptance of the agent by the Food and Drug Administration anticipated to occur within the next several months.

8. As stated in Number 6 above, there have been no serious or unexpected side-effects/complications in the subjects participating.

9. Funds utilized FY 79: None

10. Funds Requested FY 80: None

11. Publications and Abstracts FY 79: None

12. This study is considered to be an ongoing clinical observation with no determined date for completion. In this same respect there are no specific numbers of patients required before the study is completed. It is estimated that the maintenance of data as required by the Upjohn Pharmaceutical Company will be terminated once the agent is available for general use. Thus, it is very likely from present knowledge that the project in its present form will be terminated during FY 80.

Type of Report: Interim

Work Unit No: 1212

Title of Project: Computer Assisted System for Coronary Artery Disease (CASCADE).

Principal Investigator: Patrick J. Lawrence, LTC MC

The Principal Investigator, Dr. Patrick J. Lawrence, is now a civilian living in New Hampshire.

There are no other individuals on the Cardiology Service who are interested in completing this project.

Work Unit No.: 1213

Title of Project: Electron Microscopic Evaluation of Cardiovascular Guidewires.

Principal Investigator: Patrick J. Lawrence, LTC MC

The Principal Investigator, Dr. Patrick J. Lawrence, is now a civilian living in New Hampshire.

There are no other individuals on the Cardiology Service who are interested in completing this project.

DISPOSITION FORM

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

REFERENCE OR OFFICE SYMBOL	SUBJECT
HSWP-ME	Annual Progress Reports from Kyle Metabolic Unit

TO C, Clin Invest Svc FROM Asst C, KMU DATE 26 Oct 79 CMT 1

1. Sixty seven (67) annual progress reports from the Kyle Metabolic Unit are attached and are grouped by KMU ordering authorities. Seven of these are final reports (work unit numbers 1331, 1345, 1356, 1373, 1384, 1302-78 and 1306-78).

2. These 67 reports indicate that in FY-79 KMU spent $153,727 for supplies (EOE, 2600) and $68,551 for contractural services (EOE 2572) but do not include the $7,500 for supplies spent in the KMU general laboratory supply fund. The total funds spent by KMU can be calculated in three ways which are in relative good agreement.

	Annual Reports	KMU Records	CIS Records
Supplies	$161,227	$166,000	178,767
Cont. Svc	68,551	63,500	Not Available

3. The funds requested for FY-80 as indicated on the 60 annual reports total $236,075 for supplies and $91,620 for contractural services. These amounts do not reflect the funds requested for 9 work units not included in the annual reports which are 1351, 1352, 1369, 1388, 1303-79, 1306-79, 1307-79, 1311-79, 1312-79. The total funds required by KMU for FY-80 are more accurately indicated by the COBE submitted on 30 April 1979 with $257,330 for supplies and $101,720 for contractural services. The FY-80 COBE request for these elements of expense represents a 13.2% increase over the FY-79 COBE request.

H. Linton Wray, M.D.

H. LINTON WRAY, M.D.
LTC, MC
Asst. Chief, Kyle Metabolic Unit

Work Unit # 1308

Title: Inderal Kinetics in hyperthyroidism

Principal: Kenneth D. Burman

Associates: Leonard Wartofsky

Objectives: To determine if Inderal levels correlate with clinical state in thyrotoxicosis

Technical Approach: Serum Inderal levels are measured after a single dose and again after more chronic drug administration.

Progress and Results: Although no appreciable results have been obtained on this protocol we do have preliminary results that suggest the half life of Inderal is about 90 minutes. We request that this protocol be continued because we have renewed interest in this problem mainly because it has recently been shown that Inderal inhibits T4 to T3 conversion. Also, Dr. Smallridge and Dr. Jurney on our staff have been investigating the in vitro effect of Inderal in rats and also have arranged for Dr. Schand from Vanderbilt Univ to assay their samples for Inderal. Because of this demonstrated renewed interest in this problem we request that the protocol be continued and that the above mentioned investigators be added as associates.

Funds Utilized FY 79 None

Funds requested FY80	Consumable Supplies	500
	Reprints	250

Publications None

Type of Report: Interim

DISPOSITION FORM

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

REFERENCE OR OFFICE SYMBOL	SUBJECT
HSWP-ME	Response on Work Unit Number 1308, 1311, 1348 and 1353.

XX THRU C, Clin Invest Svc FROM Kenneth D. Burman, MD DATE 11 Dec 79 CMT 1
Burman/lmm/61417

TO Richard J. Summers, MD

I have the following comments and rebuttal concerning LTC Summers comments of 6 Nov 79 regarding the following protocol and progress report, "Inderal Kinetics in Hyperthyroidism, Work Unit Number 1308.

1. LTC Summers has indicated that slight progress has been made on the protocol, of which we agree. There is no deviation from the original protocol in that all of our studies have been done in humans and that Dr. Smallridge and Dr. Jurney in conjunction with Dr. Schand from Vanderbilt University are performing in vitro studies and in vivo studies of the effect of Inderal in rats. If these studies in rats performed by my co-workers on a different study protocol do indicate that thyroid hormone has an effect on Inderal kinetics we then will return to our human study involving work unit number 1308. At the present time approximately 8 patients have been studied with Inderal kinetics, there have been no side effects in the patient studies thus far. There is no plan at the moment to consider the effect of Inderal in vitro on rats to the present protocol because it is my understanding that Dr. Smallridge and Dr. Jurney have a protocol in rats for this purpose. For further clarification we are able to determine T4 to T3 conversion estimates by just obtaining T4 and T3 measurements in these patients and that is approved.

2. Response to Work Unit 1311, Treatment of Thyroid Storm with Anion Exchange Resin. We would like to thank LTC Summers for his kind comments regarding this protocol. We believe that the present price of the resin column is approximately $500.00 and that the purpose for the request for this money is so that if a patient comes in we would be able to supply the column as indicated.

3. Response to comments regarding Work Unit Number 1346, Thyroid Function Tests in Cord and Maternal Sera. We would again like to again thank LTC Summers for his kind comments regarding the progress made on this protocol. We also believe upon reconsideration that the request for FY-80 for consumable supplies of $5,000.00 is slightly excessive and we would like to lower this request to what was used in FY-79. Specifically $3,500.00. This $3,500.00 however we would like to point out, is quite necessary for us to obtain the columns, the resins, the isotopes, and the antibodies required for use in this protocol.

3. Comments regarding Work Unit Number 1353, The Regulation of T4 to T3 Conversion. We also believe upon reflection that the request for a budget of $10,000.00 for consumable supplies is slightly excessive and would request that this be lowered to $5,000.00. However, the $5,000.00 request seems quite resonable to us because at the moment we are involved in isolating the enzyme involved in T4 to T3 conversion and that the resin involved in this system are expensive anion and canion exchange resins with sophistocated columns including pH gradients and that these supplies are expensive.

DA FORM 1 FEB 62 2496 REPLACES DD FORM 96, WHICH IS OBSOLETE.

Work Unit No.: 1310

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

Investigators:

Principal: Leonard Wartofsky, COL, MC

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

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

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

Progress & Results: Approximately 550 such studies have been completed in approximately 340 subjects. Although some data is yet to be analyzed, much already has appeared in the publications listed below. Additional related studies on elucidation of abnormalities of the hypothalamic-pituitary-thyroid axis employing TRH as a probe are still underway, however.

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

Funds Utilized FY-79:

1100	Personnel	2895
2100	Travel	600
2319	Rental	100
2400	Print. & Repro.	750
2572	Contractual Svcs.	2000
2600	Cons. Supplies	750
3100	Non-Exp. Equip.	500
TOTAL		7595

Funds Requested FY-80:

1100 Personnel	3000
2600 Cons. Supplies	2000
TOTAL	5000

Publications:

1. 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.

2. Wartofsky, L., et al, Effect of Acute Increases in Serum T_3 on TSH and PRL Responses to TRH, J Clin Endocrinol & Metab, 42:451-466, 1976.

3. 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.

4. Burman, K.D., R.C. Dimond, F.D. Wright, J.M. Earll, J. Bruton, and L. Wartofsky, A Radioimmunoassay for 3,3'5'-Triiodothyronine (Reverse T_3): Assessment of Thyroid Gland Content, Serum Measurements in Conditions of Normal and Altered Thyroidal Economy, and Serum Concentrations following Administration of TRH and TSH, J Clin Endocrinol & Metab 44:660-672, 1977.

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

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

Type of Report: Interim

Work Unit 1311

Title Treatment of Thyroid Storm with anion exchange resin

Investigators: Kenneth Burman

Associate: Leonard Wartofsky

Objective: The purpose of this protocol is to have available a treatment of thyroid storm,a very serious disease, which could be used in selected circumstances. It must be stressed that when and if such a patient comes into the hospital he will be very ill and would require immediate treatment. We request that this protocol be kept active so that it could be applied in this particular instance when it would not be possible to delay. To date such a patient has not come into the hospital and we have not had the opportunity to use this protocol.

Progress and results: No patient has yet to enter the hospital.

Technical Approach: The use of hemoperfusion and circulation of the blood through an anion excahnge resin to remove the thyronines.

Funding: Utilized FY 79 None

Requested FY 80 $500.00 for a resin column

Publications in the last year: None

Interim Report

DISPOSITION FORM

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

REFERENCE OR OFFICE SYMBOL	SUBJECT
HSWP-ME	Response on Work Unit Number 1308, 1311, 1348 and 1353.

XX THRU C, Clin Invest Svc FROM Kenneth D. Burman, MD DATE 11 Dec 79 CMT 1
Burman/lmm/61417

TO Richard J. Summers, MD

I have the following comments and rebuttal concerning LTC Summers comments of 6 Nov 79 regarding the following protocol and progress report, "Inderal Kinetics in Hyperthyroidism, Work Unit Number 1308.

1. LTC Summers has indicated that slight progress has been made on the protocol, of which we agree. There is no deviation from the original protocol in that all of our studies have been done in humans and that Dr. Smallridge and Dr. Jurney in conjunction with Dr. Schand from Vanderbilt University are performing in vitro studies and in vivo studies of the effect of Inderal in rats. If these studies in rats performed by my co-workers on a different study protocol do indicate that thyroid hormone has an effect on Inderal kinetics we then will return to our human study involving work unit number 1308. At the present time approximately 8 patients have been studied with Inderal kinetics, there have been no side effects in the patient studies thus far. There is no plan at the moment to consider the effect of Inderal in vitro on rats to the present protocol because it is my understanding that Dr. Smallridge and Dr. Jurney have a protocol in rats for this purpose. For further clarification we are able to determine T4 to T3 conversion estimates by just obtaining T4 and T3 measurements in these patients and that is approved.

2. Response to Work Unit 1311, Treatment of Thyroid Storm with Anion Exchange Resin. We would like to thank LTC Summers for his kind comments regarding this protocol. We believe that the present price of the resin column is approximately $500.00 and that the purpose for the request for this money is so that if a patient comes in we would be able to supply the column as indicated.

3. Response to comments regarding Work Unit Number 1346, Thyroid Function Tests in Cord and Maternal Sera. We would again like to again thank LTC Summers for his kind comments regarding the progress made on this protocol. We also believe upon reconsideration that the request for FY-80 for consumable supplies of $5,000.00 is slightly excessive and we would like to lower this request to what was used in FY-79. Specifically $3,500.00. This $3,500.00 however we would like to point out, is quite necessary for us to obtain the columns, the resins, the isotopes, and the antibodies required for use in this protocol.

3. Comments regarding Work Unit Number 1353, The Regulation of T4 to T3 Conversion. We also believe upon reflection that the request for a budget of $10,000.00 for consumable supplies is slightly excessive and would request that this be lowered to $5,000.00. However, the $5,000.00 request seems quite resonable to us because at the moment we are involved in isolating the enzyme involved in T4 to T3 conversion and that the resin involved in this system are expensive anion and canion exchange resins with sophistocated columns including pH gradients and that these supplies are expensive.

Work Unit: 1329

Title: Lithium effects on thyroid

Investigator: Principal Kenneth Burman

Associate: Leonard Wartofsky

Objective: To ascertain the effects of Lithium on peripheral conversion

Technical Approach: The use of radiolabelled T3 and T4 to determine the T4 to T3 conversion rate. Hypothyroid subjects on exogenous T4 are treated and the kinetics and peripheral levels of T4 and T3 measured. The clinical importance of these studies are that Lithium is an agent that will be increasingly used in the treatment of thyrotoxicosis and this protocol will help determine its mechanism of action.

Progress and Results: No patients have been studied in the last year.

Conclusion: Lithium probably influences T4 to T3 conversion

Funds Utilized: FY 79 $1,070

Publications None in the last year

Type of report: Terminated

Work Unit Number: 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: Kenneth D. Burman, LTC MC

Leonard Wartofsky, COL MC

Objectives: To compare the inhibitory effect of iodine and lithium upon thyroidal release in thyrotoxicosis and evaluate whether the addition of each drug to the other achieved any additional benefit.

Technical Approach: In brief, a double isotope technique was used to measure thyroidal release and parameters of peripheral thyroid hormone metabolism. There were no modifications to the original protocol, except that some patients received slightly smaller amounts of ^{125}I- and ^{131}I-T4 than specified in the original protocol.

Progress and Results: Twenty-one 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 additional benefit was observed regardless of whether methimazole was employed. Three additional patients received iodine during both treatment periods, no additional decrease in release was seen during the second iodine treatment period, ruling out a cumulative iodine effect as the origin of the additional benefit seen when lithium was added to iodine.

Progress and Results: 1. Lithium and iodine are comparably efficacious in inhibiting thyroidal release.

2. An additional inhibition of thyroidal release is seen when lithium is added to preestablished iodine therapy.

Conclusions: There were no serious/unexpected side effects. Several patients experienced a mild increase in thirst and malaise on lithium, but these side effects were expected.

Funds Utilized, FY-79: None

Funding Requirements, FY-80: None except for reprints/page charges.

Publications: "Lithium and iodine combination therapy for thyrotoxicosis", accepted for publication in Acta Endocrinologica.

Type of Report: Project is terminated effective the date of publication; there will be no further patient entry onto the study.

Work Unit No.: 1334

Title of Project: The Regulation of T4 to T3 Conversion

Investigators: Burman, Smallridge, Latham and Wartofsky

Objective: To isolate the enzyme responsible from T4 to T3 conversion.

Technical Approach: Column chromatography

Progress and Results: This protocol overlaps with project #1353, but the major purpose of this protocol over the next several years is for us to isolate and purify the enzymes systems involved in T4 and T3 conversion. Preliminary studies, usually clinical in nature, have been published (Metab 28: 805, 1979).

Conclusions: In progress

Have there been any adverse reactions? No

Funds utilized FY-79:		Funds requested FY-80:
Travel:	$1,000	$1,000
Printing:		500
Consumable:	6,000	6,000
Total	7,000	7,500

Publication: As above

Type of report: Interim

Estimated date of completion and/or number of more studies to be performed including plan over next 1-3 years: To isolate and purify the enzymes will involve about 3 years.

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 E. Smith, MAJ, MC

Associate Investigators: Leonard Wartofsky, COL, MC, Kenneth D. Burman, MAJ, MC
Robert Kaminski, LTC, 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: 10 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 iodine (I_s), thyroidal ^{127}I (I_t) by fluorescent scan. In addition, two 24 hour urines per week will be collected and 24 hour iodide excretion (I_u) determined. At the end of each study period a perchlorate discharge test (Cl_2) will be performed.

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

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

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

Study Period II: Propylthiouracil 450 mg/day.

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

Study Period III: Propylthiouracil 1200 mg/day.

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

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

Study ends at one week.

Progress & Results: 10 patients have been studied to date and the data is presently being evaluated. Attempts are being made to recruit additional patients, although it is anticipated that there will be some delay due to the absence of the principal investigator who is on temporary duty in Germany. Studies to resume in 1980.

Conclusions: None as yet

Funds Utilized FY-79: Consumable Supplies $ .00

Funds Requested FY-80:

1100	Personnel	2000
2100	Travel	400
2319	Rental	200
2400	Print. & Repro.	400
2572	Constractual Svcs.	1000
2600	Cons. Supplies	2000
3100	Non-Expendable Equip.	0
	Total	6000

Publications: None published (One abstract submitted)

Type of Report: Interim

In response to his request for information we can state that there were absolutely no unexpected side effects or increased incidence of side effects related to any of the therapeutic manipulations detailed in the study protocol in any patients studied to date.

Work Unit: 1345

Title: Conversion of testosterone to estradiol

Principal: Kenneth Burman

Objectives: To determine if testosterone conversion is altered in Klinefelters Syndrome

Technical Approach: Isoptopes

Progress and Results: None Request that this protocol be discontinued

Funds Utilized FY 79 None

Final Report

Work Unit No: 1346

Title of Project: Thyroid Function Tests in Cord and Maternal Sera

Investigators: Burman, Smallridge, Wartofsky, Pangaro, and Cannmann

Objective: To measure levels of thyronines in cord blood and maternal blood and AF are obtained.

Progress and Results: We have completed several measurements in these fluids and have determinated that T4, T3, and T2 all exist in them. The plan is to measure other thyronines as their assays become available, for example, T1 and To

Conclusions: Reverse T3 can be used to assess thyroid status of babies in utero.

Have there been any adverse reactions? No

Funds utilized, FY-79		Funds requested, FY-80	
Travel	$2,000		$2,000
Contractual	500		
Printing			500
Consumable	1,000		5,000
Total	$3,500		7,500

Publications: JCEM 46:32, 1979, JCEM 47:1059, 1978, JCEM in press concerning 3512.

Type of Report: Interim

Date of Completion: We request extension of this protocol to cover the next three years as we develop assays for T1 and To.

DISPOSITION FORM

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

REFERENCE OR OFFICE SYMBOL	SUBJECT
	Response to CIS re protocols 1346,1353

TO CIS FROM Ken Burman,MD,LTC DATE 19 Dec 79 CMT 1

1. Re protocol 1353-125 I T3 1000uci/ug one vial (500uci) every month for 12 months- cost of each vial about 250 dollars, total cost 3000 dollars
125 I T4 one vial (500 uci) every month for twelve mohths- cost of each vial about 250 dollars, total cost 3000 dollars
125 I reverse T3 (500 uci) every month for 12 months cost of each vial about 250 dollars, total cost 3000 dollars.
Oth er consumable supplies such as reagents, chemical, columns add up to about 1000 dollars- Sephadex-400 dollars;

2. As detailed above, the budget suggested on the original progress report was and continues to be what we consider reasonable. It should be noted that this protocol constitutes the major endeavor of our group including the time of Mrs. Wright, Lukes, Dr. Latham , Dr. Tseng, and portions of the time of other individuals. In addition, we believe that sufficient progress has been documented in this and all other protocols to substantiate our request as reasonable.

3. If , however, it is not possible to fund the requested amount we respefully request that the isotope be funded every other month, but, of course, this is less desirable since the results from isotope that is over 6 weeks old may be in question.

4. Attached addendum added for protocol 1346 as requested.

5. Thank you.

Ken Burman

DISPOSITION FORM

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

REFERENCE OR OFFICE SYMBOL	SUBJECT
	Addendum to protocol 1346

TO ~~CIS~~ FROM ~~Ken Burman~~ DATE ~~19 Dec 79~~ CMT 1

1. Request that protocol 1346 be amended to allow us to measure 3,5 T2, 3'5'T2, 3'T1, TO and Tetrac in cord blood, maternal blood, and amniotic fluid. In order to perform these studies, we need to extend the number of patient studied so that we are also requesting that we be able to measure these parameters in 20 more subjects. It should be emphasized that the original consent form and volunteer agreement still apply and can be used and that there is absolutely no additional risk to this addendum.; all it actually emphasizes is that the patients will have full knowledge of all of the tests that there blood will be used for in addtion to those outlined in the original protocol.

2. Our recent advances in understanding of thyroid hormone physiology and our ability to develop newer tests of thyroid function have been made largely due to the approval of our first original protocol.

3. Thank you.

Ken Burman

Ken Burman, MD

DA FORM FEB 2 2498 EDITION OF 1 JUL 55 IS OBSOLETE.

Work Unit No: 1347

Title: Investigations into the physiology of rT3 and 3,3'T2.

Investigators: Burman, Latham, Smallridge, and Wartofsky

Objective: To determine the influences that alter conversion.

Technical Approach: Serum measurements

Progress and Results: We have performed many clinical studies and have shown that rT3 clearance is altered by thyroid state (JCEM 46:32, 1979). Our main purpose over the next several years is to investigate the factors influencing 3,3'T2 levels and clearance. Specifically, unlabelled infusions of this and other thyronines will be given during fed and fasting states and to hyper and hypothyroid subjects.

Conclusions: rT3 clearance is increased in thyrotoxicosis

Have there been any adverse reactions? No

Funds utilized, FY-79:		Funds requested, FY-80:	
Travel	$1,000		$1,000
Contractual	500		500
Consumable	2,500		2,500
Total	$4,000		$4,000

Publication: None

Type of report: Interim

To perform the studies outlined above will take about three years.

Work Unit No: 1353

Title of Project: The Regulation of T4 to T3 Conversion

Investigators: Burman, Wartofsky, Smallridge and Latham

Objective: To study the factors regulating T4 to T3 conversion.

Technical Approach: Serum measurements and isotopes

Progress and Results: This study has several aspects. We have determined serum measurements in various metabolic states of thyroid hormones (Metabolism 28:605, 1979), and have also determined in vitro factors regulating conversion such as T4 administration to rats. (Article tentatively accepted by Acta Endocrinologica.) We are in the process of extending these observations to other hormones such as 3ST3 and T1.

Conclusions: Stress, glucose and T4 alter T4 to T3 conversion.

Have there been any adverse reactions? No

Funds utilized FY-79:		Funds requested FY-80
Travel	$1,000	$1,000
Printing		500
Consumable	1,000	1,000
	$2,000	$2,500

Publication: See above.

Type of report: Interim

We will extend our studies to other lesser iodinated thyronines and will also isolate the enzymes involved in T4 to T3 conversion. Such isolation would have tremendous clinical application although this represents a full time effort for about two years.

DISPOSITION FORM

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

REFERENCE OR OFFICE SYMBOL	SUBJECT
HSWP-ME	Response on Work Unit Number 1308, 1311, 1348 and 1353.

XX THRU C, Clin Invest Svc FROM Kenneth D. Burman, MD DATE 11 Dec 79 CMT 1
Burman/lmm/61417

TO Richard J. Summers, MD

I have the following comments and rebuttal concerning LTC Summers comments of 6 Nov 79 regarding the following protocol and progress report, "Inderal Kinetics in Hyperthyroidism, Work Unit Number 1308.

1. LTC Summers has indicated that slight progress has been made on the protocol, of which we agree. There is no deviation from the original protocol in that all of our studies have been done in humans and that Dr. Smallridge and Dr. Jurney in conjunction with Dr. Schand from Vanderbilt University are performing in vitro studies and in vivo studies of the effect of Inderal in rats. If these studies in rats performed by my co-workers on a different study protocol do indicate that thyroid hormone has an effect on Inderal kinetics we then will return to our human study involving work unit number 1308. At the present time approximately 8 patients have been studied with Inderal kinetics, there have been no side effects in the patient studies thus far. There is no plan at the moment to consider the effect of Inderal in vitro on rats to the present protocol because it is my understanding that Dr. Smallridge and Dr. Jurney have a protocol in rats for this purpose. For further clarification we are able to determine T4 to T3 conversion estimates by just obtaining T4 and T3 measurements in these patients and that is approved.

2. Response to Work Unit 1311, Treatment of Thyroid Storm with Anion Exchange Resin. We would like to thank LTC Summers for his kind comments regarding this protocol. We believe that the present price of the resin column is approximately $500.00 and that the purpose for the request for this money is so that if a patient comes in we would be able to supply the column as indicated.

3. Response to comments regarding Work Unit Number 1346, Thyroid Function Tests in Cord and Maternal Sera. We would again like to again thank LTC Summers for his kind comments regarding the progress made on this protocol. We also believe upon reconsideration that the request for FY-80 for consumable supplies of $5,000.00 is slightly excessive and we would like to lower this request to what was used in FY-79. Specifically $3,500.00. This $3,500.00 however we would like to point out, is quite necessary for us to obtain the columns, the resins, the isotopes, and the antibodies required for use in this protocol.

3. Comments regarding Work Unit Number 1353, The Regulation of T4 to T3 Conversion. We also believe upon reflection that the request for a budget of $10,000.00 for consumable supplies is slightly excessive and would request that this be lowered to $5,000.00. However, the $5,000.00 request seems quite resonable to us because at the moment we are involved in isolating the enzyme involved in T4 to T3 conversion and that the resin involved in this system are expensive anion and canion exchange resins with sophistocated columns including PH gradients and that these supplies are expensive.

DISPOSITION FORM

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

REFERENCE OR OFFICE SYMBOL	SUBJECT
	Response to CIS re protocols 1346,1353

TO CIS FROM Ken Burman,MD,LTC DATE 19 Dec 79 CMT 1

1. Re protocol 1353-125 I T3 1000uci/ug one vial (500uci) every month for 12 months- cost of each vial about 250 dollars, total cost 3000 dollars
125 I T4 one vial (500 uci) every month for twelve mohths- cost of each vial about 250 dollars, total cost 3000 dollars
125 I reverse T3 (500 uci) every month for 12 months cost of each vial about 250 dollars, total cost 3000 dollars.
Oth er consumable supplies such as reagents, chemical, columns add up to about 1000 dollars- Sephadex-400 dollars;

2. As detailed above, the budget suggested on the original progress report was and continues to be what we consider reasonable. It should be noted that this protocol constitutes the major endeavor of our group including the time of Mrs. Wright, Lukes, Dr. Latham , Dr. Tseng, and portions of the time of other individuals. In addition, we believe that sufficient progress has been documented in this and all other protocols to substantiate our request as reasonable.

3. If , however, it is not possible to fund the requested amount we respefully request that the isotope be funded every other month, but, of course, this is less desirable since the results from isotope that is over 6 weeks old may be in question.

4. Attached addendum added for protocol 1346 as requested.

5. Thank you.

Ken Burman

DA FORM 1 FEB 57 2496 REPLACES DD FORM 96, WHICH IS OBSOLETE.

Work Unit No.: 1354

Title: Purification of Testosterone-estradiol Binding Globulin

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

Objective: To purify and characterize the beta-globulin which is responsible for binding testosterone and estradiol in plasma in order to study the physiologic effects of steroid binding on target tissue function and to develop a radioimmunoassay for the protein.

Technical Approach: Serial purification methods are used, e.g., perparative polyacrylamide gel electrophoresis, affinity chromatography, temperature dependent affinity chromatography, isotachophoresis, gel filtration on G-100 Sephadex and Sephacryl.

Progress and Results: Technical assistance was provided during the last 6 months from March 1979. Since that time we have established elution profiles for the protein on Sephadex G-100 and Sephacryl with an approximate 200-fold purification from the latter step. We have established a new type of affinity column using Concanavilin A with the elution solute being a linear gradient of alpha-methylmannoside and have developed the elution profile of standard proteins and testosterone-estradiol binding globulin on this column. In addition, we have used Amicon filtration for concentration of a greater than 90,000 m.w. retentate. Affinity chromatography and preparative polyacrylamide gel electrophoresis are currently being attempted.

Conclusions: Major progress has been made in establishing the techniques necessary for serial step-wise purification of testosterone-estradiol binding globulin.

Funds Utilized, FY-79: None

Funds Requested, FY-80: (Note - partial funding from grant from U.S.U.H.S.

Supplies, gnrl	$5000
Printing, publication	500
Rental	200
Isotopes	400
Travel	500
Total	$6600

Publications: None

Estimated Date of Completion: Sept. 30, 1981.

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: Timothy M. Boehm, MAJ MC

Objectives: To ascertain whether high dose steroid inhibits thyroidal release in thyrotoxicosis and to quantify effects of high dose steroid upon peripheral thyroid hormone metabolism.

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

Progress and Results: Three patients have completed study. Serious questions have arisen regarding the validity of the double isotope technique as a measure of thyroidal release. In addition, other protocols involving thyrotoxic patients have been assigned a higher priority. It is anticipated that 3-5 patients may be entered on study during FY-80. There have been no serious unexpected side effects.

Conclusions: None

Funding Requirements (FY-80): None

Funds Utilized, FY-79: None

Time Required to Complete: June 1980

Type of Report: Interim

Work Unit No.: 1356

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

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

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 patients are hyperthyroid before being put on therapy. Semen analysis performed on at least 3 occasions with motitlity, morphology, and density being analyzed. Pituitary and testicular reserve measured via LHRH and HCG tests, respectively.

Progress and Results: Of the seven patients studied, abnormal semen analysis was found in 4 of 6 in whom it was performed and the hormonal studies showed partial Leydig cell failure with abnormal feedback regulation of gonadotropins.

Conclusion: Men with hyperthyroidism have several abnormalities of the pituitary-gonadal axis which involved the Leydig cell, seminiferous tubule, and feedback regulation.

Funds Utilized, FY-79: $2,000 (2572)

Funds Requested, FY-80: None

Publications, FY-79: Kidd, G.S., Glass, A.R., and Vigersky, R.A., The hypothalamic-Pituitary-Testicular Axis in Thyrotoxicosis, J. Clin. Endo. Metab. 48: 798, 1979.

Estimated Date of Completion: Study is presently completed. This is a final report.

Work Unit No: 1357

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

Investigators:

Principal: H. Linton Wray, LTC, MC

Associates: Kenneth D. Burman, LTC, MC, Robert C. Smallridge, LTC, MC, Leonard Wartofsky, COL, 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 (T_3) and 3,3',5' triiodothyronine (reverse T_3, rT_3).

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

Progress and Results: Three hypothyroid patients treated with T_4 have shown an increase in plasma cyclic AMP and a decrease in nephrogenous cyclic AMP without a significant change in urine cyclic AMP. The data for cyclic GMP appears to show no change.

Conclusions: Thyroid hormones particularly T_3 are important in regulating extracellular cyclic AMP levels in humans.

Funds Utilized, FY-79:

2600	Supplies	$ 486

Funds Requested, FY-80:

2600	Supplies	$4,000
2572	Contract Svc	

Publications: None

Type of Report: Interim

Work Unit: 1358

Title: The effect of obesity and fasting on T 3 receptors in circulating mononuclear cells

Principal: K D Burman

Associates: K Latham, Leonard Wartofsky

Objectives: To determine if white cell receptors are altered in obese subjects both while eating and fasting

Technical Approach: Patients are studied while eating a regular diet and again while fasting. The period of fasting can last as long as 14-17 days. White cell T3 receptors are studied at each feeding or fasting interval.

Progress and results: Significant important findings relevant to thyroid hormone action has resulted from this protocol and will continue to emanate from this study over the next few years. Specifically, we have proven that T3 white cell receptors are lower in obese subjects than normal and that fasting causes an increase in white cell receptors. We have also shown that the cell binding is mediated through the lymphocytes. A very tight normal range has been derived and the assay has been found to be excellent.

Plans: Over the next several years we hope to continue in this protocol to find out exactly what type of cells mediating binding and the precise mechanism of the increased binding in fasting. The clinical protocol will remain the same but further detailed studies will be conducted in the lab to prove if the T3 receptor in white cells is similar to that in animal tissues.

Conclusion: Fasting raises T3 receptors in white cells

There have been no serious side effects to any patient in this protocol

Funds Utilized: FY 79	Personnel:	$3,000
	Consumable:	4,000
		$7,000
Funds requested FY 80:	Personnel:	3,000
	Consumable:	5,000
	Printing:	500
	Total	$8,500

Publications: Burman, KD et al, Solubilized nuclear T3 and T4 receptors in circulating mononuclear cells, Presented at the Endocrine Society, June, 79, Anaheim, Ca

Publications: An article with the same title and authors as the above mentioned abstract hasbeen submitted for publication at the Journal of Clinical Investigation. The original article was sent the fifth of May 1979 and the revised manuscript was sent Sept 7, 1979.

Type of Report: Interim

Work Unit No.: 1359

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

Investigators: Kenneth D. Burman, MAJ MC
Timothy M. Boehm, MAJ MC
Leonard Wartofsky, COL MC

Objective: To determine if reverse T3 influences T4 levels and kinetics.

Technical Approach: Reverse T3 is given and labelled, T4 is also given.

Progress and Results: About 10 patients have been studied and the data is being evaluated. It appears that reverse T3 will not influence T4 levels or kinetics. Because the data is still being evaluated, it is requested that this protocol be continued as active in case the data when finally analyzed will require the study of several more patients.

Conclusions: Reverse T3 does not influence T4 clearance rate.

Have there been any adverse reactions? No

Funds Utilized, FY-79		Funds Requested, FY-80
Personnel	$3,000	
Contractual:	5,000	$ 500
Consumable:	3,500	2,000
Non Expendable		500
Total	$11,500	$3,000

Publications: None yet

Type of Report: Interim Estimated date of completion: Within the next year.

Work Unit No.: 1360

Title of Protocol: Investigations Concerning T3 Production Rates.

Investigators: Kenneth D. Burman
Robert C. Smallridge
Charles Smith
Leonard Wartofsky
B. J. Green

Objective: To see if cold and hot (isotope) clearance rates are identical.

Technical Approach: Administer cold and hot hormones to subjects and compare MCR.

Progress and Results: This represents one major clinical area we have been working on. In short, we have determined that thyroid hormone production rates can be performed only by giving an unlabelled infusion and not giving isotope. This will make such tests much easier in the future. At present, we have only proven this works for 3'5'T2 and need to prove it for T3 and 3,3'T2 and T4. These studies will be done over the next two years. It should be noted that publication of our present results will revolutionize the way all investigators in the country measure thyroid hormone production rates.

Conclusions: PR can be performed by giving unlabelled hormones.

Have there been any adverse reactions? No

New additional investigators: B.J. Green from Abbott Labs, supplies the isotope free of charge (3'5' and 3')

Funds utilized FY-79		Funds requested FY-80
Personnel:		$1,000
Travel:	500	
Printing:		500
Consumables	1,000	1,000
Total	$1,500	$2,500

Publications: Abstract presented at annual Endocrine meeting, Anaheim, Ca, June 1979. (Full manuscript almost completed will be sent for publication this month.)

Type of Report: Interim

To continue with T3, T4 and lesser thyronines will take three years.

Work Unit: 1361

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

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

Objective: Determination of the way in which the hypothalamic-pituitary-testicular axis responds to surgery

Technical Approach: Blood sampling before and after surgery, with measurement of appropriate hormones by RIA or binding assays.

Progress, Results, Conclusions, Papers:
This project has been largely completed during the past fiscal year, and a paper has appeared in Fertility and Sterility. No additional subjects have been studied. The remaining portion of the study will involve measurement of sex-hormone-binding-globulin on the samples. Work is ongoing to set up this assay, but progress has been impeded by failure to obtain a temporary hire technician, which was approved by CIS, because of budget limitations. It is anticipated that this project will be completed during FY 80.

Funds Used FY-79: 0

Funds requested FY 80: $1,000 (2600)

Type of Report: Interim

Work Unit No.: 1362

Title of Project: Medical Treatment of Amenorrhea-Galactorrhea Syndromes with Vitamin B6 (Pyridoxine)

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

Objectives: To evaluate the effects of pyridoxine on the elevated levels of prolactin and on the symptoms of amenorrhea and galactorrhea.

Technical Approach: Pre- and post-treatment testing of LH, FSH, prolactin, growth hormone and TSH with TRH, LHRH and intravenous pyridoxine tests and the intra- and post-treatment course of the patients.

Progress and Results: The preliminary analysis of the data show that acute and chronic pyridoxine therapy have no significant effect on the prolactin levels either basally or during the provocative testing. There was a clinical response with resumption of menses in 2 of the 6 patients, however, suggesting other mechanisms of action of the drug.

Conclusions: Pyridoxine does not have an effect on the prolactin levels in patients with hyperprolactinemia and amenorrhea-galactorrhea syndromes but may be a safe method of resuming menses in some patients though the mechanism of this is unclear.

Side Effects or Complications: There have been no adverse effects associated with the use of pyridoxine.

Funds Utilized, FY-79: $2450 (2572)

Funds Requested, FY-80:

Printing and publication	$ 500
Travel	500
Total	$1000

Publications: Kidd, G.S., Dimond, R., and Vigersky, R.A., Response of Hyperprolactinemic Women to Short Term and Long Term Pyridoxine Therapy, Fert. and Ster., submitted for publication.

Estimated Date of Completion: March, 1980.

Type of Report: Interim

Work Unit No: 1363

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

Investigators:

Principal: H. Linton Wray, LTC, MC

Associates: Kenneth D. Burman, LTC, MC, John P. Alford, CPT, V.C., Leonard Wartofsky, COL, 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 T_3, rT_3).

Technical Approach: Plasma cyclic AMP, cyclic GMP and serum T_3, rT_3 and T_4 will be measured before, during and after 6 days of intramuscular administration of placebo, T_3, rT_3 or both T_3 and rT_3 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.

Progress and Results: Five groups of sheep have completed the study protocol with the following treatments (1) placebo, (2) 1.5 ug T_3/kg body weight, (3) 4.5 ug T_3/kg body weight, (4) 4 ug rT_3/kg body weight, and (5) 1.5 ug T_3/kg body weight and 2.5 ug rT_3/kg body weight. Measurement of the experimental parameters is only partially completed. Analysis of the cyclic nucleotide data revealed that only the high dose of T_3 changed the cyclic nucleotide levels. Lower dose of T_3 only or in combination with rT_3 did not change cyclic nucleotide levels. T_3 of 4.5 ug/kg caused a 52% increase in cyclic AMP without changing cyclic GMP. Measurements of the serum levels of T_3 and rT3 metabolites, 3,3'-diiodothyronine ($3,3'T_2$), 3',5'-diiodothyronine ($3',5'T_2$) and 3'-monoiodothyronine ($3'T_1$) has been performed on the samples from this study. Administration of T_3 at both doses increased $3,3'T_2$ without increasing $3',5'T_2$ or $3'T_1$. Administration of rT_3 alone or in combination with T_3 increased $3,3'T_2$ and $3',5'T_2$ with only a minimal and nonstatistically significant increase in $3'T_1$.

Conclusions: Short-term elevations of serum T_3 and rT_3 to levels associated with hyperthyroidism caused no change in plasma cyclic AMP or cyclic GMP. Higher levels of T_3 caused an increase in cyclic AMP without changing cyclic GMP. The increases noted in the thyronine metabolites suggest that; (1) T_3 and rT_3 are important precursor of $3',3'T_2$, (2) rT_3 is an important precursor of $3',5'T_2$, (3) T_3 may cause increased conversion of rT_3 to $3,3'T_2$ and (4) $3'T_1$ is present in normal sheep serum and not changed significantly by short-term increases in its putative precursors, $3,3'T_2$ and $3',5'T_2$.

Funds Utilized, FY-79:

2600	Supplies	$3,452

Funds Requested, FY-80:

2600	Supplies	$2,500

Publications:

Wray, H.L., Burman, K.D., Smallridge, R.C., Alford, J.P., Butler, V.M., Wright, F.D., Wartofsky, L., Effect of T_3 and reverse T_3 administration on serum tri-, di-, and mono-iodothyronines and plasma cyclic nucleotides in sheep, Endocrinology (submitted August 1979).

Type of Report: Interim

Work Unit: 1364

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

Investigator: Allan R. Glass, M.D., MAJ MC (principal)

Objective: To determine the role of the serotoninergic system in the regulation of gonadotropin secretion

Technical Approach: Determination of basal plasma gonadotropins and response to stimulation with estrogen or LHRH before and after administration of L- tryptophan

Progress and Results:

No subjects have been studied during the past year due to difficulty in recruiting subjects. Furthermore, failure to obtain a promised temporary hire technician, due to budget cutback, has greatly increased amount of time the principal investigator had to spend on other projects. At a recent meeting on the regulation of pituitary hormones, it became clear that such a study is needed, and therefore it is hoped to begin more active work on this protocol during FY 80.

Funds Used FY-79: 0

Funds requested FY 80: $2,000 (2600)

Type of Report: Interim

Work Unit: 1365

Title: Insulin resistance in diabetes: relative effect on glucose and amino acid

Investigators: Allan R. Glass, M.D. (Principal)
Timothy S. Boehm, M.D.
Rodolfo Bongiovanni
Charles Smith, M.D.

Objective: To determine whether, in states of insensitivity to insulin, such as obesity, whether there is insensitivity to insulin's effects on amino acids as well as its effects on glucose.

Technical Approach: Determination of the disappearance rate (IV bolus method) of glucose alone, valine alone, and glucose plus valine; in normal subjects and those with states of insulin insensitivity, including obesity

Results, Progress, and Conclusions:
The valine assay has been thoroughly developed. One paper has been published on the valine assay, and another is in preparation. Approximately 35 patients have been studied during the past year, but all the assays have not yet been run. As soon as 3 more obese subjects have been studied, the data will be compiled, and an abstract and a paper will be prepared. At that time, we will proceed with the rest of the protocol, including the study of other states of insulin insensitivity, as well as the effect of fasting. It is hoped to study 30-40 additional patients during the coming year. No side effects have been encountered.

Funds Used FY 79 (EOE 2600): 4232.00 (2572) $5,900

Funds Requested FY 80: $6,800 (2600)

$8,000 (2572)

Type of Report: Interim

Work Unit #: 1366

Title of Project: The Effect of Glucagon on Thyroidal Economy.

Investigators: Kenneth D. Burman
Leonard Wartofsky
John T. O'Brian
Robert C. Smallridge
Linda Jones

Objective: To see if glucagon alters thyroid hormone levels.

Technical Approach: Glucagon infusions for three hours and measure T3, T4 and rT3.

Progress and Results: Fifteen patients have been studied and to date it seems that small levels of T3 decreas T3 levels and it can be assumed that the drop in serum T3 during fasting is the reason glucagon levels rise.

Conclusions: T3 regulated glucagon

Have there been any adverse reactions? No

New added investigators: As above including Linda Jones from Nichols Institute in LA who is doing column chromatography.

	Funds utilized, FY-79:	Funds requested, FY-80:
Personnel:	$3,000	$3,000
Printing:		500
Contractual:	3,000	2,000
Consumable:	10,000	10,000
Total	$16,000	$15,500

Publications: Clin Rsch 27:243, 1979; Burman et al., same title as above.

Type of Report: Interim - We request continuance of this protocol so that column chromatographic studies can be done on the samples to see what molecular weight glucagon is being measured.

Perhaps 10 more patients will be done and this should take about another year and one half.

Work Unit: 1367

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

Investigators: Allan Glass, MD.. (Principal)
Nabil Gemayel, M.D.

Objective: To determine the effects of central acting alpha adrenergic agonists on release of serum LH and testosterone.

Technical Approach: Determination of basal hormone levels, pattern of pulsatile release of LH, and testosterone reserve with HCG before and after administration of aldomet or clonidine

Results, Progress, and Conclusions:
No patients were studied under this protocol during the past year, due primarily to difficulty in recruiting(collapse of the hypertension clinic at WRAMC). For FY 80, a co-investigator has been recruited to participate in this study, and it is anticipated that 10 subjects will be studied during FY 80. Emphasis will be placed on the study of clonidine, as outlined in the protocol addendum. Progress on this protocol may be hampered due to the fact that temporary hire technician, who was to work in part on this protocol, is not available due to WRAMC hiring freeze.

Funds Used FY 79 (EOE 2600): 0

Funds Requested FY 80: (EOE 2600) $4,500.00

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: Wayman W. Cheatham, CPT, MC, Joseph Bruton, Ph. D., Rodolfo Bongiovanni, CPT, MSC, Ira Mehlman, LTC, MC

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-dihydroxy-vitamin D) are changed by short-term manipulation of dietary phosphate intake in hypothyroid 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 phosphorus). During the period of phosphate restriction, phosphate-binding antiacids 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 soultion), 100 ml at 0900, 1400 and 1700). Adjustments will be made in the dosage of antiacids 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 hour 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 and Results: Six patients have undergone this protocol which was effective in regard to lowering the urinary and serum phosphate levels; however, the doubling of urinary magnesium in response to the high doses of antiacids will require the inclusion of an antiacid treated plus phosphate-repleted group of patients. The assays for the Vitamin D metabolites have not been adequately worked out and, therefore, delay the critical analyses for this study. The methodologies of these assays is presently undergoing modification and should be usable in the near future.

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

Funds Utilized - FY 79:

2572	Contract Svc	$ 200
2600	Supplies	20,291
		$20,491

Funds Requested - FY 80:

2572	Contract Svc	$ 4,000
2600	Supplies	25,000
		$29,000

Publications: None

Type of Report: Interim

Work Unit No.: 1370

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

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

Objectives: To detect, quantitate and characterize the estrogen and androgen receptors in the human thyroid gland.

Technical Approach: Thyroid tissue, obtained at the time of surgery, are homogenized in Tris-EDTA-DTT buffer and the homogenate spun at 100,000 x g. The supernatant is used to generate Scatchard plots for analysis of binding affinity and capacity and to run an sucrose density gradients and Sephadex chromatography columns to characterize the receptor physico-chemically.

Progress and Results: Technical advances in the development of methods of analysis using the rat thyroid in Protocol 1381 will permit the analysis of the human tissue that is currently frozen and tissue will be obtained during future surgical procedures.

Conclusions: None

Funds Utitlized, FY-79: $1163.36 (EOE 2600)

Funding Requirement, FY-80:

Personnel	$7,800
Supplies	5,600
Printing	300
Rentals	400
Isotopes	750
Travel	500
Total	$15,350

Publications: None

Estimated Date of Completion: Sept. 1981.

Type of Report: Interim

Work Unit#: 1371

Title: Glucose regulation in fasted subjects

Investigators: K.D. Burman, LTC, L. Wartofsky, COL, R.C. Smallridge, LTC

Objective: To see if glucose administration changes rT3 and T3 levels

Technical Approach: Subjects are studied during a fed period and agian during fasting and serum thyroid hormones are measured at both ti

Progress and Results:

15 patients have been studied and we have showm that 400 cal of pure glucose will increase T3 and decrease rT3 levels

We request continuance of this protocol so that we can moee definitively study whther it is pure carbohydrate of glucose that has this effect. Also we would like to see the effect of glucoes on T3, 3'5'T2, and 3,5T2 as well as T1.

Conclusions Glucose increases T3 levels

Have there been any adverse reactions: No

New added investigators: As above

Funds Utilized FY 79:		Funds requested FY 80
Personnel:	2000	
Travel:		500
Rental:		
Printing:	500	500
Contractual	500	500
Consumable:	2500	5000
Non expendable:		
Medcase:		
Total	5500	6500

Publications:
Clin Researcn 26:611, 1978 Metabolism 28:291, 1979

Estimated date of completion and/or number of more studies to be performed including plan over next 1-3 years:

If allowed to re study ten patients and use these newer assays we will do in one year.

Type of Report: Interim

Work Unit#: 1372

Title: Alterations in TRH stimulation in obesity and fasting

Investigators: K.D. Burman, LTC, R.C. Smallridge, LTC, L. Wartofsky, COL

Objective: To determine if TSH decreases during fasting

Technical Approach: TRH INfusions are performed during fed and fasting and TSH measured.

Progress and Results:

About 15 patients have been studied and it is clear that TRH physiology is perturbed during fasting as TSH respons decreases compared to fed state

Conclusions: TSH response decreased in fasting.

Have there been any adverse reactions: No

New added investigators: As above

Funds Utilized FY 79:		Funds requested FY 80
Personnel:	2000	
Travel:		
Rental:		
Printing:		500
Contractual:		
Consumable:	5000	7000
Non expendable:		
Medcase:	2000	____
Total	9000	7500

Publications:
Clin Research 27:248, 1979; Burman, et al, article in press, Metabolism

Estimated date of completion and /or number of more studies to be performed including plan over next 1-3 years:
Because above study was so successful and has resulted in a more clear understanding of TRH physiology we plan to now confirm and repeat above studies and measure alpha and beta subunits of TSH

Type of Report: Interim

Work Unit#: 1373

Title: The effect of protein on thyroid hormones

Investigators: K.D. Burman, LTC, L. Wartofsky, COL, J. O'Brian, Cdr

Objective: To see if protein ingestion increases T3 levels

Technical Approach: Serum is drawn both during fed and fasting periods

Progress and Results: 15 patients have been studied and 400 cal of protein does not increase T3 or decrease reverse T3

This protocol can be discontinued as study is done.

Conclusions: Protein does not increase T3

Have there been any adverse reactions: NO

New added investigators:

As above

Funds Utilized FY 79:		Funds requested FY 80
Personnel:	2000	
Travel:		
Rental:		
Printing:		
Contractual:		
Consumable:		
Non expendable:		
Medcase:		
Total	2000	0

Publications:
Clin Research 26:611, 1978 Article with above authors and title submitted t Metabolism for publication

Estimated date of completion and/or number of more studies to be performed including plan over next 1-3 years:

Final

Work Unit: 1374

Title: Evaluation of testosterone reserve in infertile men

Investigators: Allan Glass M.D. (Principal)
Robert Vigersky, M.D.

Objective: To assess the mechanism by which gonadotropins can affect the release of testosterone

Technical Approach: Determination of plasma androgen levels after various regimens of HCG stimulation of testicular output.

Results, Progress, and Conclusions:
Approximately 30 patients were studied during the past year, none with isotope infusion. A substantial number of blood samples obtained during these studies were assayed. Two papers have been submitted for publication, and an abstract was presented at a national meeting. No adverse effects were encountered. After study of 3-5 additional patients, the first phase of the study will be completed, and a final paper encompassing all the data will be prepared. At that time, work will begin on part III of the study (isotope infusion), and it is hoped to study 10 patients under this section during the next year. This project represents a top priority item for the principal investigator. Work on this project during the coming year may be hampered by the inability to obtain a temporary hire technician, which was approved by CIS committee, because of a hiring freeze.

Funds Used FY 79 (EOE 2600):	4,693.83	(EOE 2572)	$34,000.00
Funds Requested FY 80:	9,500.00		23,000.00

Type of Report: Interim

Work Unit: 1376

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

Investigators: Allan Glass M.D. (Principal)
Robert Smallridge, M.D.
Marcus Schaaf, M.D.
Richard Dimond, M.D.

Objective: To determine if the agents amitriptyline and amantadine can affect the pattern of hormone release in acromegaly.

Technical Approach: Measurement of hormone levels before and after a 4 week course of the particular medication.

Results, Progress, and Conclusions:

Though no subjects were studied during the past year, work has been ongoing on completing the assays. One paper has been published, one has been accepted for publication, and a third has been submitted for publication. In addition, an abstract was presented at the APS meeting. No work has yet been done on the amantadine portion of the protocol, and it is hoped to study 10 subjects with the amantadine protocol during the next year.

Funds Used FY 79 (EOE 2600): 122.30

Funds Requested FY 80: (2600) $2,700.00

Type of Report: Interim

Work Unit: 1379

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

Investigators: Allan Glass M.D. (Principal)

Objective: To determine how alteration in the diet affects the hypothalamic-pituitary-testicular function in rats.

Technical Approach: Measurement of hormone levels in rats after various periods on several different diets.

Results, Progress, and Conclusions:

Two separate experiments were carried out during the past year. The major limitation during the past year was inability to obtain a place to house animals and lack of assistance. The latter problem has been remedied by additional personnel, the former is still a major problem. In addition, collaborators at other institutions have been very slow to complete their portions of the work, and several major pieces of hormone measurement are still pending at their labs (in some cases for 6 months). One paper was published, one was accepted for publication, and a third has been submitted for publication. In addition, the principal investigator was invited to speak at an APS symposium to discuss his work. Additional experiments are tentatively planned for the coming year, but these will depend on the results of previous experiments (still pending in collaborators' labs) as well as the difficulty in getting space to house animals. Substantial loss of animals during one experiment was seen due to inadequate housing equipment provided by WRAIR.

Funds Used FY 79 (EOE 2600): 1730.90

Funds Requested FY 80: (EOE 2600) $7,300.00

Type of Report: Interim

Work Unit No: 1380

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

Investigators:

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

Associate: Gerald S. Kidd, M.D., MAJ, MC, Charles E. Smith, M.D., LTC, MC

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

Technical Approach: Six patients with hyperthyroidism and six with hypothyroidism will be admitted to Ward 47 for a 3 day study protocol and will be similarly studied 2 months after becoming euthyroid. During each admission the patient will undergo two 3-hour renal clearance procedures, one with PTH infusion and another with vasopressin infusion. Parathyroid hormone infusion will be given as 50 units IV push in 25 ml of D_5W and 150 units in 75 ml of D_5W over one hour. Urine will be collected for calcium, phosphate, creatinine and cyclic AMP measurements and blood for ionized calcium, total calcium, creatinine, phosphate and cyclic AMP. The vasopressin infusion will be given similarly with 0.2 units IV push and 0.6 units over one hour. Osmolarity, creatinine and cyclic AMP will be measured in blood and urine.

Progress and Results: Seven hyperthyroid and nine hypothyroid patients as well as five euthyroid patients taking thyroxine have been studied. The hypothyroid patients had a reduced excretion of an oral H_2O load, a low basal ionized calcium, high parathyroid hormone and nephrogenous cyclic AMP. The hyperthyroid patients appeared normal except for a low fractional excretion of phosphate. The responses to parathyroid hormone and vasopressin in these two groups differed only in that the hyperthyroid patients had a greater increase in plasma cyclic AMP after parathyroid hormone.

Conclusions: The delayed water excretion in hypothyroid patients and the decreased fractional excretion of phosphate in hyperthyroid patients are not associated with demonstrable changes in renal responses to vasopressin and parathyroid hormone; therefore, thyroid status has small if any effect on the hormone receptor-second systems of cyclic AMP studied in this investigation.

Funds Utilized, FY-79:

2572	Contract Svc	$ 600
2600	Supplies	9,703
		$10,303

Funds Requested, FY-80:

2572	Contract Svc	$ 4,500
2600	Supplies	8,000
		12,500

Publications:

Wray, H.L., Smallridge, R.C., Butler, V.M., Byrn, K.C., Kidd, G.S., Correlation between nephrogenous cyclic GMP and tubular reabsorption of calcium during parathormone infusion, Adv. in Cyclic Nucleotide Res. 12, 683, 1979. Presented at International Conference on Clinical Aspects of Cyclic Nucleotides in Vail, Colorado in July, 1979.

Type of Report: Interim

Work Unit No: 1381

Title of Project: Estradiol (E2) Receptors in Rat Thyroid Glands

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

Objectives: To detect, quantitate and physico-chemically characterize the receptor for estradiol in rat thryoid tissue and to see if differences occur between the receptors for male and female animals.

Technical Approach: Thirty to forty rats are sacrificed for each experiment and their thyroid tissue is pooled.Rats are previously gonadectomized with some being treated with exogenous estrogen or androgen. A 100,000 x g cytosol is prpared from the thyroid tissue homogenate and the cytosol is evauated by binding parameters, sucrose density gradient centrifugation and gel filtration on Sephadx G-100 and 0.5M Agarose for size and ch arge characteristics. Kinetic analysis of on and off rates, steroid specificity, and the ability of the receptor to translocate to the nucleus is also evaluated.

Progress and Results: An estradiol receptor has been found in the thyroid glands of both male and female rats which to this point have been identical in affinity and binding characteristics and in size and charge. Translocation studies, kinetic analysis and steroid specificity are currently being assessed.

Cnclusions: Female (E2) receptors are present in the thyroid glands of both male and female rats and to this point look very similar in their physico-chemical characteristics. Androgen receptors have not yet been evaluated.

Funds Utilized FY-79: $4067.60 (2600)

Funding Requirement FY-80:

Personnel	$ 7900
Supplies	9600
Printing	200
Rental	200
Contracts	500
Travel	500
Total	$18900

Publications: None

Estimated Date of Completion: October 1980.

Type of Report: Interim

Work Unit Number: 1382

Title of Project: Measurement of Steroids in Fluid Obtained by Micropuncture from Rat Seminiferous Tubules and Epididymis.

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

Objectives: To quantitate the levels of estradiol, testosterone and dihydrotestosterone intra-tubularly in order to help understand the reulation of spermatogenesis from a hormonal basis.

Technical Approach: Rats are anesthetized and their testes exposed through a scrotal incision. Using micropipettes made in the laboratory, tubules are punctured and small volumes (nanoliters) are withdrawn. Sperm is separated from seminal fluid by centrifugation. Micro-assays are used which measure the quantity of the sex steroid in the fluid.

Progress and Results: Over the past year we have developed the microassay for estradiol which we feel is the key steroid which controls the response of the spermatogenic process to testosterone. Technical problems with high blanks due to impure materials have plagued the progress of this assay but are now under control. The sensitivity of the assay has been finally fine-tuned so that we can measure small enough volumes of fluid to make the system practical. Progress has also been made in the dihydrotestosterone assay

Conclusions: Pending

Funds Utilized FY-79: $4206.89 (2600)

Funding Requirement FY-80:

Personnel	$ 17400
Supplies	3500
Printing	300
Rental	200
Contracts	1000
Travel	500
Total	$22900

Publications: None

Estimated Date of Completion: October 1981.

Type of Report: Interim

Work Unit No: 1383

Title of Project: Measurement os A-1-C in the Assessment of Efficacy of Diabetic Treatment.

Investigator: Timothy M. Boehm, MAJ MC

Objectives:

a) To compare hemoglobin A-1-C measurements with more established indicators of diabetic control -- namely, fasting and postprandial glucoses, outpatient single voided urines, and 24 hour urinary glucose.

b) To evaluate the response of hemoglobin A-1-C to modifications of diabetic therapy.

c) To attempt to match diabetics presenting with nephropathy and retinopathy with similar diabetics without complications regarding age, sex, duration of disease, and insulin requirement to compare hemoglobin A-1-C concentrations in the groups with and without diabetic complications.

d) 1) To establish a valid Heb A-1-C.

2) To evaluate hemoglobin A-1-C to effective and ineffective diet therapy of diabetes.

Technical Approach: During FY-79 quality control for the Hb A-1-C assay has been evaluated and is acceptable. The attached abstract describes the initial results in the study. Efforts are currently underway to expand the patiebt groups and further analyze the data.

Conclusions: None. No serious/unexpected side effects.

Funds Utilized, FY-79: $3,360

Funding Requirement, FY-80: $4,032

Publications:

"Correlations among glycosylated hemoglobins, weight reduction, and hyperglycemia in the treatment of obese diabetes mellitus". Diabetes 28:437, 1979.

Completion Date: July 1981

Type of Report: Interim

Work Unit No.: 1384

Title of Project: The Effect of Isoniazide (INH) on Prolactin, Gonadal Function, and Pyridoxine (B6) Metabolism.

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

Objectives: To evaluate whether or not INH-induced pyridoxine deficiency elevates plasma prolactin levels and/or affects gonadal function in adult men and women.

Technical Approach: Patients receiving INH for PPD conversion would receiveevaluation of their prolactin status and gonadal function status before and at 3 and 6 months after being placed in INH.

Progress and Results: This project was to be completed by Dr. Gerald Kidd when he was transferred to El Paso, TX. However, due to other commitments he was unable to do so. The project is therefore being terminated.

Conclusions: None

Funds Utitlized FY-79: None

Funding Requirememnt FY-80: None

Publications: None

Estimated Date of Completion: Project terminated.

Work Unit: 1585

Title: Serial changes in free testosterone during pregnancy

Investigators: Allan Glass, M.D. (Principal)
Thomas Klein, M.D.

Objective: To determine if maternal hormone levels reflect fetal sex

Technical Approach: Measurement of hormone levels in blood of pregnant women at various gestational ages and correlation with fetal sex.

Results, Progress, and Conclusions:
Blood samples have been obtained from approximately 40 women. No assays have been run, and none will be run until all samples have been collected, so that all samples can be run in the same assay. It is hoped that samples from 100-150 pregnant women can be obtained during the next year, at which point the assays will be run. No adverse effects have been encountered. Progress during the next year may be hindered by the inability to obtain a temporary hire technician, as approved by CIS, due to hiring freeze.

Funds Used FY 79 (EOE 2600): 798.09

Funds Requested FY 80: (EOE 2572) $4,900.00

Type of Report: Interim

Work Unit No.: 1386

Title of Project: The Effect of Delta-1-Testolactone (Teslac) in Male Infertility.

Investigators: Robert A. Vigersky, M.D. MAJ MC
Allan R. Glass M.D. MAJ MC

Objectives: To increase sperm counts in infertile men with oligospermia by lowering plasma estradiol levels.

Technical Approach: 10 men are given Teslac for 6-12 months with evaluation of seminiferous tubular and Leydig cell function before and at the end of treatment. Pre-treatment evaluation also includes testicular biopsy with routine histologic examination.

Progress and Results: 10 men have now been either started and/or completed their trial of Teslac. The mean age is 29 with an average of 4.5 years of infertility. There has been a mean increase of 154% from the basal sperm counts in these men with 8 or the first 9 apparently responding and with 3 pregnancies in these 8 men. There is an approximately 30% decrease in estradiol and a 40% increase in testosterone during therapy. No change in LH, FSH, or prolactin has been observed. There have been no complication or adverse reactions associated with taking the medication.

Conclusions: Teslac may be an effective agent in the treatment of idiopathic oligospermia.

Funds Utilized FY-79: $$8108.50 (2600) + $3250 (2572) = $11,358.50

Funding Requirement FY-80:

Personnel	12200
Supplies	13500
Drug Costs	9000
Printing	300
Contracts	3300
Travel	500
Total	38800

Publications: Vigersky, R.A. and Glass, A.R., The Effect of Teslac in Oligospermic Men, submitted for presentation to the American Society of Andrology, March 1980.

Estimated Date of Completion: We request permission to extend the drug trial for an additional two years so that we may broaden the experience with this drug by including up to another 10 patients and to vary the dose so that maximal effect may be obtained.

Type of Report: Interim

Work Unit: 1387

Title: Acute responses to estrogen in men with prostate carcinoma

Investigators: Allan Glass, M.D. (principal)

Objective: To determine if the hormonal response to estrogen is changed by chronic estrogen administration.

Technical Approach: Measuarement of plasma LH responses to estrogen before and after estrogen treatment

Results, Progress, and Conclusions:

No patients have been studied during the year due to difficulty in recruiting acceptable subjects. It is hoped that during the coming year, a co-investigator from urology service can be added to permit the study of 5-10 patients under this protocol.

Funds Used FY 79 (EOE 2600): 0

Funds Requested FY 80: (EOE 2600) $2,300.00

Type of Report: Interim

Work Unit No.: 1388

Title of Project: The Development of a Radioimmunoassay for Thyronine and 3,5-T_2

Investigator:

Principal: Keith R. Latham
Kenneth D. Burman

Objective: To obtain immunoassays for thyronine, and 3,3'T2.

Technical Approach: Antibodies are generated and tags made by labeling 1-125 artritium and serum samples are tested.

Progress & Results: We have presently made antibodies for both TO, 3,5'T2 the radiolabel for 3,5'T2 has been difficult. We have now shown that normal 3,5'T2 levels are about 4mg/dl and that 3,5'T2 increases in hypothyroidism and decreases in hypothyroidism.

Conclusions: None

Funding Requirement, FY-80:

	FY-79	FY-80
Personnel	2,000	2,000
Travel	400	400
Rental	200	200
Printing & Reproduction	300	300
Contractual Svcs	300	300
Consumable Supplies	5,000	5.000
Non-expendable Equipment	1,000	1,000
MEDCASE		
TOTAL	$9,200	$9,200

Publications: A Radioimmunoassay for 3,5'T2. Tentatively accepted to JCEM, November 1979.

Type of Report: Interim.

Work Unit#: 1589

Title: The effect of carbohydrate on T3 receptors

Investigators: K.D. Burman, LTC, L. Wartofsky, COL, Yvonne Lukes, R.C. Smallridge, LTC, A.R. Glass, MAJ

Objective: To see if glucose changes T3 receptors

Technical Approach: Rat livers and nuclei are isolated and studied during different diets

Progress and Results: Rat diets with 64 and 79 percent cho are given for three weeks and at that time nuclear receptors studied. When we performed a large scale study we noted no difference in T3 receptor levels during each diet. Serum T3 levels did change dramatically.

Conclusions: Increased T3 increases T3 receptors

Have there been any adverse reactions: No

New added investigators: As above

Funds Utilized FY 79:		Funds requested FY 80
Personnel:	500	500
Travel:		
Rental:		
Printing:	500	500
Contractual:	500	
Consumable:	1000	500
Non expendable:		
Medcase:		
Total	2500	1500

Publications:
Endocrinology 102:1925, 1978

Estimated date of completion and /or number of more studies to be performed including plan over next 1-3 years:

Request continuance of this protocol because we are now performing T3 receptor levels by a better technique involving solub lization. Hopefully, we will then be able to pick up receptor changes.

Type of Report: Interim

Work Unit#: 1390

Title: Investigations concerning the physiology of iodothyronines

Investigators: K.D. Burman, LTC, R.C. Smallridge, LTC, L. Wartofsky, COL

Objective: To detect the factors influencing iodothyronine conversions

Technical Approach: Serum measurements

Progress and Results:
We have measured serum T3 and rT3 in infections and during fasting and have published that they change reciprocally(Metab 28:805, 1979).
The plan in the furture is to measure lesser iodinated thyronines in the same conditions as this will give insight into whether the same enzymes are involved

Conclusions:

As above

Have there been any adverse reactions:
No

New added investigators:
As above

Funds Utilized FY 79:	Personnel:	500	Funds requested FY 80	500
	Travel:			
	Rental:			
	Printing:			
	Contractual:			
	Consumable:	500		500
	Non expendable:			
	Medcase:			
	Total	1000		1000

Publications:
Yes as above

Estimated date of completion and /or number of more studies to be performed including plan over next 1-3 years:

We hope to measure 3T1 and T0 in the same conditions & process that will require about one year.

Type of Report: Interim

Work Unit#: 1391

Title: Regulation of the initiation of thyroid hormone action

Investigators: K.D. Burman, LTC, Keith Latham, L. Wartofsky, COL, Yvonne Lukes

Objective: To determine the mechanism of action of thyroid hormone

Technical Approach: Rat liver and steer nuclei and receptors are isolated

Progress and Results:

This study has several aspects-one part is to determine that sulfhydryl agent affect binding, and to find receptor blockers. Both of thess aspects are done and ANS and ipodate block the receptor and binding correlated with hepatic sulfhydryl groups. The next aspect is to isolate and purify the T3 receptor - a very difficult process that is being done.

Conclusions:

ANS and ipodate block receptor binding

Have there been any adverse reactions:

No

New added investigators:

As above

Funds Utilized FY 79:		Funds requested FY 80
Personnel:		
Travel:	1000	1000
Rental:		
Printing:		
Contractual:		
Consumable:		
Non expendable:		
Medcase:	1000	1000
Total	2000	2000

Publications:

Dr. Latham has presented these findings to Natl Chemists meeting

Estimated date of completion and /or number of more studies to be performed including plan over next 1-3 years:

Isolate the T3 receptor and purify it and develop antibodies to it in rabbits

Also, a manusript desribing these findings has been sent to Science and anoth one is being sent to BBRC

Type of Report: Interim

Work Unit No.: 1392

Title of Project: Steroid Transfer Across the Blood-Cerebro-Spinal Fluid Barrier in the Rhesus Monkey.

Investigators: Robert A. Vigersky, M.D. MAJ MC
Joseph Bruton, Ph.D.

Objectives: To evaluate the kinetics of steroid entry and exit in the CSF and the effect of cancer chemotherapeutic agents on these kinetics.

Technical Approach: Rhesus monkeys with indwelling ventricular catheters are injected either i.v. or intra-thecally with cortisol, prednisone or dexamethasone in varying doses with and without the inclusion of methotrexate and/or cytosine arabinoside.

Progress and Results: No further experiments were performed in FY-79. Final publication now being written.

Conclusions: Steroids rapidly enter and exit the CSF but none of the steroid tested appeared to be more advantageous in this respect. Chemotherapy does not affect steroid CSF kinetics.

Funds Utilized FY-79: $1904.70 (2600)

Funding Requirement FY-80:

Printing	$200
Travel	500
Total	$700

Publications FY-79: None

Estimated Date of Completion: March 1980.

Type of Report: Interim

Work Unit#: 1393

Title: T3 receptors in normal and fasting rats

Investigators: K.D. Burman, LTC, Keith Latham, R.C. Smallridge, LTC, L. Wartofsky, COL

Objective: To measure T3 receptors in rat liver during fasting

Technical Approach: In vitro isolation of rat liver nuclei

Progress and Results:
We have published a landmark study in this area that was given first prior and has been quoted extensively-Endocrinology 101:1331, 1977

We are in the process of determing why T3 receptors decrease during fastin and have submitted a report for publication to Science saying that the sulfhydryl hepatic groups determine binding and that these decrease during fasting.

Conclusions:
Receptors drop in fasting due to the drop in sulfhydryl groups

Have there been any adverse reactions:
No

New added investigators:
As above

Funds Utilized FY 79:	Personnel:		Funds requested FY 80
	Travel:	2000	2000
	Rental:		
	Printing:		500
	Contractual:		
	Consumable:	500	5000
	Non expendable:		
	Medcase:		
	Total	2500	7500

Publications:
As above Also article submitted to Science

Estimated date of completion and /or number of more studies to be performed including plan over next 1-3 years:

If the article is accepted to Scinece we will then pursue the mechanism of the drop in hepatic sulfhydryl groups.
If the article is not accepted we will perform the studies the referees say in order to get it accepted.

Also this study has been extended to include the mechansim of receptor drop in ipodate and ANS treated rats . This is an outgrowth of the fasting work and is related.

Type of Report: Interim

Work Unit#: 1394

Title: The development of a radioimmunoassay for triiodothyronine

Investigators: K.D. Burman, LTC

Objective:
To develop RIA for thyroid hormones

Technical Approach:
Rabbit injection

Progress and Results:

We have been successful and the results are outlined in progree report for protocol 1300-75.

These two protocols overlap and we would like this one discontinued and we will continue our work as outlined in response to 1300-75

Conclusions:

Thyroid hormones circulate in blood

Have there been any adverse reactions:
NO

New added investigators:
As above

Funds Utilized FY 79:		Funds requested FY 80
	Personnel:	
	Travel:	
	Rental:	
	Printing:	
	Contractual:	
	Consumable:	
	Non expendable:	
	Medcase:	
	Total 0	0

Publications:
JCEM 48:32, 79

Estimated date of completion and /or number of more studies to be performed including plan over next 1-3 years:

Terminate for above reasons

Work Unit#: 1395

Title: T4 to T3 conversion:Effect of modulation of glucose metabolism

Investigators: K.D. Burman, LTC, A.R. Glass, MAJ, Yvonne Lukes, R.C. Smallridge, LTC

Objective: To see if glucose alters in vitro peripheral conversion in rat liver

Technical Approach: Rat livers are isolated and T4 to T3 conversion is determined after glucose ingestion

Progress and Results:
Numerous rat studies have determined that glucose increases T4 to T3 conversion and this effect is mediated through changes in hepatic sulfhydrul concentrain chnages. These studies have represented a major breakthough in the explanation of T4 to T3 alterations.

Conclusions: Glucose incresaes T4 to T3 conversion

Have there been any adverse reactions: No

New added investigators: As above

Funds Utilized FY 79:		Funds requested FY 80	
	Personnel: 2000		2000
	Travel:		
	Rental:		
	Printing:		500
	Contractual: 250		500
	Consumable: 1000		500
	Non expendable:		
	Medcase:		
	Total 3250		3500

Publications:
Endocrine Society presentation, Abstract 327; Manuscript tentatively accepted at Act Endocrinologi

Estimated date of completion and /or number of more studies to be performed including plan over next 1-3 years:

We would like to extend this study to see if glucose ingestion alters reverse T3 to 3,3'T2 conversion an enzyme system similar to that used above. The protocol will be identical but the in vitro substrate will be different

Type of Report: Interim

Work Unit#: 1396

Title: T4 to T3 conversion; Effect of somatostatin

Investigators: K.D. Burman, LTC, L. Wartofsky, COL, P. Thompson, LTC, Fred Coleman

Objective: To see if somatostatin decreases T4 to T3 conversion

Technical Approach: Rat liver in vitor T4 to T3 conversion plus somatostatin

Progress and Results: We have performed several studies with equivocal results because the half life of somatostain is too short. We are in the process of repeatin these studies becuase we can now infuse this agent by a continuous infusion mnipump.

Conclusions: None yet

Have there been any adverse reactions: NO

New added investigators: As above

Funds Utilized FY 79:	Personnel:	500	Funds requested FY 80 1000
	Travel:		
	Rental:		
	Printing:		
	Contractual:		500
	Consumable:	500	500
	Non expendable:		
	Medcase:		
	Total	1000	2000

Publications:
None

Estimated date of completion and /or number of more studies to be performed including plan over next 1-3 years.
Plan to continue for another 2 years to straighten out the problems mentioned above.

Type of Report: Interim

Work Unit#: 1397

Title: The effect of free fatty acids on serum T3 and rT3 levels

Investigators: K.D. Burman, LTC, L. Wartofsky, COL

Objective: To determine if lipid metabolism and thyroid function tests are inter-related

Technical Approach: Free fatty acid infusions into sheep and measure thyroid hormone levels

Progress and Results:

We have found that free fatty acids tend to cross react in our assays ans therefore have had to alter them appropriately. Also recent evidence has suggested that there is a true relationship between free fatty acids and thyroid hormone levels. Thus we request continuance of this protocol so that these studies can now be performed.

Conclusions: None yet

Have there been any adverse reactions: No

New added investigators: None

Funds Utilized FY 79:		Funds requested FY 80
	Personnel:	500
	Travel:	
	Rental:	
	Printing:	
	Contractual:	
	Consumable:	
	Non expendable:	
	Medcase:	
	Total	0
Publications:		1000

Estimated date of completion and /or number of more studies to be performed including plan over next 1-3 years:

We plan to now start this study and to complete on a two year period

Type of Report: Interim

Work Unit No: 1398

Title: Studies on the Pathogenesis of Hypocalce ia in Tumors associated with Osteoblastic Metastases.

Investigators:

Principal: R. . Smallridge , LTC

Associate: H.L. Wray , LTC
J. Horton
W. Cheatham , MAJ
R.C. Dimond , LTC
R. Sepulveda , MAJ
M. Schaaf

Objective: To determine whether the hypocalcemia seen in some patients with osteoblastic metastases is due to hypoparathyroidism, a form of secondary hyperparathyroidism, an abnormality in vitamin D metabolism, or some undentified humoral agent with osteoblastic capability.

Technical Approach: 1. 24 hour urine for calcium, PO4 =,creatinine.

2. Serum for Ca, PO4, Mg, akaline phosphatase, parathyroid hormone, calcitonin, and Vitamin D metabolites.

3. Calcium infusion and PTH infusion.

4. Tissue cultures from marrow biopsies to be tested in vitro for their ability to incorporate 3H-proline into bone collagen.

Progess and Results: FY-79 efforts were devoted to completing the developmental work on the assays for vitamin D metabolites, as these assays will be important in this study. Dr. Wayman Cheatham has joined this protocol as an investigator, and he has begun looking for patients to study.

Conclusions: Deferred

Complications: None

Funds Utilized, FY-79
Personnel- 1,000
Supplies- 8 00

Funds Requested, FY-80

Personnel	1,500
Supplies	2,500
Printing	100
	4,100

Publications, FY-79 None

Estimated date of completion 2 yrs.

Type of report: Interim

Work Unit No: 1399

Title: An assessment of Parathyroid Hormone (PTH) levels in Normal Subjects and in Patients with Disorders of Calcium Metabolism.

Investigators:

Principal: Robert C. Smallridge, LTC
Richard C. Dimond, LTC

Associate: H. Linton Wray, LTC
Marcus Schaaf

Objectives: To establish the ranges of serum PTH levels in normal subjects and patients with metabolic disorders.

Technical Approach: The protocol involves only venipunctures to obtain blood samples.

Progress and Results: Evaluation of commercial radioimmunoassays has shown them to be inadequate for our needs. Considerable effort has been spent learning the difficulties in iodinating the parathyroid hormone molecule and many of these problems have been solved. Recently we have obtained research quality PTH antisera from Dr. Mellette (VA Hospital, Houston, TX) which defects normal subjects from hypoparathyroid patients. This antesera is being furnished as part as agreement whereby cyclic AMP and cyclic GMP antesera from our laboratory are being sent to Dr. Mellette. We hope to have a usable PTH RIA within a year.

Conclusions: Deferred

Side Effects: None

Funds Utilized: FY-79

Personnel	900
Rental	200
Supplies	1,500

Funds Requested, FY-80

Personnel	900
Rental	200
Supplies	2,500
Printing	100
Total	3,700

Publications: None specifically anticipated, since this protocol is designed to establish PTH ranges in normal subjects and patients with calcium disorders. These data will supply the reference PTH ranges for all our calcium related projects.

Estimated Date of Completion: 2 yrs.

Type of Report: Interim

Work Unit#: 1300-78

Title: The development of a radioimmunoassay for 3-monoiodothyronine ($3\text{-}T_1$)

Investigators: K.D. Burman, LTC, L. Wartofsky, COL, R.C. Smallridge, LTC

Objective: To set up RIA's for thyroid hormones

Technical Approach: Rabbits are injectded with thyroid hormone conjugates and specific antibodies made

Progress and Results:

We have made ria's for T3, rT3, 3,5T2, 3'5'T2 and 3'T1 each of which has been tested and found specific. Also the have been used to measure these hormones in arious states which have overlapped with other protocols calling for their measu emnet. We ask that this protocol be continued so that we can set up ria's for T0 and 3T1.

We would like to stress that participation of this protocol is the groundwork for almost all of our other protocols which involve measurements.

Conclusions:

Have there been any adverse reactions:

No

New added investigators:

As above

Funds Utilized FY 79:		Funds requested FY 80
Personnel:		500
Travel:		
Rental:		
Printing:		
Contractual:		500
Consumable:	1350	2000
Non expendable:		
Medcase:		
Total	1350	3000

Publications:

JCEM 44:660, 77; JCEM 47:345,78; J Peds 93:118, 1978; JCEM 48:32, 79

Estimated date of completion and /or number of more studies to be performed including plan over next 1-3 years:

Plan to continue for three years

Also there is an assay involving 35T2 which is tentatively accepted in the JCEM

Type of Report: Interim

Work Unit No.: 1301-78

Title of Project: The Effect of Delta- 1-Testolactone (Teslac) on 5-alpha-reductase in Rats.

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

Objectives: To study the ability of Teslac to inhibit the conversion of testosterone to dihydrotestosterone.

Technical Approach: Immature male rats are castrated and given silastic capsules containing testosterone, dihydrotestosterone or or estradiol. Equal groups are then injected daily for 1-4 weeks with Teslac or saline. Blood is obtained at sacrifice for measurement of steroids. Weights of androgen sensitive organs are also measured at that time.

Progress and Results: Teslac appears to be an anti-androgen in that it blocks the androgen dependent growth of prostate and seminal vesicles usually induced by testosterone. It does no do this by inhibiting 5-alpha-reductase activity,however, but rather by blocking the ability of the androgens to interact with the androgen receptors in these tissues. Thus, Teslac is an anti-androgen acting at the receptor level.

Conclusions: Teslac acts as an anti-androgen receptor agent.

Funds Utilized FY-79: $5800.05 (2600)

Funding Requirement FY-80:

Personnel	$ 750
Supplies	2500
Printing	200
Rental	200
Contracts	800
Travel	500
Total	$4950

Publications: Vigersky, R.A., Mozingo, D. Eil, C., Purohit, V., Bruton, J., Anti-Androgenic Properties of Delta-1-Testolactone (Teslac), presented at the 61st Annual Meeting of the Endocrine Society, Anaheim, Ca., June 14, 1979.

Estimated Date of Completion: Oct. 1980

Type of Report: Interim

Work Unit#: 1302-78

Title: Effect of obesity in fasting on PTH and calcitonin

Investigators: K.D. Burnan, LTC, I. Mehlman, LTC, L. Wartofsky, COL

Objective: To measure PTH in fasting

Technical Approach: Serum mesurements

Progress and Results: None as yet since F llow involved has graduated

Conclusions: None

have there been any adverse reactions:

No

New added investigators:

No

Funds Utilized FY 79:		Funds requested FY 80
	Personnel:	
	Travel:	
	Rental:	
	Printing:	
	Contractual:	
	Consumable:	
	Non expendable:	
	Medcase:	
	Total	
	o	0

Publications:

None

Estimated date of completion and /or number of more studies to be performed including plan over next 1-3 years:

Request termination of above protocol since other goups have recently published similar results and the Fellow involved has graduated

Work Unit No.: 1303-78

Title of Project: Studies on the Alteration in Drug Metabolism in Hyperthyroidism

Investigators: Robert A. Vigersky, M.D. MAJ MC
Craig Holland, M.D. CPT MC

Objectives: To determine if changes in metabolism of drugs used to treat hyperthyroidism are due to the elevated thyroxine levels, per se, or mediated through beta-adrenergic effects.

Technical Approach: 10 patients will h ave the halp-life and peak plasma levels of dexamethasone and methimazole measure after IV injection while hyperthyroid, after 5 days of propranolol, and after becoming euthyroid. Cardiovascular status will be assessed by radionuclide imaging with cardiac output and ejectiion fraction being measured.

Progress and Results: The first 2 patients have been accrued into the study. There have been no complication from the infusions or from the radionuclide studies. The third part of the study on these 2 patients has not yet been completed. Patients are actively being sought for participation in the project and the laboratory aspect of this protocol is now being begun.

Conclusions: none

Funds Utilized FY-79: $179.20 (2600)

Funding Requirement FY-80:

Personnel	$ 4000
Supplies	6600
Printing	300
Rental	200
Isotopes	500
Travel	500
Total	$12100

Publications: None

Estimated Date of Completion: October 1981

Type of Report: Interim

Work Unit No.: 1304-78

Title: Radionuclide Assessment of Cardiac Function in Patients with Acromegaly.

Investigators:

Principal: Robert C. Smallridge

Associate: Sol Rajfer
Robert Kaminsky
James Davia
Marcus Schaaf
M.L. Mutter
W.J. Oetgen

Objectives: To determine whether acromegalic patients may have impaired left ventricular function before symptomatic heart disease occurs.

Technical Approach: Left ventricular function is being determined using a multiple gated acquisition (MUGA) scan. This procedure involves the injection of 99m Technetium labeled human serum albumin.

Progress and Results: Twenty-three patients have been examined with MUGA scans and the data analyzed. Radionuclide angiography has been abnormal in 9 patients, with 3 having increased and 6 having decreased ejection fractions. While several had hypertension, 6 of the patients had no explanations for there abnormal ventricular function other than acromegaly.

Conclusions: The data support the presence of an acromegatic cardiomyopathy in many patients.

Complications: None

Funds Utilized, FY-79 None

Funds Requested, FY-80
Travel $600

Publications: An abstract has been submitted for possible presentation at the annual meeting of the Amercian College of Cardiology.

Estimated Date of Completion: 1 yr.

Type to Report: Interim

Work Unit No: 1305-78

Title: Breast Carcinoma and Thyroid Hormone Receptors

Investigators:

Principal: Robert C. Smallridge
Keith R. Latham
Associate: Arthur Tischler

Objectives: To determine whether thryroid hormone receptors can be identified in human breast carcinomas.

Technical Approach: Breast tumor tissue is frozen in liquid nitrogen, processed to obtain a nuclear pellet, and T3 and T4 receptors determined in a receptor binding assay (Latham, et al, J Biol Chem 251: 7388, 1976).

Progress and Results: High affinity nuclear T_3 binding sites have been identified in 4 breast carcinomas, and in "normal" tissue from histologically uninvolved breast from one of these patients. The number of T3 binding sites was much lower than described in other human tissues (i.e. white blood cells and liver) and also lower than in one "normal" breast tissue examined.

Conclusions: Nuclear T_3 receptors have been identified in breast carcinomas. No conclusions can be drawn regarding the biologic significance of this observation, but it provides evidence that thyroid hormone could at least possibly have an influence on breast tumors. A follow-up study is under consideration to assess the significance of these findings.

Funds Utilized, FY-79

Personnel:	400
Rental:	200
Supplies:	500
Printing:	100
	$1,200

Funds Required, FY-80

Supplies:	500
Printing:	300
	$800

Publications: These results are being prepared for submission to a journal as a preliminary communication.

Estimated Date of Completion: 1 yr.

Type of Report: Interim

Work Unit No.: 1306-78

Title of Project; Thyroid Hormone Regulation of Sex-Steroid Hormone Metabolism in Fasting Men

Investigators: Robert A. Vigersky, M.D. MAJ MC
Kenneth D. Burman, M.D. MAJ MC
Leonard Wartofsky, M.D. COL MC
Elizabeth Ramos-Walker, 1LT

Objective: To study the effect of thyroid hormones in altering the pathways of metabolism of androstenedione, estradiol, estrone, estriol, and testosterone.

Technical Approach: Obese men who were hospitalized on Ward 47 had the above steroids measured in the baseline state, after 4 days of a 100 cal/day diet; after 7 days of total fasting with or without supplemental oral T3; 7 days os of total caloric fast.

Progress and Results: The above steroids were measured on 5 consecutive men and the preliminary results showed no significant changes during any of the stages. The project has thus been terminated as being unlikely to yield significant positive data.

Conclusions: Fasting with or without T3 replacement does not appear to affect steroid metabolism in obese men.

Funds Utilized FY-79: $2201 (2572)

Funding Requirement FY-80: None

Publications: none

Estimated Date of Completion: Protocol terminated.

Work Unit#: 1307-78

Title: The effect of fasting on TSH response to TRH

Investigators: K.D. Burman, LTC, R.C. Smallridge, LTC, L. Wartofsky, COL

Objective: TO see if TRH infusions result in less TSH response in fasting

Technical Approach: TRH infusions of 1 ug per hour are given and TSH measured

Progress and Results: About 15 patients have been studied and it is evident that TSH response is less during fasting

Note: This protocol is differen than 1372 because this uses infusions.

Conclusions: TSH response is less during fasting

Have there been any adverse reactions: No

New added investigators: As above

Funds Utilized FY 79:	Personnel:	3000	Funds requested FY 80	3000
	Travel:			
	Rental:			500
	Printing:			
	Contractual	1500		
	Consumable:	3000		3000
	Non expendable:			
	Medcase:			
	Total	7500		9500

Publications:
Clin Research 27:248, 1979; article with same title in press, Metabolism

Estimated date of completion and /or number of more studies to be performed including plan over next 1-3 years: The initial phase of study has been completed as published in Metabolism and the plan now is to integrate this protocol with others to see if TRH infusions are altered in conjunction with T3 receptors in white cellls

Type of Report: Interim

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Work Unit#: 1300-79

Title: Measurement of serum iodothyronines by HPLC

Investigators: K.D. Burman, LTC, L. Wartofsky, COL, R. Bongiovanni, CPT, T. Boehm, MAJ

Objective: To measure thyoid hormone levels by HPLC

Technical Approach: Develop a new HPLC method involving dansylation

Progress and Results: Lt Bongiovanni has said that he is actively involved in this protocol and has now been able to separate thyroid hormones by HPLC but needs a method with greater sensitivity. He is in process of developing such a new method which involves dansylation of hthe thyroid hormones. It is a long slow job but success is being made.

Conclusions:
None yet

Have there been any adverse reactions:

No

New added investigators:

No

Funds Utilized FY 79:	Personnel:	500	Funds requested FY 80	500
	Travel:			
	Rental:			
	Printing:			
	Contractual:			
	Consumable:	500		500
	Non expendable:			
	Medcase:			
	Total	1000		1000

Publications:
None yet

Estimated date of completion and /or number of more studies to be performed including plan over next 1-3 years:

This study will probably require about three more years to reach a successful conclusion

Type of Report: Interim

Work Unit#: 1301-79

Title: The effect of various metabolic conditions on T3 receptors in circulating mononuclear cells

Investigators: K.D. Burman, LTC, Keith Latham, L. Wartofsky, COL

Objective:
To determine T3 kinetics of receptor in various states

Technical Approach:
T3 receptors are measured in white cells by solubiliaation

Progress and Results:
We just completed a very large scale study documenting the usefulness and veracity of T3 receptors in normal and obese subjects and this paper has been tentatively accepted in the JCI . The revised manuscript was sebt back 11 Sep 1979. Since this is now done we can go ahea and perform receptor kinetics in other syndromes as outlined in the present protocol. For example, elderly, euthyroid sick. Requests this protocol be extended to measure T3 white cells receptors during glucagon infusions and after ipodate administration. Both of these agents are approved in other protocols and this just asks for another 20 ml blood.

Conclusions:
No conclusions yet

Have there been any adverse reactions:
No

New added investigators:
As above

Funds Utilized FY 79:		Funds requested FY 80
	Personnel:	3000
	Travel:	
	Rental:	
	Printing:	
	Contractual:	2000
	Consumable:	
	Non expendable:	
	Medcase:	
	Total 0	5000

Publications:
None

Estimated date of completion and /or number of more studies to be performed including plan over next 1-3 years:

This protocol will represent our major effort over the next year.

Type of Report: Interim

Work Unit No.: 1302-79

Title of Project: Prevention of Gonadal Damage in Men Treated with Combination Chemotherapy for Hodgkin's Disease and Histiocytic Lymphomas. **WRAMC #7810.**

Investigators: Robert A. Vigersky, M.D. MAJ MC
Jeffrey Berenberg, M.D. LTC MC
Ramona Chapman, M.D. MAJ MC

Objectives: To prevent the severe seminiferous tubular damage induced by chemotherapy which is most likely irreversible and to prevent the Leydig cell damage also a product of chemotherapy(whose reversibility has not yet been determined).

Technical Approach: Men undergoing chemotherapy for Stage IIIb or IV Hodgkin's disease or histiocytic lymphoma will be treated with high dose testosterone i.m. before beginning their therapy and for the duration of therapy. This is being done to suppress their own endogenous gonadotropins and thereby their own gonadal function so that they will be inactive at the time chemotherapy is begun. Evaluation of gonadal function will be assessed before, during and 6-12 months after the completion of the chemotherapy.

Progress and Results: The first 3 patients have been accrued into the study and there are no results as yet. There have been no complications from the pre-therapy testing and from the testosterone treatment.

Conclusions: None

Funds Utilized FY-79: None

Funds Requested Fy-80:

Personnel	$ 2000
Supplies	300
Contracts	9120
Printing	200
Rental	200
Travel	500
Total	$12320

Publications: None

Estimated Date of Completion: Oct. 1982

Type of Report: Interim

Work Unit No.: 1304-79

Title: Thyroid Hormones in Cerebrospinal Fluid (CSF)

Investigators:
Principal: Prentice Thompson, LTC, MC
Associates: Kenneth D. Burman, LTC, MC
Leonard Wartofsky, COL, MC
Archer D. Huott, COL, MC
Albert N. Martins, COL, MC

Objective: To determine what role the CSF plays in the transport of thyroid hormones into the central nervous system (CNS), and what role thyroid hormones in the CNS might play in various disease states.

Technical Approach: CSF of patients undergoing lumbar puncture for various disease states (such as herniated disc disease, pituitary tumor, or meningitis) will be studied. One to two ml of CSF beyond that required for routine CSF analysis will be obtained for measurement of T4, T3, rT3 and other metabolites.

Progress and Results: CSF samples from 25 patients undergoing myelogram for herniated disc disease were examined, and we were able to measure various thyroid hormones (T4, T3, reverse T3) in several of these patients. We are now prepared to measure thyroid hormones in various disease states in an effort to determine what role these hormones play in these diseases.

Conclusions: We are, indeed, able to measure thyroid hormones in CSF, and will now attempt to determine what role these hormones might have in various disease states.

Funds Utilized, FY-79: $3,825.00

Personnel:	$1,000.00
Consumable Supplies:	825.00
Contract Services:	2,000.00
Total	3,825.00

Funding Requirements FY-80: $8,150.00

Personnel:	$2,000.00
Consumable Supplies:	1,850.00
Contract Services:	3,000.00
Travel:	500.00
Reprints:	400.00
Audiovisual:	400.00
Total	8,150.00

Publications: None

Type of Report: Interim

Work Unit No.: 1305-79

Title: Thyroid Function in Liver Disease

Investigators:

Principal: Prentice Thompson, LTC, MC

Associates: Kenneth Burman, LTC, MC
George Brown, MAJ, MC
Lawrence F. Johnson, COL, MC
Robert C. Smallridge, LTC, MC
Leonard Wartofsky, COL, MC

Objective: To determine whether alterations in binding proteins for serum hormones are responsible for the abnormalities in thyroid hormone metabolism observed in patients with various liver diseases.

Technical Approach: Ten patients each will be studied with (a) acute hepatitis (acutely and during convalescence); (b) chronic active hepatitis (before and after steroid therapy); and (c) primary biliary cirrhosis. Measurements will be obtained in a baseline state and at intervals during follow-up for measurement of T1, T2, T3, T4, reverse T3, serum TRH, TBG, CBG, TeBG, and FTI. Remaining serum will be stored frozen at -40° pending evaluation of the latter results for consideration of potential assay of cortisol, estrogen, and testosterone as well. TRH stimulation tests will be performed with measurement of TSH and prolactin responses.

Progress and Results: Due to the late HSC approval date, 24 April 79, the project has not yet gotten underway.

Conclusions: NA

Funds Utilized, FY-78; FY-79: None

Funding Requirements, FY-80: $6,600

Personnel:	None (KMU Funds FY-80)	
Equipment:	None (KMU Funds FY-80)	
Supplies:	None (KMU Funds FY-80)	
Travel:		600.00
Services--Hazelton Contract:		$6,000.00
	Total	6,600.00

Publications: None

Type of Report: Interim

Work Unit No.: 1306-79

Title of Project: Thyroid Hormone Status in ob/ob Mice

Investigators:

Principal: Keith R. Latham, Ph.D.

Co-Investigators: Yueh-Chu L. Tseng, Ph.D. and Allan R. Glass, M. D.

Objectives: To determine the thyroid hormone status in ob/ob mice and to assess the potential role of thyroid dysfunction in the etiology of the ob state.

Technical Approach: In these studies we have used previously described methodologies of measuring thyroid hormones in blood and methods of measuring levels of nuclear thyroid hormone binding activity in various tissues derived from the mice.

Progress & Results: We have derived two basic results from these studies. 1. There is no difference in the levels of liver nuclear thyroid hormone receptors for T_3 and T_4 in ob/ob, ob/+ or +/+ (the lean controls). 2. There are major differences in the blood levels of T_3 and T_4 between ob/ob

mice and their thin littermates (ob/+, +,+). In this case, T_4 levels in ob/ob mice was depressed by 50% and T_3 levels slightly elevated. 3. Since we observed changes in the levels of T_4 and T_3 in the blood, we also investigated the possibility that the ob/ob defect was the result of tissue metabolism of thyroid hormones. We found in these studies that the mouse fat was a major site of thyronine metabolism.

Conclusions: We have concluded: 1. The ob/ob defect that causes obesity in this strain is not a result of modulated nucleared receptors for thyorid hormones. 2. There are major changes in blood levels of T_4 and T_3 in the ob syndrome and 3. since the obese mouse may be 50% fat fy weight and since this tissue is a major site of thyronine metabolism, it is possible that the obese mouse has a high rate of thyronine disposal through the fat, which that may contribute to the total thyroid hormone status in the obese mouse.

Funds Utilized, FY 78, FY 79: Although a great deal of work has been done on this project thus far, it has not required a high level of funding since we obtained obese mice and rats free and we were able to use supplie derived from other projects.

Funding Requirements FY 80:

Personnel: No personnel support will be required for this project.

Equipment: $600.00. Only minor equipment for pipetting and fraction collecting will be required.

Supplies: $1200.00. This will include the purchase of obese mice and their thin littermates and I^{125} T_3 and I^{125} T_4. In addition test tubes and some other general laboratory supplies will be required.

Travel: Since the latest abstract for presentation for presentation will be presented in Washington, D. C. in June, 1980, no travel money will be required.

Publications: 1. K. R. Latham, Y. L. Tseng and A. R. Glass, Thyroid status in ob/ob mice, AFCR, 1979. 2. Y. L. Tseng, A. R. Glass, K. R. Latham, Thyronine metabolism in fat and liver homogenates from rats and genetically obese mice. Endocrine Society, 1980.

Type of Report: Interim

Work Unit: 1308-79

Title: Stress-induced amenorrhea in military cadets

Investigators: Allan R. Glass, M.D. (Principal)
Leigh Wheeler, M.D.
Thomas Klein, M.D.
Mike Posner, M.D.

Objective: Determination of the cause and mechanism of amenorrhea in military cadets

Technical Approach: Measurement of hormone levels and determination of pituitary sensitivity via estradiol challenge and clomid administration in amenorrheic and non-amenorrheic cadets

Results, Progress, and Conclusions:

Approval for this recently-submitted protocol by HURO is still pending, so no work has begun yet.

Funds Used FY 79 (EOE 2600): 0

Funds Requested FY 80: $3500.00 (2600)

$3000.00 (2572)

Type of Report: Interim

Work Unit No.: 1309-79

Title of Project: The Anti-Estrogenic Effects of Delta-1-Testolactone (Teslac)

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

Objective: To study the ability of Teslac to act an an anti-estrogen in vivo and to investigate its mechanism of action.

Technical Approach: In Vivo studies are to give gonadectomized male or female rats silastic implants containing estradiol and to then inject them daily for 1-4 weeks with either saline or Teslac. The weight of the target organs is compared in the groups as is the levels of plasma steroids.

Progress and Results: There seems to be no in vivo effects of Teslac over a 1 week period. Receptor studies initially have confirmed this observation by showing no interaction of Teslac with the estrogen receptor in rat uterus.

Conclusions: Teslac appears not be be significantly anti-estrogenic in vivo and appears to act only by inhibiting conversion of testosterone to estradiol.

Funds Utilized FY-79: None

Funds Requested FY-80:

Personnel	$ 3500
Supplies	2500
Travel	500
Printing	200
Rental	300
Total	$7000

Publications: None

Estimated Date of Completion: Oct. 1980.

Work Unit No.: 1310-79

Title of Project: Pilot Investigation for the Treatment of Hirsutism with Oral Cimetidine

Investigators: Robert A. Vigersky, M.D. MAJ MC
Ira Mehlman, M.D. LTC MC
Charles E. Smith, M.D. LTC MC
Allan R. Glass, M.D. MAJ MC

Objectives: To observe the effects of Cimetidine in the treatment of hirsutism and to understand the mechanism of this effect.

Technical Approach: Ten women who are less than 50 years old and who have the diagnosis of idiopathic hirsutism are admitted for pretreatment evaluation which includes urinary and plasma steroid determinations, a TRH test, photographs, and weighing of hair shaved from an area of the face after several days of non-shaving. They will then be placed o n Cimetidine 300 mg five times daily for 3 months with re-evaluation monthly for progress and a 3... months as during the pre-treatment period.

Progress and Results: None

Conclusions: None

Side Effects and Complications: None

Funds Utiilized FY-79: None

Funds Requested, FY-80:

Supplies:	$1500
Contracts	4800
Printing	300
Travel	500
Drug Cost	705
Total	$7805

Publications: None

Estimated Date of Completion: Sept. 1981.

Work Unit #: 1406

Title of Project: Bile Salt Clearance in Chronic Active Hepatitis.

Principal Investigator: COL Lawrence F. Johnson, MC

Objective: To ascertain if the clearance rate of intravenously administered cholyl glycine can reliably relate to clinical parameters in patients with chronic active hepatitis.

Technical Approach: A radioimmunoassay for conjugates of cholic acid will be developed in rabbits by linking cholyl glycine to bovine serum albumin.

Progress and Results: A good radioimmunoassay was developed for conjugates of chenodeoxycholate acid. An intensive effort was made to develop an antibody for conjugates of cholyl glycine; and this was accomplished. However, the rabbit who had the high antibody levels to cholyl glycine died, and we were never able to again evoke a high antibody level in another animal.

Conclusions: Because of our inability to develop an antibody for conjugates of cholyl glycine, this project was terminated and more than 100% of the research chemist's (Ms Corinne Maydonovitch) time was transferred to other approved CIS-WRGH approved protocols.

Funds Utilized, FY-79: $15,432

Funds Requested, FY-80: None. Chemist, Ms Corinne Maydonovitch transferred to other CIS-WRGH Gastro Svc approved protocols.

Publications: This protocol has resulted in publication of an abstract, a presentation at a national meeting and a publication in a peer review journal.

Type of report: Terminated

Work Unit No: 1415

Title of Project: Esophageal Clearing, Quantitated by Radioisotope Scan.

Investigator:

Principal Investigator: COL Lawrence F. Johnson, MC

Coinvestigators: Andre Dubois, MD
MAJ Percy Dunagin, MC
Donald O. Castell, MD

Objective: To quantitate the peristaltic ability of the esophagus to clear a measured bolus of fluid into the stomach.

Technical Approach: Diluted .1 NHCl will be tagged with technecium, and an esophageal clearing profile will be quantitated after each swallow using manometric equipment.

Progress and Results: Five additional patients have been studied since those those commented upon in FY-78. These additional pstients have been evaluated with a new monitoring probe designed by one of the authors (LFJ), that incorporates a metallic pH sensor at the distal tip and two transistorized pressure monitors within a catheter system that is tapered down for patient comfort in the oral thorax. This new system incorporates these functions in a very small probe that formally was accomplished only by combining and then taping together several different probes. In addition, the new system now incorporates a four digit pH meter and Beckman printer that records the pH value every five seconds. These values can now be compared to scintillation counts from the isotope present in the esophagus. Early observations that bethanecol improves esophageal acid clearance as well as makes a more competent esopha-gastric junction to prevent reflux have been documented by this study.

Conclusions: Data obtained from this protocol represents an advancement in the understanding of gastroesophagus reflux disease and supports our earlier published observations.

Funding Requested, FY-80: Same as original protocol.

Publications: None

Type of Report: Interim

Work Unit No.: 1-1C

Title of Protocol: Esophageal Emptying in Achalasia: Quantitated by Radioisotope Method.

Investigators:

Principal Investigator: CAPT Lawrence F. Johnson, MC

Coinvestigators: Roy K.I. Wong, MC
LTC Robert J. Kaminski, MC
Chief, Nuclear Medicine Service

Objective: To quantitate esophageal emptying in achalasia before and after pneumatic dilation.

Technical Approach: To measure esophageal emptying of a solid meal in patients with achalasia. Technecium was tagged to cornflakes and milk and from this an esophageal emptying profile was established.

Progress and Results: The techniques proves satisfactory and distinguished asymptomatic control volunteers from symptomatic patients with achalasia. The technique also documented a significant improvement in esophageal emptying after pneumatic dilation. These data were published:

1. Gross R; Johnson LF; and Kaminsky RJ: Esophageal Emptying in Achalasia: Quantitated by Radioisotope Technique. Digestive Diseases and Sciences, vol 24, p 945, Dec 79.

We feel that there is one more manuscript in the data that is already available and this will consist of correlating esophageal manometric data with results of esophageal emptying obtained by the radioisotope technique.

Conclusions: As predicted last year this technique has aroused more objective assessment of the treatment of patients with achalasia. The unassigned investigators later this year will modify protocol #1416 and use the esophageal emptying technique to determine which pneumatic dilation technique offers the best results in terms of esophageal emptying for achalasia. This will be done in collaboration with other investigators at the Medical College of Virginia, as well as possibly the National Naval Medical Center.

Funds Utilized, FY-79: None

Funds Requested, FY-80: Same as initial protocol.

Publications: See two abstracts, FY-79, as well as enclosed publication.

Type of Report: Interim

Work Unit: 1417

Title: Plasma Ligandin in Liver Disease.

Investigator: COL Lawerence F. Johnson, M.D.

Objective: This study proposes to assess plasma ligandin levels as a potentially more sensitive indicator of hepatic information than currently available serum tests.

Technical Approach: All patients having liver biopsies at Walter Reed Army Medical Center have an aliquot of blood drawn and frozen. Plasma serum ligandin content is what is determined by sensitive and quantitative radioimmunoassay technique. Correlations between pathologic diagnosis, enzyme values and ligandin levels will be made by standard statistical techniques.

Progress and Results: Two hundred samples of serum have been forwarded to the Albert Einstein College of Medicine in New York for ligandin determinations. Results are pending.

Conslusions: Not Available.

Funds Utilized, FY 79. None.

Funds Requested, FY 80. Same as initial protocol.

Publications: None.

Type of Report: Interim.

Work Unit No: 1-19

Title of Project: Cricopharyngeal Bar: A Video Manometric Study.

Investigators:

Principal Investigator: COL Lawrence F. Johnson, MC

Coinvestigators: MAJ Roy A. H. Wong, MC
MAJ James W. Hikendall, MC
MAJ David J. Curtis, MC

Objective: To study the functional significance of a cricopharyngeal bar.

Technical Approach: This is a synchronized manometric/videotape fluoroscopic study of swallowing disorders of the hypopharynx, cricopharyngus and upper esophagus.

Progress and Results: The slow motion videotape machine procured by the Department of Radiology and its interface with Walter Reed Army Medical's TV, has functioned well. This equipment has been complimented by WRAMC-TV, acquiring a split frame apparatus that now affords televising the manometry record as well as simultaneous fluoroscopy study all on the same TV screen. This technique has functioned well in the study and documentation of pharyngeal movement and manometry findings in a patient with rumination. To perfect this technique, however, the manometry results must be displayed on a scilliscope in order for the TV equipment to adequately display it on the split frame videotape. We are very encouraged with the progress that we have made in the last year in perfecting this technique and the insight it will have in our understanding of patients with swallowing problems.

Conclusions: None

Funding Utilized, FY-79: None

Funding Requested, FY-80: Same as initial protocol.

Publications: None

Type of Report: Interim

Work Unit: 1420

Title: Adenyl Cyclase and Guanyl Cyclase Activity in the Cat Esophagus.

Investigators:

Principal investigator:	MAJ Roy K. H. Wong, M.D.
Co-investigators:	COL Lawrence F. Johnson, M.D.
	CAPT Donald O. Castell, M.D., USN

Objective: To correlate adenyl cyclase and guanyl cyclase activity with lower esophageal sphincter contraction and relaxation.

Technical Approach: Same as initial protocol.

Progress and Results:

1) We have determined that higher levels of adenyl cyclase exists in the lower esophageal sphincter (LES) of the rabbit when compared with the rest of the esophagus.

2) Cats were then used as a model for this study because the musculature of the cat esophagus is similar to that of the human. However, the anatomic location of the cat LES made it difficult to extract this LES.

3) We have found a source for opossums to be used as an animal model for this study. We have also received approval for housing these animals at WRAIR.

4) Dr. Northway (Ph.D.) from M.D. Anderson is joining the staff in the Department of Pharmacology, USUHS, has done similar work in the opossum esophagus and will add valuable expertise. Presently, we need more technical assistance in assaying adenyl and guanyl cyclase. We will submit an application for a technical assistant.

Funds Utilized, FY 79: None.

Funding Requested, FY 80: $2,500 needed for funding of animals and equipment.

Publications: Attached.

Type of Report: Interim.

Addendum to Work Unit #1420:

Both the cat and the opossum have smooth muscle in the lower 2/3 of the esophagus. In this sense they are similar anatomically to man. Many (majority) of studies have been performed on the opossum elucidating neural hormonal and muscular activity of the LES. In these studies, a technique of pinning the distal esophagus is performed and indicates fairly easy accessability to the distal esophagus. For these reasons, and also because we have now found a source of opossums, are we changing the animal model.

Gastro 68:444-447. Neural organization of esophageal peristalin role of the vagus nerve.

JCI 54:899-906. Neural control of the lower esophageal splincter: Influence of the vagal nerve.

Gastro 70:216-219. A dopamine receptor in esophageal smooth muscle of the opossum.

Work Unit: 1421

Title: Immune Characteristics of Peripheral Blood Lymphocytes in Patients on Cimetidine.

Investigators:

Principal investigator: Robert Reid, M.D.
LTC, MC

Objective: To determine if the function of human peripheral blood lymphocytes is altered during treatment with Cimetidine (Tagamet), a histamine type-2 receptor blocker.

Technical Approach: To study the classification and functional characterization of peripheral blood lymphocytes in patients receiving Cimetidine. Multiphasic immunologic testing as outlined in protocol will be performed.

Progress and Results: It has been proposed that cimetidine may enhance cellular immune function and adversely effect patients being treated for duodenal ulcer disease. Therefore, immunological parameters were studied in nine patients with duodenal ulcer disease immediately prior to, after 2-3 weeks, and after 6-8 weeks of cimetidine treatment. Thirteen normal control subjects not receiving the drug also were studied. Whole blood cimetidine and serum immunoglobulin concentrations (IgG, IgA, and IgM) were determined and peripheral blood mononuclear cells (lymphocytes and monocytes) were analyzed for their surface characteristics, cytotoxic capabilities, and responsiveness to mitogens. Circulating total leukocyte and mononuclear cell counts remained normal during the study period. The surface characteristics (esterase staining; surface immunoglobulins; E, EA and EAC-rosette formation) did not change during cimetidine treatment. Spontaneous cell-mediated cytotoxicity of K-562 cells was markedly impaired in the duodenal ulcer patients prior to treatment and returned to nrmal after 2-3 weeks of treatment. Antibody-dependent cellular cytotoxicity to either chick erythrocytes or K-562 cells, and lectin-induced cellular cytotoxicity to human erythrocytes, was not altered by cimetidine. Likewise, mitogenic responsiveness to phytohemagglutinin, concanavation A and pokeweed mitogen was unchanged. The patients' sera, all of which contained therapeutic levels of cimetidine, did not influence the results of any of the assays in comparison to simultaneous tests using fetal calf serum. Serum immunoglobulin levels as a measure of B-lymphocyte function did not change during cimetidine treatment.

Conclusions: We conclude that cimetidine therapy for up to eight weeks induces no marked enhancement or alteration of general cellular immune function.

Funding Utilized, FY 79: None.

Funding Requested, FY 80: None

Publications: R.W. Sjogren, M.J. Bertovich, I.J. Weinrieb, R.H. Reid, and R.P. MacDermott; Lack of Effect of Cimetidine Therapy on Tests of Cellular Immune Function in Patients with Duodenal Ulcer Disease. Submitted for publication to Gastroenterology.

Type of Report: Final, close-out.

Work Unit No.: 1422

Title: The Sequential Staging of the Liver in Hodgkin's Disease With Laparoscopy and Laparotomy.

Investigators:

Principal Investigator:	MAJ David A. Peura, M.D. Staff, Gastroenterology Service (Replacing MAJ Joseph S. Rice, M.D. who has been transferred to Fitzsimons AMC, Denver, CO)
Co-investigators:	CPT Morakinyo A. Oyewole, M.D. Fellow, Gastroenterology Service
	COL Lawrence F. Johnson, M.D. Chief, Gastroenterology Service
	COL Richard M. Hirata, M.D. Chief, General Surgery Service (Replacing COL Robert W. Muir, M.D.)
	MAJ Martin D. Weltz, M.D. Fellow, Hematology-Oncology Service

Objective: To evaluate the role of laparoscopy in clinical Stage III or IV Hodgkin's disease patients.

Technical Approach: See Plan Section of original protocol.

Progress and Results: Since the last report, no patients were assessed under the protocol. In checking with the Oncology Service, it was felt that the continuation of the protocol was to be encouraged and an attempt to coordinate with the Gastroenterology Service to assess all patients with the above clinical stages of Hodgkin's disease would be made.

Conclusions: No further conclusions can be reached at this time. As mentioned in the last report, there was evidence that laparoscopy seemed to be of benefit, however, further patients were needed to form statistically significant conclusions. It is anticipated that with better coordination with the Oncology Service more patients will be assessed and evaluated under this protocol.

Funds Utilized FY 79: None.

Funding Requested FY 80: None.

Publications: None.

Type of Report: Interim.

Work Unit No.: 1423

Title of Project: A Study of Trifluoroisopropyl Cyanoacrylate Polymer (MBR 4197) in the Control of Bleeding Peptic Ulcers of the Stomach and Duodenum.

Investigators:

Principal: MAJ David A. Peura, M.D.
Staff, Gastroenterology Service

Co-investigators: LTC Edward L. Burkhalter, M.D.
Fellow, Gastroenterology Service

COL Lawrence F. Johnson, M.D.
Chief, Gastroenterology Service

Gastroenterology Service, Department of Internal Medicine, Walter Reed Army Medical Center, Washington, D.C. 20012.

Objectives: To determine if the polymer is effective in preventing further bleeding in stomach and duodenal ulcers.

Technical Approach: See original protocol.

Progess: To date, 11 patients have been studied under the protocol. Seven patients have been control and four have been polymer patients. Patients in both groups had evidence of rebleeding. Since this is a multi-center study, final evaluation and eff cacy must await the return of data from all centers. It is hoped that the study will continue.

Conclusion: No definite conclusion can be made at this time.

Funds 79: None.

Funds 80:

A) Personnel: See Principal Investigators.

B) Equipment: None.

C) Consumable Supplies: $100.00

1. Sterile saline

2. CO_2 tanks

D) Travel: Presentation of paper at national scientific meeting $300.00

E) Modifications of Facilities: None

F) Other: Reprints $250.00

Publications: NA

Type of Report: Interim.

Work Unit: 1424

Title: A Double Blind Study of Long Term Maintenance Cimetidine (SKF 92334) Therapy on Gastroesophageal Reflux Disease - Protocol BO7.

Investigators:

Principal investigator: MAJ Roy K. H. Wong, M.D.

Co-investigator: COL Lawrence F. Johnson, M.D.

Objective: To determine if Cimetidine, an inhibitor of gastric acid secretion, will, on long term maintenance therapy, benefit patients with acid gastroesophageal reflux over that of conventional medical therapy.

Technical Approach: Same as initial protocol.

Progress and Results: Since the inception of this protocol (June 78), we have entered 11 patients on coded medicine. We have to admit 4 more patients to complete this protocol and hope to do so by the end of this year.

Conclusions: We hope to complete this protocol by January 1981.

Funds Utilized, FY 79: None

Funding Requested, FY 80: Same as initial protocol.

Publications: None.

Type of Report: Interim.

Work Unit No.: 1425

Name of Protocol: Pulmonary Aspiration from Gastroesophageal Reflux Defined by Pulmonary Scintiscan and Overnight Intra-Esophageal pH Monitoring.

Investigators:

Principal Investigator: COL Lawrence F. Johnson, MC

Coinvestigators: MAJ James W. Kikendall, MC
Gastroenterology Staff

LTC Robert J. Kaminski, MC
Chief, Nuclear Medicine Service

From Walter Reed Army Medical Center, Washington, D.C.

Objectives: To document the occurrence of pulmonary aspiration from nocturnal gastroesophageal reflux.

Technical Approach: Patients with symptoms of both pulmonary disease and gastroesophageal reflux are being evaluated to develop a test to see which of the patients with chronic pulmonary disease has aspiration on the basis of gastroesophageal reflux. Patients are admitted on the morning of Day 1 and a manometry catheter is placed into the esophagus for location of the lower esophageal sphincter to make sure the patients are capable of making acid. Later in the day, patients are started on pH monitoring and is continued until the following morning. This is the best parameter of reflux. Prior to bedtime, the patients are dosed with 5 mci of radioactive technicium sulfur colloid Tch^{99}. On the morning of Day 2, the patients report to Nuclear Medicine Service for a lung and abdominal scan for location of technicium. The patients are then questioned regarding their symptomatology during the night -- reflux and aspiration -- and comparison is made by a direct Chi analysis to the objective criteria of the esophageal reflux by pH monitoring, aspiration by lung scan.

Progress and Results: Thirteen patients have been entered into this study. They may be broken into two groups. The first group had abnormal distal esophageal acid exposure during the night of the study and will be designated as the reflux group. The remaining patients had either no reflux or acid exposure found within mean and two standard deviations of a previously determined control populations and will be designated a the "normal range". Both groups were distinguished by lower esophageal sphincter pressure. The reflux group had a significant lower pressure as suspected than the normal group. It was interesting that on a pulmonary history obtained after the study night and prior to looking at the data, scans and pH record, the two clinicians (LFJ, JWK) were unable to distinguish which patients refluxed and possibly had pulmonary symptoms related to aspiration. That is, we scored both groups the same. Also, all pulmonary scintiscans in the 13 patients did not show evidence of aspiration, even in those who had abnormal esophageal acid exposure on the night of the study.

We encountered several technical problems with the pulmonary scintiscan technique that we had not anticipated. First, despite evidence of impaired gastric emptying during sleep, most patients had the isotope present within the colon when scanned the morning after the study. Therefore, the isotope may have left the stomach early in the course of the study night and not been available as a gastric tag when the patient refluxed and possibly aspirated. Secondly, from talking with these patients, pulmonary symptoms of aspiration seem to occur one to three or four times per year; and therefore when attempting to document it, studying a patient for one night represents a one to three probability/over 365 days in the year. It is our intention to summarize this information and submit it to Digestive Diseases and Sciences, as follow-up data on a published pilot study that one of the authors (LFJ) participated in entitled, "Pulmonary Aspiration as a Consequence of Gastroesophageal Reflux: A Diagnostic Approach (see inclosed reprint).

This existing protocol will be modified later this year and again resubmitted to the Clinical Investigation Committee in a further effort on our part to document and study the problem of pulmonary aspiration from gastroesophageal reflux.

Conclusions: See inclosed publication.

Funds utilized, FY-79: None

Funds requested, FY-80: See originial protocol.

Publication:

Chernow B; Johnson LF; Janowitz WR; and Castell DO. Pulmonary Aspiration as a Consequence of Gastroesophageal Reflux: A Diagnostc Approach. Vol 24, p 839, 1979.

Type of Report: Interim

Work Unit: 1426

Title: The Effect of Indomethacin on Experimentally Induced Acid Stricture on the CAT Esophagus.

Investigators:

Principal Investigator: MAJ George J. Brown, M.D.

Co-Investigators: COL Lawrence F. Johnson, M.D.

CAPT D. O. Castell, M.D., USN

Objective: To prove that indocin will decrease the incidence of acid induced stricture formation in the cat by decreasing acid induced esophageal inflammation.

Technical Approach: Same as protocol.

Progress and Results:

1) We have demonstrated that the experimental model will reliably produce acid induced esophageal stricture in the cat.

2) Because of esophageal stricturing, nutrition of the animals were a problem. This has been solved with a permanent feeding gastrostomy which the animals tolerate well.

3) A semipermanent intravenous catheter needs to be develop to administer known amounts of test substances.

4) Dr. Margaret Northway at USUHS will help us develop a technique to perform a barium esophagram in the Cat.

Funds Utilized, FY 79: NONE

Funds Requested, FY 80: $2,500 for equipment, animals and animal care.

Publications: Pending.

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
HSWP-MH	Introductory Remarks, Annual Progress Report, FY 79

TO C, Clin Invest Svc FROM C, Hem-Onc Svc DATE 9 Oct 79 CMT 1

/mjh/61757

1. The Oncology Section, Hematology-Oncology Service, continued to participate in studies of the Cancer and Leukemia Group B (CALGB), investigating experimental and standard drugs, singly and in combinations, and in combination with radiation therapy, in patients with various neoplastic diseases. New WRAMC protocols were initiated during FY 1979 and others were continued from previous years.

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 Clinical Investigation and Human Use Committees and forwarded to the Human Use Review Office, Office of the Surgeon General, for approval in compliance with AR 40-7.

4. Funds in the amount of $67,425 were received from the National Cancer Institute through an Interagency Agreement. These funds were used for 50% of the salary of the Principal Investigator, three medical record technicians, patient travel, and physician travel to CALGB meetings. Because of the ceiling on travel funds imposed by the NCI, additional funds were received from WRAMC in the amount of $10,000 for physician and patient travel.

5. A new part of the research program involves the pharmacology of antineoplastic agents, particularly the anthracyclines. It is anticipated that studies supported by the Clinical Investigation Service will be fruitful in the next year.

Jeffrey L. Berenberg

Incl
Annual Report, FY 79

JEFFREY L. BERENBERG, MD
LTC, MC
Chief, Hematology-Oncology Service

DA FORM 1 FEB 62 2496 REPLACES OD FORM 95, EXISTING SUPPLIES OF WHICH WILL BE ISSUED AND USED UNTIL 1 FEB 63 UNLESS SOONER EXHAUSTED.

GPO 1968 O - 727-600

Work Unit No.: 1516

Title of Project: ALGB Protocol 7291 - Add. #5: 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. Primary objectives:

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

b. To compare, in terms of duration of remission, percentage exhibiting recurrence and survival, the effectiveness of vincristine and dactinomycin to vincristine, dactinomycin and daily oral cyclophosphamide for treatment of patients who have (1) microscopic residual disease following surgery or (2) have no demonstrable disease following complete resection of regional disease.

c. To compare, in terms of response to treatment, length of remission, percentage exhibiting recurrence, and survival, the effectiveness of vincristine, dactinomycin, and high pulse doses of cyclophosphamide to the same drug combination plus adriamycin for the treatment of patients with (1) gross residual disease following surgery, or (2) evidence of metastatic disease at time of diagnosis.

2. Secondary objectives:

a. To obtain a better understanding of the neoplasm by:

1. Defining the extent of the lesions and relating it to the response to treatment, duration of remission, percentage exhibiting recurrence, and survival.

a. Are the duration of remission and survival of patients who undergo complete tumor removal the same, irrespective of whether their disease was initially localized or regional?

b. How does the duration of remission and survival of patients with microscopic residual disease compare with those who had complete tumor removal?

2. Correlating histological types of the neoplasm and age with response to treatment, duration of remission, percentage exhibiting recurrence, and survival. Randomization to the various treatment regimens will not be based on histological type, but the correlation between histological type and response will be monitored carefully in the analysis.

Technical Approach:

Basic Protocol: 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 groups 3 and 4 will be randomized between regimen E and F.

Regimen A: Vincristine 2 mg/m^2 (maximum dose 2.0 mg) I.V. weekly for 12 doses plus
Dactinomycin 0.015 mg/kg/day (max. 0.5 mg) I.V. for 5 days to be repeated at 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) I.V. for 5 days to be repeated at 9, 18, 27, 36 and 45 weeks plus
Vincristine 2 mg/m^2 (max. 2 mg) I.V. weekly for six doses.

Regimen E: Vincristine 2 mg/m^2 (max. 2 mg) I.V. weekly for 12 doses plus
Dactinomycin 0.015 mg/kg/day (max. 0.5 mg) I.V. for 5 days to be repeated at 18, 30, 42 and 54 weeks plus
Cytoxan 10 mg/kg/day I.V. 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 area of spread to be started at six weeks.

Regimen F: Vincristine 2 mg/m^2 (max. 2.0 mg) I.V. 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 2, 33, 45 and 57 weeks plus

Regimen F: (Cont'd) Cytoxan 10 mg/kg/day I.V. 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 I.V. 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 (max 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.

Addendum #1: Change effects patients in Groups 3 and 4 and is as follows:

Cyclophosphamide 300 mg/m^2/day I.V. for 5 days starting on day 0. In addition, for children 2 years of age and older (excluding those who have the bladder included in the radiation portal or are to have large volumes of bone marrow irradiated, such as whole abdomen including the pelvic bones), cyclophosphamide 300 mg/m^2 I.V. is to be administered as a single dose on days 28, 42 and 56, concomitant with radiation.

Radiotherapy to the tumor-bed as well as to the metastatases, as outlined in Section 9.0 of protocol, is to be started at 4 weeks (day 28). If the disease is progressive after 2 weeks of chemotherapy, radiotherapy may be initiated. If the disease is stable, radiotherapy should be withheld until 4 weeks.

At week 11 (day 77), the patient is to receive one of the following two treatment regimens:

Regimen H: Starting at week 11 (day 77) and at 4-6 week intervals (according to tolerance) thereafter up through week 101 or 103, the following course is to be given:

Vincristine 2 mg/m^2/day I.V. on days 0 and 4 (max. single dose 2 mg) plus
Dactinomycin 0.45 mg/m^2/day for 5 days starting on day 0 (max. single dose 0.5 mg) plus
Cyclophosphamide 300 mg/m^2/day I.V. for 5 days starting on day 0.

OR

Regimen I: Starting at week 11 (day 77) and at 8-12 week intervals (according to tolerance) thereafter up through week 95 or 99 the following course is to be given:

Vincristine 2 mg/m^2 I.V. on day 0. (max. single dose 2 mg) plus
Cyclophosphamide 500 mg/m^2 I.V. on day 0 plus
Adriamycin 30 mg/m^2/day I.V. for 3 days starting on day 0.

(If patient has received pulmonary or mediastinal irradiation, adriamycin should be stopped after the 5th course, otherwise it should be stopped after the 6th course.

Starting at week 15 or 17 (day 105 or 119) and at 8-12 week intervals (according to tolerance) thereafter up through week 101 or 103 the following course is to be given:

Vincristine 2 mg/m^2/day I.V. on days 0 and 4 (max. single dose 2 mg).plus
Dactinomycin 0.45 mg/m^2/day for 5 days starting on day 0 (max. single dose 0.5 mg) plus
Cyclophosphamide 300 mg/m^2/day I.V. for 5 days starting on day 0.

Addendum #3 refers to cyclophosphamide schedule toxicity.

Addendum #4 refers to surgical guidelines.

Addendum #5 refers to patients with nasopharynx-nasal cavity, paranasal sinuses, and middle ear primary sites.

Progress and Results: WRAMC entered eleven patients. One was lost to follow-up shortly after entry on the study. One patient expired with progressive disease on day 40 and one had progressive disease on day 117. One relapsed on day 660 and one on day 323. One has relapsed at 436 days and expired on day 606. One has completed two years of therapy and is free of disease.

Conclusions: Four hundred and twenty three children have been entered and two hundred and seventy eight are evaluable for analysis. Details of results according to stages have recently been published.

Side Effects/Complications: One patient had disseminated intravascular coagulation during therapy. One has developed radiation necrosis of the brain.

Funds Utilized FY 79/Requested 1980: See Introductory Remarks to Annual Progress Report.

Publications: Maurer et al: The Intergroup Rhabdomyosarcoma Study. Cancer 2015, 1977.

Type of Report: Interim

Work Unit No.: 1520

Title of Project: ALGB Protocol 7411 Add. #4 - 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 regimen 1 or 2. Patients at increased risk will be allocated to regimens 2 or 3.

Regimen I:

Vincristine 2.0 mg/m^2/week I.V. 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 I.V. for 10 consecutive days from day 29-38.

Regimen II:

Vincristine 2.0 mg/m^2/week I.V. for 4 weeks on days 1,8,15 & 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 6 doses on days 1,15, 22,43,50 and 57 (last 3 injections coincide with cranial irradiation)plus
L-asparaginase 1000 IU/kg/day I.V. for 10 consecutive days from day 29-38 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 I.V. for 4 weeks on days 1,8,15 and 22 plus
Prednisone 40.0 mg/m^2/day po 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 6 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 I.V. for 3 days on days 1,2,and 3 for those 2 years and over and 22.5 mg/m^2/day I.V. for 3 days on days 1,2 and 3 for those under 2 years of age plus
L-asparaginase 1000 IU/kg/day I.V. for 10 consecutive days from day 29-38 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 p.o. plus
MTX 15.0 mg/m^2/week p.o. on the 1st day of each week
Reinforce with vincristine and prednisone at monthly intervals for 5 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 I.V. 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 as the 13th and 25th week of maintenance, 45.0 mg/m^2/day I.V. x 2 beginning on the last day of the vincristine plus prednisone reinforcement.

Regimen B: Intermittent intensification oral 6-MP and oral MTX:
6-MP 200 mg/m^2/day p.o. for 5 days plus
MTX 7.5 mg/m^2/day p.o. for five days, wait 9 days and then repeat, wait 9 days and then 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 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 I.V. 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 p.o. 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. x 2 beginning on the first day of vincristine plus prednisone reinforcement.

Addendum #1 dated 13 June 1974 changes the randomization timing for postoperative and systemic therapy.

Addendum #2 dated 27 June 1974 changes dose schedule in Regimen C for C. Parvum

Addendum #3 dated 31 July 1974 modifies dosage of C. Parvum and immunotherapy.

Addendum #4 dated 11 November 1974 changes treatment schedule in Regimen A for L-PAM.

Progress and Results: WRAMC entered 16 patients. Ten achieved a complete remission. Six patients remain in complete remission from day 1196 to day 1596. Two have relapsed on days 56 and 738. Two were not evaluable for maintenance.

CALGB entered 472 patients. Median duration of remission is 50 + months at this time with very few relapses after three years. Those patients who are greater than 2 years or less than 30,000 were shown to be at increased risk for relapse. These results are comparable to those shown for other study groups and at the St. Judes Hospital there was no difference in treatment regimens.

Conclusions: Daunorubicin does not improve remission duration in these patients at increased risk for relapse. This was subsequently confirmed in a study at St. Judes Hospital. This is in contradistinction to recent data in adult acute lymphocytic leukemia. Here the addtion of daunorubicin to vincristine, prednisone and L-asparaginase improves overall complete remission rate.

Side Effect/Complications: No unusual/unexpected side effects were encountered.

Funds Utilized FY 79/Requested FY 80: See Introductory Remarks to Annual Progress Report.

Publications: Abstract: Burgert EO: Risk Factors in Planning Treatment for Children with Acute Lymphocytic Leukemia. Proceeding of AACR and ASCO, #C, 262, 372, 1978.

Type of Report: Interim-Study was discontinued in November L976.

Work Unit No.: 1528

Title of Project: ALGB Protocol 7391 - Add. #1: 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. x 6 plus
Cyclophosphamide 500 mg/m^2 I.V. x 6 plus
Radiotherapy to the lesion.

Regimen II - Vincristine 1.5 mg/m^2/week x 6 plus
Cyclophosphamide 500 mg/m^2/week I.V. x 6 plus
Radiotherpay to the lesion and both lung fields

Continuation Plan: Actinomycin-D 15 mcg/kg daily I.V. x 5 at 3 months; after one week's 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.

Addendum #1 - Group I Randomization:

Regimen I - Radiotherapy to primary lesion will be substituted by radiotherapy to primary lesions plus cyclophosphamide (NSC 26271) Vincristine (NSC 67574) Dactinomycin (NSC 3053) and Adriamycin (NSC 123-127).

Regimen II - Remains the same.

Additional material to Objectives: Compare the time interval from clinically localized tumor to appearance of metastases using:

Irradiation of the primary tumor plus systemic chemotherapy (cyclophosphamide, vincristine, dactinomycin and adriamycin).

Adriamycin 60 mg/m^2 I.V. (Not used in Regimen II).

Regimen I - Initial phase concomitant with radiotherapy (day 0 and weekly x 6) included both cyclophosphamide and vincristine but no dactinomycin. The first dose of adriamycin is given the sixth week of therapy on day 35 along with the last dose of vincristine and cyclophosphamide.

Continuation phase begins three months after beginning of the initial phase and is repeated every three months through 18 months (six courses). Dactinomycin, 1t mcg/kg is given I.V. daily for 5 days (day 1-5). After a nine day rest, vincristine 1.t mg/m^2 and cyclophosphamide 500 mg/m^2 is given I.V. weekly for five weeks (day 14, 21, 28, 35 and 42). Adriamycin 60 mg/m^2 is given I.V. in the seventh week (day 42) along with the dose of vincristine and cyclophosphamide. A rest period extends from day 42 to day 90 when the next continuation course begins.

Regimens II & II: Remain unchanged.

Progress and Results: WRAMC entered seven patients. One relapsed on day 582. One went off study shortly after entry, and a third patient relapsed. One patient

died on day 356; one patient is free of disease on day 783, and one on day 335, a third patient has no evidence of disease on day 395.

Conclusions: There are statistically significant differences in times to relapse related to the site of the primary lesion. Superior disease-free intervals are obtained in patients with distal versus proximal versus rib versus pelvic primary tumors. Likewise, patients with complete or incomplete resection of primary tumors fared much better than those whose tumors were biopsied only.

Side Effects/Complications: No unusual/unexpected side effects were encountered.

Funds Utilized FY 79/Requested FY 80: See Introductory Remarks to Annual Progress Report.

Publications: ASCO Abstract #C-425, 413, 1978. Prognostic Factors on Ewing's Sarcoma. Burgert O, etal.

Type of Report: Interim

Work Unit No.: 1532

Title of Project: ALGB Protocol 7451 - Add. #2 - 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:

Basic Protocol: Regimen I: Total nodal radiation therapy with the mantle port above the diaphragm and inverted "Y" below the diaphragm plus the spleen of splenic pedicle area and optionally the porta hepatis.

Regimen II: Chemotherapy consisting of:
Vincristine 1.4 mg/m^2/week I.V. x 2 with a max. 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 I.V. on day 1.

Each course will consist of 2-weeks treatment and two-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/procabazine/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.

Addendum #1 states changes in the shielding procedure for radiotherapy consisting of: In the areas above the diaphragm the lungs will be shielded; individually constructed lead blocks will be used whenever possible. When arms are brought over the head to full extension, the lungs are shielded more adequately and consequently, a greater proportion of the upper ribs are also shielded. However, because of the upward rotation of the axillary nodes in the vicinity of the humeral heads, the humeral heads should not be shielded. The irradiation of the humeral heads is compensated by the better shielding of the upper ribs. If the akimbo position is employed, the humeral heads will be shielded during the whole course of treatment.

In the split course technique, it is expected that reactive mucositis of the larynx will be avoided, but it is left to the clinical judgement of the radiation therapist to shield the larynx when this is considered appropriate.

Addendum #2 states changes in the chlorambucil maintenace therapy for regimen II: Chlorambucil maintenace for Regimen II is to be given such that the patients will have received a total treatment period of two years as measured from the onset of protocol therapy (Induction and Maintenance).

At completion of that therapy, patients will be re-evaluated for the completeness of the remission. Those patients judged to be in complete remission by the investigator will be followed with no further therapy until disease progression. Those patients judged to be only in partial response will be taken off study. Indicated on the flow sheets all tests done and their results at that time of assessment for the extent of response.

Progress and Results: Fifteen patient have been entered on this study. Ten have achieved complete remissions. Two have relapsed and one of these has died. Three of these patients have been lost to adequate follow-up currently. One patient has failed therapy. Four patients have been disqualified.

Conclusions: Protocol 7451 therapy has prolonged survival overall for both stage IIIA and B patients. Complete remission for stage IIIA was 82%, 76%, 63% and 88% respectively for the four treatment arms and for IIIB was 58%, 70%, 70% and 85% respectively. Although the chemotherapy-radiotherapy regimen has the highest complete remission frequency, it is associated with the highest number of treatment related deaths. No disease relapse has been observed as yet in the 15 patients who completed the radiotherapy phase of the chemotherapy-radiotherapy regimen.

Side Effects/Complications: No unusual/unexpected side effects were encountered.

Funds Utilized FY 79/Requested FY 80: See Introductory Remarks to Annual Progress 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 multipel myeloma.

Technical Approach:

Regimen I - L-PAM 150mcg/kd/day x 7 p.o. plus
Prednisone 0.8 mg/kg/day x 14 p.o. beginning on day 1
0.4 mg/kg/day x 14 p.o.
0.2 mg/kg/day x 14 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 addtional therapy.

Regimen B Indicates that the patient should continue with his initial therapy and in addition re eive
Vincristine 1.0 mg/m^2 I.V. x 1 on day 154 and every 8 weeks thereafter plus
Prednisone 0.6 mg/kg/day p.o. x 7 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 and Results: WRAMC entered six patients. Their courses were well detailed in the 1978 report. Since then, one remaining patient has progressed and died on day 640. No follow-up is available on the disqualified patient who was in remission on day 809 last year.

CALGB entered 558 patients. Median survival was 25 months essentially unimproved from previous studies. Oral L-PAM 49% and I.V. L-PAM 44% proved somewhat more effective than BCNU 34% or CCNU 32%. Overall 25% of patients are surviving at 4 years.

Conclusions: L-PAM I.V. or p.o. with prednisone give significantly better response rates than prednisone plus nitrosoureas - BCNU or CCNU.

Side Effects/Complications: Low rate of drug associated deaths in this study - 3%. There was about 2% incidence of allergic reactions to I.V. L-PAM

Funds Utilized FY 79/Requested FY 80: See Introductory Remarks to Annual Progress Report.

Publications: Cornwell CG.: Hypersensitivity Reactions to Intra-Venous L-Phenylalanme Mustard. Accepted for publication in Cancer Treatment Reports.

Type of Report: Final-Protocol closed to entry in September 1977.

Work Unit No.: 1534

Title of Project: ALCB Protocol 7521 Add. #2: A Comparative Study of the Value of Immunotherapy with MER as Adjuvant to Induction and Two Maintenance Chemotherapy Programs in Acute Myelocytic Leukemia.

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 1-7 plus
Daunorubicin 45 mg/m^2/day by rapid I.V. 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. q 12 hrs for 10 injections plus
Thioguanine 100 mg/m^2 p.o. q 12 hrs for a total of 10 doses plus MER

Regimen B: Cytosine Arabinoside 100 mg/m^2 s.c. q 12 hrs for a total of 10 injections plus
Thioguanine 100 mg/m^2 p.o. q 12 hrs for a total of 10 doses.

Alternate with Second five day course:

Cytosine Arabinoside 100 mg/m^2 s.c. injection q 12 hrs, total of 10 injections on days 1-5 plus
Vincristine 2 mg/m^2, (max. 2 mg), 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 days 1-5 plus
Intradermal MER

Regimen C: 5-day course repeated q 4 weeks

Cytosine Arabinoside 100 mg/m^2 s.c. q 12 hrs, total of 10 injections plus
Thioguanine 100 mg/m^2 p.o. q 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. q 12 hrs total of 10 injections plus
daunorubicine 45 mg/m^2/day by rapid I.V. injection on days 1-2.

Addendum #1 dated 10 December 1975 modifies the protocol to provide uniform treatment for CNS leukemia when it occurs and alters the schedule of MER administration.

Addendum #2 dated 14 February 1977 states that MER will be given as a single dose during Induction Phase of patient entry.

Progress and Results: WRAMC has entered 28 patients. Twelve patients (13%) obtained a complete remission. Six of whom relapsed from day 114 to day 403. One patient in complete remission died of drug related causes (presumed sepsis). Five of the six patients who relapsed have died, one is alive after a bone marrow transplant. Four patients had partial response. Three of these have died and one remains in remission following a marrow transplant.

CALGB results 629 patients entered. 287 (46%) attained a complete remission. Overall survival of patients to date is a median of 8 months. Median survival of patients attaining a complete remission is 19.8 months. MER treatment during induction appears to benefit the duration overall remission rate (52%) vs 43%. Overall survival also appears to be influenced by skin test reactivity + 11 months vs - 6 months. No difference in remission duration has been seen with the different maintenance regimens.

Conclusions: 46% of patients treated in CALGB achieved a complete remission. This translated into a median survival of 19.8 months for this group. The survival for all patients treated was 7.7 months. MER treatment during induction or skin reactivity prior to treatment appear to increase the likelihood of complete remission and therefore survival. [It is of interest that two patients at WRAMC have apparently benefited from Bone Marrow Transplantation].

Side Effects/Complications: One patient died in complete remission of sepsis following maintenance chemotherapy. This is unfortunately seen occasionally in the treatment of acute leukemia.

Funds Utilized FY 79/Requested FY 80: See Introductory Remarks to Annual Progress Report.

Publications: An abstract of this protocol was reported by Cuttner et al: A Controlled Trial of Chemoimmunotherapy in Acute Myelocytic Leukemia (AML). Proceedings of AACR and ASCO, Vol. 20, March 1979 pp 333, 1978.

Type of Report: Interim - Protocol was closed to patient entry June 1977.

Work Unit No.: 1535

Title of Project: ALGB Protocol 7581 - Add. #2: 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 p.o. for 42 consecutive days plus
Methotrexate 40 mg/m^2/week I.V. for 6 consecutive weeks
EXCEPT patients 60 years of age are to receive 30 mg/m^2/week I.V.plus
5-FU 500 mg/m^2 I.V. for 6 consecutive weeks plus
Vincristine 1.0 mg/m^2/week I.V. for 6 consecutive weeks (max. dose 1.5 mg per dose) plus
Prednisone 40 mg/m^2/day p.o. 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 p.o. for 42 consecutive days plus
Methotrexate 40 mg/m^2/week I.V. for 6 consecutive weeks, EXCEPT patients 60 years or older are to receive 30 mg/m^2/week I.V. plus
5-FU 500 mg/m^2/week I.V. for 6 consecutive weeks.

Regimen III: Cytoxan 80 mg/m^2/day p.o. for 42 consecutive days plus
Methotrexate 40 mg/m^2/week I.V. for 6 consecutive weeks EXCEPT patients 60 years or older are to receive 30 mg/m^2/week I.V. plus
5-FU 500 mg/m^2/week I.V. for 6 consecutive weeks plus
MER 200 ug intradermally in each of 5 sites (total 1 mg) at weeks, 1,3&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 p.o. days 1-14 of each cycle plus
Methotrexate 40 mg/m^2 I.V. 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 I.V. day 1 and 8 of each cycle plus
Vincristine 1.0 mg/m^2 I.V. day 1 and 8 of each cycle (max. dose 1.5 mg/dose) plus
Prednisone 40 mg/m^2.day p.o. 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 p.o. days 1-14 of each cycle plus
Methotrexate 40 mg/m^2 I.V. days 1 and 8 of each cycle EXCEPT patients 60 years or older are to receive 30 mg/m^2 plus
5-FU 500 mg/m^2 I.V. day 1 and 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 p.o. days 1-14 of each cycle plus
Methotrexate 40 mg/m^2 I.V. days 1 and 8 of each cycle EXCEPT patients 60 years or older are to receive 30 mg/m^2 plus
5-FU 500 mg/m^2 I.V. day 1 and 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 p.o. days 1-14 of each cycle plus
Methotrexate 40 mg/m^2 I.V. on day 1 and 8 of each cycle EXCEPT patients 60 years or older are to receive 30 mg/m^2 plus
5-FU 500 mg/m^2 I.V. on day 1 and 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.

Addendum #1 dated 13 September 1975 mandates patient eligibility with 1-3 involved axillary nodes for protocol.

Addendum #2 dated 28 October 1978 states that Regimen III is closed to patient entry and that all new patients will be placed on either regimen I or II of the protocol.

<u>Progress and Results:</u> WRAMC has entered 33 patients. One patient was not eligible. Five patients have relapsed on days 240, 832, 861, 588 and 302. All other patients remain in complete remission from 183 to 1368 days.

Conclusions: As of 1 June 1979 there is as yet no statistical difference between the regimens.. The CMF plus MER regimen has been discontinued based on ALGB Breast Committee recommendation. There is no difference in disease free interval related to the time between mastectomy and onset of chemotherapy up to eight weeks postoperatively. The failure rate appears to be lower in patients with only one to three positive nodes compared with four or more for both pre and post menopausal patients.

Side Effects/Complications: No unusual/unexpected side effects were encountered.

Funds Utilized FY 79/Requested FY 80: See Introductory Remarks to Annual Progress Report.

Publications: None

Type of Report: Interim

Work Unit No.: 1537

Title of Project: ALGB Protocol 7551 - Add. #2: 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 75mg/m^2 p.o. day 1 plus
Vinblastine 4 mg/m^2 I.V. day 1 & 8 plus
Procarbazine 100 mg/m^2 p.o. days 1-14 plus
Prednisone 40 mg/m^2 p.o. days 1-14

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 course, 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.

Addendum #1 dated 17 March 1978 states that chlorambucil maintenance therapy be shortened.

Addendum #2 dated 1 September 1978 states that after all disease parameters that were abnormal at the time of protocol entry for chlorambucil maintenance must be carefully reassessed. If all parameters are normal, the patient should be followed with no further therapy until disease progression. The same is indicated for new patients entered on induction and all other patients presently on induction therapy.

Progress and Results: WRAMC has entered 8 patients. Four are in complete remission at 176 to 768 days. One had a partial remission on day 258 and subsequently expired and a second had a partial remission on day 355 and currently is not evaluable due to inadequate follow-up. One patient has failed therapy and one is too early for evaluation.

Conclusions: Survival estimates are too early to establish trends. Coded regimen Q is showing a very early trend of superiority with respect to complete response frequency.

Side Effects/Complications: No unusual/unexpected side effects were encountered.

Funds Utilized FY 79/Requested FY 80: See Introductory Remarks to Annual Progress Report.

Publications: None

Type of Report: Interim

Work Unit No.: 1538

Title of Project: CALGB Protocol 7552, Add #6: 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 I.V. on days 1 and 8 plus
Procarbazine 100 mg/m^2 p.o. on days 1-14 plus
Prednisone 40 mg/m^2 p.o. on days 1-14.

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 or Regimen IIB	Bleomycin 5 u/m^2 I.V. on days 1 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 chemoptherapy, 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 or Regimen IIIB	Will consist of 12 courses of induction therapy. Each course will consist of 2 weeks of chemotherapy, and a course will be given q 4 weeks.

Regimen III will be alternated 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 #1 dated 21 April 1976 changes patient eligibility to regardless of stage patients may be entered provided other criteria for protocol study are met.

Addendum #2 dated 22 October 1976 decreased the dose of streptozotocin.

Addendum #3 dated 15 July 1977 adds follow-up evaluation reassessments.

Addendum #4 dated 17 March 1978 shortens the chlorambucil maintenance therapy time frame.

Addendum #5 dated 1 September 1978 states for patients currently on maintenance and induction chlorambucil therapy, a reassessment of their abnormal disease paramenters must be obtained and if all parameters are normal after the assessment that patient should be followed with no further therapy until disease progression.

Addendum #6 dated 10 February 1979 changes MER randomization which was discontinued and for treatment during induction (all patients currently receiving MER will continue to receive the agent for the twelve month period). For Maintenance therapy - after the twelve month administration of MER during the Induction Phase no further immunotherapy will be given.

Progress and Results: WRAMC entered 5 patients, one of whom was disqualified because he refused MER five out of nine courses. Four achieved complete remissions. One developed AML and began induction chemotherapy on day 360 and is now off protocol; one is now off protocol since he stopped chlorambucil at 1 1/2 years of maintenance due to increasing restrictive pulmonary disease. At that time he had no evidence of disease at day 1045.

Conclusions: Addendum #5 discontinued the MER randomization since MER failed to show any advantage with respect to complete response or survival. The three chemotherapy programs continue to be tested. The survival of patients who have had prior radiotherapy (median not yet reached) is superior to those who have had prior chemotherapy (no MER 21.8 months, MER 10.9 months).

Side Effects/Complications: No unusual/unexpected side effects were encountered.

Funds Utilized FY 79/Requested FY 80: See Introductory Remarks to Annual Progress Report.

Publications: None

Type of Report: Interim

Work Unit No.: 1539

Title of Project: CALGB Protocol 7541: 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, and 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 x 3 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 x 3 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 q 4th 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, providing 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 threshold 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 and Results: Five patients have been entered at WRAMC. One patient was ineligible because of prior treatment. Two patients have expired on day 89 and day 700. Follow-up is pending on the other two.

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

Side Effects/Complications: Skin reactions to MER immunotherapy.

Funds Utilized FY 79/Requested FY 80: See Introductory Remarks to Annual Progress Report.

Publications: None

Type of Report: Interim

Work Unit No.: 1541

Title of Project: CALGB Protocol 7542: 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 standary lymphoma-type maintenance with high dose intermittent Cyclophosphamide and Vincristine-steriod 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 I.V. 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 I.V. push x 1 beginning on day 36 of study and q 4 weeks thereafter plus
Vincristine 2 mg/m^2 I.V. push x 1 beginning on day 36 and q 4 weeks thereafter plus

Dexamethasone 6 mg/m^2 p.o. daily x 7 days q 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 1000 mg/m^2 I.V. push x 1 beginning on day 36 and q 4 weeks thereafter plus
Vincristine 2 mg/m^2 I.V. push x 1 beginning on day 36 and q 4 weeks thereafter plus
Dexamethasone 6 mg/m^2 p.o. daily x 7 days q 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 I.V. x 4 doses given on days 1,8,15 & 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 I.V. x 3 doses given on days 36,57 and 78 of study plus
Dexamethasone 6 mg/m2 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 start of the high dose MTX (500 mg/m^2) plus
Methotrexate 500 mg/m^2 1/3 I.V. push and 2/3 I.V. drip over 24 hours given on days 26,57 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 I.V. 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 I.V. push x 1 beginning on day 36 of study and q 4 weeks thereafter plus
Vincristine 2 mg/m^2 I.V. push x 1 beginning on day 36 and q 4 weeks thereafter plus
Dexamethasone 6 mg/m^2 p.o. daily x 7 days q 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 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 and Results: WRAMC entered 3 patients. The one patient with a complete remission maintained at day 572 at last report has had no further follow-up. The other two patients have died.

Conclusions: CALGB status unknown. Recommend this protocol be discontinued at WRAMC.

Side Effects/Complications: No unusual/unexpected side effects were encountered.

Funds Utilized FY 79/Requested FY 80: See Introductory Remarks to Annual Progress Report.

Publications: None

Type of Report: Interim

Work Unit No.: 1542

Title of Project: CALGB Protocol 7583 - Add #1: Adjuvant Chemotherapy in Osteogenic Sarcoma, Adriamycin vs Sequential Adriamycin, High Dose Methotrexate--Citrovorum Factor vs Sequential Adriamycin-Cyclophosphamide.

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 20 mg/m^2 daily x 3 days I.V. to be repeated q 4 weeks for 6 courses. The treatment will begin no sooner that 4 days and not later than 4 weeks following operation.

Regimen II
Day 1-3, adriamycin 30 mg/m^2 I.V. daily
Day 28-30, 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 IM q 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 IM q 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 1-3, adriamycin 30 mg/m^2 I.V. daily
Day 28-30, 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 course for cyclophosphamide.

Addendum #1 dated 10 June 1977 closes Regimen III to patient entry.

Progress and Results: WRAMC entered seven patients. Treatment had to be stopped in one patient on day 73 because of toxicity. Three relapses have been noted on days 134, 563 and 448 respectively. One patient is free of disease at 534 days. Follow-up is pending on the other two patients.

Conclusions: Adriamycin appears equivalent, if not superior to high dose methotrexate as employed.

Side Effects/Complications: Side effects noted were mucositis and renal dysfunction.

Funds Utilized FY 79/Requested FY 80: See Introductory Remarks to Annual Progress Report.

Publications: None

Type of Report: Interim

Work Unit No.: 1543

Title of Project: ALGB Protocol 7651 - Add #3: 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.

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 I.V. 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 q 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 I.V. plus
Vincristine 1 mg/m^2 (max. 2 mg) I.V. 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.

Addendum #1 dated 22 October 1976 changes patient selection and eligibility and preliminary requirements for induction phase and randomization for maintenance Phase II regimens.

Addendum #2 dated 23 March 1978 states noted toxicity from radiation bath of abdomen with reinforcement vincristine with results of radiation hepatitis at doses under 1500 rads with this combined treatment.

Addendum #3 dated 26 June 1979 mandates restaging of patients with completion of 3 years of maintenance chemotherapy. After restaging, if patient continues in complete remission, all maintenance chemotherapy will be discontinued and patient will be followed untreated on study. However, if after restaging, patient shows evidence of disease in areas previously established by biopsy to be normal, patient should be removed from study as relapsed. If patient shows areas of not previously noted disease patient will be considered a partial responser.

Progress and Results: WRAMC entered a total of 17 patients. To date 5 patients have achieve a complete remission and 4 patients remain in complete remission at 125 to 933 days. One patient relapsed after 9 months in remission; 5 patients have achieved a partial remission at 78 to 1181 days; 4 patients have failed therapy. Three patients have been disqualified.

Conclusions: An addendum amended the protocol to omit vincristine during the course of abdominal radiation, since three or possibly more patients developed radiation hepatitis at doses under 1500 rads with this combined treatment. Although P consolidation is favored at this time, it is too early for any meaningful statistical test of significance because of the small number of deaths.

Side Effects/Complications: No unusual/unexpected side effects were encountered at WRAMC.

Funds Utilized FY 79/Requested FY 80: See Introductory Remarks to Annual Progress Report.

Publications: None

Type of Report: Interim

Work Unit No.: 1544

Title of Project: CALGB Protocol 7652 - Add #2: 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.

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 I.V. 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 q 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 I.V. 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 fourth 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 I.V. q 3 weeks x 3
plus
Vincristine 1 mg/m^2 I.V. 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 q 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 180-200 rad fractions daily.

Addendum #1 dated 16 November 1976 made two changes in Patient Selection and Eligibility (initial work-up) and stated that patients with mixed histiocytic lymphocytic lymphoma are not eligible for this protocol. Under the Induction Phase of chemotherapy patients are randomized to receive radiotherapy with chemotherapy, radiotherapy forms must be obtained and forwarded to main office at the time of entry. All staging procedures must be listed and results posted on flow sheets. Under Phase II Consolidation and Maintenance, randomization was added.

Addendum #2 dated 16 October 1978 states that patients on maintenance chemotherapy for two years or over must be reassessed and after reassessment, if no disease is noted patient will be followed without further chemotherapy. If any disease is documented patient will be taken off study and considered treatment failure.

Progress and Results: This study was closed to entry of new patients 16 June 1977. Three patients were previously entered at WRAMC; one remains in complete remission at 1370 days and the other two patients failed therapy.

Conclusions: Therapeutic regimens on this protocol are inferior to current treatment methods. The study has been closed.

Side Effects/Complications: No unusual/unexpected side effects were encountered.

Funds Utilized FY 79/Requested FY 80: See Introductory Remarks to Annual Progress Report.

Publications: None

Type of Report: Interim

Work Unit No.: 1546

Title of Project: CALGB Protocol 7611: Treatment of Primary Untreated Acute Lymphocytic Leukemia in Patients under 20 Years with Vincristine (NSC 57674), 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. x 4 on days 1,8, 15 and 22 (max dose 2 mg) plus
Prednisone 40 mg/m^2/day p.o. daily x 4 weeks and then tapered over 10 days plus
Methotrexate 12 mg/m^2 IT x 3 on days 15,22, 29 (max dose 15 mg) plus
L-Asparaginase 1000 iu/kg/day I.V. on days 29-38.

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

Regimen A - High dose methotrexate 500 mg/m^2 over 24 hrs on days 43,64 and 85 plus
Leucovorin 24 hrs after completion of each course of methotrexate at a dose of 12 mg/m^2 plus
Methotrexate 12 mg/m^2 IT x 3 doses on days 43,64 and 85 plus
Vincristine 2 mg/m^2 I.V. on day 78 plus
Prednisone 40 mg/m^2 p.o. daily x 7 days beginning on day 78.

Regimen B - Methotrexate 12 mg/m^2 IT x 3 on days 43,50 and 57 (max dose of IT MTX 15 mg) plus
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 place on:

Maintenance Phase: 6-Mercaptopurine 90 mg/m^2/day p.o. plus
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 q 12 weeks until relapse.

Progress and Results: WRAMC entered 7 patients. One patient went off study on day 42 because local physician refused to give maintenance therapy. Six achieved complete remission. Two have since relapsed between day 87 and day 219. Four remain in complete remission between day 78 through day 373.

CALGB has entered 491 patients. 90% have attained complete remissions. Greater than 70% remain in complete remission at three years. There is no difference in the remission duration between the two types of CNS prophylaxis.

Conclusions: The overall rate of complete remission and duration of remission appear at least comparable to other studies. It is too early to see any difference in disease free survival between CNS prophylactic regimens.

Side Effects/Complications: High dose methotrexate produced more severe mucositis.

Funds Utilized FY 79/Requested FY 80: See Introductory Remarks to Annual Progress Report.

Publications: None

Type of Report: Interim-Study was closed to entry of new patients on 16 July 1979.

Work Unit No.: 1547

Title of Project: CALGB Protocol 7682 Add #1: Combination Chemotherapy or Chemoimmunotherapy for Metastatic Recurrent or Inoperable Carcinoma of the Breast. Three Treatment Regimens: Cyclophosphamide, Adriamycin, 5-Fluorouracil vs Cyclophosphamide, Adriamycin, 5-Fluorouracil, Vincristine, Prednisone vs Cyclophosphamide, Methotrexate, 5-Fluorouracil, All with or without MER. 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 plus 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 to be repeated q 28 days.
Regimen IB	Same as Regimen IA plus MER.
Regimen IIA	Cyclophosphamide 100 mg/m^2/day p.o. days 1-14 plus Adriamycin 25 mg/m^2 I.V. days 1 and 8 to a total dose of 450 mg/m^2 plus 5-Fluorouracil 500 mg/m^2 I.V. days 1 and 8. This cycle to be repeated q 28 days.
Regimen IIB	Same as Regimen IIA plus MER.
Regimen IIIA	Cyclophosphamide 100 mg/m^2 p.o. days 1-14 plus Adriamycin 25 mg/m^2 I.V. days 1 and 8 to a total dose of 450 mg/m^2 plus 5-Fluorouracil 500 mg/m^2 I.V. days 1 and 8 plus Vincristine 1.0 mg/m^2 I.V. days 1 and 8 with max dose of 2 mg plus Prednisone 40 mg/m^2/day p.o. days 1-14 This cycle to be repeated q 28 days.
Regimen IIIB	Same as Regimen IIIA plus MER.

Addendum #1 dated 23 February 1978 changes randomization of patients with pleural metastases to visceral metastases rather than soft tissue.

Progress and Results: WRAMC has entered 10 patients on study. One had progressive disease on day 179; one on day 286; one on day 136; one on day 732 and one on day 177. Two patients have expired, one at day 130 and one at day 485. One patient had a partial response at day 151 and two patients have complete remissions at 110 and 993 days.

Conclusions: Due to a decrease in survival among those patients receiving MER, randomization to MER was discontinued as of 28 October 1978. Recommendation to general membership by CALGB Breast Committee was to discontinue MER.

Groupwide there is presently no difference in survival by coded chemotherapy (as of 1 June 1979).

Side Effects/Complications: No unusual/unexpected side effects were encountered at WRAMC.

Funds Utilized FY 79/Requested FY 80: See Introductory Remarks to Annual Progress Report.

Publications: None

Type of Report: Interim

Work Unit No.: 1548

Title of Project: CALGB Protocol 7681 Add #1: 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. q 4 weeks to a max dose of 550 mg/m^2.
Regimen IB	Adriamycin plus MER 1 mg intracutaneously on days 1 and 8 to be repeated q 4 weeks.
Regimen IIA	Adriamycin 25 mg/m^2 on days 1,2 and 3, to be repeated q 4 weeks to a max dose of 550 mg/m^2.
Regimen IIB	Adriamycin plus MER 1 mg intracutaneously on days 1 and 8 q 4 weeks.

Patients who are in a remission or who have no evidence of progressive disease and who have received the max 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 1-5. Cyclophosphamide and DTIC will be repeated q 4 weeks. Patients who are on MER should be continued on MER.

Addendum #1 dated 8 November 1977 for all new patients entered onto 7681 they will not receive MER immunotherapy.

Progress and Results: WRAMC entered five patient on study. Three had progressive disease at days 28, 86 and 92 and subsequently expired. Two patients are lost to follow-up at the present time.

Conclusions: The 25% range of complete and partial response is the same as that of other cooperative groups employing adriamycin alone or in combination.

Side Effects/Complications: No unusual/unexpected side effects were encountered.

Funds Utilized FY 79/Requested FY 80: See Introductory Remarks to Annual Progress Report.

Publications: None

Type of Report: Interim

Work Unit No.: 1549

Title of Project: CALGB Protocol 7482: Combination Chemotherapy of Patients with Metastatic, Recurrent or Inoperative Carcinoma of the Breast.

This protocol was closed to patient entry on 11 October 1976. Final approval was not received on this protocol until 15 February 1977.

Work Unit No.: 1550

Title of Project: CALGB Protocol 7631: Resistant Phase of Chronic Granulocytic Leukemia: A Study of Chemo-Immunotherapy; A Phase III Study: Daunorubicin, Hydroxyurea, 6-Mercaptopurine, Cyclophosphamide, Prednisone, MER.

This protocol was closed to patient entry in November 1977. No patients were entered on the protocol.

Work Unit No.: 1551

Title of Project: CALGB Protocol 7612 Add #3: 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 x 3 plus
Prednisone 40 mg/m^2 p.o. daily for 21 days plus
L-Asparaginase 500 iu/kg MV daily for 10 days beginning on day 22.

Regimen II

Vincristine 2 mg I.V. weekly x 3
Prednisone 40 mg/m^2 p.o. daily for 21 days
Daunorubicin 45 mg/m^2 I.V. daily x 3 days followed by
L-Asparaginase 500 iu/kg I.V. daily for 10 days staring on day 22
Prednisone will be tapered over 10 days.

Addendum #1 dated 18 October 1976 corrects the incorrectly listed dose of vincristine, on the schema.

Addendum #2 dated 21 July 1977 mandates that patients not achieving an M1 marrow after induction therapy will not be randomized to maintenance therapy but will be given daunorubicin in an attempt to induce complete remission and then will be randomized to maintenance therapy.

Addendum #3 dated 28 October 1978 mandates that all patients will receive chemotherapy provided in Regimen II and not be treated by the indicated randomization number given on study cards.

Progress and Results: WRAMC entered 10 patients. Eight attained complete remission. One patient stopped therapy on day 41, began taking laetrile and relapsed. Six patients have relapsed from day 141 to day 414. One patient remains in complete remission. One patient obtained a partial response but has relapsed. One patient failed to respond and expired on day 40.

CALGB has entered 91 evaluable patients to date. 61 (67%) have attained complete remissions. Evidence at this time indicates benefit for the group receiving daunorubicin (Regimen II). 82% complete remissions vs 51% for group not receiving daunorubicin (Regimen I). Therefore all entries will be to Regimen II.

Conclusions: Daunorubicin adding to vincristine, prednisone and L-asparaginase significantly increases the complete remission rate in adult acute lymphocytic leukemia from 51% to 82%.

Side Effects/Complications: No unusual/unexpected side effects were encountered.

Funds Utilized FY 79/Requested FY 80: See Introductory Remarks to Annual Progress Report.

Publications: None

Type of Report: Interim-This study will probably be closed to entry within the next fiscal year.

Work Unit No.: 1552

Title of Project: CALGB Protocol 7632 Add #1: 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. q 28 days.

Addendum #1 dated 5 November 1977 clarifies eligibility requirements.

Progress and Results: WRAMC has entered two patients. One was randomized to follow-up alone and is stable on day 93. One is too early for evaluation.

CALGB has entered 27 patients.

Conclusions: It is too early to make any conclusions.

Side Effects/Complications: No unusual/unexpected side effects were encountered.

Fund Utilized FY 79/Requested FY 80: See Introductory Remarks to Annual Progress Report.

Publications: None

Type of Report: Interim-Fifty additional patients must be entered.

Work Unit No.: 1554

Title of Project: CLGB Protocol 7691 (WRAMC Add #1): Comparison of Involved Field Radiotherapy with Adjuvant MOPP Chemotherapy and Extended Field Radiotherapy in the Treatment of Stage I and II Hodgkin's Disease in Children.

Investigators:

Principal: Johannes Blom, M.D.

Objectives: To compare the effectiveness of IF radiotherapy, IF radiotherapy followed by MOPP chemotherapy, and EF radiotherapy, in treating laparotomy confirmed Stage I and II Hodgkin's Disease in children in terms of: a) duration of disease-free interval following completion of initial therapy, b) the type and extent of disease extensions following initial therapy, and c) survival.

To determine the retrievability of new disease following primary therapy for each of the three regimens, using specified retrieval plans.

To determine the effect of specific histology on results of primary and retrieval therapy for each of the three regimens.

To determine the comparative effects of the three treatment regimens with respect to:

a) Linear growth, bi-acromial and bi-cristal diameters.
b) Incidence of hypothyroidism and sterility.
c) Incidence of second malignancies.
d) Complications following staging celiotomy and splenectomy, immediate and remote, including fulminating infections.
e) Effectiveness of penicillin prophylaxis in the prevention of post-splenectomy infectious complications.

Technical Approach: Initial therapy for all patients will be irradiation, either IF or EF. Therapy must be initiated within 28 days of the staging celiotomy.

Involved regions should be treated to a total basic tumor dose of 3500-4000 rad at a rate of 850-1000 rad tumor dose per week. Additional or "booster"

treatment may be given for residual disease through very limited fields at the same or a slightly higher tumor dose rate for a total of 500-1000 rad, provided the tolerance of the normal tissues is not exceeded. Doses over 4000 rad delivered in 4 weeks should be avoided in the spinal cord, gastrointestinal tract and heart.

In patients randomized to receive MOPP therapy, it is recommended that the lower limit of the tumor dose described on previous page by employed, i.e., 35 rad in 20 fractions in 4 weeks.

For extended field radiotherapy, the lower limit of radiation dose i.e., 3500 rad in 20 fractions is recommended.

Radiation Dose Modifications for extended field radiotherapy:

Age (Years)	Dose
$\geq$ 11	3500 rad in 20 fractions in 4 weeks
6-10	3000 rad in 20 fractions in 4 weeks
$\leq$ 5	2500 rad in 20 fractions in 4 weeks

Chemotherapy treatment schedule:

Within 4 weeks following the completion of IF radiotherapy, patients randomized to receive adjuvant chemotherapy will begin MOPP chemotherapy (6 courses) provided the adequacy of the hematologic status has been demostrated by a white blood count $>$ 4,000 mm^3 and a platelet count $>$ 100,000 mm^3.

M	Nitrogen Mustard	6 mg/m^2 I.V. days 1 and 8.
O	Vincristine	1.4 mg/m^2 I.V. days 1 and 8.
P	Procarbazine	50 mg p.o. day 1; 100 mg/m^2 p.o. in 2 or 3 divided doses, days 2-14.
P	Prednisone	40 mg/m^2/day p.o. in 3 divided doses, days 1-14. FIRST AND FOURTH COURSES ONLY.

Subsequent courses and dosage adjustments: Following the initial MOPP course, subsequent courses will be intitiated on days 29,57, 85,113 and 141 provided the white blood count is $>$ 4000 mm^3 and the platelet count is $>$ 100,000 mm^3. If the counts are below these levels, treatment will be delayed and doses adjusted on the subsequent course as shown on next page:

Day 29	WBC >4000 mm^3 platelet $>100,000$ mm^3	- Proceed with full dose MOPP, i.e. 100% all drugs.
29	WBC <3000 mm^3 platelet $<100,000$ mm^3	- Wait 3 days and repeat blood count.
32	WBC >4000 mm^3 platelet $>100,000$ mm^3	- Proceed with full dose MOPP i.e. 100% all drugs.
32	WBC <4000 mm^3 platelet $<150,000$ mm^3	- Wait 3 or 4 days and repeat blood count.
35 or 36	WBC >3000 mm^3 platelet $>100,000$ mm^3	- Full dose VCR & Prednisone 25% dose HN_2 & Procarbazine.
	WBC 2,000-3,000 mm^3	- Full dose VCR & Prednisone 25% dose HN_2 & Procarbazine.
	WBC 1000-2000 mm^3	- 50% VCR; no HN_2 or Procarbazine.
	Platelet 50,000-60,000 mm^3	- Full dose VCR & Prednisone 25% HN_2 and 25% Procarbazine.
	$<50,000$ mm^3	- No therapy.

When patients have first relapse they may receive another 6 courses of MOPP chemotherapy.

Addendum #1 (WRAMC) states that prior to WRAMC patient entry all patients must obtain thyroid function studies (T3, T4, TSH and FSH).

Progress and Results: No patients have been entered on study.

Conclusions: None

Side Effects/Complications: No unusual/unexpected side effects were encountered.

Funds Utilized FY 79/Requested FY 80: See Introductory Remarks to Annual Progress Report.

Publications: None

Type of Report: Interim

Work Unit No.: 1555

Title of Project: CALGB Protocol 0702 (Pilot Study) Add #1: Evaluation of Galactitol 1, 2:5, 6-Dianhydro in the Treatment of Advanced Carcinoma of the Lung and Melanoma.

Investigators:

Principal: Johannes Blom, M.D.

Objectives: To determine the antitumor effect of galactitol in small cell, large cell, squamous and adenocarcinoma of the lung and melanoma.

Technical Approach: Chemotherapy Regimen:

Patients who have received prior cytotoxic chemotherapy will be required to wait three weeks from the date of the last dose of chemotherapy before starting on Galactitol.

Galactitol Dosage: 60 mg/m^2 as a slow intravenous push q 7 days.

Dose Modifications:

WBC (mm^3)	Platelets (mm^3)	Dosage
> 4000	> 100,000	Full
3-4000	75-100,000	75%
2-3000	50-75,000	50%
< 2000	< 50,000	Wait for counts to recover

Dose Adjustment: If after four injections of Galactitol the white blood count does not nadir below 4000 or the platelet count below 100,000, the dose of Galactitol will be increased to 75 mg/m^2 intravenously each 7 days.

Concomitant Therapy: Concurrent use of steroids, antibiotics or other treatment modalities to be used as indicated.

Palliative radiation to be used as indicated. this does not remove patient from study unless it is used to control progressive disease or all the measurable disease.

Addendum #1 states that the only patients to be entered on this study at WRAMC are patients that are resistant to conventional chemotherapy.

Progress and Results: WRAMC entered 21 patients on study. One patient has malignant melanoma. This patient had intially stable disease, then expired of progressive disease on day 44. Of the twenty registered lung cancer patients, 16 had progressive disease ranging from day 18 to day 328, and subsequently expired. One patient expired on day 3 and was considered non-evaluable. Two patients refused treatment on days 15 and 42 and later expired. One patient has shown significant response, and remains on study on day 335 with no evidence of disease.

Conclusions: This protocol was closed to entry of new patients effective 1 June 1979 because of poor response rate (3% overall for CALGB patients).

Side Effects/Complications: No unusual/unexpected side effects were encountered.

Funds Utilized FY 79/Requested FY 80: See Introductory Remarks to Annual Progress Report.

Publications: None

Type of Report: Interim

Work Unit No.: 1556

Title of Project: CALGB Protocol 7721 Add #2: A Comparative Study of Adriamycin vs Daunorubicin at Two Dose Levels for Induction and of 4-Week Cycle vs 8-Week Cycle for Maintenance Chemotherapy in Acute Myelocytic Leukemia by Cancer and Leukemia Group B.

Investigators:

Principal: Johannes Blom, M.D.

Objectives: A. Induction Phase:

1. To test whether Daunorubicin at a reduced dose of 30 mg/m^2 produces complete remissions with the same frequency as Daunorubicin at the standard dose of 45 mg/m^2, and whether the same duration of remission and the same survival are produced by both doses.

2. To test whether another anthracycline, Adriamycin, at a dose of 30 mg/m^2 produces complete remissions wtih the same frequency as Daunorubicin at the standard dose of 45 mg/m^2, and whether the same duration or remission and the same survival are produced by both doses.

B. Maintenance Phase:

1. To test whether the duration of remission is equivalent in patients receiving maintenance chemotherapy at 8-week intervals when compared with patients receiving maintenance q 4 weeks. The comparison will also be made with respect to survival from onset of the protocol and from the onset of maintenance.

2. To test whether prolong exposure to anthracyclines (Daunorubicin and Adriamycin) in maintenance, as achieved by the use of reduced doses (30 mg/m^2), increases the duration of remission as compared to the standard dose of Daunorubicin (45 mg/m^2) given to the same cumulative total dose.

Technical Approach: Induction Phase Treatment Schedules:

Regimen I — Daunorubicin 45 mg/m^2/day by rapid I.V. injection on days 1,2 and 3 plus
Cytosine Arabinoside 100 mg/m^2/day by continuous I.V. infusion on days 1-7

Regimen II — Daunorubicin 30 mg/m^2/day by rapid I.V. injection on days 1,2 and 3 plus
Cytosine Arabinoside 100 mg/m^2/day by continuous I.V. infusion on days 1-7

Regimen III — Adriamycin 30 mg/m^2/day by rapid I.V. injection on days 1,2 and 3 plus
Cytosine Arabinoside 100 mg/m^2/day by continuous I.V. infusion on days 1-7

Patients will be placed on maintenance regimens after completion of induction phase.

Maintenance Phase Treatment Schedules:

Regimen AI — Give courses of chemotherapy q 4 weeks

Cytosine Arabinoside 100 mg/m^2 SC q 12 x 10 (total dose p/course 1000 mg/m^2) courses 1-21 plus
Thioguanine 100 mg/m^2 p.o. q 12 hr x 10 (total dose p/course 1000 mg/m^2) courses 1,5,9,13,17,19 and 21 plus
Vincristine 2 mg/m^2 (max dose 2 mg) I.V. I.V. on day 1 of each course. Courses 2,4,6,8,10,12,14,16,18 and 20 plus
Prednisone 40 mg/m^2 p.o. in 3 divided doses daily on days 1-5 (max dose 100 mg, total dose per course $\leq$ 500 mg) courses 2,4,6,8, 10,12,14,16,18 and 20 plus
Daunorubicin 45 mg/m^2 rapid I.V. injection on days 1 and 2 of courses 3,7, (11), (15)

If 3 courses of DNR were required for induction, discontinue after 7th course, substitute thioguanine.
If 2 or 3 courses of DNR were required for induction, discontinue after 11th course, substitute thioguanine.
If 1 course of DNR was required for induction, discontinue after 15th course, substitute thioguanine.

Regimen AII: — Give courses of chemotherapy q 4 weeks

Cytosine Arabinosie 100 mg/m^2 SC q 12 x 10 (total dose p/course 1000 mg/m^2) courses 1-21 plus
Thioguanine 100 mg/m^2 p.o. q 12 hrs x 10 (total dose p/course 1000 mg/m^2) courses 1,5,9,13,17,19 and 21 plus
Vincristine 2 mg/m^2 I.V. on day 1 of each course (total dose 2 mg) courses 2,4,6,8, 10,12,14,16,18 and 20 plus

Prednisone 40 mg/m^2 p.o. in 3 divided doses daily on days 1-5 (max dose 100 mg, total dose p/course $\leq$ 500 mg) courses 2,4,6,8,10, 12,14,16,18 and 20 plus
Daunorubicin 30 mg/m^2 rapid I.V. injection days 1 and 2 of courses 3,7,11,15 and19

If 3 courses of DNR were required for induction, discontinue after 19th course and substitute with thioguanine.
If 2 or 3 courses of DNR were required for induction, discontinue after 23rd course and substitute with thioguanine.
If 1 course of DNR was required for induction, discontinue after 27th course and substitute with thioguanine.

Regimen AIII

Give courses of chemotherapy q 4 weeks

Cytosine Arabinoside 100 mg/m^2 SC q 12 x 10 (total dose p/course 1000 mg/m^2) courses 1-21 plus
Thioguanine 100 mg/m^2 p.o. q 12 hrs x 10 (total dose p/course 1000 mg/m^2) courses 1,5,9,13,17,19 and 21 plus
Vincristine 2 mg/m^2 I.V. on day 1 of each course (max dose 2 mg) courses 2,4,6,8,10, 12,14,16,18 and 20 plus
Prednisone 40 mg/m^2 p.o. in 3 divided doses daily on days 1-5 (max dose 100 mg, total dose p/course $\leq$ 500 mg) plus
Adriamycin 30 mg/m^2 rapid I.V. injections days 1 and 2 of courses 3,7,11,15 and 19

If 3 courses of ADM were required for induction, discontinue after 19th course and substitute with thioguanine.
If 2 or 3 courses of ADM were required for induction, discontinue after 23rd course and substitute with thioguanine.
If 1 course of ADM was required for induction, discontinue after 27th course and substitute with thioguanine.

Regimen BI

(Give chemotherapy q 8 weeks)

Cytosine Arabinoside 100 mg/m^2 SC q 12 x 10 total dose p/course 1000 mg/m^2, courses 1-21 plus
Thioguanine 100 mg/m^2 p.o. q 12 hrs x 10 total dose p/course 100 mg/m^2, courses 1,5,9,13,17,19 and 21 plus
Vincristine 2 mg/m^2 I.V. on day 1 of each course (max dose 2 mg) courses 2,4,6,8,10, 12,14,16, 18 and 20 plus

Prednisone 40 mg/m^2 p.o. in 3 divided doses daily on days 1-5 (max dose 100 mg, total dose p/course $\leq$500 mg) courses 2,4,6,8,10, 12,14,16,18 and 20 plus
Daunorubicin 45 mg/m^2 rapid I.V. injection days 1 and 2 of courses 3,7,(11), and (15)

NB noted same as Regimen AI

Regimen BII

(Give chemotherapy q 8 weeks)

Cytosine Arabinoside 100 mg/m^2 SC q 12 x 10 (total dose p/course 1000 mg/m^2) courses 1-21 plus
Thioguanine 100 mg/m^2 p.o. q 12 hrs x 10 (total dose p/course 1000 mg/m^2) courses 1,5,9,13,17,19 and 21 plus
Vincristine 2 mg/m^2 I.V. on day 1 of each course (max dose 2 mg) courses 2,4,6,8,10, 12,14,16,18 and 20 plus
Prednisone 40 mg/m^2 p.o. in 3 divided doses daily on days 1-5 (max dose 100 mg) courses 2,4,6,8,10,12,14,16,18 and 20 plus(total dose $\leq$500 mg)
Daunorubicin 45 mg/m^2 rapid I.V. injection days 1 & 2 of courses 3,7,11,15 and 19

NB noted same as Regimen AII

Regimen BIII

(Give chemotherapy q 8 weeks)

Cytosine Arabinoside 100 mg/m^2 SC q 12 x 10 (total dose p/course 1000 mg/m^2) courses 1-21 plus
Thioguanine 100 mg/m^2 p.o. q 12 hrs x 10 (total dose p/course 1000 mg/m^2) courses 1,5,9,13,17,19 and 21 plus
Vincristine 2 mg/m^2 I.V. on day 1 of each course (max dose 2 mg), courses 2,4,6,8,10, 12,14,16,18 and 20 plus
Prednisone 40 mg/m^2 p.o. in 3 divided doses daily on days 1-5 (max dose 100 mg, total dose p.course $\leq$ 500 mg) courses 2,4,6,8,10, 12,14,16,18 and 20 plus
Adriamycin 30 mg/m^2 rapid I.V. injection days 1 and 2 of courses 3,7,11,15 and 19

NB noted same as Regimen AIII

Addendum #1 dated 1 July 1977 amends the cytosine arabinoside dosage to read 30 mg/m^2 q 4 days until there is no malignant cells, instead of every day x 4.

Addendum #2 dated 5 November 1977 clarifies eligibility requirements

Progress and Results: WRAMC has entered 23 patients. Twelve had no response and died from day 3 to day 31. Two obtained partial remissions but progressed and died on days 210 and 337. Nine patients obtained a complete remission. Six remain in remission between day 80 and day 549. One patient died in remission possibly of drug induced sepsis. One relapsed; was reinduced and off study but in remission. One relapsed on day 127 and died on day 450.

CALGB has entered 452 patients of whom 401 are evaluable. 213 (53%) achieved complete remission to date. The induction regimens are still coded but there appears to be no difference to date.

Conclusions: Remission rates appear comparable to previous studies.. It is too early to evaluate maintenance regimens.

Side Effects/Complications: About 40% of patients in the whole CALGB study, have experienced severe toxicity secondary to infection during induction. 20% have had serious bleeding problems. It is typically difficult to assign these problems to the underlying leukemia or to drug treatment.

Funds Utilized FY 79/Requested FY 80: See Introductory Remarks to Annual Progress Report.

Publications: None

Type of Report: Interim-A total of 540 patients will be required. 74% of evaluable patients necessary have been entered. The requisite number necessary should be achieved in one year.

Work Unit No.: 1557

Title of Project: CALGB Protocol 0704 (Pilot Study): A Phase II Trial of Neocarzinostatin in Carcinoma of the Bladder, Kidney, Pancreas, Stomach, Uterus, Ovary, Hepatoma, Acute Leukemia or Malignant Melanoma.

Investigators:

Principal: Johannes Blom, M.D.

Associate: M. Robert Cooper, M.D.
Robert L. Comis, M.D.

Objectives: To evaluate response rate, duration of response and survival of patients with acute leukemia, pancreatic, stomach, bladder, ovarian, uterine, liver and renal carcinoma, and malignant melanoma treated with a new agent, neocarzinostatin (NCS). To determine the frequency and severity of different organ system toxicities in patients with advanced cancer treatment with neocarzinostatin.

Technical Approach:

Patients with acute leukemia (all types) receive the following treatment:

Neocarzinostatin 2500 u (2.5 mg)/m^2/day I.V. bolus over 30 minutes x 5 days, repeated at intervals of 7-10 days if necessary to obtain a remission (3 courses of 5 days considered an adequate trial).

All patients with solid tumors of pancreas, liver, stomach, kidney, bladder, ovary and uterus, and malignant melanoma meeting the eligibility requirements who have received prior chemotherapy or or radiotherapy will start at:

1500 u/m^2/day (1.5 mg) x 5 days and, 2250 u/m^2/day (2.25 mg) x 5 days.

Patients not previously treated with chemotherapy or radiotherapy will start at:

2250 u/m^2/day (2.25 mg) x 5 days.

Courses will be repeated q 35 days.
Neocarzinostatin will be discontinued if no response is seen after three courses.

Progress and Results: Twelve patients have been entered at WRAMC. All have expired. Six patients had one course of treatment only; 3 had progressive disease, 1 refused further therapy and 2 expired after 1 course only. Four patients expired after 2 courses, 2 with progressive disease, and two with stable signs of disease. Two patients died with progressive disease, one after 3 courses and one after 4 courses.

Conclusions: With the exception of 2 patients with stabilization of disease, none of the patients entered at Walter Reed have responded to treatment. At the CALGB meeting on 2 June 1979, there were 2 partial responses reported in 15 patients with hepatoma. It is anticipated that this protocol will be officially closed at the upcoming CALGB meeting in October.

Side Effects/Complications: No unusual/unexpected side effects were encountered.

Funds Utilized FY 79/Requested FY 80: See Introductory Remarks to Annual Progress Report.

Publications: None

Type of Report: Final

Work Unit No.: 1558

Title of Project: CALGB Protocol 7761 Add #1: A Study to Determine the Effectiveness of Single vs Multiple Alkylating Agents with or without Adriamycin in the Primary Treatment of Multiple Myeloma.

Investigators:

Principal: Johannes Blom, M.D.

Objectives:

1. To test the hypothesis that three alkylating agents given sequentially produce:
   a. Higher frequency of good respon e and
   b. Longer duration of disease control than the same alkylating agents given in combination.
2. To test the hypothesis that addition of adriamycin to a combination of three alkylating agents:
   a. Increases the frequency of good response and
   b. Prolongs the duration of disease control.
3. To test the hypothesis that:
   a. The frequency of good response and
   b. The duration of disease control are the same after treatment with intravenous L-PAM as after treatment with triple alkylating agents.
4. To compare the duration of remission maintained with oral L-PAM in patients induced with combination chemotherapy regimens and with I.V. L-PAM, and to compare duration of disease control with these regimens against historical controls maintained on intravenous therapy with triple alkylating agents.
5. To evaluate psychosocial function in patients with myeloma before and during treatment and to investigate differences in psychosocial function in patients receiving different treatment.
6. To determine if new experimental regimens prolong the survival of patients with multiple myeloma compared to historical controls.

Technical Approach:

Regimen I — Combination Alkylating Agents plus Prednisone

L-PAM 8 mg/m^2 I.V. on day 1
Cyclophosphamide 300 mg/m^2 I.V. on day 1
BCNU 100 mg/m^2 I.V. day 1

Each cycle - 6 weeks
Repeat for 12 cycles (72 weeks)

If BUN is >30 and creatinine is >1.5 give 1/2 dose.

Prednisone during first 6 weeks only:

0.8 mg/kg p.o. single dose, days 1-14
0.4 mg/kg p.o. single dose, days 15-28
0.2 mg/kg p.o. single dose, days 29-42

D/C after day 42
Begin maintenance therapy in 73rd week

Regimen II — Sequential Alkylating Agents plus Prednisone

L-PAM 16 mg/m^2 I.V. day 1
Cyclophosphamide 600 mg/m^2 I.V. day 22
BCNU 150 mg/m^2 I.V. day 43

Each cycle - 12 weeks
Repeat for 6 cycles (72 weeks)

If BUN is >30 and creatinine is >1.5 give 1/2 dose.

Prednisone during first 6 weeks only (See Regimen I)

Begin maintenance therapy in 73rd week

Regimen III — Combination Alkylating Agents plus Adriamycin plus Prednisone

L-PAM 8 mg/m^2 I.V.
Cyclophosphamide 300 mg/m^2 I.V.
BCNU 100 mg/m^2 I.V.

Give chemotherapy for 10 courses on days 1,43,106,148,211,253,316,358,421 and 463.

Adriamycin 45 mg/m^2 I.V.
for 4 courses on days 85,190,295 & 400

Prednisone (as per Regimen I)

Begin maintenance therapy in 73rd week

Regimen IV — I.V. L-PAM plus Prednisone

L-PAM 16 mg/m^2 I.V. on days 1,15,29.43 and 71 and q 4 weeks thereafter until day 491 then D/C.

Total of 20 doses

Prednisone as per Regimen I

Begin maintenance therapy in 73rd week

MAINTENANCE THERAPY

L-PAM 0.05 mg/kg p.o. daily until relapse, progression of disease or 2 years from day 1 of induction

Addendum #1 dated 28 October 1978 modifies all chemotherapy dosages for elevated BUN and elevated creatinine.

Progress and Results: WRAMC has entered 6 patients. One died on day 40. Five had measurable response but two have developed progressive disease on days 431 and 283.

CALGB have entered 231 patients. It is still early to determine whether one treatment program is better. The treatment arms are still coded and most patients are continuing on study.

Conclusions: Too early

Side Effects/Complications: The dose modifying addendum dated 28 October 1978 was implemented because of increased hematologic toxicity seen in these patients with renal failure. One case of possible BCNU pulmonary toxicity was seen at another institution.

Funds Utilized FY 79/Requested FY 80: See Introductory Remarks to Annual Progress Report.

Publications: None

Type of Report: Interim--About 200 more patients will have to be entered for a total of 440 evaluable patients. This will require two more years.

Work Unit No.: 1559

Title of Project: CALGB Protocol 7781-Add #3: Small Cell Carcinoma of the Lung: Localized Disease. A Phase III Study. Combination Chemotherapy vs alternating Chemotherapy Plus Radiotherapy with or without Immunotherapy.

Investigators:

Principal: Johannes Blom, M.D.

Objectives:

1. To test whether chemotherapy (with either of two combinations of agents) and radiotherapy (to the primary site and brain) produce a higher frequency of response (complete or partial) in patients with localized small cell (oat cell) carcinoma of the lung, as compared to historical controls.

2. To test whether combination chemotherapy and radiotherapy produce longer durations of response in these patients as compared to historical controls.

3. To test whether combination chemotherapy and radiotherapy affect patterns of relapse in these patients, as compared with historical controls.

4. To test whether combination chemotherapy and radiotherapy prolong survival in these patients, as compared to historical controls.

5. To test whether the two combinations of drugs, used with radiotherapy, have significantly different effects on:

   a. frequency and/or duration of response
   b. pattern of relapse or
   c. survival in patients with localized small cell carcinoma of the lung

6. To test whether immunotherapy with MER (methanol extraction residue of Bacillus Calmette-Guerin), added to combination chemotherapy (with either of two regimens) significantly affects:

   a. duration of response and/or
   b. pattern of relapse and/or
   c. survival

   in patients with localized small cell carcinoma of the lung initially responsive to combination chemotherapy and radiotherapy.

7. To evaluate psychosocial function in patients with localized small cell carcinoma of the lung before, during and after treatment using:

   a. the rating of psychosocial function
   b. the handicap rating scale
   c. the profile of mood states
   d. demographic data.

Technical Approach:

Induction Phase:

Regimen I

Methotrexate 30 mg/m^2 I.V. plus
Adriamycin 35 mg/m^2 I.V. plus
CCNU 30 mg/m^2 p.o. plus
Cyclophosphamide 400 mg/m^2 I.V.

All drugs are given on the first day of the cycle.

Two cycles of chemotherapy will be given on days 1 and 21, followed by radiotherapy in a split course technique (the first part of a split course of radiotherapy will consist of 2500 rads in 10 treatment days beginning on day 42. This will be followed by a two week rest period. Then 2000 rads will be given in a further 10-day period beginning on day 70. In addition, 3000 rads in 10 treatments will be given to the whole brain of all patients entered into this study). To be followed by two further cycles of chemotherapy on days 84 and 105.

Adriamycin is omitted from the third cycle of MACC, which is given one week after the completion of radiotherapy. This should prevent the exacerbation of radiation esophagitis and esophageal stricture formation. Adriamycin will be reinstituted on day 105 at the beginning of the fourth cycle of chemotherapy.

Regimen II

Cyclophosphamide 700 mg/m^2 I.V. plus
CCNU 70 mg/m^2 p.o. plus
Vincristine 1.0 mg/m^2 (no greater than 2.0 mg in any single dose will be given)
(FIRST COURSE GIVEN ON DAY ONE)

Adriamycin 50 mg/m^2 I.V. plus
Vincristine 1.0 mg/m^2 (no greater than 2.0 mg in any single dose will be given)
(ON DAY 21 OF EACH SIX WEEK CYCLE)

As in Regimen I, radiotherapy will begin on day 42 by the split course technique (see description in Regimen I), chemotherapy will be reinstituted on day 84.

The induction phase of protocol consists of four cycles of chemotherapy, two prior to the institution of radiotherapy, and two subsequent to the completion of radiotherapy.

Maintenance Phase:

Regimen A	Patient should continue with his initial chemotherapy (Reg I or II) at three week intervals.
Regimen B	Patient should continue with his initial chemotherapy (Reg I or II) and in addition receive immunotherapy with MER, given q 6 weeks, starting on the day of randomization and coinciding with first maintenance course of chemotherapy.
Regimen I with Regimen B Maintenance	Methotrexate 30 mg/m^2 I.V. given on days 136,157,178,199,220,241,262,283,304,360, Adriamycin 35 mg/m^2 I.V. given on days 136,157,178,199,220,241,262 and 283 Cyclophosphamide 400 mg/m^2 I.V. given on days 136,157,178,199,220,241,262,283, 304,360,416,472,528,584,640 and 696 CCNU 30 mg/m^2 p.o. given on days 136,157, 178,199,220,241,262,283,304,360,416, 472,528,584,640 and 696 MER immunotherapy given on days 136,178, 220,262,304,360,416,472,528,584,640 and 696 (treatment plan listed after Regimen II with Regimen B Maintenance)
Regimen II with Regimen B Maintenance	Cyclophosphamide 700 mg/m^2 I.V. given on days 136,178,220,262,304,416,528 and 640 CCNU 70 mg/m^2 p.o. given on days 136,178, 220,262,304,416,528 and 640 Vincristine 1.0 mg/m^2 I.V. (2 mg max dose) given on days 136,157,178,199,220,241, 262,283,304,360,416,472,528,584,640 and 696 Adriamycin 50 mg/m^2 I.V. given on days 157, 199,241 and 283

MER immunotherapy given on days 136,178,220, 262,304,360,416,472,528,584,640 and 696

The total dose of adriamycin (induction and maintenance) for patients treated with Reg I will be 385 mg/m^2 for patients treated with Reg II, the total dose will be 300 mg/m^2.

Patients will receive maintenance chemotherapy (or chemoimmunotherapy) until day 696 or until relapse, whichever comes first. Patients completing the maintenance phase of protocol will be followed until relapse or until death.

MER IMMUNOTHERAPY

At the time of the first schedule administration, 200 ug of MER should be injected intradermally into each of three sites on the anterior body surface. Sites should be chosen so that each site is drained by a different group of lymph nodes. In addition, doses of 200, 100, 10, 1, 0.1 and 0.01 ug should be injected in a linear array of sites on an anterior thigh. Acceptable sites for MER injection, in addition to the proximal thighs, are the upper and lower abdominal wall and the intraclavicular areas. Sites where the regional lymph nodes have been excised or irradiated should not be used. Areas which might be irritated by friction from clothing, etc., should be avoided.

Radiation Therapy:

1. Evaluation of the area to be irradiated must be made prior to commencing chemotherapy. The volume to be included in the irradiated field is defined as the original tumor size and its drainage because of recurrence which may develop in any part of the area or original involvement despite marked shrinkage after two courses of chemotherapy.

2. Radiation therapy to the primary tumor will commence on day 42 after two courses of chemotherapy. Radiotherapy will be given by a split course technique as stated in Regimen I.

3. Radiation of megavoltage quality (1 MeV or greater) will be used preferably with an isocentric gantry apparatus with a source to axis distance greater than or equal to 80 cm.

4. Radiotherapy portals shall include the primary disease site, the whole width of the mediastinum extending superiorly above the suprasternal notch and inferiorly 4 cm below the carina. More generous margins may be desirable superiorly for upper lobe lesions and inferiorly for lower lobe lesions. With this field coverage, subcarinal lymph node groups as well as groups of lymph nodes of the lymphatic drainage of the thoracic duct will be covered. The supraclavivular fossi bilaterally, will be included in all cases using an anterior field only.

5. The tumor dose will be 2500 rad in 10 sessions over two weeks. AP PA parallel opposing fields will be used. Following a two week rest period, an addtional 200 rad in 10 sessions to the same volume will be delivered. This is designed to give a TDF of 75.

6. Dose calculations shall be done on the basis of midplane doses i.e., the dose to the central axis point midway between the anterior and posterior entrance points. The dose to the spinal cord at the suprasternal notch should be calculated and recorded in each patient. For sharply sloping chests, it may be necessary to calculate the dose in more than one plane. If a variation in the midplane dose of more than 10% at the different planes is noted, a compensator will be required. If tissue compensation is employed, it should be clearly indicated in all the records sent to the Radiotherapy Office.

7. The supraclavicular fossi will receive a given dose of 4500 rads + 5%, calculated at a depth of 3 cm. The dose of these areas should be calculated and recorded as reference doses into the Radiotherapy Reporting Forms. The depth of the recorded dose should be 3.0 cm from the skin surface. This will require the addition of boosts to the supraclavicular fossae only. The inferior border is defined as the lower edge of the clavicle at the sternoclavicular joint.

8. During the second course of treatment, the field arrangement should be appropriately modified so that no part of the spinal cord receives a dose in excess of 4200 rads (or a TDF of 69).

9. If field arrangements other than AP PA parallel opposed portals are to be used, the dose distributions are to be calculated and isodose maps are to be plotted at the midplane and at other planes of interest.

10. For purpose of this study, no corrections are to be applied for lung or bone attenuation. Doses will be described in rads to muscle.

Addendum #1 dated 5 November 1977 clarifies eligibility requirements.

Addendum #2 dated 11 July 1978 requests that pathology review of slides be sent directly to the CALGB Pathology Office to monitor protocol requirements.

Addendum #3 dated 14 August 1978 amends patient eligibility to patients who present with a malignant pleural effusion with positive cytology will be considered to have extensive disease and will be eligible for randomization to protocol

Progress and Results: WRAMC entered 5 patients. One died on day 7. One had one course of treatment, refused further treatment and died on day 120. Three had partial remissions-two progressed on days 119 and 166 and subsequently died. One patient remains in remission at day 560 +.

CALGB entered 125 patients. Overall about 30% have responded to therapy. The three treatment arms are still coded.

Conclusions: Too early for definite analysis.

Side Effects/Complications: No unusual/unexpected side effects were encountered.

Funds Utilized FY 79/Requested FY 80: See Introductory Remarks to Annual Progress Report.

Publications: None

Type of Report: Interim-270 patients are estimated to be required for completion of this study.

Work Unit No.: 1560

Title of Project: CALGB Protocol 7782 Add #3: Small Cell Carcinoma of the Lung, Extensive Disease

Investigators:

Principal: Johannes Blom, M.D.

Objectives:

1. To test whether the alternating combination (CCV-AV) will prolong the disease control interval as measured from the start of protocol to the first documented disease progression or recurrence when compared with the continuous MACC program. Comparisons between these two programs will also be made with respect to objective response frequencies, remission duration, and survival.

2. To test whether the addition of irradiation to the primary lesion and draining lymph nodes in conjunction with MACC will prolong the disease control interval when compared with the continuous MACC program. Comparisons between these two programs will also be made with respect to objective response frequencies, remission duration, relapse patterns and survival.

3. To evaluate psychosocial function in patients with localized small cell carcinoma of the lung before, during and after treatment using:

   a. The rating of psychosocial function
   b. The handicap rating scale
   c. The profile of mood states
   d. Demographic data

Technical Approach: Patients will be categorized into two groups:

A Good Risk-Performance scores 0 or 1
B Poor Risk-Performance scores 2 or 3

Regimen I

Methotrexate 30 mg/m^2 I.V. q 3 weeks
Adriamycin 40 mg/m^2 I.V. q 3 weeks
CCNU 30 mg/m^2 p.o. q 3 weeks
Cyclophosphamide 400 mg/m^2 I.V. q 3 weeks

Adriamycin is given on day 1 of each 3 week cycle.

Two cycles of chemotherapy will be administered followed by radiation therapy (written after Regimen III). After completion of the radiotherapy, chemotherapy will be re-instituted and continued until relapse.

Adriamycin will be omitted from the 3rd cycle of MACC which is given one week after the completion of radio-therapy in an attempt to decrease the incidence of "recall" phenomena. On day 84 MACC including Adriamycin will be reinstituted. The max dose for Adriamycin will be 450 mg/m^2. When the total dose of Adriamycin has been reached, Methotrexate, CCNU and Cyclophosphamide will be continued q 3 weeks until relapse.

Regimen II

Methotrexate 30 mg/m^2 q 3 weeks I.V.
Adriamycin 40 mg/m^2 I.V. q 3 weeks
CCNU 30 mg/m^2 p.o. q 3 weeks
Cyclophosphamide 400 mg/m^2 I.V. q 3 weeks

Adriamycin is given on day 1 of each 3 week cycle

Therapy will be continued until relapse. The total dose of Adriamycin is as stated in Regimen I.

Regimen III

CCNU 70 mg/m^2 p.o. days 0 and 84
Cyclophosphamide 700 mg/m^2 I.V. on days 0,21,84 and 105
Vincristine 2 mg I.V. on days 0,21,42,63,84 & 105
Adriamycin 75 mg/m^2 I.V. on days 42 and 63

The alternating CCV-AV chemotherapy regimen will be continued until relapse. The total dose of Adriamycin will be 450 mg/m^2. When the total dose of Adriamycin has been reached, CCNU q 6 weeks and Cyclophosphamide and Vincristine q 3 weeks will be continued until relapse.

Radiation Therapy: Radiotherapy will be administered in Regimen I only. Radiation therapy will commence on day 42 after 2 full cycles of MACC as stated in Regimen I. Chemotherapy with methotrexate, cyclophosphamide and CCNU omitting Adriamycin will resume one week following the completion of radiation therapy. The complete MACC regimen including Adriamycin will be reinstituted three weeks later.

Radiation of megavoltage quality (1 or MeV or greater) will be used, preferably with an iso-centric gantry apparatus with a source to axis distance greater than or equal to 80 cm.

The radiotherapy portals shall include the primary disease site, the whole width of the mediastinum. extending superiorly above the supersternal notch and inferiorly 4 cm below the carina. More generous margins may be desirable superiorly for upper lobe lesions and inferiorly for lower lobe lesions. With this field coverage, sub-carinal lymph node groups as well as groups of lymph nodes of the lymphatic drainage of the thoracic duct will be covered.

The tumor dose will be 3000 rads administered in 10 treatments over 12 days. AP PA parallel opposing fields will be used. Both fields will be treated each day.

Dose calculations shall be done on the basis of the dose at the central axis point midway between the anterior and posterior entrance points. If other fields of entrance are used, a dose distribution is to be calculated at the mid-plane and at other planes of interest.

No corrections are to be applied for lung or bone attenuation. Doses will be prescribed in rads to muscle.

Evaluation of Psychosocial Function:

1. Rating of Psychosocial Function (RPF): Done by physician.
2. Handicap Rating Scale: Done by physician.
3. Profile of mood states (POMS): Filled out by patient.
4. Demographic data: Supplied by patient.

Psychosocial evaluation will be performed:

1. Before treatment
2. On achievement of remission or on diagnosis of treatment failure in induction.
3. (For responders): on relapse
4. For patients continuing in remission, when 50% of patients have relapsed.

Evaluation of Psychosocial Function:

1. Rating of psychosocial function (RPF): Done by physician.
2. Handicap rating scale: Done by physician.
3. Profile of Mood States (POMS): On PSY-2 Form.
4. Demographic data: Supplied by patient.

Ratings will be obtained:

1. Prior to treatment
2. At the conclusion of radiotherapy
3. At the time of randomization for MER
4. At the time of relapse; when 50% of patients have relapsed, the remaining patients will be rated.

Addendum #1 dated 26 January 1978 makes corrections to the schema.
Addendum #2 dated 30 March 1978 states that in addendum #1 the MER schedule was incorrect. The radiotherapy was incorrect also.
Addendum #3 dated December 1978 revises the complete radiotherapy section for this protocol.

Progress and Results: WRAMC entered 8 patients. Five have progressed and died from day 250 to 405. Two had partial remissions and remain stable on days 182 & 270. One had a partial resonse but progressed on day 599 and is off study.

CALGB has entered 100 patients. Treatment arms are still coded but approximately 50% are achieving some form of remission.

Conclusions: Too early to compare treatment regimens

Side Effects/Complications: Moderate esophagitis following radiation.

Funds Utilized FY 79/Requested FY 80: See Introductory Remarks to Annual Progress Report.

Publications: None

Type of Report: Interim-Another 80 patients have to be entered on this study.

Work Unit No.: 1561

Title of Project: CALGB Protocol 7783: Surgical Adjuvant Therapy for Non-Small Cell Bronchogenic Carcinoma, Stage I and II Disease.

This protocol was closed to patient entry in June 1979. No patients were entered on the protocol.

Work Unit No.: 1562

Title of Project: CALGB Protocol 7802 (Pilot Study) Add #1: The Treatment of Advanced Non-Small Cell Bronchogenic Carcinoma with Cytoxan, CCNU, Hexamethylmelamine and Methotrexate

Investigators:

Principal: Johannes Blom, M.D.

Objectives: 1. To assess the response frequencies of the major subtypes of non small cell bronchogenic carcinoma to the 4 drug treatment program.

2. To assess the duration of responses produced by the 4 drug treatment program.

Technical Approach: Treatment cycles are 21 days in length.

Cytoxan 500 mg/m^2 I.V. given on day 1 of each cycle
CCNU 50 mg/m^2 p.o. given on day 1 of q other cycle (q 42 days) beginning with cycle 1.
Hexamethylmelamine 150 mg/m^2/day p.o. given on days 2-8 inclusive of each cycle of chemotherapy. (Single dose just before bedtime)
Methotrexate 20 mg/m^2 p.o. given on days 10,13 and 17 of each cycle. The full days dose of MTX should be taken all at once on each of the treatment days.

Addendum #1 dated 12 February 1979 gives treatment schedule for patients who have not had previous radiation therapy to their lung primary and is as follows:

Cytoxan 600 mg/m^2 I.V. given on day 1 of each cycle
CCNU 60 mg/m^2 p.o. given on day 1 of q other cycle (q 42 days) beginning with cycle 1.
Hexamethylmelamine 180 mg/m^2/day p.o. given on days 2-8 inclusive of each chemotherapy cycle) Single dose just before bedtime.
Methotrexate 20 mg/m^2 p.o. given on days 10, 13 and 17 of each cycle. Full days dose should be taken at one time of each treatment day.

Progress and Results: WRAMC entered 11 patients. Data is available on 9 at this time. One of the patients with squamous cell carcinoma attained a partial remission and is alive on day 243. Seven patients failed to respond and are dead from day 7-120.

CALGB entered 125 patients of whom 94 were considered evaluable. The overall response rate (Complete and partial remissions is 15%). Interestingly it was 25% for squamous cell and large cell carcinomas, but only 3% for adenocarcinoma. 13/14 responses occured in patients with performance indices of 0 or 1 (good performance).

Conclusions: A modest response activity for the combination was seen for squamous and large cell carcinomas.

Side Effects/Complications: One patient at WRAMC experienced profound anorexia, nausea and vomiting secondary to hexamethylmelamine.

Funds Utilized FY 79/Requested FY 80: See Introductory Remarks to Annual Progress Report.

Publications: None

Type of Report: Interim-All unused hexamethylmelamine was returned to the NCI and the study was closed to entry of new patients on 1 June 1979.

Work Unit No.: 1563

Title of Project: CALGB Protocol 7751 Add #2: The Comparative Effectiveness of Combination Chemotherapy Alone and with Radiation Therapy by Involved Field or Extended Field, in Poor Risk Patients with Stage I or II Hodgkins' Disease.

Investigators:

Principal: Johannes Blom, M.E.

Objectives:

1. To test if combination chemotherapy alone is as effective as extended field radiotherapy prior to start of adjuvant chemotherapy in achieving complete remission in poor prognosis Hodgkin's Disease patients with Stages I and II.

2. To test if extended field radiotherapy plus 6 cycles of CVPP prolongs the total duration of remission compared to involved field radiotherapy plus 6 cycles of CVPP or combination chemotherapy alone in poor prognosis patients.

3. To test if combination chemotherapy alone or involved field radiotherapy + chemotherapy significantly decreases the morbidity and/or mortality compared to extended field radiotherapy and chemotherapy.

4. To determine the relapse patterns of disease, whether in nodal or extranodal sites, inside or outside of the irradiated fields, for each treatment program.

5. To test the influence of the three treatments upon overall survival.

Technical Approach: Patients are randomized from two stratification categories according to their Ann Arbor Stage being either:

Stage IA or Stage IIA - Mixed cellularity and lymphocyte depletion
Stage IB or IIB

Regimen I — Involved field radiation therapy followed by chemotherapy. (Written after Regimen III) Following a four-week rest period, chemotherapy with CCNU, vinblastine, prednisone and procarbazine will be initiated for six cycles.

Patients who are in complete remission after six cycles of CVPP will receive two addtional courses of chemotherapy and then begin observation phase.

Regimen II — Extended field radiation followed by chemotherapy.

After a four-week rest, chemotherapy with CCNU, vinblastine, prednisone and procarbazine will be initiated for six cycles.

Patients who are in complete remission at the end of 6 cycles of CVPP will receive two addtional courses of chemotherapy and then begin the observation phase.

Regimen III — Chemotherapy with CCNU, vinblastine, prednisone and procarbazine will be initiated for six cycles.

Patients who achieve complete remission after 6 cycles will receive two addtional courses of chemotherapy and will then begin observation phase.

CHEMOTHERAPY SCHEDULE AND DOSAGES:

Patients randomized to Reg I or II will receive 6 courses of chemotherapy beginning four weeks after the completion of radiotherapy pending criteria of entry to that phase of the study are satisfied. Patients randomized to Reg III will receive 6 courses immediately starting after randomization. Each course will consist of 2 weeks of chemotherapy followed by a 2 week rest period. A course will be given every 4 weeks.

CCNU 75 mg/m^2 p.o. on day 1 plus
Vinblastine 4 mg/m^2 I.V. on days 1 and 8 plus
Procarbazine 100 mg/m^2 p.o. on days 1-14
(In the initial course, stepwise dose escalation from 50 mg/m^2 on day 1, 75 on day 2 to 100 mg/m^2 per day thereafter may diminish nausea) plus
Prednisone 40 mg/m^2 p.o. on days 1-14 (Course 1 and 4 only).

Radiation Therapy: Only megavoltage radiation is to be used. Isodose distributions are to be plotted.

Doses will represent midplane doses; minimum and maximum doses at the midplane skin peak doses, and applied dosages will be calculated and entered into records.

For area above diaphragm-5 reference points: neck, supraclavicular, axilla, mid-and-lower mediastinum.
For below diaphragm-5 reference points: upper and mid-periaortic area, splenic pedicle, iliac areas and groin; calculation of dose at different points is less critical if variation in thickness is found to be less than 5%.
Areas that have received a low dose will be boosted at the end aiming for a prescribed dose to the overall volume of ± 5%.
Doses at the different points should be calculated by the use of scatter air method.
A dose of 3500-4000 rads in 4 weeks is to be delivered. A boost of 500 rads to bulky disease is acceptable. The daily dose may be as high as 200 rads per day but no less than 150 rads per day. Anterior and posterior fields will be employed and the daily dose is equally divided between them.

Addendum #1 dated 1 July 1978 revises the psychosoical schema and instuments.

Addendum #2 dated 12 February 1979 revises the closing of Regimen II to new patient entry, expands patient eligibility criteria, change in pathology review and statistical considerations.

Progress and Results: No patients have been entered on this study at WRAMC.

Conclusions: No conclusions can be made at this time.

Side Effects/Complications: No unusual/unexpected side effects were encountered.

Funds Utilized FY 79/Requested FY 80: See Introductory Remarks to Annual Progress Report.

Publications: None

Type of Report: Interim

Work Unit No.: 1564

Title of Project: CALGB Protocol 7772: Phase II Study of Chlorozotocin (NSC 178248)

Investigators:

Principal: Johannes Blom, M.D.

Objectives:

1. Yield information concerning the efficacy and safety of this agent.
2. See evidence of activity in tumors of interest to the Group. Activity will be judged by:
   a. Percentage of patients achieving an objective response, complete or partial.
   b. Duration of response while patient is maintained on continuous chlorozotocin therapy.
   c. Quality of response and its relationship to ultimate patient survival.
3. Provide experience in the design of a phase III protocol, should this phase II study be promising.
4. Enter up to 200 patients with advanced neoplastic disease in the categories of gastrointestinal, pancreatic, lung tumors, melanoma and lymphoma.

Technical Approach: Dose and Administration of chlorozotocin

Chlorozotocin 120 mg/m^2 q 6 weeks. The drug will be administered in a bolus over a period of 30 seconds via the tubing of a running intravenous infusion.

The failure to achieve a response following the administration of three doses of the drug, will be cause for removal from study.

Progress and Results: WRAMC entered 10 patients. Ten have not responded and five have expired. Another five remain alive with progressive disease.

CALGB has entered 212 patients. To date only a small number (9) patients have improved.

Conclusions: More patients with melanoma, breast and lymphoma need to be studied.

Side Effects/Complications: Four percent of patients treated have experienced thrombocytopenia.

Funds Utilized FY 79/Requested FY 80: See Introductory Remarks to Annual Progress Report.

Publications: None

Type of Report: Interim-Another 80 patients need to be accrued on this study. This should be accomplished within the year.

Work Unit No.: 1565

Title of Project: CALGB Protocol 7804 (Pilot Study) Add #2: Cyclophosphamide, Adriamycin, Vincristine, Prednisone in Combination with Low Dose 5-Day I.V. Infusion Bleomycin in the Treatment of Poor Histology Lymphomas and Nodular Poorly Differentiated Lymphocytic Lymphomas.

Investigators:

Principal: Johannes Blom, M.D.

Objectives:
1. Determine the response rate, disease-free interval and survival of patients with poor histology lymphomas and nodular poorly differentiated lymphocytic lymphoma treated with cyclophosphamide, vincristine, adriamycin, prednisone and low dose infusion bleomycin.
2. To determine the toxicities of this regimen.
3. To determine, in appropriate patients, the pharmacokinetics of low dose bleomycin infusions.

Technical Approach: Dose Schedule

Cyclophosphamide 750 mg/m^2 I.V. bolus day 1
Adriamycin 50 mg/m^2 I.V. Bolus day 1
Vincristine 1.4 mg/m^2 I.V. Bolus day 1
(max 2 mg)
Bleomycin 2 u/day continuous I.V. Infusion
Days 1-5
Prednisone 100 mg/day p.o. days 1-5

Courses to be repeated at 21 day intervals.
Total of 6 courses are to be given.

Max dosages for adriamycin and bleomycin are to be 300 mg/m^2 and 30 units.

Courses 4-6 will be as indicated above except that no bleomycin will be administered.

Addendum #1 dated 29 March 1979 revises the objectives to:
Determine the response frequencies, disease-free interval, and survival

durations of patients in the following three histologic categories:

a. Nodular Pattern
b. Diffuse Poorly Differentiated or Mixed Lymphoma
c. Diffuse Histiocytic

and revises the statistical considerations.

Addendum #2 dated 18 June 1979 removes entry of new patients to the diffuse histiocytic category.

Progress and Results: WRAMC has entered six patients. Two patients had DHL (diffuse histiocytic lymphoma), one had stage III disease obtained a partial remission but taken off study by physician in Indiana because total bilirubin was 1.6 at onset of treatment. The other patient had stage IV disease and achieved a partial remission after two courses however, due to tachycardia and increase left ventricular dilatation had the adriamycin discontinued and received CVP-Bleo until progression. Two patients have PDL-N (Poorly Differentiated lymphocytic lymphoma-Nodular); one with stage III disease had a complete remission and is alive at day 192 without disease and one with stage IV disease is too early to evaluate. The last two patients had mixed histiocytic lymphocytic type; one with nodular stage IV disease had no response to several prior regimens but is in complete remission with CHOP-BLEO at day 330. The other patient had stage III diffuse disease not previously treated but in complete remission at day 510.

CALGB have entered a total of 69 patients of which 58 are evaluable however, too few numbers of patients in each of the 6 histiologic subtypes makes evaluation difficult at this time.

Conclusions: Too early for statistical analysis however, protocol looks very favorable.

Side Effects/Complications: See Progress and Results

Funds Utilized FY 79/Requested FY 80: See Introductory Remarks to Annual Progress Report.

Publications: None

Type of Report: Interim-25 patients in each of the 6 categories will be needed for statistical analysis. Date of completion by CALGB probably 1982.

Work Unit No.: 1566

Title of Project: CALGB Protocol 7811: Remission Induction and T-COAP vs T-MOP Maintenance for the Treatment for Recurrent Childhood ALL.

Investigators:

Principal: Johannes Blom, M.D.

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

Objectives: 1. To induce remissions in children with ALL who have relapsed following a first or later remission.

2. To compare the effectiveness of a maintenance treatment program of intermediate dose methotrexate/thioguanine/vincristine/prednisone (T-MOP) with one of vincristine/prednisone/cytosine arabinoside/cyclophosphamide/6-thioguanine (T-COAP) in maintaining:

a. Systemic control of leukemia,
b. Central nervous system control of leukemia.

Technical Approach:

INDUCTION PHASE: All patients recieve the following therapy:

Vincristine 2 mg/m^2/week I.V. on days 1,8,15and 22 (Single dose max. 2 mg) plus
Prednisone 120 mg/m^2/day p.o. in 3 divided doses on days 1-28, then taper over 12 days 60 mg/m^2 x 3, 30 mg/m^2/day x 3, 10 mg/m^2/day x 3, 5 mg/m^2/day x 3 plus
Methotrexate 12 mg/m^2/week IT on days 8,15,22 (max dose (single) 15 mg)

The bone marrow must be examined on day 22 (at the time of the fourth VCR administration). If the bone marrow is not an M1 marrow give:

Adriamycin 25 mg/m^2/day I.V. on days 23,24 and 25
L-Asparaginase 1000 u/kg/day I.V. on days 29-38.

The bone marrow must be examined on day 45 following administration of L-Asparaginase. If marrow is an M1, patient will be randomized for maintenance. If marrow is not an M1 patient will receive:

Adriamycin 25 mg/m^2/day I.V. on days 46,47 and 48.

In this group of patients, re-examine the marrow on day 62. If the marrow is M1 or M2, patient may be randomized to maintenance phase. If not M1 or M2 marrow, patient will be taken off study.

Patients will receive a uniform induction therapy consisting of 4 weekly courses of vincristine plus daily prednisone and 3 doses of IT methotrexate, followed by a 10 day course of L-Asparaginase.

MAINTENANCE PHASE Patients will be randomized to Regimen I or Regimen II consisting of:

Regimen I Each 28 day cycle consists of:

Methotrexate 500 mg/m^2/I.V. 1/3 by I.V. push and 2/3 by continuous infusion over 24 hrs.
Methotrexate 12 mg/m^2 IT give two hrs after the onset of the MTX infusion. (max single dose 12 mg) EXCLUDE FROM 7th and LATER COURSES.
Citrovorum Factor 25 mg/m^2 I.V. give 48 hrs after onset of the MTX infusion
6-Thioguanine 75 mg/m^2/day p.o. days 2-11
Vincristine 2 mg/m^2 I.V. on day 22
Prednisone 120 mg/m^2/day p.o. in 3 divided doses on days 22-24. Taper 60 mg/m^2 x 1 day, 30 mg/m^2 x 1 day, 10 mg/m^2 x 1 day, 5 mg/m^2 x 1 day on days 25-28.

Repeat this sequence of therapy q 28 days to relapse.

Regimen II Each 28 day cycle consists of:

Cyclophosphamide 300 mg/m^2 I.V. on day 1
Cytosine Arabinoside 50 mg/m^2 subcutaneously q 12 hrs x 8 on days 1-4
Methotrexate 12 mg/m^2 IT on day 1 (max single dose 12 mg) EXCLUDE FROM 7th AND LATER CYCLES.
6-Thioguanine 75 mg/m^2/day p.o. on days 2-11.
Repeat this sequence of therapy q 28 days until relapse.
Vincristine 2 mg/m^2 I.V. on day 22
Prednisone 120 mg/m^2/day p.o. in 3 divided doses on days 22-24. Taper over 4 days: 60 mg/m^2 x 1 day, 30 mg/m^2 x 1 day, 10 mg/m^2 x 1 day, 5 mg/m^2 x 1 day on days 25-28.

Progress and Results: No patients have been entered at WRAMC.

Conclusions: Too early for any conclusions.

Side Effects/Complications: As noted in protocol L-Asparaginase may cause anaphylaxis.

Funds Utilized FY 79/Requested FY 80: See Introductory Remarks to Annual Progress Report.

Publications: None

Type of Report: Interim-210 patients (evaluable) need to be entered.

Work Unit No.: 1567

Title of Project: CALGB Pilot Study Protocol 0703 Add #2: Cis-Platinum Diamminedichloride in Advanced Malignant Lymphomas.

Investigators:

Principal: Johannes Blom, M.D.

Objectives: To determine the efficacy of Cis-Platinum (II) Diammine-dichloride (DDP) in adult patients with advanced Hodgkin's and non-Hodgkin's Lymphomas.

Technical Approach: DRUG SCHEDULE

DDP 70 mg/m^2 I.V. once q 3 weeks. DDP should be injected in the tubing of a running infusion over a period of no less than 20 minutes and no more than 1 hours. The administration of mannitol diuresis with DDP is MANDATORY.

ADMINISTRATION PROCEDURE

Pretreatment hydration of D5W with half normal saline and appropriate potassium supplement as determined by serum electrolytes. Starting infusion rate 250-300 cc/hr. Either start the night before treatment or hydrate orally with at least 2 1/2 liters of fluid. Hydration must result in urine output of at least 100 cc/hr or greater for 4 consecutive hours before treatment. (No diuretics should be used). Patients must either urinate hourly or have foley catheter for hourly urine output measurements.

After 4 hours of adequate urine:
-Mannitol 12.5 gm I.V. push then
-Start 25% mannitol infusion at 0 to 5 grams per hour to maintain urine output at least 100cc/hr for 2 hrs during cis-platinum infusion and 6 hrs afterwards. Continue I.V. infusion at 250-300 cc/hour.
-Cis-platinum as above
-After diuresis is complete, I.V. should be maintained until patient is able to take oral fluids well.

All patients are to be evaluated after two courses (6 weeks).
Patients who show no response (no change or progressive disease) after 6 weeks of therapy, go off study and are considered treatment failures.
Patients in either complete or partial remission after 6 weeks continue therapy to relapse.

Addendum #1 dated 5 November 1977 states that creatinine clearance must not be less than 60 cc/min rather than 75%.

As stated in the technical approach the amended dosages for mannitol and cis-platinum are as follows:

After 4 hrs of adequate urine:
-Mannitol 12.5 grams I.V. push then
-Simultaneously with giving Platinum start mannitol infusion at 10 grams/hr for six hrs to maintain urine output at least 100 cc/hr during the twenty minute platinum infusion and for six hours afterwards. Hydration should be continued at a rate of 250-300 cc/hr.
-After diuresis is complete, the I.V. should be maintained until patient is able to take oral fluids well.

Addendum #2 dated 22 February 1979 adds 5 new treatment facilities.

Progress and Results: No patients have been entered at WRAMC,

Conclusions: Too early

Side Effects/Complications: No unusual/unexpected side effects were encountered.

Funds Utilized FY 79/Requested FY 80: See Introductory Remarks to Annual Progress Report.

Publications: None

Type of Report: Interim

Work Unit No.: 1571

Title of Project: CALGB Protocol 7891 Add #1: Intergroup Rhabdomyosarcoma Study -: II: ALVEOLAR Rhabdomyosarcoma of the Extremity in Clinical Groups I and II Patients.

Investigators:

Principal: Johannes Blom, M.D.

Objectives: The objectives of the study are to answer the following questions:

1. (Clinical Group I Disease) Can cyclophosphamide be dropped from the standard VAC regimen with radiation omitted without jeopardizing disease control and survival, and if so, would there be less side effects without it, particularly testicular, ovarian, and renal dysfunction?
   (Comparison: Standard VAC x 2 years vs VA x 1 year- both arms identical save for cyclophosphamide. No radiation is given in either arm. FSH, LH, and testosterone levels, growth rate, and cystitis incidence are compared as well.)
2. (Clinical Group II Disease) Will repetitive courses of "pulse" VAC improve the duration of complete remission and survival beyond that which is now achievable for microscopic residual disease with cyclic-sequential vincristine and dactinomycin, all patients receiving post-operative radiation to the tumor bed?
   (Comparison: Repetitive "pulse" VAC x 1 yr vs cyclic-sequential VA x 1 yr. XRT is given in both arms.) Hormonal levels, growth rate and cystitis incidence are also compared.
3. (Clinical Groups III and IV Disease) Will adriamycin if given in pulse combination with vincristine and cyclophosphamide ("pulse" VADRC), improve the complete remission rate and prolong the duration of remission and survival beyond that now achievable with "pulse" VAC, all patients receiving radiation to the tumor bed and sites of metastases?

   Will two years of repetitive pulse therapy be superior to the non-repetitive pulse regimens previously employed in IRS-I for Groups III and IV disease (Regimens E and F)?

(Comparison: Induction - "pulse" VAC vs "pulse" VADRC, (+ XRT)
Maintenance - "pulse VAC qmo vs "pulse" VADRC ALT qmo with "pulse" VAC in 1 yr "Pulse" VAC qmo for all patients in year 2.
(VADRC = VCR, Adriamycin, Cyclo)

4.. (Extremity Rhabdomyosarcoma Requiring Primary Amputation) Will two years of repetitive "pulse" VAC improve the duration of remission and survival in patients subjected to primary major amputation for primary tumors localized to the extremity?

5. (Rhabdomyosarcoma Localized to the Nasopharynx-Nasal Cavity, Middle Ear and Paranasal Sinus) Will "prophylactic" local meningeal radiation with or without intrathecal chemotherapy prevent direct meningeal extension of disease and improve the duration of remission and survival in these patients?

6. (Rhabdomyosarcoma Localized to the Pelvis (vagina, uterus, bladder, prostate) Can a primary chemotherapeutic approach avoid the disability associated with radical surgery without jeopardizing local disease control and survival?
(Certain events such as subsequent exenteration will be designated as treatment "failures". No improvement in survival rate is expected).

7. (Lymphatic Involvement in Rhabdomyosarcoma) What is the frequency and significance or regional lymph node involvement in relation to primary site of tumor origin?

8. (Pathology) What are the relationships between the special undifferentiated cell types I and II (Ewing's tumor of the soft tissue) and classical rhabdomyosarcomas in terms of biological behavior, ultrastructural features, and response to therapy?

What are the patterns of lymph node metastases at autopsy?

What are the specifiic pathological features of CNS involvement from direct extension of tumor from parameningeal sites or from distant metastasis from other primary sites?

Based on evaluation of autopsy material, what are the toxicities of the treatment programs under investigation?

Technical Approach: PATIENTS WILL BE RANDOMIZED ACCORDING TO THEIR DISEASE GROUP.

EACH INSTITUTION WILL DECIDE REGARDING WHICH SPECIFIC PELVIC RHABDOMYOSARCOMA TREATMENT PLAN (PRIMARY SURGERY VS PRIMARY CHEMOTHERAPY) WILL BE UTILIZED DURING THE DURATION OF IRS-2.

Groups Ia & Ib: Patients who had complete resection of a localized tumor (no regional node involvement and/or evidence of distant metastases) will be randomized to one of two chemotherapy regimens. No postoperative radiotherapy is to be given. (For patients in Group I subjective to primary extremity major amputation as defined under Amputation in protocol will be assigned to regimen 25 but postoperative radiation therapy will be omitted to the tumor bed as the tumor bed will have been removed.)

Regimen 21

Vincristine 2 mg/m^2 I.V. weekly for 12 doses, starting on day 0. (max single dose 2 mg)
Dactinomycin 0.015 mg/kg/day I.V. for 5 days starting on day 0. (max single dose 0.5 mg) This is to be repeated at weeks 12, 24, 36 48 (last course).
Cyclophosphamide 2.5 mg/kg/day p.o. starting on day 42 and continuing through 24 months.

Regimen 22

Vincristine 2 mg/m^2 I.V. weekly for 12 doses starting on day 0. (max dose (single) 2 mg)
Dactinomycin 0.015 mg/kg/day I.V. for 5 days starting on day 0. (max single dose 0.5 mg) This is to be repeated at weeks 12, 24, 36 and 48 (last course).

Groups IIa, IIb and IIc: Patients who had(a) gross resection of the tumor (no nodes involved) but microscopic residual disease, or (b) complete resection of regional disease (nodes may or may not be involved) or (c) gross resection of regional disease including involved nodes, but microscopic residual disease, and no evidence of distant metastases will be randomized to one of two treatment regimens. (For pts in Group II subjected to primary extremity major amputation as defined under Amputation in protocol will be assigned to regimen 25 but postoperative radiation therapy will be omitted as tumor bed will have been removed.)

Regimen 23

1. Post-operative radiotherapy to the tumor-bed is to be started on day 0 as outlined in section Radiotherapy.
2. Dactinomycin 0.015 mg/kg/day I.V. for 5 days starting on day 0 (max single dose 0.5 mg) This is to be repeated at weeks 9, 18, 27, 36 and 45 (last course).
3. Vincristine 2 mg/m^2 I.V. weekly for 6 doses starting on days 21 (3 weeks), 84 (12 weeks), 147 (21 weeks), 210 (30 weeks), 273 (39 weeks), and 336 (48 weeks, last course) (max single dose 2 mg).

Regimen 24

(DAYS 0-83) (WEEKS 0-11)

1. Vincristine 2 mg/m^2 I.V. weekly for 12 doses starting on day 0 (max single dose 2 mg).
2. Dactinomycin 0.015 mg/kg/day I.V. for 5 days starting on day 0. (max single dose 0.5 mg).
3. Cyclophosphamide 10 mg/kg/day I.V. for 3 days starting on day 0 and then one dose of 20 mg/kg/I.V. on days 21, 42 and 63. However, cyclophosphamide should be omitted on days 42 and 63 in children who have the bladder included in the radiation portal or are to have large volumes of bone marrow irradiated, such as whole abdomen including the pelvic bones.
4. Post-operative radiotherapy to the tumor-bed is to be started on day 42 as outlined in Radiotherapy section.
5. (DAYS 84-371) (WEEKS 12-52): The following VAC "pulse" course should be given repetitively q 4 weeks from day 84 (week 21) - day 371 (week 52) and then stopped:
   Vincristine 2 mg/m^2 I.V. on days 0 and 4 (max single dose 2 mg)
   Dactinomycin 0.015 mg/kg/day I.V. for 5 days starting on day 0 (max single dose 0.5 mg)
   Cyclophosphamide 10 mg/kg/day I.V. for 3 days starting on day 0.

Groups III & IV

(Exclusive of Group III patients with primaries in either the bladder, vagina, uterus or prostate who are to be treated by the primary chemotherapeutic approach.

Patients who had only a biopsy or incomplete removal of the primary with gross residual disease, or who had evidence of distant metastases at the time of initial evaluation will be randomized to one of two treatment regimens.

Regimen 25

1. Same as Regimen 24, except that pulse VAC courses are to be given repetitively q 4 weeks from day 84 (week 12) - day 742 (week 104) i.e., - year 2 from the date on study.
2. Radiotherapy to the tumor bed as well as to the metastases as outlined in section Radiotherapy is to be started on day 42 (6 weeks) If the disease is progressive after 2 weeks of chemotherapy, radiotherapy may be initiated. If stable, radiotherapy should be withheld until week 6.

Regimen 26

(DAYS 0-83) (WEEKS 0-11)

1. Vincristine 2 mg/m^2 I.V. weekly for 12 doses starting on day 0., (max dose (single) 2 mg).
2. Adriamycin 30 mg/m^2/day I.V. on days 0,1,21 and 22.
3. Cyclophosphamide 10 mg/kg/day I.V. for 3 days starting on day 0 and then one dose of 20 mg/kg/I.V. on days 42 and 63. However, cyclophosphamide should be omitted on days 42 and 63 in children who have bladder included in the radiation portal or are to have large volumes of bone marrow irradiated, such as the whole abdomen including the pelvic bones.
4. Radiotherapy to the tumor-bed as well as to the metastases as outlined in section Radiotherapy is to be started on day 42 (6 weeks). If the disease is progressive after 2 weeks of chemotherapy, radiotherapy may be initiated. If disease is stable, radiotherapy should be withheld until week 6.

(DAYS 84-371) (WEEKS 12-52)
Pulse VADRC and pulse VAC courses are given alternately q 4 weeks from day 84 (week 12) through day 371 (week 52) as follows:

5. Pulse VADRC Course (q 8 weeks)(Weeks 12,20,28, 26,44 and 52):
Vincristine 2 mg/m^2 I.V. on day 0. (max single dose 2 mg)
Adriamycin 30 mg/m^2/day I.V. on day 0 and 1.
Cyclophosphamide 10 mg/kg/day I.V. for 3 days starting on day 0.
6. Pulse VAC Course (q 8 weeks) (Weeks 16,24,32, 40 and 48):
Vincristine 2 mg/m^2 I.V. on day 0 and 4. (max single dose 2 mg).
Dactinomycin 0.015 mg/kg/day I.V. for 5 days starting on day 0 (max single dose 0.5 mg).
Cyclophosphamide 10 mg/kg/day I.V. for 3 days starting on day 0.

7. (DAY 373-742) (WEEKS 53-104)
Pulse VAC courses should be given repetitivity q 4 weeks from day 372 to day 742 (weeks 52-104).
Pulse VADRC is not to be given in this phase so as to avoid adriamycin cardiac toxicity.
(The total cumulative adriamycin dose is 480 mg/m^2 in this regimen.

Special Sites:

Primary Chemotherapy Regimen for Primary Pelvic Sites.
(Study confined to patients in Clinical Groups I-III with primary tumors in the vagina-uterus, bladder or prostate). Patients treated with primary surgery are excluded from this study.

After initial biopsy through the perineum or rectum, patient is to be registered on study and receive 2 pulse VAC courses, the first starting on day 0 (week 0) and the second starting on day 28 (week 4) as follows:

Vincristine 2 mg/m^2 I.V. on days 0 and 4
(max single dose 2 mg)
Dactinomycin 0.015 mg/kg/day I.V. for 5 days starting on day 0 (max single dose 0.5 mg)
Cyclophosphamide 10 mg/kg/day I.V. for 3 days starting on day 0.

If patient is in CR or PR status, additional courses of pulse VAC are to be given starting on days 56 and 84 (weeks 8 and 12).

If patient shows no response, surgery should be performed. If excision would require exenteration, an option to employ radiation therapy to known extent of tumor. If no microscopic residual disease is present following surgery and nodes are negative or positive being completely excised, patients are to be randomized to regimen 26. Starting at week 12 of regimen given q 4 weeks through week 52 (VADRC) and VAC given q 4 weeks starting at week 53-week 104. If incomplete tumor removal with either gross or microscopic residual disease following surgery, patient is to receive radiotherapy to the postoperative tumor bed and area of incompletely removed positive nodes and then placed on regimen 26.

<u>Radiotherapy and IT Chemotherapy for Patients with Nasopharynx-Nasal Cavity, Paranasal Sinuses, and Middle Ear Primary Sites at Risk of Meningeal Extension:</u>

Evidence of meningeal extension in continuity with primary tumor (by laboratory, clinical or radiographic examinations) or by spinal fluid contamination or established spinal disease should be treated as follows:

The entire craniomeninges should be treated in continuity with the site of primary origin of tumor and the entire spinal meninges should be treated Day 0 and Week 6 respectively. The split course is recommended because spinal irradiation during the first six weeks of the protocol, with intensive systemic chemotherapy, may cause undue marrow suppression. IT chemotherapy is administered beginning on day 0 of cranial cavity irradiation with hope of controlling spinal meningeal disease prior to spinal axis irradiation, in addition to its effect in contolling craniomeningeal disease.

Intrathecal Chemotherapy Dosage Schedules
"Prophylactic" Intrathecal Chemotherapy:

The three drugs listed below are administered intrathecally in combination at days 0 and 14 and then at weeks 4,8,14 and then q 8 weeks thereafter up to 18 months from the date on study.

Cytosine Arabinoside 60 mg/m^2 I.T. (no top dose)
Hydrocortisone 30 mg/m^2 I.T. (no top dose)
Methotrexate 15 mg/m^2 I.T. (top dose 15 mg)
Leucovorin 15 mg/m^2 I.V., I.M. or p.o. should be given 24 hours after the I.T methotrexate injection for protection against systemic effects of methotrexate.

Intrathecal Chemotherapy for Established CNS Disease at Diagnosis:
Induction Phase
If CSF cytology is positive or spinal cord is involved, triple chemotherapy plus leucovorin rescue as defined above, are administered once a week until CSF remission is achieved.
IT Chemotherapy and cranial or craniospinal radiation are to be started at the same time.

Maintenance Phase
When complete CSF remission is achieved, triple chemotherapy plus leucovorin rescue as indicated above are administered at weeks 4,8,14 and q 8 weeks thereafter up to 2 years from the date of diagnosis of CNS disease.

Radiation Therapy

Group I	No radiation therapy
Group II	Patients of all ages are to receive no less than 4000 rad (min dose) and no more than 4500 rad (max dose) to a volume of tissue which should encompass the "tumor bed" including the most distal margins of resection and also including a 5 cm margin beyond the limites of resection in all directions. However, the maximum volume to be irradiated is the muscle bundle of origin.

Group III

Children less than six years of age:

When the tumor is less than 5 cm*
(*Tumor size is to be determined after surgical resection but before initiating chemotherapy).
(at the time of commencement of chemotherapy) the doses of radiation are to be a minimum of 4000 rad and a maximum of 4500 rad.

When the tumor is equal to or greater than 5 cm. at the time of beginning chemotherapy, the doses of radiation should be 4500 rad minimum and 5000 rad maximum.

Children equal to or greater than six years of age:

When the tumor is less than 5 cm (at time of commencement of chemotherapy) the doses of radiation are to be a minimum of 4500 rad and a maximum of 5000 rad.

When the tumor is equal to or greater than 5 cm. at the time of beginning chemotherapy, than the doses of radiation should be 5000 rad minimum and 5500 rad maximu.

Group IV

Patients in clinical Group IV should be treated to the primary site as decribed for patients with clinical Group III disease.

However, in addition to treating the primary site of involvement, these patients should receive radiation therapy to sites of metastatic disease.

Doses have been adjusted for age as described above; no further adjustments of dose for age is thought to be necessary.

Supervoltage irradiation is to be used. Isodose distributions should be plotted, including doses to offaxis points of interest.
180-200 rad fraction should be delivered, at the rate of 1 fraction per day, for a dose schedule of 5 fractions per week. This will deliver 900-1000 rad per week.
Daily fractions may be reduced to 150 rad tumor dose (750 rad per week) when larger volumes (i.e. whole chest, whole abdomen) are included in the portals.

Split course is permissible, if in the opinion of the radiation therapist, The normal tissue tolerance would be exceeded otherwise. In such instances, the same daily dose rate and total dose should be used, except if the rest period is two weeks or longer, the total dose should be increased by no less than 10%*. (*TDF calculations should be used). In instances of split course irradiation, the rationale for the use of the split course should be noted on the radiation therapy checklist.

Usually, balanced parallel paired opposing portals will be used and tumor doses are mid-plane values alone the central axis. Preferably, each portal will be treated each day in all patients.

For asymmetrical tumors, unbalanced parallel paired opposing portals may be used. In such instances, minimum and maximum doses within the tumor along the central axis should be stated as well as the dose at the midplane of the tumor.

For other techniques, such as wedge pairs or rotational fields, the minimum and maximum doses should be stated. The minimum dose should be considered as tumor dose.

Addendum #1 dated 12 March 1979 states that All patients in Clinical Groups I and II with alveolar extremity primary tumors will be assigned regimen 25 (repetitive "pulse" VAC, section 8.42 of protocol) for 2 years. However, only the Group II patients are to receive radiation therapy (beginning at 6 weeks, not day 0). Radiation therapy will be omitted in Group I patients.

Progress and Results: No patients have been entered at WRAMC.

Conclusions: Too early

Side Effects/Complications: No unusual/unexpected side effects were encountered.

Funds Utilized FT 79/Requested FY 80: See Introductory Remarks to Annual Progress Report.

Publications: None

Type of Report: Interim

Work Unit No.: 1602

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

Investigator: Johannes Blom, MD

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 and Results: Five patients were entered on this study. Three patients had no response or progressive disease. One patient had minimal response, but progressed. One patient had initial subjective improvement but progressed on day 110.

Conclusions: This study was closed.

Side Effects/Complications: No unusual/unexpected side effects were encountered.

Funds Utilized FY 79/Requested FY 80: See Introductory Remarks to Annual Progress Report.

Publications: None

Type of Report: Final

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

Investigator: Johannes Blom, MD

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 mg/m^2 and DIC 200 mg/m^2 for 5 days.

Progress and Results: Fifty-five patients have been entered on study. Of the 43 histologic tissue for review, there were 23 patients with astrocytoma grade III and IV; ten patients with astrocytoma grade I and II; one patient each with cerebellar astrocytoma and ependymoblastoma; and eight with metastatic disease. Six patients were lost to follow-up or no recent information is available. Twenty-nine patients were begun on treatment after completion of surgery and radiation to the brain. Two of these had grade II astrocytomas with recurrence for which they received further radiation therapy and were then placed on chemotherapy. One patient relapsed on day 762 and the other on day 889. Four of these 29 patients had grade II astrocytomas and are stable from 274 to 1355 days, however one relapsed at 577 days. Twenty patients remained stable or became asymptomatic until they had progressive disease and subsequently expired from 15 to 549 days. One remaining patient has been stable for 205 days at last follow-up. The other remaining patient expired on day 450. Eleven patients were placed on study when they had evidence of progressive disease, one obtained a complete remission and relapsed on day 594. Ten patients remained on study until further progression or death from 37 to 625 days. Twenty-four patients had progressive disease and all expired shortly thereafter. One patient had an improvement of his clinical condition but progression of his disease by day 594.

Twenty-two 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. Five patients remain on study from 180 to 1800 days at last follow-up. The mean survival on this protocol is now 54 weeks with a median of 47 weeks.

Conclusions: Treatment efficacy is found to be minimal. The efficacy of the chemotherapy after surgery and radiation therapy will need further evaluation, possibly with different agents, combinations or radiosensitizing drugs.

Side Effects/Complications: No unusual/unexpected side effects were encountered.

Funds Utilized FY 79/Requested FY 80: See Introductory Remarks to Annual Progress Report.

Publications: None

Type of Report: Interim. No patient entries have been made since September 1978. Those patients surviving will continue to be followed.

Work Unit No.: 1604

Title of Project: WRAMC Protocol 7205 - Phase II Protocol Combination Chemotherapy with Dimethyl-Triazeno Imidazole Carboxamide (DTIC) and Adriamycin in Soft Tissue and Bone Sarcomas

Investigator: Johannes Blom, MD

Objectives: To determine the efficacy of combination chemotherapy with DTIC and adriamycin in patients with soft tissue and bone sarcomas, and to evaluate the toxicity of this combination of agents.

Technical Approach: Good risk patients:
Adriamycin 60 mg/m^2 day 1 in rapid I.V. infusion
DTIC 250 mg/m^2 I.V. x5 days

Poor risk patients:
Adriamycin 45 mg/m^2 day 1 in rapid I.V. infusion
DTIC 200 mg/m^2 I.V. x5 days

Progress and Results: Thirty-eight patients have been entered on the study. Nine patients are lost to follow-up or no recent follow-up is available; two patients are not evaluable; one patient refused treatment, and one was invalid because at autopsy the diagnosis was renal cell carcinoma. One patient had a complete remission and relapsed at day 677. One patient remains in complete remission at day 924. One patient received the treatment as adjuvant, but had progressive disease by day 44. Three patients had a partial remission, ten had progressive disease, and ten had stable disease or no response.

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. The study was closed to patient entry on 18 May 1978. Five patients are still being followed for survival studies.

Side Effects/Complications: No unusual/unexpected side effects were encountered.

Funds Utilized FY 79/Requested FY 80: See Introductory Remarks to Annual Progress Report

Publications: None

Type of Report: Interim

Work Unit No.: 1610

Title of Project: WRAMC Protocol 7307 - Phase I-II Evaluation of Dibromodulcitol in Previously Treated Patients with Metastatic Carcinoma of the Breast (NCI B134)

Investigator: Johannes Blom, MD

Objectives: Evaluation of dibromodulcitol in patients who have been treated with and are resistant to standard modes of therapy.

Technical Approach: Dibromodulcitol p.o. days 1-10 each 21-day cycle

Progress and Results: Fifteen patients have been entered on study. One patient is free of disease on day 1082. All other patients had progressive disease.

Conclusions: Twenty-nine patients were entered by all participating institutions. A response was observed in four patients.

Side Effects/Complications: Low blood counts.

Funds Utilized FY 79/Requested FY 80: See Introductory Remarks to Annual Progress Report

Publications: None since 1976.

Type of Report: Interim. The study was closed to patient entry in December 1977.

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

Investigator: Johannes Blom, MD

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 and Results: WRAMC entered four patients on this study. Two patients had chemotherapy and two patients had radiation therapy. Both patients who received chemotherapy relapsed. The patients who received radiation therapy have been lost to follow-up.

Conclusions: None

Side Effects/Complications: None

Funds Utilized FY 79/Requested FY 80: See Introductory Remarks to Annual Progress Report

Publications: None

Type of Report: Final. 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.

Work Unit No.: 1621

Title of Project: WRAMC Protocol 7208 - Phase II Protocol 5-Azacytidine in Acute Leukemia.

Investigator: Johannes Blom, MD

Objectives: To determine the effectiveness of 5-azacytidine in the treatment of acute leukemia resistant to standard therapy.

Technical Approach: 5-azacytidine 250 mg/m^2 I.V. daily x5 in 3 divided infusions every 8 hours. This course will be repeated every 2 weeks.

Progress and Results: Fourteen patients were entered on the study. None were entered during the past year. Thirteen patients had myelogenous leukemia in a blastic phase resistant to standard agents. One patient had acute lymphocytic leukemia. One patient was lost to follow-up, one had a complete remission but relapsed and died within 1 month, one had a partial remission, and ten had no response.

Conclusions: 5-azacytidine is a minimally effective agent in the treatment of resistant adult acute myelogenous leukemia. This protocol was closed to new patient entry in August 1979.

Side Effects/Complications: It is very hard to separate the toxicity from the extremely ill health and deteriorating status of these patients. Other than one possible episode of drug-related fever, no extraordinary complications were encountered.

Funds Utilized FY 79/Requested FY 80: See Introductory Remarks to Annual Progress Report.

Publications: None

Type of Report: Final

Work Unit No.: 1626

Title of Project: WRAMC Protocol 7405 - Treatment of Advanced Renal Cell Carcinoma with a Combination of 1-(chlorethyl)-3-cyclohexyl-1-nitrosourea (CCNU)(NSC 79037) and Bleomycin (NSC 125066)

Investigator: Johannes Blom, MD

Objectives: To evaluate the effectiveness of CCNU and bleomycin in the treatment of advanced renal cell carcinoma and to measure survival of these patients.

Technical Approach:

Basic Protocol - Induction: CCNU 130 mg/m^2 p.o. every 6 weeks
Bleomycin 15 mg I.V. once a week

Maintenance: CCNU 130 mg/m^2 p.o. every 6 weeks
Bleomycin 15 mg I.V. every 3 weeks, not to exceed the maximum total dose of 210 mg/m^2.

Patients with complete or partial remissions after 3 induction courses will receive maintenance therapy.

Addendum #1 - The following changes were made to the basic protocol:

Bleomycin will be given I.M. and the dose on day 22 of the maintenance phase is deleted.

Progress and Results: Thirty-one patients were entered on study. Ten patients were entered for adjuvant treatment of whom eight remain without evidence of disease from 848 to 1812 days. Two patients relapsed at 152 and 222 days. Two patients are lost to follow-up and one chart was non-evaluable. In four patients the drugs were discontinued because of drug toxicity (two pancytopenia, two increased dyspnea). Two patients developed severe pulmonary toxicity with dyspnea after total doses of bleomycin of 180 mg and 270 mg, and both subsequently died. None of 16 patients with metastatic disease had a response to the treatment.

Conclusions: No patients with metastatic disease have responded to treatment. Two patients given adjuvant treatment have died of progressive pulmonary toxicity. Lack of results in metastatic disease and high risk of bleomycin drug toxicity have led to closure of this protocol.

Side Effects/Complications: See above.

Funds Utilized FY 79/Requested FY 80: See Introductory Remarks to Annual Progress Report

Publications: None

Type of Report: Interim.

Work Unit No.: 1627

Title of Project: WRAMC Protocol 7404, with 2 addenda - Immunological Evaluation and Immunotherapy of Patients with Carcinoma of the Lung

Investigator: Johannes Blom, MD

Objectives:
1. To investigate the therapeutic efficacy of BCG given by 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:

Basic Protocol - Patients were put into three broad groups based on the extent of disease:

A patients - surgically resectable disease (no clinically detectable tumor after surgery)

B patients - surgically treatable for the bulk of tumor, but not completely locally resectable (palliative resection), or residual disease treatable by local radiotherapy (after 1) or primary disease treatable by radiotherapy (patients in whom surgery is contra-indicated).

C patients - patients with metastatic disease.

Radiotherapy - 1) "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 1000-15000 rads to the primary tumor only.
2) "Palliative Intent" - To be given to the primary site of tumor in all C patients and may be given at the discretion of the physician to local tumor masses in C patients during chemotherapy

for metastatic disease if clinical symptoms warrant it. 3000 rads over 2 weeks will be administered to the local symptomatic area only.

Chemotherapy - A patients - no chemotherapy

B patients - will be treated with chemotherapy as C patients after they have finished their radiotherapy.

C patients - All patients will be treated with chemotherapy as follows:
Cytoxan 500 mg/m^2
Methotrexate 40 mg/m^2
Vincristine 2.0 mg
total dose intravenously on days 1 and 8 of a 28-day cycle. Chemotherapy will continue for a two-year period. Patients randomized to receive BCG or a BCG plus allogeneic tumor will receive these materials on days 1 and 21 of the 28-day cycle.

Immunotherapy - All patients will be randomized into 3 groups:

1) Control Group - no immunotherapy.
2) Non-specific active immunotherapy (BCG only) every 2 weeks by Heaf gun dermal scarification.
3) Specific active immunotherapy (BCG _ allogeneic cells). These patients will receive BCG as outlined above and in addition will receive allogeneic tumor cells in the extremity at the same visit. These cells will be intradermally and subcutaneously injected adjacent to the BCG scarification.

Addendum #2 - 1) Because of early results indicating no objective value of immunotherapy and chemotherapy vs chemotherapy alone in class B and C patients, the scope of this protocol will be reduced, and only those patients classified as "A" or Stage I will be eligible for treatment.

2) Immunotherapy:

a) Following surgical resection of their disease, patients classified as "A" (the equivalent of Stage I or T_1, N_0, M_0, T_1, N_1, M_0) will be randomized to one of two treatment groups.

b) Group I will be a control group who will receive no therapy; group II will receive nonspecific immunotherapy consisting of BCG given by Heaf gun scarification every 2 weeks or as tolerated. Specific active immunotherapy with BCG plus allogeneic cells will not be utilized.

Addendum #1 - 1) Modification of chemotherapy dose because of significant hematologic toxicity:

Cytoxan 250 mg/m^2	I.V. days 1
Methotrexate 20 mg/m^2	and 8 of 28-
Vincristine 1.4 mg/m^2 (2 mg maximum)	day cycle

2) Immunotherapy: The first administration will be BCG alone. Each subsequent administration will be BCG and tumor cells. The tumor cells, however, will be injected intradermally and subcutaneously within 2 cm (lateral or medial) of the previous site of BCG scarification (i.e. the site which is about 2 weeks old).

Progress and Results: No patients were entered during the last year. Thirty-nine patients were entered on the study. Sixteen patients with Stage A(I) were entered. One was non-evaluable. Of the six control, five have relapsed and one remains with no evidence of disease. However, seven of nine patients treated with BCG remain in remission. One patient has developed a marginal recurrence and is now in remission after radiation therapy. Only one of the Stage B patients (treated with BCG) remains in remission. The others have all relapsed.

Conclusions: Based on results at WRAMC, National Naval Medical Center, and Portsmouth Naval Hospital, patients with early stage disease (A) treated with BCG appear to have an improved survival. No benefit is seen in B and C patients. A new study is being developed which includes specific and nonspecific immunotherapy.

Side Effects/Complications: One case of chronic hepatitis was seen. This may have been secondary to BCG administration.

Funds Utilized FY 79/Requested FY 80: See Introductory Remarks to Annual Progress Report.

Publications: A recent update of this study by Perlin et al will be published in the International Journal of Radiation Oncology.

Type of Report: Interim. The remaining patients on study will be followed for a minimum of three more years to determine the actual rather than projected five-year survival. The protocol was closed to new patient entry on 16 February 1979.

Work Unit No.: 1628

Title of Project: WRAMC Protocol 7406 - Chemoimmunotherapy of Carcinoma of the Large Bowel. Revised December 1976

Investigators:

Principal: Johannes Blom, MD

Associate: MAJ Salvatore J. Scialla, 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/MeCCNU.

Technical Approach:

All patients are classified according to Duke's C classification:

Type II	(Stage B_1)	- Extension into but not through muscularis
	(Stage B_2)	- Extension to or through serosa; negative nodes
III	(Stage C_1)	- Limited to serosa; positive nodes
	(Stage C_2)	- Extension through serosa; positive nodes
IV		- Locally metastatic disease beyond lymphatics, the bulk of which can be removed, but with some tumor remaining
		- Cannot tolerate surgery
		- Tumor of such size or fixed so that surgery would not be undertaken
V	(Stage D)	- Distant metastases

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 - "Currative 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 judgment of the physician the patient can tolerate chemotherapy, these patients will receive 5-FU 10 mg/kg p.o. days 1-5 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 two years.

Type IV2 - After two weeks (10 doses) of radiation, these patients will be treated as V patients.

Type IV1 - About three 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 - 5-FU 325 mg/m^2 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 two weeks (days 8 and 22) thereafter for at least two years.

Type IV and V - Patients randomized to receive BCG will have it administered on days 22, 27, 57, etc.

The BCG will be a lyophilized preparation (Phillips 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.

Addendum #3 - BCG was discontinued for all new entries and discontinued for patients who had received BCG for six months.

Addenda #1 and #2 were incorporated into the revised protocol.

Progress and Results: Seventy-seven patients have been entered on study. Twenty-nine patients were treated in an adjuvant setting with either 5-FU or 5-FU plus BCG. There is no evidence of disease in 20 patients from 570 to as long as 1740 days. Four patients have progressed, three on 5-FU alone on days 131, 365, and 395. One patient on 5-FU/BCG progressed by day 438 who was a stage B2. Two of the 5-FU alone treated patients were B2 and one was stage C. There were four patients on whom recent follow-up was not available. One patient was non-evaluable receiving less than one course of treatment.

Forty-eight patients were treated for metastatic disease. There were 28 evaluable patients. Five patients received 5-FU, MeCCNU, and BCG - all have progressive disease from 108 to 300 days. Twenty-two patients received 5-FU and MeCCNU with stabilization and subsequent progression in 21 patients from as short as 41 days to as long as 450 days. One patient has been stable without progression on day 587. One patient was treated with 5-FU and BCG with progression by day 136. Eight patients were non-evaluable not completing a single course of treatment. Seven patients were not evaluable because they were either not treated as the schedule indicated, there was no measurable disease, or there was no histologic confirmation of a colorectal primary. On four patients there is no recent follow-up.

Conclusions: It is too early to evaluate the effect of chemotherapy or chemoimmunotherapy in the adjuvant setting. This chemotherapy or chemoimmunotherapy has no effect in the management of colorectal carcinoma in metastatic disease as far as response or ultimate survival. Adjuvant patients will have to be followed five years to evaluate its effect on survival.

Side Effects/Complications: Cumulative, but reversible, thrombocytopenia has occurred with MeCCNU.

Funds Utilized FY 79/Requested FY 80: See Introductory Remarks to Annual Progress Report

Publications: None

Type of Report: Interim. The protocol has been closed to patient entry.

Work Unit No.: 1629

Title of Project: Chemoimmunotherapy of Malignant Melanoma. WRAMC 7407

Investigator: Johannes Blom, MD

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, treatment with BCG by dermal scarification weekly x3 months and then every other week x21 months.
- Stage II - ICDT 700 mg/m^2 day 1 every 21 days
  BCG on day 7, 12 and 17 every 21 days
  This treatment will continue for at least 2 years after complete remission is achieved until there is evidence of progressive disease.
- Stage III - 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, patients will receive chemoimmunotherapy as described under stage II. Therapy is continued until there is evidence of disease progression.

Progress and Results: Forty-three patients have been entered.

Stage I - 16 patients entered
- 2 no recent follow-up
- 3 relapses on days 284, 315 and 730+
- 11 remain with no evidence of recurrence from 250 to 1092 days

Stage III - 15 patients entered
- 2 no recent follow-up
- 8 relapsed with progressive disease from day 28 to 1094
- 5 remain with no evidence of disease

Stage IV - 12 patients entered
1 lost to follow-up
11 no response to treatment and died
from day 27 to 119

Conclusions: Chemoimmunotherapy with DTIC and BCG have minimal effectiveness in advanced melanoma. A 68% disease-free survival at three years for stage I melanoma is not better than disease-free survival without BCG immunotherapy.

Side Effects/Complications: Local inflammation was experienced with BCG as expected. There were no disseminated BCG diseases.

Funds Utilized FY 79/Requested FY 80: See Introductory Remarks to Annual Progress Report

Publications: None

Type of Report: Interim. This study was closed to patient entry on 19 May 1978.

Work Unit No.: 1630

Title of Project: WRAMC Protocol 7408 - Comparative Trial of Tamoxifen and Fluoxymesterone plus Tamoxifen in Metastatic Breast Cancer

Investigator: Johannes Blom, MD

Objectives: Response rates and durations will be compared to assess the relative therapeutic benefit of the two regimens and also the quality of survival. Prognostic importance of a variety of pretherapy stratification factors will be evaluated.

Technical Approach: Regimen A - Tamoxifen 2 mg/m^2 p.o. tid

Regimen B - Fluoxymesterone 7 mg/m^2 p.o. bid
Tamoxifen 2 mg/m^2 p.o. bid

The dose of tamoxifen will gradually be increased.

Addendum #1 changed the tamoxifen dose to bid.

Progress and Results: Thirty-eight patients have been entered, one of whom is invalid because of taking improper dose. One patient is too early for evaluation. One patient was removed from study when estrogen receptors were found to be negative. Twenty-nine patients had no response or progressive disease. Six patients had improvement or stable disease from 37 to 1030 days.

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.

Side Effects/Complications: Recent data from the tamoxifen studies indicates that ophthalmic abnormalities may occur after prolonged use of tamoxifen. Dr. Muriel Kaiser at NIH is conducting free eye examinations on all tamoxifen patients. In the WRAMC group of patients, one individual developed fundoscopic changes at a tamoxifen dosage of 180 mg per day. Current maximum dosage is 50 mg per day.

Funds Utilized FY 79/Requested FY 80: See Introductory Remarks to Annual Progress Report

Publications: None

Type of Report: Interim

Work Unit No.: 1634

Title of Project: WRAMC Protocol 7412 - Metastatic Breast Carcinoma Study to Evaluate the Effect of Cyclophosphamide, Adriamycin and 5-Fluorouracil vs 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: Johannes Blom, MD

Objectives: The response rates obtained with the two induction regimens will be compared for their value as primary induction therapy. Both programs will be compared for their impact upon response duration. 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. days 1-14
Adriamycin 20 mg/m^2 I.V. days 1 and 8
5-FU 500 mg/m^2 I.V. push days 1 and 8

Each cycle is 28 days. Treatment will continue for two full cycles and thereafter until patient has progressive disease or no change or until a total dose of adriamycin (500 mg/m^2).

Regimen B - Adriamycin 45 mg/m^2 I.V. day 1
Dibromodulcitol 150 mg/m^2 p.o. days 1-10
Vincristine 1.2 mg/m^2 I.V. days 1, 8, and 15

Each cycle is 28 days. This regimen is given for three consecutive cycles after which the patient is switched to:

Cytoxan 100 mg/m^2 p.o. days 1-14
Methotrexate 40 mg/m^2 I.V. push days 1 and 8
5-FU 600 mg/m^2 I.V. push days 1 and 8

Each cycle is 28 days. Treatment is continued for three full cycles after which the patient undergoes sequential therapy with adriamycin, dibromodulcitol, vincristine alternating with cytoxan, methotrexate and 5-FU after

each three 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 - Cytoxan 100 mg/m^2 p.o. days 1-14
Methotrexate 40 mg/m^2 I.V. push days 1 and 8
5-FU 600 mg/m^2 I.V. push days 1 and 8

Each cycle is 28 days long.

Progress and Results: Twelve patients were entered on study at WRAMC. Although all patients showed improvement or stabilization of disease initially, all twelve patients have since demonstrated progressive disease from 136 to 1427 days.

Conclucions: 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.

Side Effects/Complications: No unusual/unexpected side effects were encountered.

Funds Utilized FY 79/Requested FY 80: See Introductory Remarks to Annual Progress Report

Publications: None since 1977.

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: 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 and Results: Since the activation of the study only one patient has presented with bleeding and an inhibitor to factor VIII. She was ineligible for study because of concomitant liver disease.

Conclusions: I desire to keep the study open in order to have the ability to utilize this investigational agent available for the treatment of this difficult management problem.

Funds Utilized, FY-79: None

Funding Requirement, FY-80: 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

Investigators:

Principal: Johannes Blom, MD

Associate: MAJ Salvatore J. Scialla, 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

Addendum #1 modified the cis-platinum administration to reduce the toxic side effects.

Progress and Results: Thirty-nine patients have been entered on study. Fourteen patients had widespread metastatic prostate carcinoma. One patient had stabilization of disease for 454 days, however later progressed. One patient had a partial remission with decrease of alkaline phosphatase from 294 to 91; one patient had relief of bone pain but progressive disease at day 120. Eight patients had progressive disease from day 12 to day 246. One patient was not evaluable receiving cis-platinum alone and two patients were lost to follow-up. There were two patients with adenoid cystic carcinoma; one obtained relief of bone pain but progressed at day 119; the other patient had no response and progression on day 90. There were two ovarian patients; one with stabilization at 270 days, the other with progressive disease by day 65 who

expired on day 82. The 17 remaining miscellaneous tumors included squamous cell carcinoma of the floor of the mouth, retromoral trigone, squamous cell and adenocarcinoma of the lung, esophagus, bladder, tongue, renal, thyroid, myeloma, soft tissue rhabdomyosarcoma and embryonal rhabdomyosarcoma of the nasopharynx. One patient with squamous cell of the esophagus had a partial remission in a metastatic lymph node, but expired of hypercalcemia on day 121. The remaining patients had minimal responses with progression of disease from day 15 to day 158. Three additional patients were non-evaluable because one ovarian patient was lost to follow-up, one patient with epitheloid tumor of the foot received only cis-platinum, and one patient with primary urethral carcinoma had no measurable disease. One patient was entered on study, but never received any chemotherapy. The one breast patient could not be evaluated because she was given megase with her chemotherapy.

Conclusions: Because of the diversity of patients no conclusions can be made about the small number of similar diseases entered. Although subjective bone pain relief was seen in the prostate patient, more patients must be entered to evaluate the objective response rate.

Side Effects/Complications: The two patients with esophageal carcinoma and prior radiation had a WBC nadir of 700. One patient had a partial response. The one patient with prostate carcinoma with a response also had a WBC of 900 and platelet count of 10,000 at nadir. Dose modifications will have to be adhered to for massive bone involvement plus prior radiation therapy.

Funds Utilized FY 79/Requested FY 80: See Introductory Remarks to Annual Progress Report

Publications: None

Type of Report: Interim. If the same type of tumors continue to be entered, an additional 60 patients will be needed for statistical analysis. It is estimated that this accrual will be completed in 1985.

Work Unit No.: 1649

Title of Project: WRAMC Protocol 7602 - Chemoimmunotherapy of Prostatic Carcinoma

Investigators:

Principal: Johannes Blom, MD

Associate: LTC Charles F. Miller, 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 days 14 and 21

Regimen B - Cyclophosphamide 1000 mg/m^2 I.V. on day 1
5-fluorouracil 600 mg/m^2 I.V. on days 1 and 8

This cycle to be repeated every 28 days.

Addendum #1 changed the BCG vaccine to the Pasteur strain, $2-8x10^8$ viable units.

Progress and Results: Eighteen patients have been entered on this study. Two of these patients have been lost to follow-up and three patients are alive as of September 1979. One patient has had complete remission of pulmonary metastases and continues on therapy 14 months from initiation of therapy. Two other patients have had partial remissions with durations of 9-11 months. One patient had a mixed response with complete remission of nodal disease and stable bony metastases (duration 9.5 months). Of interest is the observation that all objective responses occurred in either nodal or pulmonary metastases. No objective responses of bone metastases were noted, however subjective disease in pain was frequent. Median survival on study is 38 weeks from onset of therapy. The response rate seen (PR+CR) with this combination is approximately 22% which is favorably comparable to other studies.

Conclusions: Continue study until 20 evaluable patients have been entered.

Side Effects/Complications: One patient developed sepsis secondary to a urinary tract infection at the nadir of his chemotherapy bone marrow suppression. This patient died on day 12 of therapy. His chemotherapy dosage had been decreased by 50% for known bone marrow involvement. His sepsis was due to urinary tract infection associated with foley catheterization for treatment of neurogenic bladder due to cord compression by tumor.

Funds Utilized FY 79/Requested FY 80: See Introductory Remarks to Annual Progress Report

Publications: None

Type of Report: Interim. Twenty evaluable patients are desired prior to closure of this study. These patients should be entered during the next year.

Work Unit No.: 1651

Title of Project: WRAMC Protocol 7604 - Combination Chemotherapy for the Treatment of Advanced Gastric Carcinoma with either 1-Tetra-Hydro-2-Furanyl-5-Fluorouracil (Ftorafur), Adriamycin and Mitomycin-C vs 5-Fluorouracil, Adriamycin and Mitomycin-C. (Addendum #1 eliminated the use of Ftorafur. This is a study in cooperation with the Oncology Service, Georgetown University Hospital.)

Investigator: Johannes Blom, MD

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. days 1-5 during week 1 and 5 of each 8-week cycle
Adriamycin 30 mg/m^2 I.V. days 1 and 29
Mitomycin-C 10 mg/m^2 I.V. day 1 of each 8-week cycle

5-fluorouracil 600 mg/m^2 I.V. days 1 and 8 and days 29 and 36 of each 8-week cycle
Adriamycin 30 mg/m^2 I.V. days 1 and 29 of each 8-week cycle
Mitomycin-C 10 mg/m^2 I.V. day 1 of each 8-week cycle

Ftorafur was discontinued on 1 July 1977.

Progress and Results: WRAMC entered 18 patients. Of four patients receiving ftorafur, adriamycin and mitomycin-C, two patients had progressive disease by day 41 and day 559, one was non-evaluable receiving one course of therapy, and one patient was lost to follow-up. Of the remaining 14 patients, one had a complete remission of esophageal disease documented on E6D and is alive on day 349; one patient had greater than 60% remission of esophageal metastases by the end of the second course of treatment and is alive at day 260. Five patients had stabilization and subsequent progression from as short as day 110 to as long as 347 days. Three patients were non-evaluable because two received one course of therapy or less, one had no measurable disease. Three patients were lost to follow-up. The final patient has follow-up pending.

Conclusions: In a small number of evaluable patients some activity was noted. This regimen warrants further investigation in a larger comparative study.

Side Effects/Complications: One patient on Ftorafur had adriamycin cardiotoxicity at a total dose of 865 mg (limit 880 mg).

Funds Utilized FY 79/Requested FY 80: See Introductory Remarks to Annual Progress Report

Publications: None

Type of Report: Interim. This study has been closed to patient entry.

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, MD

Associate: COL Frederick B. Ruymann, 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, 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 and Results: WRAMC entered six patients, one with extraosseous Ewing's sarcoma who was not evaluable. One patient with osteosarcoma had stable disease for 300 days. Two osteosarcoma, one osteochrondrosarcoma, and one rhabdomyosarcoma had progressive disease.

Conclusions: The study was closed to patient entry on 19 May 1978.

Side Effects/Complications: No unusual/unexpected side effects were encountered.

Funds Utilized FY 79/Requested FY 80: See Introductory Remarks to Annual Progress Report.

Publications: None

Type of Report: Final

Work Unit No.: 1654

Title of Project: WRAMC Protocol 7601A - The Treatment of Unresectable Bronchogenic Carcinoma with CCNU (1-(2-chlorethyl)-3-Cyclohexyl-1-Nitrosourea), Cyclophosphamide, Adriamycin, Procarbazine, Hexamethylmelamine, Methotrexate, and Irradiation

Investigator: Johannes Blom, MD

Objectives: To determine the efficacy of combination chemotherapy with CCNU, cyclophosphamide, adriamycin, procarbazine, hexamethylmelamine, 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
Cytoxan 500 mg/m^2 I.V. push day 1
Adriamycin 30 mg/m^2 I.V. push day 2
Hexamethylmelamine 6 mg/kg p.o. days 8-22
Procarbazine 100 mg/m^2 p.o. days 8-18
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
Cytoxan 250 mg/m^2 I.V. push day 1
Adriamycin 15 mg/m^2 I.V. push day 2
Hexamethylmelamine 6 mg/kg p.o. days 8-22
Procarbazine 50 mg/m^2 p.o. days 8-18
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
Cytoxan 375 mg/m^2 I.V. push day 1
Adriamycin 25 mg/m^2 I.V. push day 2
Hexamethylmelamine 6 mg/kg p.o. days 8-22
Procarbazine 75 mg/m^2 p.o. days 8-18
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.

Addendum #1 added the hormone nandralone deconate or normal saline by randomization procedure.

Progress and Results: WRAMC entered 37 patients, one of which was never begun on treatment. Six patients received less than one full cycle of treatment. Three patients had a complete remission and five had a partial remission. Twenty-two patients had no significant response at all. Only one of the three patients in complete remission remains in remission on day 882.

Conclusions: Overall response rate of 25% was correlated with a prolonged median survival. However, the toxicity associated with this treatment program was greater than that seen with other equally effective, but less intensive, treatments.

Side Effects/Complications: Profound nausea, vomiting, anorexia, and weight loss were experienced. These effects appeared to be primarily associated with the combined administration of procarbazine and hexamethylmelamine.

Funds Utilized FY 79/Requested FY 80: See Introductory Remarks to Annual Progress Report

Publications: Miller CF, Weltz MD, Heim WJ, Blom J: Six-drug combination chemotherapy for nonresectable bronchogenic carcinoma. Cancer Treatment Reports (in press).

Type of Report: Interim. The protocol was closed to patient entry on 31 May 1977. Hexamethylmelamine was returned to the NCI.

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, MD

Associate: LTC Charles F. Miller, 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 and Results: WRAMC entered seven patients. One patient with extensive neuroblastoma metastatic to lung had progressive disease on day 15. One patient who received radiation therapy has no evidence of active tumor on day 890. Five patients progressed between day 30 and day 120. They have all died.

Conclusions: Based upon two studies in the recent literature and the preliminary results here, high dose methotrexate does not appear to be efficacious in lung carcinoma. Therefore, the study was closed to new patient entry on 2 January 1979.

Side Effects/Complications: No unusual/unexpected side effects were encountered.

Funds Utilized FY 79/Requested FY 80: See Introductory Remarks to Annual Progress Report.

Publications/Abstracts: None

Type of Report: Interim. The remaining patient will continue to be followed. Supplies of high dose methotrexate and BCG were returned to the National Cancer Institute.

Work Unit No.: 1657

Title of Project: WRAMC Protocol 7701 - Velban, Bleomycin, and Cis-Platinum in the Treatment of Head and Neck Malignancies

Investigators:

Principal: Johannes Blom, MD

Associate: MAJ Archie W. Brown, Jr., MC
LTC Jeffrey L. Berenberg, MC
COL Guillermo Garcia-Guerrero, MC
COL Robert L. Henderson, MC

Objectives: To evaluate the efficacy of the combination of velban, bleomycin, and cis-platinum in squamous cell carcinoma of the head and neck recurring after radiation, surgery, or previous chemotherapy. To evaluate the efficacy of this regimen as pre-operative or pre-radiation treatment in preventing recurrence.

Technical Approach:

Pre-Operative/Pre-Radiation Induction:

Velban 4.0 mg/m^2 I.V. day 1
Bleomycin 15 mg I.M. qd days 1-7
Cis-platinum 60 mg/m^2 I.V. day 8, plus mannitol and fluids

This regimen can be repeated every three weeks, if tolerated, as long as there is continued tumor regression, up to a maximum of three courses. Following surgery/radiation/recovery from myelosuppression the patient will be continued on the induction regimen until the total dose of bleomycin reaches 250 mg/m^2 (approximately four induction courses).

Maintenance:

Methotrexate 20 mg/m^2 p.o. twice weekly to begin on day 15 from onset of final induction course.
Cis-platinum 60 mg/m^2 will be given every 29 days x3 courses then every 57 days x3 courses.

Methotrexate will be held the week following cis-platinum to avoid excessive mucositis or myelosuppression. After completion of six maintenance courses of cis-platinum, methotrexate alone will be continued at 20 mg/m^2 twice weekly for a total of two years.

Recurrent Disease:

Patients with recurrent disease after previous definitive treatment will be treated with the induction regimen every three weeks as long as there is continued tumor regression until the maximum dose of bleomycin (250 mg/m^2) has been reached.

Addendum #1 modified the administration of cis-platinum to reduce the toxic side effects.

The original protocol has been modified in certain circumstances:

Several patients with squamous cell carcinomas originating in other areas have been treated with this approach (e.g. esophagus, anus, cervix).

The maintenance therapy specified has frequently been omitted because of geographic inaccessibility of many patients.

One patient with very limited cancer of the larynx was treated first with this regimen and then with laser therapy because she refused standard surgical therapy.

Progress and Results: Eighty-one patients have been entered on study. After receiving chemotherapy, most patients on this study were treated with other modalities such as radiation or surgery. Therefore, only response to chemotherapy can be evaluated, however overall survival resulting from response to chemotherapy cannot.

		RESPONSE			STATUS LAST F/U		
TUMOR TYPE	# PTS	CR	PR	OTHER	DEAD	NED	OTHER
Head and Neck	69	8	29	32	18	16	35
Uterine Cervix	6	0	0	6	4	0	2
Esophagus	3	0	0	3	2	0	1
Anus	1	1	0	0	0	0	1

Records could not be found on two patients.

Conclusions: The combination of velban, bleomycin, and cis-platinum has substantial activity in squamous cell carcinoma of the head and neck, especially in patients without prior surgery or radiation. This regimen can be given with reasonable safety from severe toxicity, and without compromising subsequent surgery or radiation.

Side Effects/Complications: Certain side effects have been observed. However, they were not unexpected. They include the well-recognized toxicities of these three chemotherapeutic agents.

Funds Utilized FY 79/Requested FY 80: See Introductory Remarks to Annual Progress Report.

Reprints: $300.00 (FY 80)

Type of Report: Interim. Patients are still being entered onto the study. At the present time we are considering other studies to be built on the results of this one, but no formal requests to change this protocol have been formulated.

Publications: Brown AW Jr, Blom J, Garcia-Guerrero G, Richardson MF, Henderson RL: Combination chemotherapy with vinblastine, bleomycin, and cis-diamminedichloroplatinum (II) in squamous cell carcinoma of the head and neck. Cancer (in press).

This study is being considered for a pilot study of the Cancer and Leukemia Group B.

Work Unit No.: 1658

Title of Project: WRAMC Protocl 7702 - Adjuvant Chemotherapy of Prostatic Carcinoma with Adriamycin and Cis-Diammine-dichloroplatinum II

Investigators:

Principal: LTC Charles F. Miller, MC

Associate: Johannes Blom, MD

Objectives: To compare the efficacy of radiation therapy alone versus the combination of radiation therapy plus chemotherapy in the treatment of patients with operatively staged and histologically proven stage D1 prostatic carcinoma.

Technical Approach: Regimen A - Whole pelvic irradiation to a total dose of 4600 rads with an additional 2000 rads to the prostate bed.

Regimen B - Radiation therapy as above
Adriamycin 60 mg/m^2 I.V. day 1 every 28 days
Cis-Platinum 60 mg/m^2 I.V. day 1 every 28 days

Addendum #1 increased type of patients eligible for this protocol.

Addendum #2 modified administration of cis-platinum to decrease toxic side effects.

Progress and Results: Two patients have been entered. One patient had one course of chemotherapy and refused further treatment. The second patient completed his adjuvant treatment with no evidence of recurrence at day 485.

Conclusions: Too early for appropriate evaluation.

Side Effects/Complications: Cis-platinum administration was modified to reduce toxic side effects.

Funds Utilized FY 79/Requested FY 80: See Introductory Remarks to Annual Progress Report.

Publications: None

Type of Report: Interim. Study requires a minimum of 14 patients. Accrual is expected to be completed by 1984.

Work Unit No.: 1659

Title of Project: WRAMC Protocol 7703 - Hepatic Artery Infusion with 5-fluorouracil.

Investigators:

Principal: Johannes Blom, MD

Associate: MAJ Salvatore J. Scialla, MC

Objectives: To study incidence of response of hepatic metastatic disease to this form of therapy as opposed to other forms of systemic therapy. Also, to provide palliation and prolonged survival to this patient group.

Technical Approach: Angiographic study of the vascular anatomy and placement of the catheter(s) will be performed by the special procedures team. Transbrachial catheterization is preferred over the transfemoral approach. At least weekly, and where otherwise indicated, the catheter position should be confirmed angiographically.

Dilute 5-FU in appropriate volume of infusage and continue on 24-hour perfusion for preferably 21 days. Suggested dosage: 5-FU 20 mg/kg/24 hours x4 days, subsequently 5-FU 15 mg/kg/24 hours x17 days.

Progress and Results: Seven patients have been entered on the study. Four patients had colorectal carcinoma, and one each with hepatoma, cholangiohepatoma, and metastatic breast carcinoma. Seven patients received less than a 21-day course as per protocol. One of these patients developed gastric ulceration and severe diarrhea; another had embolization to the distal upper extremity digits with subsequent vascular necrosis. The hepatoma patient received only a 10-day course with minimal improvement; she expired six weeks later. The patient with the cholangiohepatoma had no response to a 20-day course. The breast cancer patient had a 12-day course with mouth ulcers, diarrhea, leukopenia and thrombocytopenia secondary to malpositioning of the catheter. She had a partial remission with decreased LFT's and liver size, but expired two months later. One patient with pancreatic metastases had a slight decrease in liver size with stabilization of LFT's during a 15-day infusion. A patient with well differentiated adenocarcinoma of

the rectum with hepatic metastases had an 11-day course and 19-day course with some improvement, however shortly thereafter expired. The one patient with a complete 21-day course had progressive disease at day 119 and subsequently developed pulmonary metastases and expired.

Conclusions: Due to technical difficulties the response to prolonged infusion is difficult to evaluate. The short infusions were minimally active.

Side Effects/Complications: As noted above.

Funds Utilized FY 79/Requested FY 80: See Introductory Remarks to Annual Progress Report.

Publications: None

Type of Report: Final. Protocol was closed to patient entry in July 1979.

Work Unit No.: 1661

Title of Project: Polycythemia Vera Study Group (PVSG) Protocols

Investigators:

Principal: Daniel B. Kimball, Jr., LTC, MC

Associate: Staff and Fellows of Hematology/Oncology Service

Objectives: To study therapeutic modalities and natural history of several myeloproliferative diseases.

Technical Approach: See details of each protocol listed in Progress & Results Section.

Progress & Results: In FY 1979, WRAMC followed 6 patients registered on PVSG Protocols. (Protocol 01, Protocol 05, and Protocol 10.)

Protocol 01: Ms. E J continues to be followed on this protocol, periodically being phlebotomized and doing well. This study was designed to compare three therapuetic modalities for the treatment of polycythemia rubra vera namely phlebotomy vs radiation therapy in the form of P32 vs oral alkalater therapy in the form of chlorambucil. This study has been closed to further a patient accrual but data continues to be collected on the 431 eligible patients randomized. 109 patients have died; 98 patients had an initial thrombotic episode and 31 patients have developed varieties of cancer with 22 patients having developed leukemia. The median time on study is 4.8 years. The risk for a thrombotic event appears to be roughly 2 time greater for patients treated with phlebotomy as compared to those treated with P32 or chlorambucil. There were an excessive incidence of leukemia in the chlorambucil treated group and for this reason the PVSG voted to discontinue the use of chlorambucil therapy in this protocol. The median survival of chlorambucil treated patients is 8 years, P32 treated patients 10 years and the median has not been reached in the phlebotomy treated patients. These differences are not statistically significant at the present time and follow-up continues.

Protocol 05: As noted above, the major difficulty in treating patients with phlebotomy alone for their polycythemia rubra vera was the high rate of thrombotic events in these patients. Because of this, it was decided to compare phlebotomy combined with P32 against phlebotomy combined with continuous aspirin and persantine therapy. The aspirin and persantine, it was hypothesed, would reduce the functional intergity of the circulating platetet so that the number of thrombotic events will be decreased. Ms. N B continues to be followed on this study receiving aspirin therapy. She has been disqualified nationally since her persantine therapy had to be discontinued because of persistent cutaneous toxicity. The patient continues to do well. Mr. A N was randomized to this protocol in January 1979 and is also being treated with phlebotomy and combined with aspirin and persantine therapy. He has experienced no significant toxicity to the therapeutic regimen and his hematocrit has been well controlled with phlebotomy. Mr. R B was just randomized to the study (September 1979) and is also receiving phlebotomy therapy combined with aspirin and persantine therapy without problems. Nationally 82 patients have been randomized to this study. The time on study has been insufficient to permit meaningful analysis. No deaths and no major complications have occurred. Four patients have been removed from the study because of toxicity associated with the antiaggegating agents (aspirin or persantine) including gastrointernal bleeding (2), gastrointernal intolerance (1), and skin rash (1). The study continues to accrue patients nationally.

Protocol 10: Two patients at WRAMC have been randomized to this study which is designed to compare the therapeutic efficacy of P32 vs an Oral Alkalating agent phenylalanine mustard (Alkeran) for the control of primary thrombocytosis. Ms. R B continues on study with her platelets count controlled in the normal range on oral Alkeran therapy. She has experienced no major toxicity and continues to do well. Mr. B C was randomized to this protocol on December 1978 and is receiving daily oral Alkeran therapy for the control of his platelet count. His

platelet count which was in the range of 1.5 million at the beginning of therapy gradually fell and is currently maintained in the normal range of 260 to 300 thousand on 1 mg to 0.5 mg per day of Alkeran therapy. The patient has experienced no significant toxicity other than a transient leukopenia in the range of 3600 white count. Nationally 41 patients have been randomized to the primary thrombocytosis study and are available for review. The data indicates date both Alkeran and P32 are comparably effective in acheiving good responses in patients with this disease within a period of 3 months time. The overall response rate for Alkeran was approximately 90% while it was 70% for radioactive phosphorus (P32). There was no significant toxicity to either agent. With a short time of follow-up to date it appears that the duration of response to radioactive phosphorus be superior to Alkeran therapy. Two cases of acute leukemia have developed in this study, 1 in a patient treated with Alkeran alone and 1 in a patient treated with Alkeran for 2 years and then switched to radioactive phosphorus. Since it is known that acute leukemia on occasion is a terminal manifestation of acute primary thrombocytosis the significance of the development of leukemia in these patients as it relates to there primary mode of therapy is uncertain.

Funds Utilized in FY 1979: The PI was provided TDY support for 2 meetings of the PVSG which met in New York in November 1978 and May 1979.

Funds Requested for FY 1980: Request that TDY funds to support the travel of PI and 1 Hematology/Oncology Fellow to the Semi-Annual Meeting of the PVSG to be held in New York would be continued.

Type of Report: Interim

Work Unit No.: 1664

Title of Project: WRAMC Protocol 7705 - Metastatic Colorectal Carcinoma

Investigators:

Principal: Johannes Blom, MD

Associate: MAJ Martin D. Weltz, MC
MAJ Salvatore J. Scialla, MC

Objectives: To investigate the therapeutic efficacy of mitomycin-C alone versus mitomycin-C plus ICRF-159 in patients with advanced colorectal neoplasms. To evaluate the hypercoagulable state which exists in metastatic colon patients.

Technical Approach: Regimen I - Mitomycin-C 7 mg/m^2 I.V. every 6 weeks

If there is progression after one dose, or stabilization after two doses, switch over to Regimen II.

Regimen II - Mitomycin-C 7 mg/m^2 I.V. every 6 weeks
ICRF-159 500 mg/m^2 p.o. day 1,2,3 every 3 weeks in divided doses every 8 hours

If there is objective progression after one course, the patient is to be taken off protocol.

Addendum #1 changed the randomization. All patients will be entered on the ICRF-159 plus mitomycin-C regimen only.

Progress and Results: There have been 25 patients entered on study. Of the 12 patients receiving two or more courses of chemotherapy, there were no responses. There was stabilization with progression of disease from 90 to as long as 135 days. There were five patients non-evaluable because of receiving inadequate dosages or less than two courses of treatment. Three patients have no recent follow-up and five patients were lost to follow-up.

Conclusions: The present regimen has no efficacy in colorectal carcinoma as far as response and survival is concerned.

Side Effects/Complications: One patient was a protocol violation receiving chemotherapy only five days after completion of radiation therapy. She had sustained, but reversible, leukopenia.

Funds Utilized FY 79/Requested FY 80: See Introductory Remarks to Annual Progress Report

Publications: None

Type of Report: Interim. This protocol has been closed to patient entry.

Work Unit No.: 1665

Title of Project: WRAMC Protocol 7706 - Treatment of Refractory Gastrointestinal Tumors with Chlorambucil and Methotrexate

Investigators:

Principal: Johannes Blom, MD

Associate: MAJ Martin D. Weltz, MC

Objectives: To test the therapeutic efficacy of chlorambucil and methotrexate in patients with advanced gastrointestinal tumors.

Technical Approach: Chlorambucil 6.0 mg/m^2 days 1-14
Methotrexate 10 mg/m^2 days 1,4,8,12 (p.o.)

This course is repeated every 28 days. For patients who have had prior chemotherapy or radiotherapy, 75% of the dosage is given for the first cycle.

Addendum #1 listed drug dose modifications for kidney dysfunction.

Progress and Results: WRAMC has entered 16 patients on study. Bethesda Naval Hospital has entered eight patients. Of the WRAMC patients, two have had stabilization of disease, one as long as 180 days without progression. Nine patients have had progression of disease with a period of onset of chemotherapy to death ranging from 43 to 231 days. One patient was non-evaluable because of a gall bladder primary. Two patients have no recent follow-up, and two patients were lost to follow-up. The Naval Center evaluation is pending.

Conclusion: This combination has no effect on response or survival in patients with colorectal carcinoma.

Side Effects/Complications: No unusual/unexpected side effects were encountered.

Funds Utilized FY 79/Requested FY 80: See Introductory Remarks to Annual Progress Report.

Publications: None

Type of Report: Interim. The protocol has been closed to new patient entry.

Work Unit No.: 1666

Title of Project: WRAMC Protocol 7801 - Protocol for Immunological Evaluation and Phase One Immunotherapy of Patients with Various Carcinomas

Investigator: Johannes Blom, MD

Objectives: To perform detailed immune evaluation in patients with tumor present and with tumor entirely resected, following immunization with either BCG or C. parvum in an attempt to ascertain changes in cytotoxicity induced by immune agents and to determine if immune depression in cancer patients can be reversed. A similar evaluation will be performed in patients before and after anesthesia and general surgery.

Technical Approach: Following baseline evaluation of immune status, patients will receive one of eight possible immunosensitizations with various doses of either BCG or C. parvum. Repeat doses to be determined following analysis of original response to immunization. Tests to be performed include:

Lymphoproliferative response to PHA, MLC, tetanus toxoid, PPD or C. parvum (depending on agent used) 15 ml.

Growth inhibition assay using lymphoid tumor cell line (5 ml).

Cytotoxicity in ^{51}Cr-release assay, against K562 (for NK) and antibody-coated Chang cells (for ADCC) (10 ml).

E-RFC, 29° and 4° assays (10 ml).

Serum (5 ml): To measure antibodies active in ADCC, antigen-antibody complexes, possible presence of blocking factors in assays of cell-mediated immunity.

Plasma (volume recovered from separation of heparinized blood for assays 1-4 will be saved in aliquots and stored at -70°C): To measure CEA, possible presence of human lung tumor-associated antigen, immunoglobulin levels.

Agents and doses to be studied include:

BCG (Pasteur, lyophilized), 2-10 x 10^8 viable organisms in 0.5 ml, inoculated percutaneously by Heaf gun, in a 5x5 cm^2 area on thigh

C. parvum (Wellcome clinical preparation as supplied by NCI, DCT), 1.18 mg/m^2 subcutaneously.

BCG, 2-10 x 10^7 viable organisms in 0.5 ml by Heaf gun

C. parvum, 1 mg I.V.

BCG 2-10 x10^6 organisms/0.5 ml by Heaf gun

C. parvum 0.12 mg/m^2 subcutaneously

C. parvum 10 mg/m^2 subcutaneously
C. parvum 5 mg I.V.

Patients to have studies performed as a baseline and then on days 1,3,7 or 8, 14 or 15. Skin tests with PPD, mumps, SKSD, and tetanus toxoid to be performed on days 7 or 8 and 14 or 15.

Patients with malignant and benign disease undergoing similar types of anesthesia and general surgery will have the following tests performed:
Lymphoproliferative response to MLC and PHA
LMI, indirect agarose microdroplet assay, with allogeneic tumor extracts
NK and K cell cytotoxicity
E-RFC 29° and 4° assays
Serum and plasma (described above)

In addition to evaluation prior to surgery, these studies will be repeated on days 7, 14 and 28 with skin tests performed on days 7 and 28.

Progress and Results: Nine patients have been entered on study from 123 to 365 days. Seven patients have been vaccinated with C. parvum; two patients were evaluated and not vaccinated.

Conclusions: Too early for evaluation.

Side Effects/Complications: No unusual/unexpected side effects were encountered.

Funds Utilized FY 79/Requested FY 80: See Introductory Remarks to Annual Progress Report

Publications: None

Type of Report: Interim. Fifty patients are required for this study. It is expected that accrual will last for approximately two years.

Work Unit No.: 1667

Title of Project: WRAMC Protocol 7803 - Metastatic Breast Carcinoma

Investigators:

Principal: Johannes Blom, MD

Associate: Martin D. Weltz, MAJ, MC

Objectives: To evaluate response rates, mean duration of response and survival in two patient populations with advanced breast carcinoma. In the first group, patients who have failed CMF chemotherapy or single or combination therapy not to include adriamycin will be randomized to treatment with BCNU and mitomycin-C vs adriamycin alone, in an attempt to determine if BCNU and mitomycin-C provide an equivalent or improved response rate when compared to adriamycin. In the second group, patients who have progressed on CAF regimens and who have had prior exposure to methotrexate will be randomized to treatment regimen consisting of BCNU, methotrexate and vincristine, with and without cytoxan, in an attempt to test the synergism of BCNU and cytoxan.

Technical Approach: Those patients who have progressed on CAF or adriamycin combinations will be randomized to 1 of 2 regimens.

Regimen I - BCNU 100 mg/m^2 I.V. infusion day 1
Cytoxan 400 mg/m^2 I.V. push day 1
Vincristine 1.4 mg/m^2 I.V. push day 1
Methotrexate 30 mg/m^2 I.V. push day 21

This cycle will be repeated every 28 days

Regimen II - BCNU 100 mg/m^2 I.V. in 30 cc of 5% D5W over 30 minutes on day 1
Vincristine 1.4 mg/m^2 I.V. push day 1
Methotrexate 30 mg/m^2 I.V. push day 21

This cycle will be repeated every 28 days.

If there is progression on Regimen I after two courses, the patient is removed from protocol and followed for survival. If there is progression on Regimen II after two courses the patient will receive Regimen I. If there is progression on Regimen I after two complete courses the patient is taken off protocol and followed for survival.

Progress and Results: Eleven patients have been entered on study, nine as CMF failures and two as adriamycin failures. One adriamycin failure treated with BCNU, cytoxan, methotrexate, and mitomycin-C died with progressive disease on day 80 and the other adriamycin failure was treated with BCNU and mitomycin-C and progressed after two courses. Nine patients were treated as CMF failures. Of four patients randomized to adriamycin, one refused further therapy on day 86, one expired with progressive disease on day 361, one is stable at day 365, and one progressed on day 93 and was then treated with BCNU and mitomycin-C and remains stable as of day 85. Of five patients randomized to BCNU and mitomycin-C, one progressed on day 74 and expired on day 48 after being crossed over to adriamycin; one refused further therapy after one cycle; one progressed on day 57 and remains stable at day 223 after being crossed over to adriamycin; one had progressive disease at one year and was treated with megace; and one remains stable as of day 78.

Conclusions: Too early

Side Effects/Complications: No unusual/unexpected side effects were encountered.

Funds Utilized FY 79/Requested FY 80: See Introductory Remarks to Annual Progress Report

Publications: None

Type of Report: Interim. Sixty patients will be required for this study. Therefore, the protocol will remain open for approximaely three years.

Work Unit No.: 1668

Title of Project: WRAMC Protocol 7807 - Effect of N-Acetyl-Cysteine on Adriamycin-Induced Acute Cardiac Damage

Investigators: Johannes Blom, MD
MAJ Martin D. Weltz, MC

Objectives: To test the effect of N-acetyl-cysteine on adriamycin's acute cardiac toxicity. The study will provide information on the development of acute and chronic cardiomyopathy and the possible protective effect of N-acetyl-cysteine. ECG-gated cineangiography will be obtained at regular intervals in patients receiving adriamycin with or without N-acetyl-cysteine and the rate of progression of the cardiomyopathy will be determined in "protected" versus "non-protected" patients.

Technical Approach:

A. Randomization
   Regimen A - Oral placebo followed in 1 hour by adriamycin 60 mg/m^2 I.V. every 4 weeks
   Regimen B - Oral N-acetyl-cysteine 5.6 mg/m^2 followed in 1 hour by adriamycin 60 mg/m^2 I.V. every 4 weeks

B. ECG-gated radionuclide cineangiography will be performed before and again 24 hours after the first, fourth, and ninth dose of adriamycin.

C. Echocardiography and systolic time intervals will be performed immediately following the radionuclide studies.

D. Blood studies to be performed prior to adriamycin therapy and then 6, 24, 48, 72 hours after adriamycin. These studies will be done to establish additional biochemical markers of cardiac damage or evidence of free radical damage.

Progress and Results: This is a joint study with the National Cancer Institute. Approval was recently granted for the use of N-acetyl-cysteine. Thus far, the NCI has entered 9 patients, four on adriamycin plus N-acetyl-cysteine and five on adriamycin alone. Two patients on the adriamycin alone have developed congestive heart failure; no patients on adriamycin plus N-acetyl-cysteine have developed CHF. No patients have been entered at WRAMC because of eligibility requirements, however several patients were considered.

Conclusions: Too early for appropriate evaluation.

Side Effects/Complications: No unusual/unexpected side effects were encountered.

Funds Utilized FY 79/Requested FY 80: See Introductory Remarks to Annual Progress Report.

Publications: None

Type of Report: Interim. Twenty patients will be accrued for this study with expected completion date October 1982.

Work Unit No.: 1672

Title of Project: Tumor Tissue for Extract Preparation

Investigator: Johannes Blom, MD

Objectives: Evaluation of immunotherapy in carcinoma of the colon using an antigen prepared from human colon tumor tissue.

Technical Approach: Obtain tumor tissue remaining after the Department of Pathology has obtained the necessary samples for diagnostic purposes. Tissue should not be deposited in formalin, should be kept sterile, and rinsed with normal saline. Tumor tissue should be trimmed of fat and other tissue as much as possible. Tissue will be sent to Dr. Ariel Hollingshead at George Washington University.

Progress and Results: No tissue obtained to date.

Conclusions: No data for evaluation.

Side Effects/Complications: N/A

Funds Utilized FY 79/Requested FY 80: See Introductory Remarks to Annual Progress Report

Publications: N/A

Type of Report: Interim

1. Work Unit No.: 1801

2. Title of Project: Direct Immunofluorescence in MCTD

3. Investigators:
   a. Principal: ROBERT A. DAVIS, LTC, 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, 1978 and June 30, 1979 102 skin biopsies were submitted for examination by direct immunofluorescence. All of the tissue, except 2, were submitted by the Department of Dermatology. The Department of Allergy and Oral Surgery each submitted one tissue for direct immunofluorescence examination. Biopsy specimens were submitted with the following diagnosis, MCTD, SLE, DLE, Bullous Pemphigoid, Erythema Multiforme, DH, Pprphyria Cutanea Tarda, Autoerythrocyted Sensitization, Pemphigus Vulgaris, Pemphigus Foliaceous, Allergic Vasculitis, Scleroderma, Exfoliative Erythroderma. Final diagnoses could not be obtained in 43 tissues, secondary to unavailability of records. Of the remaining 59 tissues, 3 positives were obtained. Positive direct immunofluorescence cases were, 1 case of DH (IgA deposition Dermal Papillae), 1 case of Pronestyl induced LE (IgG Basement Membrane), and 1 case of DLE (IGG, IgM, C3 at Basement Membrane Zone). Inconclusive or non specific findings were found in 4 cases: 1. C3 deposition at the basement membrane in a questionable case of Subcorneal Pustular Dermatosis, 2. IgG deposition at the basement membrane, the significance of which is unknown since no clinical data was found, 3. Interceullular IgG, IgA, C3 staining in a case reported as EM. 4. IgG deposition at the basement membrane in a case of questionable autoerythrocyte sensitization.

7. Conclusions:
   1. Procedures for improved record keeping have be ituted.
   2. Controls run regularly
   3. Discrimination used in tissue submitted for direct immunofluorescent study will be encouraged.
   4. Specimens for direct immunofluorescence from departments other than dermatology will be sought.
   5. Tissues analized for MCTD were negative.

8. Funds Utilized - FY-77:
   a. Personnel: ROBERT A. DAVIS, LTC, MC
   b. Equipment: None
   c. Supplies: $1,187.00
   d. Travel: None
   e. Other: None
   f. Funds not Utilized: $290.00

9. Funds Requested - FY-78:
   a. Personnel: ROBERT A. DAVIS, LTC, MC
   b. Equipment: None
   c. Supplies: Immunologic reagents, glassware and miscellaneous Items - $3,000.00
   d. Travel: $500.00 Immunofluorescent Technique Course, Dr. Beutner
   e. Other: None

10. Publications: None

11. Type of Report: Interim

Unit No.: 1901

Title of Project: The Efficacy of Antisera to Gram Negative Endotoxin in the Treatment of Gram Negative Sepsis

Investigators:

Principal: Jerald Sadoff, M.D.
Associate: John B. McClain, M.D.

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 antisera were 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 in San Diego, who is coordinating this multi-center study.

Progress and Results: During FY 79, 11 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. Only 40 more units need to be given, in the nationwide trial before the code will be broken. This should occur sometime in FY 1980 at which time a final progress report on the entire study will be submitted.

Laboratory Studies: It was noted in earlier progress reports that normal sera contained J-5 antibody by solid phase radioimmunoassay. Accordingly gamma globulin pools from Parke Davis, Armour Pharmaceutical, Green Cross of Japan, Cutter Pharmateutical, and Hyland were tested for anti-J-5 antibody levels were found in the 3.5-10.0 mgm/ml range. Experimental lots prepared by these manufacturers for intravenous use were then tested for J-5 antibody and found to have similar levels on a microgram of J-5 antibody per microgram antibody protein. One of these lots (Armour) is being tested in burned rats and neutropenic rabbits for efficacy.

Conclusions: 1) J-5 serum from vaccinated humans may be effective against shock and to gram negative sepsis but definite answers await completion of the study which should occur mid-FY 1980.

2) Gamma globulin prepared for I.V. use may provide the same protection as serum from vaccinated patients. Intravenous gamma globulin may provide a better route for J-5 administration.

Funds Utilized FY 79:

Funding Requirements FY-80: $1000.00

Publications: None

Type of Report: Annual Report. Interim

Work Unit No.: 1903

Title of Project: Persistence of T. Pallidum in Neurosyphilis

Investigators:

Principal Investigator: Edmund C. Tramont, LTC MC

Associate Investigator: Shannon Harrison, CPT MC

Objective: To determine the frequency with which Treponema pallidum can be isolated from the cerebrospinal fluid (CSF) of patients who have received 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: The CSF of 14 patients were studied by injecting rabbit testes. The experiments were carried through 3 passages. No rabbits were positive.

An attempt to determine the minimal infective dose was unsuccessful due to problems with the strain of rabbits.

Conclusions: It is too early to determine the results of these studies.

Funding Requirements FY-79:

Funding Requirements FY-80: $10,000.00

Publications:

Tramont, E.C., Chapter 180, Treponema pallidum (syphilis). in Principles & Practice of Infectious Disease, 1979. Editors Mandell, Bennett and Douglas, McGraw Hill, New York.

Type of Report: Interim.

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Work Unit No.: 1904

Title of Project: Access Shunt Infections on Patients Undergoing Kidney Dialysis.

Investigators:

Principal Investigator: Alan S. Cross, M.D.

Objective: To study the value of access shunt cultures in the diagnosis of infection.

Progress and Results: Sixty-four sets of quantitative blood cultures from both the access site and a peripheral vein were obtained in twenty-six patients suspected of having an access site infection. These were compared to 65 sets of quantitative cultures from 16 control patients. Three patients had a significantly higher bacterial colony count at the access than from the peripheral culture ("step-up") suggestive of an access site infection. Four patients with bacteremia had no set-up in bacterial counts indicating another source of infection. One hundred-seven sets of cultures from 16 control and 16 study patients were negative. None of these patients followed for up to one year developed an access site infection. Quantitative cultures were helpful both in the diagnosis and management of access site infections in patients undergoing chronic hemodialysis (Table 1 and Table 2).

Conclusions: This technique is now being used to assess access shunt infections in our dialysis patients.

Funding Requirements, FY-79: $5,000.00

Funding Requirements, FY-80: $5,000.00

Publications:

Cross, A.S. (abstract) Diagnosis of Access Site Infections in Patients Undergoing Chronic Hemodialysis. Submitted for publication.

Type of Report: Interim.

1. The numbers of patients studied are not large enough to be statistically significant, especially positive patients.

2. Improved methods of culture should help our recovery.

Table 1. Characteristics of Study and Control Patient Groups

	Patients with Suspected Access Site Infection		Controls		Total
Access Site Culture	+	-	+	-	
	no.	no.	no.	no.	
Patients	10	16	0	16	42
Patients with A-V Fistula	8	16	0	14	38
Patients with A-V cannula	1	1	0	2	4
No. of access site cultures	11	53	11	54	129
No. of peripheral cultures	10	49	11	54	124
Signs of Infection					
Erythema	1*	9			10
Pain	0	10			10
Edema	0	10			10
Drainage	8	6			14
Hematoma	0	9			9
Bacteremia	4	5			9
Fever alone	0	9			9
	13	58			71
Antibiotic use at the time of culture					
Inappropriate †	1*	3	0	1	5
Culture-negative episode before therapy	0	3	0	1	4
Therapy for previous culture-positive episode	0	9	0	4	13
Culture positive on appropriate therapy	10	0	4	0	14
Other cause of fever found	0	3	0	4	7
	11	18	4	10	43

* = episodes

† = antibiotic not active against S. aureus or Pseudomonas aeruginosa

Table 2. Patients with Positive Access Site Cultures

Patient	Date	Colony Count (CFU/ml) A	/	P	Organism	Duplicate	Day First Turned Positive	Interpretation	Comment
1	10/29	1	0	15	S. epidermidis	No	3	No A.S. infection	
	11/12	0	0	2	S. epidermidis	NO	4	No A.S. infection	Benign appearing A.S.; A-V cannula later removed because of recurrent bleeding.
	11/25	1	5	0	S. epidermidis	Yes	1	Possible infection	
	12/10	> 300 T	NO	137	Enterococcus	Yes	4		
	12/17	> 300	> 300	0	Enterococcus	Yes	2	Access site infection with both arterial and venous port involvement	
	12/22	7,300	11	0	Enterococcus	Yes	2		
	12/29	9,300	47,000	4	Enterococcus	Yes	2		
	1/7	3,200	30,300	0	Enterococcus	Yes	2		
	1/14	29,000	9,000	0	Enterococcus	Yes	2		
2	2/2	9	---	0	S. epidermidis	Yes	4	Possible infection arterial port	Three other studies negative
3	4/22	6	---	0	S. epidermidis	No	1	Possible infection arterial port	All organisms with same antibiogram. No overt clinical infection at A.S. Possible aneurysm of A-V fistula by contrast study
	4/23	25	---	0	S. epidermidis	Yes	7		
	4/26	6,000	---	0	S. epidermidis	Yes	2		
	4/29	100	---	0	S. epidermidis	Yes	1		
4	3/24	15	---	0	S. aureus	Yes	2	Arterial port infection	A.S. removed. Follow-up cultures negative
5	9/22	10	---	54	K. pneumoniae	Yes	1	Bacteremia with primary focus outside A.S.	Catheter-related phlebitis below site of peripheral sampling source of sepsis
6	9/27	6	---	4	Salmonella Gp B	Yes	4	Bacteremia with primary focus outside A.S.	
7	10/7	0	---	4	S. epidermidis	No	1	Probably contaminant	Two other studies negative
8	1/11	34	---	58	Ps. capacia Cryptococcus neoformans	Yes	1	Infection with primary focus outside A.S.	Infected aortic graft. Died
9	3/15	4	3	12	Enterococcus	Yes	1	Infection with primary focus outside A.S.	Died of aspergillus pneumonia
10	11/27	111	11	14	S. aureus	Yes	1	Infected A.S.	Draining lesion developed 2 days into therapy. Cleared with A.S. left in place.
	11/29	3	2	NO	S. aureus				

A = arterial culture; / = venous culture; P = peripheral culture; NO = not done, T = not diluted out; A.S. = access site
A-/ = arteriovenous

Work Unit No.: 1905

Title of Project: Immune Response to Neisseria gonorrhoeae in Humans.

Investigators:

Principal Investigator: Edmund C. Tramont, LTC MC
Associate Investigators: John Boslego, MAJ MC
Jennie Ciak, GS 12

Objective: To study the immune response to the mucosal infection caused by Neisseria gonorrhoeae.

Progress and Results: Much of the past years efforts have been devoted to improving the existing assays to measure the immune response.

INHIBITION OF ATTACHMENT ASSAYS

The inhibition of attachment assay measures the functional ability of antipilus antibody. The test which is done by direct microscopic examination is simple, accurate and reproducible but is tedious and time consuming. The need for a new and equally sensitive assay is paramount. Three approaches have been taken, 1) radiolabelling organisms, 2) determining limulus lysate activity and 3) radiolabelling high titered specific antiserum.

N. gonorrhoeae has been labelled with ^{3}H adenine. The surface of a GC agar plate is coated with 500 ul of a balanced buffered salt solution containing 50 ul of ^{3}H adenine (1mCi/ml). This solution is allowed to dry on the plate surface. The GC plate is then streaked with bacteria, and incubated for 18 hrs. The labelled bacteria can now be used in the standard IEA assay. The percentage of bacteria attached to the cells is determined by the amount of radioactivity associated with the cells. This method is being developed in conjunction with the tissue culture project because the sensitivity of this test is related to the ability of N. gonorrhoeae to attach to the cells. Our results have confirmed the feasibility of this approach but have also emphasized the need for using a cell line to which the bacteria adhere at a high percentage. The limulus lysate activity of N. gonorrhoeae attached to tissue culture cells can be determined. To do this requires that the IEA test be performed in a well in which a tissue culture cell line is growing. At the completion of the IEA test the mixture in the well is removed and the cells washed with sterile distilled water. The limulus reagents are then added directly to the well. Those wells in which sufficient bacteria are attached to the cell will cause the limulus test to gel and will be related to the titre of the sample being tested. This system has proven to be very sensitive. The usefulness of it is limited by the requirement that the sample being tested be free of bacterial, LPS and proteolytic enzyme contamination.

High titered GC specific antiserum has been raised in rabbits, fractionated with ammonium sulfate, absorbed with the tissue culture cells with which it will be used and labelled with ^{125}I. This labelled antiserum is used to enumerate the bacteria adhering to the TC cells. The results of these studies are incomplete.

N. GONORRHOEAE ADHERENCE TO TISSUE CULTURE

Several mammalian cell lines are being examined for the ability of N. gonorrhoeae to attach to them. Nine cell lines have been examined and the percentage of attachment has ranged from 1.5% to 35%.

The day to day variance in buccal epithelial cells obtained from a pool of human volunteers and its influence on the ability of N. gonorrhoeae to attach is a continuing problem.

An approach to solving this problem is to propagate a stable cell line using tissue culture techniques. The ability of two different strains of N. gonorrhoeae to adhere to nine mammalian cell lines has been examined. The percentage of bacteria adhering to a specific number of tissue culture cells was determined using both a viable bacteria count and radiolabelled N. gonorrhoeae. The percentage of gonococci attaching to each cell line varied considerably and was different for each cell line (Table 1, Table 2).

Gonococcal pili were found to be broadly cross reactive when examined with regard to their ability to block attachment of gonococci to epithelial cells.

Gonococcal pili have previously been demonstrated to have considerable antigenic heterogenicity. However, by using the assay which measures inhibition of attachment of whole gonococci to human epithelial cells (see Annual Report 1975), gonococcal pili were demonstrated to be broadly cross reactive. This was demonstrated by competitive inhibition and by absorption of vaginal antibody. Gonococcal pili were capable of competitively inhibiting the attachment of heterologous strains of gonococci to human epithelial cells, although not as efficiently as they inhibited the homologous strain. When genital antibody was absorbed with the homologous pili, this blocking activity was completely removed; while absorption with the heterologous pili removed all of the inhibiting activity against the heterologous strains, but only partially reduced the titer against the infecting strain (Table 3). Thus there appears to be a common set of antigenic determinants on gonococcal pili which mediate attachment and the human local antibody response is directed at least in part against this common set of determinants.

Funding Requirement FY-79:

Funding Requirement FY-80:$27,000.00

Publications:

Tramont, E.C., Hodges, W., Ciak, J., Gilbreath, M. Importance of Differences in Attachment Antigens in Gonococcal Reinfection. J Clin Lab Med 93:730-735.

Tramont, E.C., Ciak, J., McChesney, D., Boslego, J., Brinton, C. Cross Reactivity of Gonococcal Pili as Determined by Inhibition of Epithelial Cell Attachment. (Abstract) presented ICCAC, Boston, Mass. 1979.

Tramont, E., Boslego, J., Sadoff, J., Zollinger, W., Lolik, A., Bryan, J., Brinton, C. Safety and Immunogenicity Study of Gonococcal Pilus Vaccine. (Abstract) presented ICCAC, Boston, Mass. 1979.

Nature of Report: Interim.

Table 1

Comparison of Mean Percentages of Attachment and Number of Bacteria Attached/Cell

Cell Line	Percentage of Bacterial Attachment	Bacteria Attached per Cell
	P3-2	
BHK-21	1.47[a]	9.2[a]
Hep-2	2.18[b]	9.2[b]
Vero	13.6[b]	9.7[b]
HenLe	2.27[b]	7.8[b]
HeLa	5.39[c]	17.3[c]
Foreskin	1.26[c]	2.6[c]
Tonsil	2.78[c]	7.9[c]
	CG418	
BHK-21	3.54[d]	6.7[d]
Hep-2	3.70[b]	6.6[b]
Vero	1.89[e]	4.4[e]
HenLe	2.19[b]	2.8[b]
HeLa	1.28[c]	9.8[c]
Foreskin	7.86[c]	34.5[c]
Tonsil	14.58[c]	15.8[c]

a The mean is derived from 7 individual tests run at two separate times.
b The mean is derived from 10 individual tests run at two separate times.
c The mean is derived from 5 individual tests run at one time.
d The mean is derived from 8 individual tests run at two separate times.
e The mean is derived from 9 individual tests run at two separate times.
All cell lines were counted using a hemocytometer and a bacterial suspension was made in M199 + 2% w/v BSA. The bacteria and cells were combined in a 50:1 ratio and incubated for 30 minutes at 37°C. Dilutions were made of the mixture of cells and bacteria and were then counted by the bacterial plate counting method.

Table 3

Mean Percentages of Attachment
and Number of Bacteria Attached per Cell

Cell Line	Percentage of Bacterial Attachment	Bacteria Attached per Cell
	P3-2	
Flow 1000	35.5[a,b]	105[a,b]
HeLa	19.7	18
BHK	3.7	3
Hep-2	13.3	11
Vero	6.5	6
HenLe	6.4	5
Flow 2000	ND	ND
Tonsil	ND	ND
Foreskin	ND	ND
	418	
Flow 1000	19.2[a]	18[a]
HeLa	17.1	5
BHK	3.5	1
Hep-2	10.5	2.9
Vero	8.3	2
HenLe	6	1
Flow 2000	13.7	3.1
Tonsil	ND	ND
Foreskin	8	2

a The mean is derived from 5 individual tests

b All cell lines were counted using a hemocytometer. A bacterial cell suspension was made in M199 + 2% PSA. The percentage of attachment and the bacteria attached per cell were determined from the amount of radioactivity associated with each cell line.

Table 3

INHIBITION OF ATTACHMENT BY VAGINAL SECRETIONS
ABSORBED WITH HOMOLOGOUS AND HETEROLOGOUS PILI

	STRAINS		
Vag. sec. 418	418	135	149
Unabsorbed	1:32	1:4	1:32
abs. with 418 pili	0	0	0
abs. with 135 pili	1:8	0	0
abs. with 149 pili	1:1	0	0

Work Unit No.: 1906

Title of Project: The Limulis Lysate Assay for the Determination of Gram Negative Meningitis Septic Arthritis and Contamination of Intravenous Fluids.

Investigators: Arthur Dobek, Ph.D.
Charles Oster, MAJ MC
Edmund Tramont, LTC MC

Objective: To select a reliable and sensitive test to determine the presence of bacterial endotoxin in fluids, especially cerebrospinal fluid, from clinical cases chosen by the Infectious Disease Service.

Technical Approach: The manufacture of the LAL kit (Millipore Corp) has altered the method of plotting the standard curve of known concentrations of endotoxin (range: .0625 to .5 ng/ml). The former method, for which certain data will be presented, involved subtracting the optical density (OD) of the LAL control from each "observed" OD of the known concentrations of endotoxin to obtain a "corrected" OD which was plotted on ordinary graph paper. The new procedure requires that the LAD control OD no longer be subtracted, but rather that the "observed" OD of each endotoxin concentration either be plotted on log-log graph paper or that these OD's be converted to logarithms and then plotted on ordinary graph paper. We are using log-log graph paper.

Progress and Results: The following data in Table 1 have been obtained by the former method previously described:

Table 1

Patient designation	Endotoxin (ng/ml)	Time interval with multiple specimens
A	.075	
B	.080	
C	.070	A day
	.197	A + 4
D	.075	A day
	.188	A + 4
E	.125	
F	.076	
G	.075	A day
	.075	A + 2
H	.125	
I	.025	
J	.075	
K	.188	

In addition, 9 research samples were tested.

The following data in Table 2 have been obtained using the new method, previously described:

Table 2

Patient designation	Endotoxin (ng/ml)	Time interval with multiple specimens
L	.039	
M	.1075	A day
	.095	A + 9
	.103	A + 13
N	.220	
O	below standard curve	
P	.047	
Q	.022	
R	below standard curve	
S	.015	
T	.064	
U	.050	A day
	.060	A + 11
V	.022	
W	below standard curve	A day
	.068	A + 1
X	.047	
Y	.041	

In addition 4 research samples were tested

Conclusion:

Since the manufacturer at present indicates no endotoxin level which could be considered clinically significant, the interpretation of the test readings must be based upon clinical findings for each patient. The manufacturer is seeking FDA approval for this test kit, subsequent to clinical trial studies. The package insert includes under "Precautions",page 4: "Not for Determination of Endotoxemia in Man".

Funding Requirement FY-79:

Funding Requirement FY-80: $10,000.00

Publications:

Dobek, A.S., Klayman, D.L., Tramont, E.C. (Abstract) In vitro of Neisseria gonorrhoeae and thiosemicarbazones. ASM Los Angeles, CA 1979.

Nature of Report: Interim.

Work Unit No.: 1908

Title of Project: Evaluation of Sodium Stibogluconate (Pentostam^{R}) in the Treatment of Cutaneous Leishmaniasis.

Investigators:

Principal: Jeffrey D. Chulay, M.D., LTC MC

Associate: Edmund C. Tramont, M.D., LTC MC

Craig J. Canfield, M.D., COL MC

Larry D. Hendricks, Ph.D., MAJ MSC

Charles L. Pamplin, III, M.D., MAJ MC

Robert E. Desjardins, M.D., MAJ MC

Objectives: (a) To evaluate the clinical efficacy of sodium stibogluconate (Pentostam^{R}) for the treatment of cutaneous leishmaniasis.

(b) To observe for long term sequelae of cutaneous leishmaniasis and its treatment in military personnel.

Technical Approach: Patients diagnosed as having cutaneous leishmaniasis are offered treatment with sodium stibogluconate (Pentostam^{R}) either according to the standard treatment plan (manufacturer's recommended therapy for visceral leishmaniasis) or the investigational treatment plan (random assignment to one of three treatment groups: group A, single daily dose; group B, loading dose followed by continuous 24 hour drug infusion; group C, loading dose followed by three equally spaced doses per day). Each course of therapy consists of 10 mg/kg/day (maximum 600 mg/day) for 10 days. Patients are evaluated by clinical appearance of lesions and cultures of lesions. Evidence of toxicity is obtained by monitoring CBC, urinalysis, SMAC-20, and chest x-ray weekly, and EKG daily. For the first five patients in each group of the investigational treatment plan, blood is obtained at intervals for measurement of drug levels to determine the pharmacokinetics of sodium stibogluconate (Pentostam^{R}).

Patients will be reevaluated by interview, physical examination and culture of lesions three months and one year following treatment. A questionnaire is being developed for follow-up by mail yearly thereafter.

Progress and Results: An additional 6 patients have been enrolled in the project during FY-79, bringing the total to 23 patients. The geographic origin of infection for these patients was: Panama, 18; Brazil, 2; Iran, 2; Kenya, 1.

A total of 17 patients volunteered for the investigational treatment plan and were randomly assigned to treatment A (a single daily dose, 4 patients), treatment B (a continuous 24 hour infusion, 6 patients), or

treatment C (three equally spaced doses per day, 7 patients). All patients in group A, 4 of 6 patients in group B, and 6 of 7 patients in group C had clinical healing of their lesions and negative cultures for leishmania after a single ten day course of therapy. One patient in group B had improvement in the appearance of lesions but culture 3 days after finishing treatment was still positive. He was retreated (treatment A) with further healing and negative cultures immediately after and 3 months after therapy. Another patient in group B had slow clinical healing but with negative cultures during the month after therapy. A culture 6 months later was again positive, and he received treatment C, and cultures up to 3 months after therapy have remained negative. One patient who had a very large, deep ulcer, had a positive culture after treatment C. Culture remained positive after treatment B, but was negative after treatment A. There was progressive clinical improvement in his lesion, and at follow-up 1 month after his last treatment, culture is negative and the lesion appears clinically healed.

The response rate (clinical healing with negative cultures after one course of therapy) was not significantly different between any two groups ($p > 0.005$, Fisher's exact test).

Six patients elected treatment with the standard treatment plan. One of these, the only patient who was treated on the basis of exposure history and a compatible clinical picture but without a positive culture, failed to respond to two 10 day courses of therapy. His lesions persisted more than a year, and eventually was diagnosed as having prurigo nodularis which improved with topical steroids and excision of the larger nodules. Four patients were cured, three with a single course and one with three courses of therapy. The remaining patient, a 7 year old girl who acquired disease in Kenya, failed to improve after 5 courses of Pentostam^{R} (3 here and 2 in Canada). She subsequently received local heat therapy, and 2 months later her lesion healed and became culture negative.

Side effects occurring in the 15 patients who have completed therapy were: no side effects in 10; headache in two; and skin rash, local phlebitis, tinnitus, blurred vision, diarrhea and epigastric discomfort in one each. Abnormal laboratory tests were limited to transient elevation of SGPT in two patients and serum triglycerides in one patient. There were no apparent changes in electrocardiograms.

Sixteen patients have been seen for follow-up evaluation at least three months after treatment, and another two patients one month after treatment (or retreatment). All were clinically well with healed lesions and negative cultures.

Blood samples from 12 patients (4 in each group) have been assayed for antimony levels. Peak whole blood levels after an initial 600 mg dose were 13-22 mcg/ml. Drug elimination best fit a 3 compartment model. An initial distribution phase, accounting for 20% of the area under the curve,

Work Unit No.: 1909

Title of Project: Immunological evaluation of patients with cutaneous leishmaniasis

Investigators:

Principal: Jeffrey D. Chulay, M.D., LTC MC

Associate: David J. Wyler, M.D.
Edmund C. Tramont, M.D., LTC MC

Objectives: To study antigen-specific and nonspecific humoral and cellular immune responses in patients with cutaneous leishmaniasis.

Technical Approach: Patients with suspected or documented cutaneous leishmaniasis are asked to volunteer to have 50 to 200 ml. of blood obtained by venipuncture for in vitro tests of their immune status. These tests include lymphocyte transformation in response to mitogens and antigens, lymphokine generation, intracellular parasite growth in cultivated monocytes and assessment of "helper" and "suppressor" activity.

Progress and Results: A total of eight patients were studied since the inception of this investigation. This included five with cutaneous leishmaniasis acquired while soldiers were undergoing jungle warfare training in Panama, one who acquired cutaneous leishmaniasis while posted in Iran, and a young girl (Canadian diplomat's daughter) referred to WRAMC who acquired a cutaneous lesion in northern Kenya.

Three of the eight patients had significant in vitro lymphoproliferative responses to leishmanial antigens prior to therapy (stimulation index > 2 with 1 ug/ml of antigen). When tested two weeks to six months after treatment two additional patients developed significant responses, and one patient with significant pre-treatment responses markedly increased these responses after treatment. In the two patients who developed responses after treatment, there was an associated appearance of ulceration of the papules which characterized these mild infections.

Additional studies revealed that in four of six patients so tested, cultivation of peripheral blood lymphocytes in the presence of fetal calf serum resulted in greater anti-leishmanial proliferative response than when these cells were tested in the presence of autologous plasma. In one patient, there were no differences observed. In another patient, responses to 10 ug/ml antigen were greater in FCS but responses to 1 ug/ml antigen less in FCS than in autologous plasma.

Conclusions: These preliminary studies suggest possible modulation of T-cell responsiveness during the evolution of the disease, and raise the possibility that serum factors may play a role in this modulation.

Funds Utilized FY-79: $2000.00

Funds Requested FY 80: $5000.00

Publications: None

Type of Report: Interim.

Work Unit No.: 1909

Title of Project: Immunological evaluation of patients with cutaneous leishmaniasis

Investigators:

Principal: Jeffrey D. Chulay, M.D., LTC MC

Associate: David J. Wyler, M.D.
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Conclusions: These preliminary studies suggest possible modulation of T-cell responsiveness during the evolution of the disease, and raise the possibility that serum factors may play a role in this modulation.

Funds Utilized FY-79: $2000.00

Funds Requested FY 80: $5000.00

Publications: None

Type of Report: Interim.

Addendum: Because of personnel reassignments, the list of investigators for FY-80 will be:

Principal: Charles N. Oster, M.D., MAJOR, MC

Associate: Franklin A. Neva, M.D.
Eskild A. Petersen, M.D.
National Institutes of Health
Edmund C. Tramont, M.D., LTC, MC
Jeffrey D. Chulay, M.D., LTC, MC

Annual Progress Report for Work Unit #1909

Addendum re: Budget increase

In FY-79 a total of only eight patients were studied. Since January 1980, when I became the Principal Investigator on this protocol, I have already studied seven patients. I anticipate continued increased activity under this protocol for the remainder of the fiscal year.

Immunological studies of our patients with leishmaniasis are very important. Leismaniasis is a disease which, like leprosy, may evoke host responses ranging from virtually none at all to very strong reactions; prognosis in individual cases is directly related to thi- ability of the host to mount an effective immune response.

In my limited experience treating WRAMC patients, I have already had two that did not respond to conventional chemotherapy (pentavalent antimonials). Both of these patients, when tested immunologically, responded poorly to leishmanial antigens. In my view, it is imperative that we continue to study our patients, not only to advance our basic knowledge of the immunology of leishmaniasis, but also to be able to monitor patients, such as these two, that develop suboptimal immunity and respond poorly to chemotherapy. Only with adequate immunologic data will we be able to formulate novel approaches to treatment of the unresponsive patient (i.e. transfer factor, levamisole), and be able to monitor our therapy to see if, in fact, it is benefitting the patient.

Funding requirements for these immunological studies is modest, as we require no major equipment, no new personnel, etc., in order to continue our work. However, we do have need to purchase expendable supplies, and it is for these that we requested additional funds. It costs about $100.00 to study one patient one time. Therefore, with $2,000.00 we could only study twenty patients one time, and fewer if we did serial studies (which are especially important in following patients who respond poorly to chemotherapy,as noted above). With the $5,000.00 requested, we would have the needed capability to study our expected patient population adequately.

Charles N. Oster

CHARLES N. OSTER, M.D.
MAJOR, MC
Infectious Disease Service

WORK UNIT NUMBER: 1910

Title: Longitudinal Survey of Candida Serology and Antigenemia with Special Reference to Dissemination.

Investigator: J. Bruce McClain, M.D., CPT MC

Objective: To observe the natural history of Candida serology and antigenemia in the altered host to determine the predictive value and significance of these laboratory procedures.

Progress and Results: Due to the PCS of the principal investigator, no work was done on this protocol.

Conclusion: In the absence of Dr. McClain, this protocol should be terminated.

Funds Utilized, FY 79: $2400.00

Funds Required, FY 80: None

Publications: None

Type of Report: Terminal

Work Unit No.: 1911

Title of Project: In Vitro inhibitory activity of a series of 2-Acetylpyridine thiosemicarbazones toward a group of clinically significant bacterial genera.

Investigators:

Arthur Dobek, Ph.D.
Edmund Tramont, M.D., LTC, MC
Daniel Klayman, Ph.D.

Progress and Results: A total of 67 compounds were tested of which 25 were N^4-monsubstituted, 25 were N^4-disubstituted, 9 were thiosemicarbazone derivatives other 2-acetylpyridines and 7 were miscellaneous compounds related to the 2-acetylpyridine thiosemicarbazones. These compounds were used to determine MIC values of selected bacterial isolates described in the protocol.

Table 1 lists the most effective compounds tested and the MIC range for each group of isolates. Table 2 lists the molecular structures of these compounds.

Conclusions:

1. Of the 67 compounds tested 35 were found to be effective against one or more genera of bacteria.

2. The heterocyclic N^4, N^4-disubstituted group shows the most universal inhibitory activity especially compound 48, and was the largest group with 17 compounds. The least inhibitory activity was in the N^4-monosubstituted and in the miscellaneous related compounds groups (A and E).

3. None of the compounds were very inhibitory toward the gram negative enteric microorganisms (Pseudomonas, Klebsiella, Shigella, E. coli, Proteus).

4. Inhibitory activity toward S. aureus and gp D enterococcus was primarily confined to the N^4, N^4-disubstituted heterocyclic group and the thiosemicarbazone derivatives of other 2-acetylpyridines. Inhibition of S. aureus did not necessarily imply inhibition of gp D enterococcus (8 compounds inhibited both, 6 compounds only one or the other) although they are both gram positive.

5. The greatest inhibitory activity, i.e. lowest MIC, occurred with the two Neisseria species, and involved the same compound groups associated with the gram positive genera.

6. Of the effective monosubstituted and noncyclic disubstituted groups (groups A and B), 7 of 9 are methyl, ethyl or cyclohexyl substitutions of the thiosemicarbazone derivatives. Of other 2-acetylpyridines (group D) all have at least one ethyl or methyl substitution. The effective disubstituted heterocyclic compounds (Group C) and the miscellaneous related compounds (group E) all have at least one ring containing nitrogen as the substitution. Future investigation will involve primarily compounds with such substitutions.

Table 1

MOST INHIBITORY

Organisms (no. of isolates)	A				B					C															
	1	2	18	23	25	26	27	29	30	32	33	34	35	36	39	40	41	42	43	44	45	46	47	48	49	50
S. aureus (5)				x			x		x		x			x									x	x		
gp D enterococcus (5)									x		x												x	x	x	
Pseudomonas (5)						x	x	x	x	x			x	x		x							x	x		x
Klebsiella (5)																								x		x
Shigella (4)	x	x			x	x		x		x	x	x	x	x	x	x						x		x	x	x
E. coli (1)	x				x		x	x	x	x	x	x	x	x	x	x					x	x	x	x	x	x
Proteus (5)					x	x	x	x	x	x		x	x	x	x						x			x		
N. meningitidis (5)					x	x		x			x		x					x	x		x					x
N. gonorrhoeae (34)			x		x	x				x	x		x			x		x	x	x	x					x

A: N^4-Monosubstituted
B: N^4, N^4 - Disubstituted (noncyclic)
C: N^4, N^4 - Disubstituted (heterocyclic)
D: Thiosemicarbazone derivatives of other 2-acetylpyridine
E: Miscellaneous related compounds

OMPOUNDS

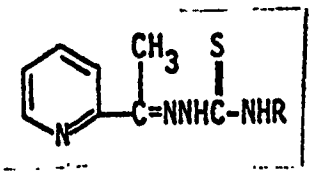
D								E	MIC range (ug/ml)
51	52	53	54	55	56	57	58	65	
		x		x	x	x	x		.125–1 (.5)*
	x	x		x		x	x		.25–2 (.5)*
	x	x	x	x		x		x	64–128 (128)*
									64–128 (128)*
x	x		x	x		x	x		32–256 (64)*
x	x		x	x	x	x	x	x	32–128 (64)*
x	x	x	x	x					64–128 (128)*
	x	x	x	x	x	x			.015–.125 (.031)*
x			x		x				.002–.062 (.031)*

* Majority of MIC=( )

Table 2

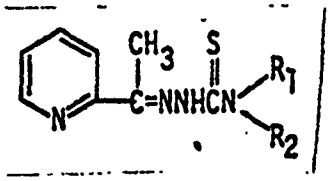
Molecular Structures of Compounds in Table 1

A



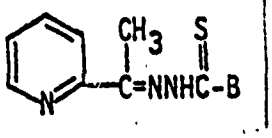
R
1. CH_3
2. C_2H_5
18. $4ClC_6H_4$
23. cyclohexyl

B



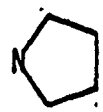
	R_1	R_2
25	CH_3	CH_3
26	C_2H_5	C_2H_5
27	isobutyl	isobutyl
29	CH_3	cyclohexyl
30	CH_3	cyclooctyl

C

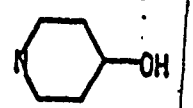


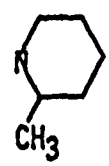
B

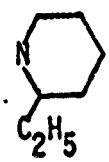
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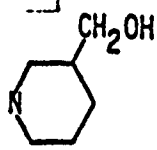
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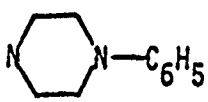
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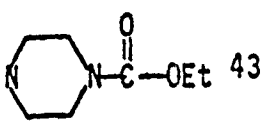
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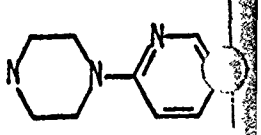
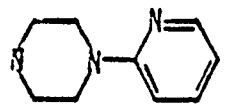
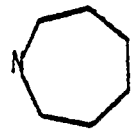
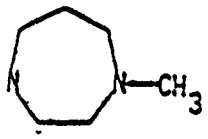
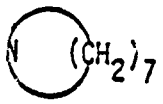
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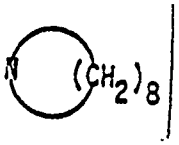
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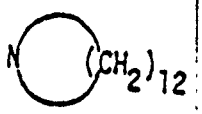
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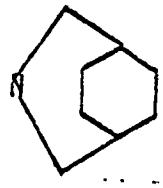
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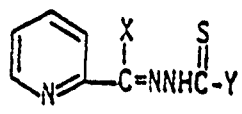
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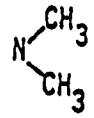
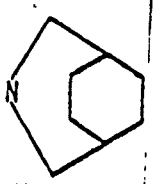
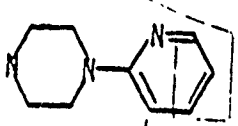
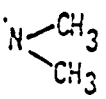
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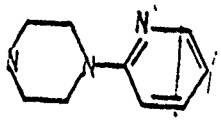
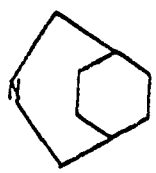
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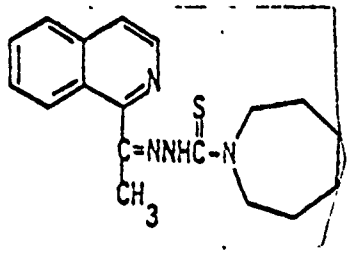
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	X	Y
51	C_2H_5	
52	C_2H_5	
53	C_2H_5	
54	C_2H_5	
55	$CH(CH_3)_2$	
56	$CH(CH_3)_2$	

	X	Y
57	$CH(CH_3)_2$	
58	$CH(CH_3)_2$	

E

65 

Funding Requirement FY-79:

Funding Requirement FY-80: $10,000.

Publications:

Dobek, A.S., Klayman, D.L., Tramont, E.C. (Abstract) In-vitro of Neisseria gonorrhoeae and thiosemicarbazones. ASM Los Angeles, CA, 1979.

Nature of Report: Interim.

Funding Requirement FY-79:

Funding Requirement FY-80: $10,000.

Publications:

Dobek, A.S., Klayman, D.L., Tramont, E.C. (Abstract) In-vitro of Neisseria gonorrhoeae and thiosemicarbazones. ASM Los Angeles, CA, 1979.

Nature of Report: Interim.

Additional information/clarification on Work Unit #1912

a. There were no subjects studied in FY-79. This protocol was for the development of an assay for vancomycin, and as such, required only laboratory work. A follow-up protocol will be submitted to study the clinical pharmacology/toxicology of vancomycin using this assay.

b. Funding is required for this project for FY-80 so that this new, rapid assay for vancomycin can be studied further. Two objectives should be met before this work unit is concluded:

1. Development of an internal stardard. This would increase the accuracy and reproducibility of the assay, and shorten the time required for reporting the results to attending physicians when patient samples are assayed.

2. More comprehensive studies are needed to determine if other antibiotics or commonly used pharmaceuticals will interfere with this assay.

3. Estimated date of completion - 31 March 1980.

Type of report: Interim

Work Unit No.: 2000

Title of Project: The Effects of Gastric Surgery on the Release of Pancreatic Polypeptide

Investigators:

Principal: John W. Harmon, MAJ, MC

Associate: Lawrence Johnson, COL, MC
Daniel Rosenthal, COL, MC
Ian Taylor, MD
Richard Hirata, COL, MC

Objectives: To determine the roles of the vagus nerve and the antrum of the stomach in the release of pancreatic polypeptide into the blood from the pancreas.

Technical Approach: To compare meal stimulated serum pancreatic polypeptide values in patients before and after surgery on the stomach.

Progress and Results: Serum samples were collected from 15 patients in anticipation of surgery. Thirteen patients have had surgery of whom 8 have had repeat collection of serum samples. Dr. Harmon will bring the samples to Los Angeles for measurement of serum pancreatic polypeptide in April 1980 when he goes to present a paper at the FASEB meeting in Anaheim.

Conclusions: Satisfactory progress has been made in collecting specimens. No unexpected problems have arisen. The protocol has not interfered significantly with patient care.

Funding requiresments:

FY 1979 - none
FY 1980 - Travel for meeting at Center for Ulcer Research and Education to discuss progress of the project and future plans $600.00

Publications: Taylor, IL, Harmon, JW, Trout, HH, Walsh, JH: The effect of antrectomy on the pancreatic polypeptide response to food. Gastroenterology 76:1259, 1970.

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 N. Rich, MC
Associate: LTC George J. Collins, Jr., MC, and LTC Paul T. McDonald, MC

An annual report for our long term follow-up of vascular patients cannot be written this year because funding ceased.

R&D Command Headquarters has not responded to previous communications over the last eighteen months.

The project will have to be terminated.

Work Unit No.: 2104

Title of Project: Evaluation of the Efficacy of Suppressing Platelet Activity in Patients with Intermittent Claudication

Investigators:

Principal: LTC George J. Collins, Jr.

Associate: MAJ Salvatore Scialla, COL Norman M. Rich, MAJ Earl Ferguson, MAJ Patrick Clagett, and Mr. Charles Barr

Objectives:

1. To determine the relative effectiveness of several platelet active drugs in suppressing in vivo and in vitro platelet function.

2. To determine whether or not these drugs cause a lowering of coagulation factors.

3. To determine if suppression of platelet function in patients with intermittent claudication results in objective improvement in exercise tolerance.

Technical Approach: Patients ranging in age from 40 to 70 years of either sex with intermittent claudication documented by lowering of ankle pressure after exercise have been randomized into four treatment groups. One treatment group receives placebo, one receives 600 mg per day of aspirin, one receives 600 mg per day of aspirin and 100 mg per day of persantine and one receives 200 mg of sulfinpyrazone four times daily. Patients have a full coagulation screening battery including prothrombin time, activated partial thromboplastin time, fibrinogen, factors II, V, VII-X, VIII antigen, IX, X, XI, XII, antithrombin III, fibrin split products, and protamine sulfate para-coagulation. The tests are done before taking medicines, after being on medications for two weeks, after being on medications for two months, and after being on medications for six months. In addition to this, patients have arm and ankle pressures before and after treadmill exercise at the same time intervals.

Progress & Results: The study continues to go along quite well. So far, 98 patients have been entered into the study. Sixty of these have completed the study. The remaining 38 have to have one or more subsequent clinic visits and/or laboratory determinations. Still, only one patient had to drop out of the protocol because of a difficulty with the medications.

Conclusions: The study is on-going and no conclusions can be drawn at this time.

Funds Utilized, FY-78: $2,640.00

Funding Requirements, FY-79:

Supplies:	$3,000.00
Travel:	300.00
Publication costs:	$200.00
Total:	$3,500.00

Publications and Abstracts FY 79: None

Estimated Date of Completion: It is estimated that the project will be completed by 30 June 1980.

Type of Report: Interim

Work Unit No.: 2105

Title of Project: Rapid Screening for Coagulation Abnormalities

Investigators:

Principal: LTC George J. Collins, Jr.

Associate: Donald Christopher, LTC Daniel Kimball, COL Norman M. Rich, MAJ Salvatore Scialla, and Mr. Charles Barr

Objectives: To develop techniques whereby sizable numbers of patients can be screened for hypercoagulability. The objective of the study is to be able to screen as many as twenty patients per day.

Technical Approach: Patients from the Peripheral Vascular Surgery and Hematology/Oncology Clinics with suspicion of hypercoagulability will have coagulation screening batteries and thromboelastography performed. In addition, twenty healthy volunteers will be examined. After the determinations are made, the results of thromboelastography will be compared to the results of the screening battery. If the results of thromboelastography agree with the results of broad screening with coagulation tests, thromboelastography will then become the principal mode of screening.

Progress & Results: All equipment for the project has been purchased. So far, the entire battery of patients has had thromboelastography. A date in January has been established to perform the expanded coagulation battery on specimens that have been saved. Presently, we are totally out of reagents to perform these tests and will not be able to purchase them until FY-80 funds are made available. A total of twenty controls and fifty patients as outlined in the original protocol have been studied.

Conclusions: Firm conclusions regarding the accuracy of thromboelastography cannot be made since the coagulation batteries have not yet been performed. However, it can be stated that this is an extremely easy test to perform. Some extremely interesting patterns suggesting hypercoagulability have been identified in a number of patients.

Funds Utilized, FY-80: $1,287.95

Funding Requirements, FY-79:

Supplies:	$1,500.00
Travel:	$300.00
Publication Costs:	$200.00
Total:	$2,000.00

Publications and Abstracts FY-79: None

Estimated Date of Completion: 1 May 1980

Type of Report: Interim

Work Unit Number: 2106

Title of Project: Management of the Hemodynamically Significant, Asymptomatic Carotid Bruit

Investigators:

Principal: MAJ G. Patrick Clagett

Associates: LTC George J. Collins, Jr.
COL Norman M. Rich
LTC James M. Salander
MAJ Michael J. Spebar

Objectives: (1) To determine the most appropriate management of patients with asymptomatic, hemodynamically significant carotid bruits, (2) To determine the natural history of asymptomatic extracranial vascular disease; (3) To determine the role of non-invasive diagnostic techniques in the management of patients with asymptomatic extracranial vascular disease.

Technical Approach: Consenting patients who are asymptomatic for cerebrovascular disease who have hemodynamically significant carotid stenoses (as determined by non-invasive studies) are eligible for randomization into two groups. Patients ineligible for randomization include those who have had carotid endarterectomy on the side in question, those judged too frail to undergo carotid endarterectomy, and those who don't consent. Patients randomized into the surgical group will undergo arteriography and carotid endarterectomy if an operable lesion is found. Patients randomized into the second group will be treated with aspirin, 650 mg twice daily, and followed closely (every 3 months). If patients in the second group develop symptoms, they will then undergo arteriography and carotid endarterectomy.

Progress and Results: Since April 1979, 15 patients eligible for entry have been identified. Of these, 11 have consented to join the study and 4 have refused. Of those who have entered, 7 were randomly assigned to the aspirin group. They have been followed for an average of six months (range 3-9 months). All have remained asymptomatic for cerebrovascular disease and there have been no complications of aspirin therapy. There has been one death from myocardial infarction. In the surgical group (4 patients), 2 have undergone uneventful arteriography and carotid endarterectomy and one is awaiting admission for arteriography in anticipation of endarterectomy. One patient became symptomatic (amaurosis fugax) in the interval between entry into the study and admission to the

hospital. He underwent arteriography and suffered a probable analyphylactic response to contrast agent and probable myocardial infarction. He is currently considered unable to undergo surgery and is being followed as an outpatient. He is on aspirin and is presently asymptomatic for cerebrovascular disease. The 4 patients who refused entry are being followed and treated with aspirin and they remained asymptomatic.

Conclusion: The number of patients is too small and the follow-up period too brief to draw any conclusions. The study will probably have to be continued for 4-5 years to reach meaningful conclusions.

Funding Requirements: None.

Publications: None.

Type of Report: Interim.

Work Unit Number: 2107

Title of Project: Perioperative Thrombosis Prophylaxis in Patients with Peripheral Vascular Disease

Investigators:
Principal: Maj. Michael J. Spebar

Associate: LTC. George J. Collins, Jr.
COL. Norman M. Rich
LTC. Isamn Y. Kang
MAJ. G. Patrick Clagett
LTC. James M. Salander

Objectives: To determine the efficacy and safety of low-dose heparin prophylaxis of deep venous thrombosis in patients undergoing peripheral vascular surgery.

Technical Approach:
Those patients scheduled for a surgical procedure by the Peripheral Vascular Surgery Division were asked to participate in this study after informed consent. Volunteers were then randomly assigned to recieve perioperative, low-dose heparin (5,000 units subcutaneous, twice daily). Both groups received 100 microcuries of I^{125} labeled fibrinogen. Their lower extremities were scanned daily for approximately one week.

Progress & Results:
All necessary equipment has been purchased and is operational. A feasibility study was conducted in May and June 1979 which involved eight patients. A group of one hundred patients, to comprise the study group, was begun in September 1979. To this date, 20 patients have participated, but 7 of these were eliminated due to cancellations of proposed surgical procedures or surgical complications. At present, funds to continue purchase of the isotope labeled fibrinogen are exhausted.

Conclusions: No firm conclusions can be drawn from the data in this early phase of the study. At present rate of patient volunteer participation, three years will be required to accumulate the necessary one hundred patients.

Funds Utilized, FY-78:	$6,000.00
Funds Required, FY-79:	
Supplies:	$5,500.00
Travel:	$300.00
Publications	$200.00
Total:	$6,000.00
Estimated Completion:	1 January, 1983

Type of Report: Interim

Work Unit No.: 2306

Title of Project: Clinical Quantification of Intraocular Malignant Melanoma Volume

Investigators:

Principal: Kenyon K. Kramer, LTC, MC, USA

Objective:

To develop a technique to quantitate the size of intraocular malignant melanomas in vivo, since this is an important prognostic and management parameter.

Technical Approach:

A and B Scan ultrasonography after the method of J. Coleman, M.D., will be used to measure intraocular malignant melanoma in vivo. The Bronson Turner ultrasound device will be used in a similar manner. Dimensions obtained from the histopathology and report will be used to evaluate the accuracy of the ultrasound devices.

Progress and Results:

Five additional lesions have been measured in vivo and have come to histopathology with the following results:

4th Report

Single Longest Dimension
% Error

	Coleman		Bronson Turner
14	+100		+14*
15	+5		-19
16	+7		
17			-2
18	+69		
	+45	Mean Algebraic % Error	+40
	+45	Mean Absolute % Error	+53

Conclusions:

A reanalysis of the total series of eighteen cases suggests that tumor location has a significant effect on the accuracy of the ultrasound measurements. No improvement in accuracy has been achieved over the past year.

Serious or Unexpected Side Effects: None

Funds Utilized FY 79: None

Funding Requirement FY 80: None

Publications: None

Estimated Date of Completion: Six months

Type of Report: Interim

WORK UNIT NUMBER: 2308

TITLE: Scleral Buckling for Retinal Detachment 1973-1976.
A Retrospective View

PRINCIPAL INVESTIGATOR: Cary L. Burton, CPT, MC

OBJECTIVES: The purpose of this clinical review, therefore, is to present our experience in scleral buckling and to draw some conclusions from our experience.

TECHNICAL APPROACH: Attempts will be made to create a listing of all cases, to include demographic information, diagnosis, indications for surgery, hard preoperative data (fundus drawings, etc.), surgical procedures performed (to include type of element utilized, method of placement, drainage versus nondrainage), complications of surgery and postoperative results with specific interest on resultant visual acuity as compared to degree of detachment preoperatively.

Attempts will also be made to obtain follow-up data on as many patients as possible, This will be accomplished by contacting the patients themselves, their referring physicians, or both.

Arrangements will be made for as many patients as possible to undergo a follow-up exam at WRAMC. If this is not feasible, the patient will be requested to visit the nearest Army Medical facility for a follow-up examination by an ophthalmologist. A questionnaire will be devised to provide the examiner with guidelines so that base-line data for the study will be obtained.

PROGRESS AND RESULTS: Dr. Burton is continuing with the review of inpatient records following Dr. Pomerance's completion of residency. A preliminary report based on the first 60 cases reviewed by Dr. Pomerance was presented to the Walter Reed Postgraduate Ophthalmology Course. Completion of the addition record review is anticipated by April 1980 and a supplementary report will be presented to the Ophthalmology Postgraduate Meeting at that time. 150 cases will be reviewed.

CONCLUSIONS: The reattachment success rate in this series is currently identical to that reported in other published series. There have been no unexpected side effects or complications.

FUNDS UTILIZED, FY79: None

FUNDS REQUESTED, FY80: None

PUBLICATIONS & ABSTRACTS, FY79: None

ESTIMATED DATE OF COMPLETION: April 1980

Type of Report: Interim

Work Unit No.: 2309

Title of Project: A Study of Eye Trauma and Treatment in the Military

Investigators:

Principal: Howard P. Cupples, CAPT, MC, USN

Associate: Paul V. Whitmore, LTC, MC, USA

Objectives:

1. To determine the role of vitreous surgery in the management of ocular trauma.

2. To compare the results of ocular trauma cases managed by vitreous surgery with the results of ocular trauma cases managed in the past by convential methods.

3. To use animal studies in order to refine vitreous surgery techniques and to develop new approaches to problems in the management of ocular trauma.

4. To develop plans for the efficient management of ocular combat injuries based upon the analysis of data collected during the study.

Technical Approach:

A series of 100 cases of ocular trauma managed by vitreous surgery techniques will be compared with a similar series drawn retrospectively from records of NNMC and WRAMC during the Vietnam era and managed by conventional surgical techniques.

Progress and Results:

To date, thirty-two (32) cases of ocular trauma have been managed at Walter Reed Army Medical Center using vitreous surgery techniques. Fifty-six (56) cases have been completed at NNMC, Bethesda, bringing the combined series to eighty-eight (88) at this time. It is anticipated that the series of 100 cases will be completed in the next year. The retrospective study of Vietnam era cases has been begun.

Conclusions:

Conclusions as to the effectiveness of vitreous surgical techniques will be reviewed at this time, until comparison can be made with the group treated by conventional surgery. No serious unexpected side effects to vitreous surgery have been found.

Funds Utilized FY 79: None

Funding Requirements FY 80: None

Publications: No additional publications during FY 79

Type of Report: Interim (Annual)

Work Unit No.: 2310

Title of Project: Intraocular Lenses

Investigators:

Principal: LTC Kenyon K. Kramer, MC

Associates: COL Floyd L. Wergeland, Jr., MC

CPT Donald J. Bergin, MC

Objectives: To evaluate intraocular lenses with regard to safety in the treatment of aphakia

Technical Approach: Intraocular lens will be implanted in selected patients either at the time of cataract extraction or at a second operation following the cataract extraction. This is part of a nationwide collaborative study to determine the incidence of adverse effects.

Progress and Results: 20 eyes in 19 patients have had lens implants or attempted lens implants. One patient has suffered an adverse effect, i.e. a hyphema with delayed resolution. The lens has been removed. The residual pupillary membrane is to be removed at surgery.

Conclusions: The generally good results (95%) indicate sufficient value to continue with this protocol.

Serious or Unexpected Side Effects/Complications: The adverse result listed in "Progress and Results" is not an unexpected complication.

Funds Utilized, FY-1979: $4300

Funding Requirements, FY-80: $6000 for intraocular lenses

Publications: None

Estimated Date of Completion: One year. (FDA will determine termination date)

Type of Report: Interim

Work Unit No.: 2312

Title of Project: Corneal Endothelial Cell Loss Following Various Cataract Extraction Techniques

Investigators:

Principal: CPT R. Jeffrey Bergquist, MC

Associates: N/A

Objectives: To compare the difference in endothelial cell damage between two techniques of cataract extraction.

Technical Approach: Pre and postoperative photographs are taken of the patient's corneal endothelial. Cell counts and size are the parameters of damage in comparing the surgical techniques. The photos are taken by the specular corneal endothelial microscope in a manner similar to the routine glaucoma test by applanation tonometry.

Progress and Results: To date, 2 patients have been studied with a total goal of 15 standard cataract patients and 10-15 small incision cataract patients. There are no investigational drugs being used. There have been no modifications in the protocol.

Conclusions: Statement of results deferred until more data obtained. There have been no complications or deleterious effects from this study, nor are any anticipated.

Funds Utilized, FY-1979: $65.00

Funding Requirements, FY-1980: None

Publications: None

Estimated Completion Date: May 1980

Type of Report: Interim

Work Unit #: 2400

Title of Protocol: Effect of Acute Anterior Cruciate Ligament Reconstruction in the Monkey.

Principal Investigator: LTC R. R. Protzman, MC
Hand Fellow
Orthopaedics Service

LTC Protzman has been reassigned and his project not taken up by anyone else. This project may be considered discontinued with no prospect of picking it up.

Work Unit No.: 2512

Title of Project: Effects of Hearing Impairment and Acoustic Filtering on the Perception of Speech

Investigators:

Principal: Brian E. Walden, Ph.D.

Associate: Allen A. Montgomery, Ph.D.
Daniel M. Schwartz, Ph.D.
Robert A. Prosek, Ph.D.

Objectives: 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 have been obtained for 13 adults with unilateral hearing impairments. The consonants were presented without any external distortion to the impaired ear. For the normal ear, however, the stimuli were presented through a multi-filter network which was adjusted to match the configuration of the hearing loss in the impaired ear. In addition, pairs of consonants were presented sequentially to the two ears for judgment of consonant similarity using an equal appearing interval scale. The resulting data were analyzed to reveal which consonants (and classes of consonants) are perceived differently through the impaired ear and the filter network. As a check on the validity of the supra-threshold audiogram matching procedure, consonant confusion matrices have been obtained for 6 normally-hearing adults. Frequency distortion of varying amounts were introduced into the audio circuit to one ear via two passive band-pass filters. The multi-filter was then used to match the frequency distortion in the opposite ear using the audiogram matching procedure. Frequency responses of the two filter networks were obtained in order to compare them for similarity, and consonant confusion matrices were obtained for both ears.

Progress and Results: Data were obtained for six normally-hearing subjects and 13 unilaterally impaired subjects. It was intended that additional subjects would be run. A breakdown in the spectrum shaper, however, prevented further data acquisition. Data for 5 of the 13 unilaterally impaired subjects had to be discarded because the nature of their hearing impairments (i.e., flat audiometric configurations) resulted in very few confusions in the normally-hearing ear when listening through the multi-filter. As a result, standard analyses could not be applied to these matrix data. The confusion matrix data for the normally-hearing subjects and the hearing impaired subjects were analyzed

via INDSCAL and KYST multidimensional scaling programs to derive the underlying perceptual features. The features derived from the multidimensional scaling analysis were then used as criterion dimensions for the SINFA analysis of the confusion matrices for each subject. Since all ears were treated separately, the resulting data consisted of a SINFA analysis of 28 confusion matrices - 16 for the 8 hearing impaired subjects and 12 for the 6 normally-hearing subjects. Crossed products between the feature weights for each ear and every other ear were computed. These data, as well as additional recognition data, were analyzed to determine which consonants and features were perceived differently through the impaired ear and the normal ear listening through the multi-filter.

Conclusions: See attached manuscript.

Funds Utilized, FY-79: None

Funding Requirements, FY-80: Reprint costs.

Publications: The results of this experiment were presented at the joint meetings of The Acoustical Society of America and The Acoustical Society of Japan meeting in Honolulu, in November, 1978. A manuscript based on this research was submitted to the Journal of Speech and Hearing Research and has been accepted, pending minor revisions to the manuscript.

Type of Report: Final

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 the California Consonant Test (CCT) as a tool in clinical hearing aid evaluation on the population with limited high-frequency hearing loss.
Assessment of benefit of amplification for individuals with hearing loss limited to frequencies above 2000 Hz.

Technical Approach: Completed

Progress & Results: Three pilot studies have been presented as papers at different national and international scientific meetings. Two of these papers have also been published in the scientific literature and the third manuscript is in final stages for submission for publication. The last stage of this study is nearly completed. All the data have been collected and a paper submitted and accepted for presentation at the American Speech and Hearing Association Convention this November in Atlanta, GA. The results show that the CCT is not an effective tool in clinical hearing aid evaluation procedure for individuals with limited high-frequency hearing loss. Follow-up evaluation using two questionnaires assessing daily usage and subjective benefit suggest that many of these individuals with limited hearing loss benefit from amplification.

Conclusions: The results suggest that extended high frequency amplification can be beneficial for at least some individuals with limited high-frequency hearing loss who experience hearing handicaps. In light of these findings hearing aid use should be considered but clinical assessment of benefit needs further exploration.

Funds Utilized: FY-77: Travel to Chicago, ILL, in Nov., 1977 for paper presentation.
FY-78: None.
FY-79: Purchase of reprints for one publication, the other one was purchased by the authors.

Funding Requirements: FY-80: Travel: Presentation of paper in Atlanta, GA November, 1979 (copy of acceptance letter attached).

Publications: Schwartz, D.M., Surr, R.K.: Three Experiments on the California Consonant Test, J. Speech Hear Disord., February, 1979.
Schwartz, D.M., Surr, R.K. et al: Performance of High Frequency Impaired Listeners with Conventional and Extended High Frequency Amplification, Audiology, 18, 1979.

Copies of the above have been forewarded to CIS.

Type of Report: Interim.

AMERICAN SPEECH-LANGUAGE-HEARING ASSOCIATION
10801 Rockville Pike
Rockville, Maryland 20852

EXTENDED HIGH FREQUENCY...
Rauna K. Surr
Walter Reed Army Medical Center
Washington, D.C. 20012

Dear Colleague:

On behalf of the Program Committee for the 1979 American Speech-Language-Hearing Association Convention, it is my pleasure to inform you that your proposal, which is referenced above, has been accepted as a traditional platform presentation. It has been scheduled as follows:

SA-22, Sat., Nov. 17, 2:00 pm
Marriott-North BR

The coordinator for your session will be: Angela Loavenbruck

Please note that the standard audiovisual equipment to be provided in Atlanta will include a 2X2 projector, an overhead projector, an appropriate screen, and a microphone. No additional equipment will be provided unless you requested it when your proposal was submitted, and unless it is noted below.

Please remember that the standard time limit for your presentation will be ten (10) minutes. If you requested a longer presentation time, and if your request was approved, your time limit will be noted below.

The September, 1979, ASHA magazine will carry more details regarding placement of your presentation in the Program and your proposal's abstract. We will not be sending additional notices to your co-authors (if any), and ask that you please notify them of the acceptance of your proposal.

We wish to thank you for your interest in participating in the 1979 Program and feel that your presentation will have a significant impact on its quality. If you have any questions, please do not hesitate to call me or Heather Murphy at (602) 626-4606.

Sincerely,
Ted Glatthe
Theodore J. Glatthe
1979 Program Chairman

Audiovisual:

Time:

TP

Work Unit No.: 2517

Title of Project: Evaluation of a Specialized Technique for Training Audiovisual Integration in Hard-of-Hearing Patients

Investigators:

Principal: Allen A. Montgomery, Ph.D.

Associate: Brian E. Walden, Ph.D.
Daniel M. Schwartz, Ph.D.
Robert A. Prosek, Ph.D.

Objective: This study is designed to evaluate the effectiveness of a newly-developed training procedure for improving patients' ability to use the audible and visible aspects of speech simultaneously.

Technical Approach: This study was divided into two parts.

Evaluation of Treatment Procedure: Part II of this study followed a standard pretest, treatment-posttest paradigm with an experimental group receiving training in AVI and a control group not receiving training in AVI.

a. Subjects: The subjects in Part II were 30 hearing-impaired patients from the inpatient Aural Rehabilitation Program in the Army Audiology and Speech Center. The patients will be assigned randomly to experimental and control groups of 15 patients each; in addition, 15 normal hearing subjects were tested to evaluate learning effects of the test.

b. Materials: The pre- and post-training materials and procedures developed in Part I of this study (reported last year) were employed.

c. Procedure: The pre- and post-training testing were conducted on all patients to obtain measures of their ability to utilize simultaneously the auditory and visual components of speech prior to and following training (or following a comparable period of nontraining for the control group and normal group).

The training in AVI was done individually without noise in ten one-hour sessions employing a two-room environment. The training was done by audiologists and speech pathologists who rotated assignments such that no patient received more than one half of his sessions from any one of the clinicians.

d. Data Analysis: The primary analysis involves the comparison of mean pre- and post-test results for the control and experimental groups. In addition, analysis is made of the learning curves of individual patients and of the errors on test items to provide insight into the nature of the learning which has taken place and the effects of training.

Progress and Results: Part II of the study, which uses the test to evaluate the effectiveness of our specialized training procedures, is nearing completion. We have trained 12 of the 15 patients needed for the experimental group and tested all of the 15 control patients. In

addition, 15 normal subjects have been tested. The results to date indicate that the technique is quite successful in improving the experimental patients' ability to perceive speech in noise, with improvement averaging 17% following training. In addition, the patients' reaction to the technique is quite favorable.

Our plans are that the new technique be incorporated into the clinical routine of the Aural Rehabilitation Section on an experimental basis. Its effectiveness and its role in the overall program will continue to be monitored there, under our guidance. We have completed the transfer of the Army Audiology and Speech Center to the New Treatment Facility and have implemented the technique in the Aural Rehabilitation Program.

Conclusions: At the present time the technique appears to be beneficial to the patients and easy to administer. Final conclusions and recommendations will be made following a clinical trial in the Aural Rehabilitation Program. The clinical trial is now in progress.

Funds Utilized, FY-79: None

Funding Requirements, FY-80: Publication and reprint charges.

Publications: A manuscript is being prepared for submission to the Journal of the Academy of Rehabilitative Audiology.

Type of Report: Interim

Work Unit No.: 2518

Title of Project: The Effects of Analytic Training on the Sentence Recognition Ability of Hearing-Impaired Soldiers

Investigators:

Principal: Brian E. Walden, Ph.D.

Associate: Allen A. Montgomery, Ph.D.
Daniel M. Schwartz, Ph.D.
Robert A. Prosek, Ph.D.

Objectives: The purpose of this investigation is to determine the effects of analytic lipreading and auditory training on the ability of hearing-impaired soldiers to recognize sentences audiovisually.

Technical Approach: The subjects of this investigation were 30 hearing-impaired soldiers selected from the inpatient Aural Rehabilitation Program of the Army Audiology and Speech Center. 20 of these subjects were assigned at random to two experimental groups of 10 subjects each, designated as the auditory and visual groups. The remaining 10 subjects constituted a control group. All subjects were administered a variety of test materials before and after a two-week training period. Test materials consisted of a 400-item test of auditory and visual consonant recognition and a 50-item test of audiovisual sentence recognition. Each of the tests were recorded on videotape and presented under controlled conditions to the subjects. The training materials consisted of 38 exercises designed to improve consonant recognition ability. The 38 exercises were graduated in difficulty with the earlier exercises having fewer consonants and only those which were easily identified by the hearing-impaired soldiers. Later exercises included a larger number of consonants, many of which were frequently confused by the subjects.

Subjects in the auditory group received a test of auditory consonant recognition and the auditory-visual sentence test before and after two weeks of analytic auditory training. Subjects in the visual group received a test of visual consonant recognition and the audiovisual sentence test before and after two weeks of analytic lipreading training. The other 10 subjects constituted a control group and received the standard two-week group-oriented Aural Rehabilitation Program but did not receive any analytic auditory or lipreading training.

Progress and Results: The results of the 400-item videotaped tests were organized into confusion matrices for each subject group. Separate matrices were prepared for the pre-training and post-training test results. These matrices were analyzed to determine the effects of training on phoneme perception. The overall correct recognition score for the sentence test was compared for the pre-training and post-training administrations for each group. This comparison revealed that the analytic training had a substantial, beneficial effect on the audiovisual sentence recognition ability of both experimental groups. The amount

of the improvement, however, was comparable for both groups, suggesting that neither analytic auditory training or analytic lipreading training was superior to the other in improving audiovisual sentence recognition ability. The results for the control group of the 10 subjects revealed that they also showed improvement in audiovisual sentence recognition ability as a result of the standard Aural Rehabilitation Program. The magnitude of this improvement, however, was approximately half that of the experimental subjects receiving the analytic training. Additional analyses were conducted on the consonant recognition data for both groups to reveal the effects of the analytic training on phoneme recognition.

Conclusion: See attached manuscript.

Funds Utilized, FY-79: None

Funding Requirements, FY-80: Reprint costs.

Publications: A manuscript based upon this research is being prepared and will be submitted to the Journal of Speech and Hearing Research within the next few weeks.

Type of Report: Final

Work Unit No.: 2520

Title of Project: The Effect of the Change of Body Position on Nystagmus during the Electronystagmography (ENG)

Investigators:

Principal: Ms. Sylvia K. Allen, M.A.

Associates: Mrs. Rauna K. Surr, M.S.
Mrs. Nan K. Lukmire, M.Ed.

Objectives: To measure how sudden shifts in patient position during the ENG procedure may induce or alter nystagmus. To correlate this nystagmus with vestibular pathology.

Technical Approach: Testing was planned to have been done in conjunction with routine patient referral for ENG. However, the project has been cancelled.

Progress and Results: After Ms. Allen left WRAMC in 1978, it was anticipated that the Associate Investigators would continue the project. However, this has not occurred, and the project has been shelved.

Conclusions: None

Funds Utilized, FY-79: None

Funding Requirement, FY-80: None

Publications: None

Type of Report: Final

WORK UNIT NUMBER: 2521

TITLE: Reaction Times of Stutterers and Nonstutterers

INVESTIGATORS: Principal: Robert A. Prosek, Ph.D.
Associate: Allen A. Montgomery, Ph.D.
Brian E. Walden, Ph.D.
Daniel M. Schwartz, Ph.D.

OBJECTIVES: a) To determine if the reaction times of stutterers and nonstutterers differ from each other for a variety of speech and non-speech activities. b) To determine if the speech reaction times of stutterers and nonstutterers differ from each other with respect to the onset of laryngeal EMG activity. c) To determine the effects of training on the reaction times of stutterers and nonstutterers.

TECHNICAL APPROACH: Recent stuttering research (Adams and Hayden, 1976; Starkweather, Hirschman and Tannenbaum, 1976; Luper and Cross, 1978; Cross and Luper, 1979; Cross, Shadden and Luper, 1979) has demonstrated simple reaction time differences between stutterers and nonstutterers in acoustic voice initiation following an acoustic or visual stimulus. The results indicate that stutterers have difficulty in promptly initiating phonation. The implication of this research for the treatment of stuttering is that fluency may be improved by improving the control of laryngeal activity as it relates to respiration and articulation (Starkweather, et al., 1976). The voice reaction time data reported to date have consisted primarily of measures of the onset of the acoustic signal. It is not known whether comparable reaction time differences exist between stutterers and nonstutterers at other levels of the phonatory mechanism. The purpose of the present study was to examine the reaction times of stutterers and nonstutterers using acoustic and laryngeal-region surface electromyographic (EMG) measures. In addition, manual and lingual reaction time tasks were included for comparative purposes.

Ten stutterers, selected randomly from the patients seen in Speech/Language Pathology Section, Army Audiology and Speech Center, WRAMC, comprised the experimental group for this study. Ten nonstutterers, volunteers from the WRAMC staff, served as the control group. None of the subjects reported a history of neuromuscular disorders.

Three reaction time measures were recorded in the experiment. The first, referred to as manual reaction time, was defined as the time elapsed between the onset of a stimulus and the onset of a button-push. The second, referred to as acoustic reaction time, was defined as the time elapsed between the onset of a stimulus and the onset of an acoustic response (either a tongue-click or the production of a vowel-consonant monosyllabic word). The third measure, referred to as laryngeal reaction time, was defined as the time elapsed between the onset of a stimulus and the onset of the laryngeal-region EMG activity associated with the production of a vowel-consonant (VC) word. Laryngeal EMG activity was sensed by means of bipolar surface electrodes placed over the cricothyroid region of the subject and amplified by

means of a high-gain differential amplifier. A previous investigation (Prosek, Montgomery, Walden and Schwartz, 1978) determined that this electrode site provided excellent recordings of laryngeal-region EMG activity but was relatively insensitive to movement artifacts, such as head turning, head retroflexion and mandibular movements.

Three stimuli were used in the experiment. The first was a flash of light which was gated on for 40 msec for each presentation. The light was mounted at eye level at a distance of 75 cm from the subject. The second stimulus was a 1000 Hz pure tone which was presented monaurally via earphones at 80 dB SPL. The tone was gated on for 100 msec with rise and fall times of 10 msec. The interstimulus intervals for the light and tone were randomly selected to be three, four or five seconds.

The third stimulus was one of 16 VC monosyllabic words such as "ape," "abe," "ice" or "eyes." Each word was presented twice, resulting in 32 stimuli per task. Three randomizations of the words were prerecorded on audio tape by a single male talker experienced in live-voice recording. The particular word list for a given task was selected randomly. The words were presented monaurally via earphones at 80 dB SPL ($\pm$ 3 dB) with interstimulus intervals of five, six or seven seconds.

The experiment consisted of nine tasks, each of which was repeated on five consecutive days for every subject. Each task represented a combination of one of the three stimuli and one of three responses as outlined in Table 1. The order in which the tasks were performed was randomized for each subject and experimental session. Digital logic modules were used to synchronize the onset of the stimuli to the activation of a free-running time base which produced pulses at the rate of one per msec. The pulses were counted by high-speed electronic event counter.

For Tasks 1-3, the subject was instructed to push a hand-held button as quickly as possible when he saw or heard the stimulus. The button was connected to a switch which deactivated the time base, and the reaction time, in milliseconds, was read directly from the counter. For Tasks 4-6, the subject was instructed to click his tongue as rapidly as possible when he saw or heard the stimulus. Each subject practiced the tongue-click maneuver a few times prior to beginning the task. A microphone, placed 5 cm from the subject's lips, was used to register the tongue-click. The microphone was connected to a voice-actuated switch which disabled the time base when the subject clicked his tongue. Again, the reaction time was recorded directly from the counter.

For Tasks 7-9, the subject was instructed to produce a VC word as quickly as possible in response to the stimulus. When the stimulus was a light or tone (Tasks 7 and 8), the response word was written on a card placed in front of the subject so that he knew the desired response prior to stimulus presentation. When the stimulus was a word (Task 9), the subject was instructed to repeat the word as quickly as possible. For these tasks, the stimuli activated two time bases, and the pulses produced by these modules were counted by two electronic event counters. The first time base was deactivated when the laryngeal-region EMG activity exceeded a value of approximately 15 μV. The amplified EMG signal was used to deactivate the time base, and laryngeal reaction time

was read directly from the corresponding event counter. The exact threshold EMG level used to deactivate the time base was determined independently for each subject. The second time base was deactivated by the microphone and voice-actuated switch. The subject's acoustic production of the response word closed the voice switch which deactivated the second time base, and the acoustic reaction time was read directly from the corresponding event counter. For Tasks 7-9, then, laryngeal and acoustic reaction times were measured simultaneously.

PROGRESS AND RESULTS: The response latency data were analyzed by means of a multifactor analysis of variance in which the factors were groups (stutterers and nonstutterers), stimulus (light, tone and word), response (manual, tongue-click, acoustic speech signal, and laryngeal EMG signal) and experimental sessions (five repetitions of each task). The manual reaction time data are summarized in Figure 1 in which the mean response latencies of the stutterers and nonstutterers are shown as a function of experimental sessions for each type of stimulus. Of particular interest is the observation that the analysis revealed no significant main effects or interactions for the two groups ($p = 0.2$). That is, in contrast to the data of Luper and Cross (1978), manual response latency was not influenced by whether the subject was a stutterer. The analysis also revealed no significant differences in reaction time as a function of the number of experimental sessions for any stimulus, although some reduction in response latency is observed in Figure 1. The data obtained using a light stimulus, however, were significantly different ($p < 0.05$) from that obtained with the tone or word stimuli. Thus, the manual reaction times of the subjects used in this experiment were affected only by the type of stimulus used.

The tongue-click reaction time data are shown in Figure 2 where the mean response latencies of the stutterers and nonstutterers are displayed as a function of experimental sessions for each type of stimulus. Again, the analysis revealed no significant main effects or interactions for the two groups. In Figure 2B, for the third experimental session, a large difference in response latency for the stutterers and nonstutterers, on the order of 40 msec, was observed. This difference was attributable almost entirely to one of the stutterers, and when this subject's data are removed, the two data points are nearly coincident. Even when that subject's data are included, however, the two groups are not significantly different. The analysis of variance also disclosed that the response latencies for the light stimulus were significantly different ($p < 0.05$) from those obtained using the tone or word stimuli. In addition, for Task 6 (Figure 2C), the response latencies of the first and second experimental sessions were significantly different from the remaining three sessions, indicating a learning effect for this task. Thus, the lingual reaction times of the subjects were affected by the type of stimulus, and, to a lesser degree, by the number of experimental sessions.

The mean response latencies obtained for the tasks requiring a verbal response are shown in Figure 3. The filled rectangles represent the mean acoustic reaction times of the stutterers while the open rectangles represent the mean acoustic reaction times of the nonsutterers.

Although the analysis of variance revealed no significant main effects or interactions for the groups, an individual comparisons test (Winer, 1962) of the acoustic data of the stutterers and nonstutterers was significant at the 0.06 level. Since the 0.06 level is not used in conventional practice, the effect size index of the acoustic data also was calculated. The index is a metric-free measure, not dependent on sample size, which is used to estimate the "size" of an observed difference (Cohen, 1969). The effect size for the acoustic data was 0.71, which, according to Cohen's guidelines, would indicate a large effect. The analysis of variance did reveal significant differences as a function of experimental sessions especially for the tone and word stimuli where the data obtained for the first two sessions were significantly different from the data of the last three sessions. Further, the data obtained for the word repetition task (Figure 3C) were significantly longer than that of the light and tone stimuli for the first two sessions. The acoustic response latencies, then, were affected by group membership, the type of stimulus and by practice. The longer acoustic reaction times of the stutterers are consistent with the data reported by Adams and Hayden (1976), Starkweather, et al. (1976), Cross, Shadden and Luper (1979) and Cross and Luper (1979).

Figure 3 also presents the laryngeal-region EMG response latencies. The X's represent the mean reaction times of the stutterers while the triangles represent the data of the nonstutterers. The figure shows that the two groups are indistinguishable when the EMG response latencies are examined, and individual comparisons tests of these data were not significant ($p > 0.3$). A significant practice effect was observed only for the word repetition task (Figure 3C), but the type of stimulus did not affect the laryngeal-region reaction times. These data indicate that there is no consistent difference in laryngeal-region response latency comparable to that observed in the acoustic data of the stutterers and nonstutterers.

CONCLUSIONS: The manual reaction time data in Figure 1 do not agree with that of Luper and Cross (1978). Those authors reported a mean difference between stuttering and nonstuttering adults of approximately 28 msec. Additional research on the manual reaction times of stutterers and nonstutterers is certainly warranted since the results affect hypotheses attempting to explain reaction time differences. That is, longer reaction times for stutterers involved in manual tasks would indicate a generalized timing problem as opposed to a difficulty specific to speech production.

Response latencies for tongue-clicks were obtained in the present study in order to determine if reaction time differences existed between stutterers and nonstutterers at levels of the speech production mechanism other than the larynx. The data of Figure 2 indicate that simple response latencies of a major, extra-laryngeal articulator are not different for stutterers and nonstutterers.

The acoustic response latencies shown in Figure 3 agree with the results of previous research in that the average difference between groups is consistent and obvious. On the other hand, no comparable difference in laryngeal-region reaction time was observed, implying that

the acoustic differences cannot be accounted for solely by slowness in the onset of laryngeal activity. Although the time relationship between the onset of surface EMG activity and vocal fold vibration is not clearly established, the data argue that speed alone is not a sufficient measure of laryngeal involvement in stuttering.

The results of this study do not invalidate the statements of Starkweather, et al. (1976) that fluency might be improved by improving control, particularly timing, of laryngeal activity. In the present study, laryngeal-region responses occurred, and no audible stuttering was observed. The nature of the EMG response, however, is not known. It is conceivable that the laryngeal responses of the stutterers, while as fast as those of the nonstutterers, were abnormal or incoordinated. That is, the initial laryngeal gesture may occur with normal latency, but the release of the gesture or the onset of airflow may be abnormally long. The results of this study do indicate that analysis of a single variable, such as reaction time, is inadequate to measure a behavior as complex as disfluency, and that the pattern of activity at different levels of the speech production mechanism needs to be examined.

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FUNDS UTILIZED, FY-79: None

FUNDING REQUIREMENTS, FY-80: None

PUBLICATIONS: The manuscript, "Reaction Time Measures of Stutterers and Nonstutterers," has been accepted for publication in the Journal of Fluency Disorders. A copy of the manuscript is attached.

TYPE OF REPORT: Completed

Table 1. Outline of reaction time tasks used in the experiment.

	STIMULUS		
RESPONSE	Light	Tone	Speech
Button Push	Task 1. Push button as quickly as possible when light flashes.	Task 2. Push button as quickly as possible when tone is heard.	Task 3. Push button as quickly as possible when word is heard.
Tongue Click	Task 4. Click tongue as quickly as possible when light flashes.	Task 5. Click tongue as quickly as possible when tone is heard.	Task 6. Click tongue as quickly as possible when word is heard.
Speech	Task 7. Say word as quickly as possible when light flashes.	Task 8. Say word as quickly as possible when tone is heard.	Task 9. Repeat word as quickly as possible.

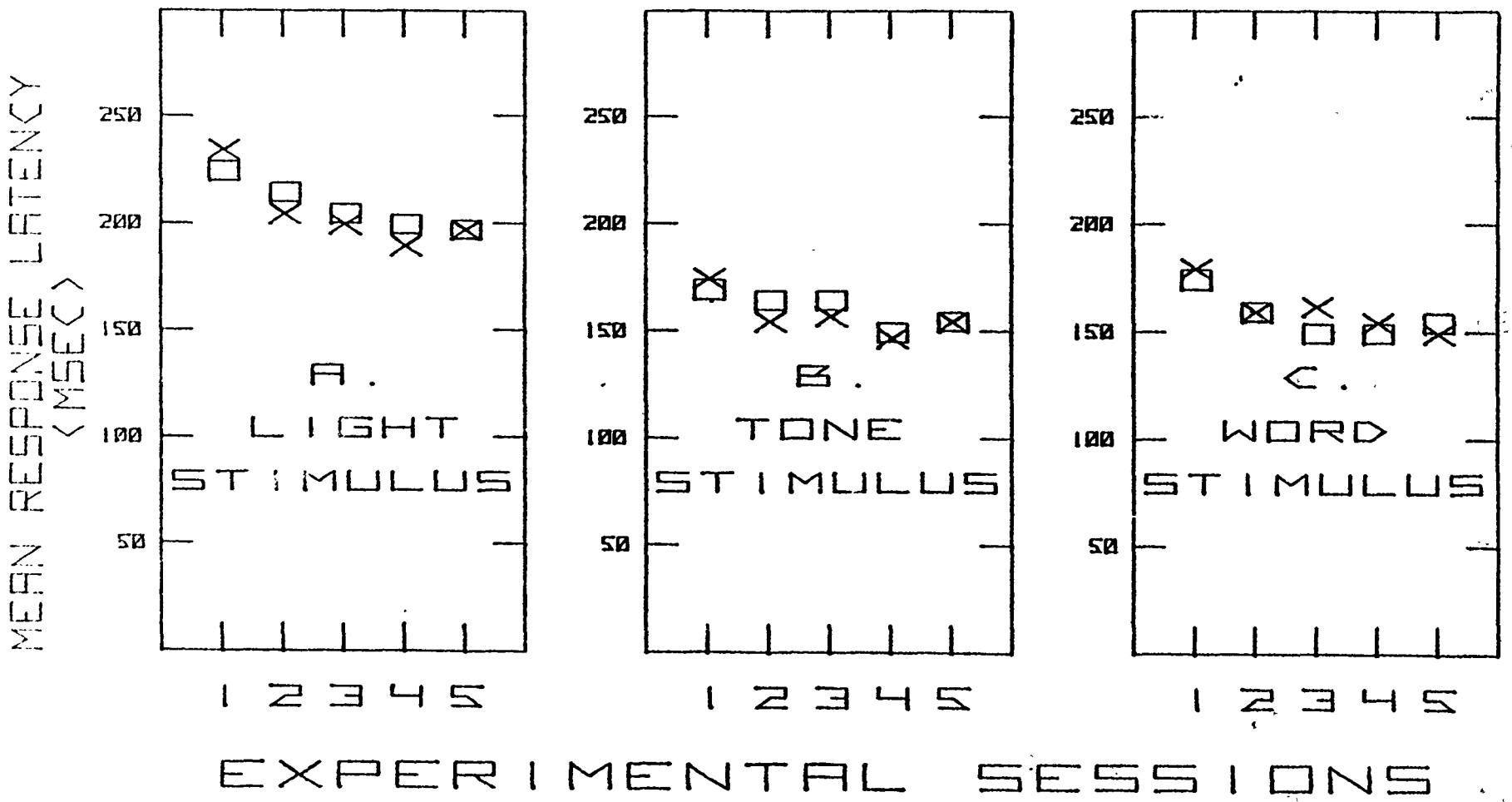


Figure 1. Mean reaction time as a function of experimental sessions obtained in the manual reaction time tasks for A) light, B) tone, and C) VC monosyllabic word stimuli. Rectangles represent data obtained from stutterers; X's represent data obtained from nonstutterers.

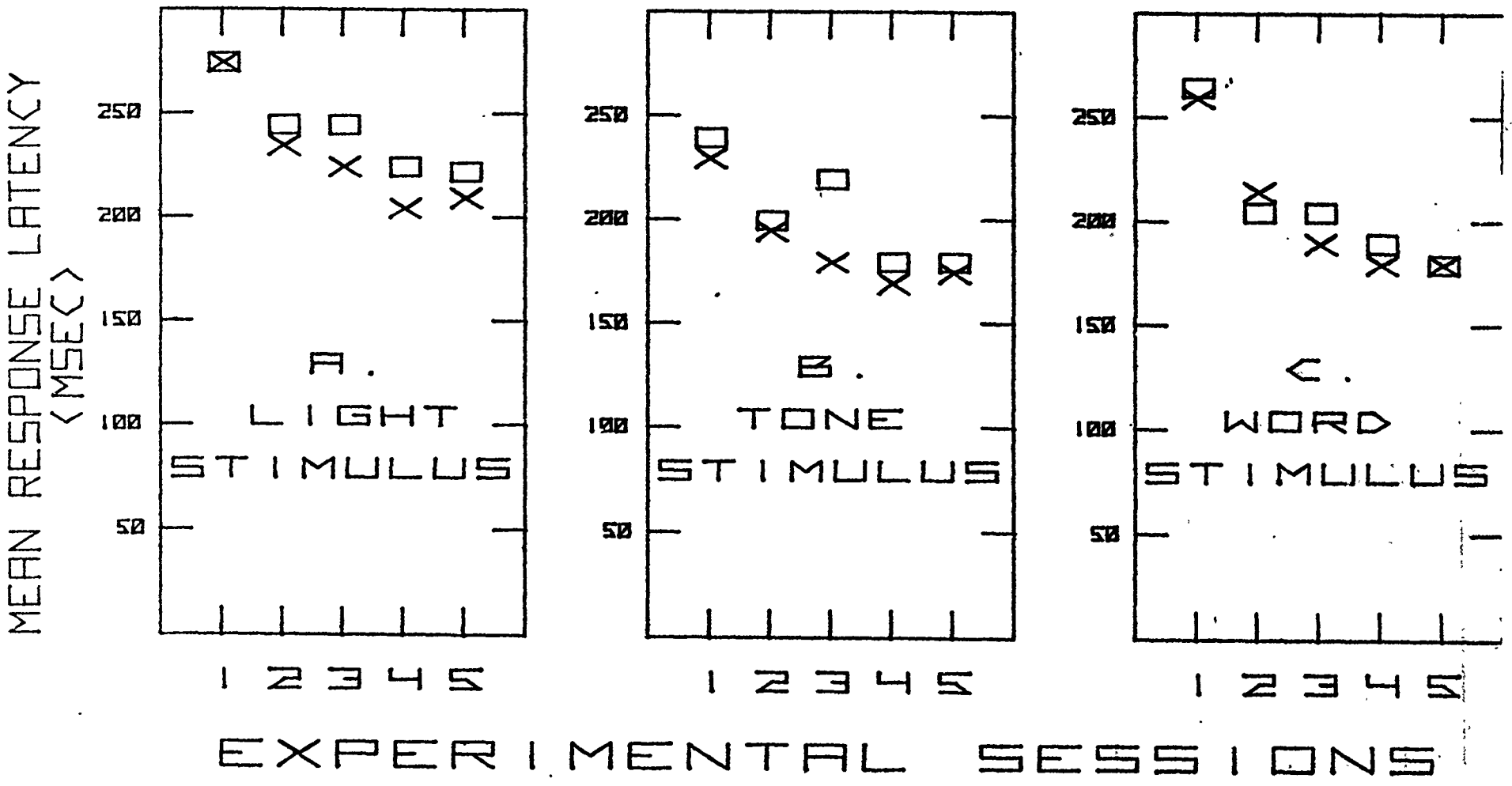


Figure 2. Mean reaction time as a function of experimental sessions obtained in the lingual reaction time tasks for A) light, B) tone, and C) VC word stimuli. Rectangles represent data obtained from stutterers; X's represent data obtained from nonstutterers.

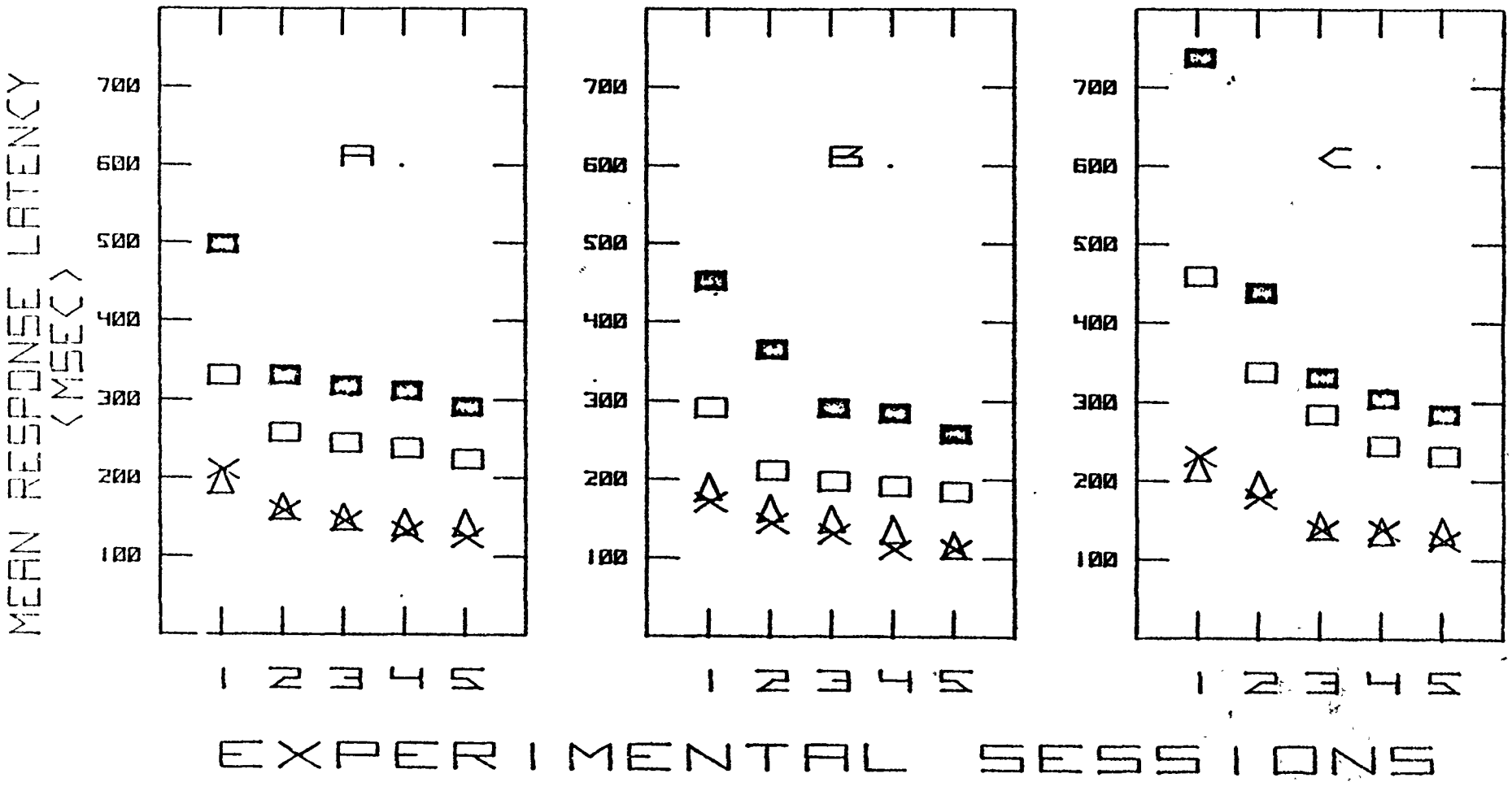


Figure 3. Mean reaction time as a function of experimental sessions obtained in tasks requiring a vocal response for A) light, B) tone, and C) VC word stimuli. Key: Filled rectangles - acoustic data of stutterers; open rectangles - acoustic data of nonstutterers; X's - laryngeal-region data of stutterers; triangles - laryngeal-region data of nonstutterers.

Work Unit No.: 2522

Title of Project: Monaural Versus Binaural Amplification for Hearing Impaired Listeners

Investigators:

Principal: Daniel M. Schwartz, Ph.D.

Associate: Nan K. Lukmire, M.Ed.
Allen A. Montgomery, Ph.D.
Robert A. Prosek, Ph.D.
Brian E. Walden, Ph.D.
Roy K. Sedge, MAJ, MSC, Ph.D.

Objectives: To determine the efficacy of binaural hearing aids for improving word and sentence recognition in noise for hearing impaired listeners.

Technical Approach: The procedure outlined in the proposal for determining the benefits of binaural amplification when the subject is surrounded by speech babble and required to respond to monosyllabic word and sentence materials has been discontinued. Recent research has demonstrated that the benefits of binaural hearing aids cannot be shown by assessing speech discrimination with monaural and binaural amplification. This, in fact, was supported by the 15 subjects employed in this study since no observable difference was obtained. It appears that a more appropriate assessment of the binaural advantage would be that of a horizontal sound localization task which, unfortunately requires the use of an anechoic chamber. Hence, this project has been discontinued. A paper reviewing the advantages of binaural hearing and binaural hearing aids, in addition to a critical review of research related to this topic was presented at an International Symposium on Amplification at Vanderbilt University, School of Medicine, September 27, 1979. This is presently being prepared for publication.

Progress and Results: Data were gathered on 15 subjects, none of which displayed marked differences in performance between monaural and binaural conditions. A complete review of all literature published to date has led to a manuscript related to the limitations involved in doing research on binaural hearing aids with speech stimuli.

Conclusions: Discontinue this research paradigm.

Funds Utilized, FY-79: None

Funding Requirements, FY-80: N/A

Publications: Binaural Hearing Aids: A Paradox: In Bess, F. H., Amplification in Education (in press).

Type of Report: Final

Work Unit No.: 2523

Title of Project: The Relationship Between Electroacoustic Parameters and Perceived Sound Quality of Hearing Aids

Investigators:

Principal: Daniel M. Schwartz, Ph.D.

Associate: Allen A. Montgomery, Ph.D.
Brian E. Walden, Ph.D.
Robert A. Prosek, Ph.D.

Objectives: To determine the relationship between various perceptual dimensions and physical characteristics of hearing aids in judging the sound quality of hearing aid amplified speech.

Technical Approach: A 20 second passage from the book "Tom Sawyer" was recorded through 20 different hearing aids mounted on a Knowles Electronics Maniken for Acoustics Research. In addition, 17 measures of the electroacoustic characteristics of each hearing aid were obtained as the aid was mounted on the maniken.

The hearing aid recorded speech samples from each of the 20 hearing aids were then paired with every other hearing aid and spliced onto a master tape resulting in 190 pairs of hearing aid recorded speech.

Ten normal hearers and 10 hearing impaired listeners listened to the hearing aid recorded speech samples as transduced through an insert receiver having a flat acoustic spectrum through 10,000 Hz. Each listener was seated in a sound-isolated test room and was presented with a two position switch which allowed him to hear a speech sample recorded through each pair of hearing aids. The subject was instructed to judge which of the two hearing aids in each of the 190 pairs he preferred on the basis of sound quality. Second, each listener was required to judge how similar the two hearing aids were with respect to sound quality and to rate similarity on a seven point equal appearing interval scale.

Data for each subject were collected in three separate test sessions in an effort to determine the reliability and consistency of both the preference and similarity ratings. That is, each subject judged the similarity and preference of 190 pairs of hearing aids on each of three test sessions.

Progress and Results: Data have been obtained on 10 normal hearing, 10 high frequency sensorineural and 10 flat sensorineural hearing loss subjects. These data have been organized into matrices via program INDSCAL for ultimate correlation of the stimuli in the psychological space with the electroacoustic characteristics of the 20 hearing aid pairs used in this study. We continue to await purchase of the FONIX 10,000 Hearing Aid Test System to obtain electroacoustic response measurements on the 20 hearing aids before this study can be finalized. All other data, however, have been collected.

Conclusions: Not applicable at this time.

Funds Utilized, FY-79: None

Funding Requirements, FY-80: $17,000.00 (for FRY ELECTRONICS MODEL 10,000 Hearing Aid Analyzer)

Publications: Results of this experiment are to be presented at the annual convention of the American Speech and Hearing Association, Atlanta, Georgia, November 1979.

Type of Report: Interim

Work Unit No.: 2524

Title of Project: The Effects of Assertiveness Training on Hearing Impaired Soldiers

Investigators:

Principal: Allen A. Montgomery, Ph.D.

Associate: Suzanne K. Sedge

Objective: To determine the effects of assertiveness training on the levels of assertiveness and self-concept in hearing impaired soldiers.

Technical Approach: Hearing impaired patients from the two-week Aural Rehabilitation Program are assigned to either a control group which receives only traditional rehabilitative techniques, or to an experimental group which receives communication-centered assertiveness training as well as aural rehabilitation. Evaluation of the effectiveness of the assertiveness training is performed by administering two standardized tests, the Adult Self-Expression Scale and the Tennessee Self-Concept Scale, at the beginning and end of the training period, as well as by debriefing patients and therapists. Standard descriptive and correlation techniques and the analysis of variance are used to analyze the results.

Progress and Results: The assertiveness training program has been designed and tested, and data collection on both control and experimental groups is complete. Data analysis is completed. It was found that the control group showed little or no improvement in either assertiveness or self-concept, while the experimental group demonstrated significant gains on both measures. Both groups of patients show high test-retest reliability, and the results of the post-training tests are in good agreement with the information from the debriefings. Detailed description of results follows:

Adult Self Expression Scale (ASES) - The descriptive data for the ASES is presented in Table 1. The total score can range from 0 to 192. Gay's 1975 study with 640 adults demonstrated a mean of approximately 115 with a standard deviation of approximately 20. Thus, scores falling above 135 would be considered high scores, while those falling below 95 would be low scores. Therefore, both the experimental and control groups were slightly above the mean pre-treatment; yet not approaching the high range. Also at post-test the control group's mean was still very close to the normative mean -- demonstrating no change; whereas the experimental group's mean changed from 128.3 to 139.9 post-treatment which is in the high range of over 135.

In addition, a repeated measures analysis of variance was performed on the data from the ASES. This analysis focused on control versus experimental groups and pre- versus post-performances. Statistically significant differences were observed both between groups and between pre- and post-treatment at the .05 level. In summarizing simple main

effects, it was determined that the experimental and control groups were not significantly different at pre-treatment; yet they were highly significantly different at post-treatment. Also there was no difference between pre- and post-treatment conditions for the control group; yet, there was a high level of significance between pre- and post-treatment conditions for the experimental group. This indicates a strong treatment effect and strongly supports the hypothesis that assertion training results in increased levels of assertiveness as measured by the ASES.

Tennessee Self-Concept Scale - The descriptive data for the TSCS's total positive scores are presented also in Table 1. Fitts (1965) arrived at a mean of 345.57 and a standard deviation of 30.70 with a group of 626 subjects. The present study's control group's pre- and post-test means were slightly below the normative mean and remained basically the same pre- and post-treatment. The experimental group's mean was slightly above the mean initially and reached 364.7 post-treatment. A change of 16.6 points was noted between pre- and post-test means.

The scores from the TSCS were also statistically examined by a repeated measures analysis of variance. Here too, the focus was on control versus experimental group and pre- versus post-performance. In examining the analysis of variance, there was a significant difference both between the experimental and control groups and between pre- and post-treatment conditions. In reviewing the simple main effects, there were no significant differences found between the groups at pre-treatment or between the pre- and post-treatment for the control group which was as expected. There were significant differences between the groups at post-treatment between the pre- and post-training for the experimental group. This is indicative of a highly significant treatment effect and supports the hypothesis that assertiveness training will result in increased levels of self-concept as measured by the TSCS.

Conclusions: This study was designed to investigate the effects of assertiveness training on hearing-impaired military males. Forty hearing-impaired subjects participated in one of two conditions: 1) control condition where twenty subjects participated in all the regular components of the on-going aural rehabilitation program; or 2) treatment condition where twenty subjects received all the regular components of the aural rehabilitation program, plus an assertiveness training module specifically designed for the hearing impaired. The assertiveness training utilized included: covert and overt behavior rehearsal, modeling, coaching, role-playing, mini-lectures, relaxation training, homework assignments, audio tapes, and canned situations of problems specific to the hearing impaired. The two standardized assessment instruments utilized in this study were: the Adult Self-Expression Scale to assess assertiveness level and the Tennessee Self-Concept Scale to assess self-concept. The subjects were pre- and post-tested with these instruments and two repeated measures analyses of variances were conducted on the data obtained. The results from both instruments indicated a statistically significant improvement demonstrated by the experimental group on both assertiveness and self-concept and no improvement for the control group on either construct. It was recommended that Assertiveness Training be given serious consideration as a

component of adult aural rehabilitation programs, and assertiveness training has been added to the Army Audiology and Speech Center's rehabil'tation program.

Funds Utilized, FY-79: None

Funding Requirements, FY-80: Publication and reprint costs.

Publications: A manuscript is being prepared for submission to the Journal of Speech and Hearing Disorders.

Type of Report: Final

Table 1

Summary of Descriptive Data from the Adult Self-Expression Scale (ASES) and the Tennessee Self-Concept Scale (TSCS) fo' both experimental and control groups.

	Pre-Test			
Groups	Mean	Standard Deviation	Mean	Standard Deviation
ASES				
Group 1				
(Controls)	120.1	15.7	118.6	15.4
Group 2				
(Experimentals)	128.3	16.2	139.9	14.8
TSCS				
Group 1				
(Controls)	342.5	33.7	342.1	32.3
Group 2				
(Experimentals)	348.1	27.3	364.7	33.5

Work Unit No.: 2525

Title of Project: Generation and Evaluation of Synthetic Facial Images for Studying and Training Lipreading

Investigators:

Principal: Allen A. Montgomery, Ph.D.

Associate: Brian E. Walden, Ph.D.
Robert A. Prosek, Ph.D.
Daniel M. Schwartz, Ph.D.

Objective: This study is designed to evaluate the feasibility of simulating on a computer graphics system, the information-bearing elements of the talker's mouth and face during speech, for the purpose of studying lipreading in hard-of-hearing patients.

Technical Approach: The present paper is the second report on a long range project aimed at developing the capability to synthesize realistic images of the visual aspects of speech. What we foresee is an algorithm, in the form of a FORTRAN program with graphic I/O subroutines, which allows the researcher or clinician to request (by typing on the keyboard) the materials that he or she desires. The computer would then generate the stimuli according to rules that had been developed and display the speech in the form of a face whose lips and jaws move in appropriate ways. Our interest in synthetic visual speech stems from the following reasoning.

One of the innovations most useful for studying speech perception was the development of the ability to generate synthetic speech -- speech that was intelligible and reasonably natural, yet whose acoustic properties were under the control of the experimenter. Hundreds of studies of speech perception by normal and hearing-impaired listeners have been conducted with the aid of synthetic speech.

Given the value of synthetic stimuli for studying auditory perception of speech, it seems apparent that the ability to generate the visual analog of synthetic (auditory) speech would be of potentially great value for studying lipreading. That is, if we could generate on a computer-driven graphics system, an animated facial image whose lips, mandible, and surrounding areas moved in a way that closely simulated the movements of real talkers, such images could be used to study the process of lip reading (and auditory-visual integration) in great detail.

Last year we compared intelligibility and confusion patterns of synthetic and natural CV stimuli and demonstrated that computer-displayed synthetic lip movements could, in most cases, preserve the essential characteristics of speech.

This year we have turned our attention to a specific question concerning the effects of coarticulation on lipreading intelligibility, as a way of evaluating and demonstrating the usefulness of synthetic visual speech.

The purpose of the present study is to examine in VCV stimuli the effects of vowel context on consonant visual intelligibility.

The subjects are 15 hearing-impaired soldiers (inpatients at Walter Reed Army Medical Center) with moderate noise-induced losses and 15 normally-hearing adults.

The stimuli are VCV bisyllables where the initial and final vowels are the same. Vowels used are /i,a,ɔ,u/, consonants are /b,v,w/. The stimuli are prepared in both natural and synthetic form. The natural stimuli are obtained by videotaping three talkers each producing the combinations of vowels and consonants in random order at each of three rates of articulation. The synthetic stimuli are prepared by programming a computer-driven graphics terminal to produce comparable stimuli according to rules.

The stimuli are presented for identification and are arranged randomly within each stimulus type with a large number of "foils" to prevent viewers from focusing on the three primary consonants. Data are analyzed for intelligibility and confusions.

Progress and Results: The results to date are incomplete, but preliminary indications are that the data confirm conventional knowledge about lip reading: the rounded vowel context exerts a powerful negative influence on visual intelligibility, as do higher rates of articulation. More importantly, the model of visible coarticulation which underlies the rules for generating the synthetic stimuli seems to be quite adequate for portraying the effects of vowel lip rounding and speech on the consonants (some problems remain in conveying degree of lip rounding in a graded "linear" manner).

Conclusions: N/A

Funds Utilized, FY-79: Travel - to annual convention, Nov 1978

Funding Requirements, FY-80: Travel - $178.00
Equipment - $5,571.00*
Supplies - $580.00
Publication and reprint costs

Publications: Montgomery, A.A. Generation and Evaluation of Synthetic Facial Images for Lip Reading. Paper presented at the American Speech and Hearing Association convention, Nov. 1978.

Type of Report: Interim

*Unfunded request carried over from FY-79.

Work Unit No.: 2526

Title of Project: Evaluation of a Communication Self-Assessment Inventory of the Hearing-Impaired Soldier (Previously "Development of a Communication Self-Assessment Inventory of the Hearing-Impaired Soldier")

Investigators:

Principal: Brian E. Walden, Ph.D.

Associate: Sue E. Anderson, M.A.
Allen A. Montgomery, Ph.D.
Roy K. Sedge, MAJ, MSC, Ph.D.

Objective: The objective of this project is to evaluate a communication self-assessment inventory being used in the inpatient Aural Rehabilitation Program of the Army Audiology and Speech Center, WRAMC. The specific purposes of this inventory are: a) To assess progress in environmental control and in emotional, social, familial and vocational adjustment to the handicap as a result of the aural rehabilitation program; b) To establish a baseline for planning the patient's environmental control training and adjustment counseling in the aural rehabilitation program; c) To provide prognostic indicators of short-term success in the program; and d) To provide prognostic indicators of long-term success in communication after returning to the duty station.

Technical Approach: As proposed in the original Application for Clinical Research Project, it was proposed that the Government contract for the development of a self-assessment inventory of communication ability. A review of the available inventories at that time revealed that none were appropriate to the specific purposes of the Government. Since the time that the original protocol was approved by the Clinical Investigation Service, attempts have been made to obtain funding for this project. Specifically, requests for funding were made of the Medical Research and Development Command and the Health Services Command. In both cases funding was not obtained.

Recently, a new communication self-assessment inventory appeared in the literature. The Hearing Performance Inventory (T.C. Giolas, E. Owens, S.H. Lamb and E.D. Schubert, Journal of Speech and Hearing Disorders, May, 1979) appears to have potential for use with the military population. Given that funding was not obtained for the original proposal to develop a new self-assessment inventory, the project has been revised to be an evaluation of the Hearing Performance Inventory (HPI). Among the specific goals of this evaluation are the following:

a) To determine the clinical applicability of the HPI for the military population;

b) To accomplish a detailed statistical analysis of the reliability of the HPI. In its present form, the HPI is too long for the Government's purposes, taking over an hour to administer. The HPI will, therefore, have to be revised and shortened. To accomplish this, a detailed item analysis of the test must be completed; and

c) To determine the prognostic value of the HPI for the military population. This will involve relating performance on the self-assessment inventory to other indices of hearing and communication ability through empirical investigation.

These goals represent a modification of those set forth in the original Application for Clinical Investigation Project. Since the HPI was not developed specifically for the military population, certain of the Government's purposes cannot be fulfilled by this inventory. The corpus of potentially useful items in the HPI, however, represent a major advantage to the Government, in that extensive item development is not required. Several statistical and validation studies of the inventory will be needed in order to determine the appropriateness of the HPI for use with the military population.

Progress and Results: To date, the HPI has been administrered to approximately 40 soldiers attending the inpatient Aural Rehabilitation Program at the Army Audiology and Speech Center. The statistical analyses and follow-up studies of the inventory must wait for the accumulation of considerably more data.

Conclusions: None

Funds Utilized, FY-79: None

Funding Requirements, FY-80: The expertise in psychometrics required to evaluate the HPI does not exist at the Army Audiology and Speech Center or within WRAMC. The required analyses will require several months of work. It is, therefore, necessary to hire on a temporary basis a psychometrist with the appropriate statistical and programming capabilities to accomplish this work. Given the present rate of data acquisition this person must be available from mid-June through mid-September 1980. It is also quite likely that the summer would be the only time that we could recruit a qualified person for a temporary hire. Estimated cost: $7,500.

Publications and Abstracts, FY-79: None

Estimated Date of Completion: 1981-82

Type of Report: Interim

WORK UNIT NUMBER: 2527

TITLE: Assessing Laryngeal Function via Residue Inverse Filtering

INVESTIGATORS: Principal: Robert A. Prosek, Ph.D.
Associate: Robert L. Henderson, M.D., COL, MC
Allen A. Montgomery, Ph.D.
Daniel M. Schwartz, Ph.D.
Brian E. Walden, Ph.D.

OBJECTIVE: To establish the relationship between voice quality ratings and acoustic measurements obtained by means of Linear Predictive Coding for patients with voice disorders.

TECHNICAL APPROACH: Patients with various voice disorders who are being seen at the Army Audiology and Speech Center and the ENT Service, WRAMC, are the subjects of this study. Each subject records the vowel /a/ as in "father" on FM recording tape at a comfortable pitch and loudness. A 400 msec segment of each vowel is digitized at 10,000 samples per second and stored on disk using the Speech and Hearing Data Acquisition System (SHDAS) of the Army Audiology and Speech Center. Each sample is inverse filtered by means of Linear Predictive Coding (LPC) to obtain a residue signal which appears to be correlated with intuitive notions of vocal behavior. Each residue signal in turn is analyzed to obtain measures of pitch perturbation quotient, amplitude perturbation quotient, pitch amplitude, coefficient of excess, spectral flatness of the inverse filter, and spectral flatness of the residue signal. These measures, known as residue features, constitute the independent variables of the study.

Once all of the vowel samples have been obtained, they will be randomized on audio tape and presented to a panel of speech-language pathologists for voice quality judgments. These judgments will be averaged for each sample, and the mean voice quality judgments will constitute the dependent variable of the study. Correlation and regression techniques will be used to establish the relationship between voice quality judgments and residue features. The magnitude of the relationship will determine which, if any, of the residue features are potentially useful in the clinical evaluation of patients with voice disorders.

PROGRESS AND RESULTS: Software for SHDAS has been written and tested which accomplishes the analog-to-digital conversion, calculates and applies the LPC inverse filter, and measures the residue signal. The software has been written in modular form such that a clinical version of the program, based on the results of the current study, can be implemented with minimal delay.

Thirty patients with voice disorders have been recorded to date. Preliminary examination of the residue feature values obtained for these subjects reveals that all of these data can be used in the study. The correlation and regression analyses, however, require more subjects, and, thus, further analysis must await the recording of additional

patients. It is estimated that a minimum of 25 additional subjects is required. The subjects recorded to date vary widely in age, severity of disorder, type of disorder and residue feature values, indicating that the desired heterogeneous sample of voice disorders is being obtained.

CONCLUSIONS: Not applicable at the present time.

FUNDS UTILIZED, FY-79: $400.00

FUNDING REQUIREMENTS, FY-80: $400.00 (for FM recording tape as requested in the original protocol)

PUBLICATIONS: Not applicable at the present time.

TYPE OF REPORT: Interim

Work Unit Number: 2610

Title: Antilymphocyte Globulin and Kidney Transplantation: A Controlled Double Blind Study

Investigators:

Principal: Jimmy A. Light, COL, MC

Associate: M. R. Alijani, MAJ, MC

Objective: To define the value of antilymphocyte globulin in clinical transplantation.

Progress and Results: This protocol, approved in 1973, has never been implemented. It has been carried in an inactive status pending the availability of a suitable ALG for use in this project. The study purposed, although original in design at the time of its inception, is now in progress or has been completed at a number of transplantation centers. In its present form it is no longer a useful protocol. However it continues to provide a useful background in information for the clinical use of antilymphocyte globulin. Data from various transplant centers continue to show improved graft survival in patients receiving ALG with decreased morbidity from infection and steriod toxicity. The ATG from the Navy Laboratories is still not available, however we do have access to a quality reagent from the University of Minnesota. Administration of this ALG to patients undergoing irreversible, steriod resistant allograft rejection (100% graft loss) has resulted in 100% graft salvage. Dose is adjusted by these total rosette count, maintaining it approximately 5% of control values. A protocol delineating patient eligibility and parameters suitable for scientific investigation is being evolved. Preliminary thoughts included:

1. Serial transplant biopsy with tissue identification of lymphocyte sub populations over the rejection and treatment period.
2. Correlation of ALG dose with blood levels and T-rosette responses.
3. Comparison of short with prolonged treatment regimens.

Conclusions and Plans: These are patients who otherwise would have had their transplant removed from irreversible rejection. The results clearly demonstrate the short term benefits of this therapeutic intervention. The task now is to attempt to determine optimal timing for intervention, dose and duration of therapy, and attempt to further understand the pathophysiology of the acute and chronic rejection response.

Funds Utilized, FY-79: None

Funds Needed, FY 80:

1. ALG - purchased through operating funds (See WRAMC 40-3)
2. Biopsy interpretation - provided by USAR pathologist as part of his AD military obligation.

3. Rosette monitoring - provided by present personnel in Transplant Clinical Investigation lab.
4. Serum ALG leve's will be done by present technical staff, using available resources. Small amount of funds may be needed for plates and reagents.

Publications and Travel: $1,000.00

Publications and Abstracts: None in FY 79. Expect minimum of 3 abstracts from present work in FY 80:

1. Correlation of ALG doses, serum levels and T-rosettes.
2. Steroid resistant rejection reversal with ALG.
3. Serial transplant biopsy following allograft rejection.

Type of Peport: This will be an ongoing study for a minimum of 2 years. The number of subjects will be determined by their clinical course and the activity of the transplant service.

Work Unit Number: 2615

Title: Immunological Monitoring of the Transplant Recipient

Investigators:

Principal: Jimmy A. Light, COL, MC

Associate: D. Strong, S. Metz

Progress, Results and Conclusions: Under this work unit, there are three separate areas of study, which overlap to some degree because of the nature of the studies.

I. Pre transplant immune assessment.

A. Mitogen assays (PHA, ConA, PWM) - over 1700 assays have been performed. In contrast to the literature, "responder" status could not be prediced by these assays over a 3 year study period. Similarly they were not helpful in detecting the degree of immunosuppression post transplant. The assays were not predictably affected by pretransplant imuran administration. This work is no longer performed.

B. Mixed lymphocyte Culture - Nearly 200 MLC's have been performed in the last three years. MLC responsiveness to frozen pooled stimulator cells was not helpful in predicting "responder" status and rejection episodes. MLC's were performed in all living related donor recipient pairs. We have assessed our results over an 8 year period. The assessment was made more difficult by having had several technologists, a variety of procedural changes, changing labs, etc. Only about 65% of the tests are valid, because of problems with one of the controls, one of the stimulators, or not performing the transplant. Since Jan 1979, techniques have been refined, standardized and may now be more useful with changing laboratory supervision and technologists. Despite these obvious limitations, we were able to develop mathematical ratios which reliably predicted a favorable outcome in 83% of parent-child pairs. Predictive parameters could not be established for haplo-type mismatched siblings in the "one-way" MLC model. "Two-way" micro MLC results are now being assessed.

Future work in this area will be directed at improving the reliability and predictability of the one-way and two-way study so it can be used to select or reject living related donor recipient pairs. Cochrum has worked extensively in these areas and is willing to come as a consultant to discuss our efforts. Future work will include research with primed lymphocytes (PLT) to help type for HLA-D more rapidly, especially for application in cadaver kidney transplantation. PLT will be compared with HLA-DRW serological typing done in the histocompatibility laboratory. (B cell typing)
$1,000.00 consultant travel should be included.

C. DNCB - in vitro and in vivo-With the Rolley report correlating failure to develop a DHS reaction to DNCB with successful transpant outcome in 1975, we began working with DNCB.

Approximately 40 patients have been skin tested - without clear cut conclusions regarding their post transplant course. There were a number of logistical problems associated with the prolonged testing period (2-4 weeks) and the fact that most of our patients are not from this area. This led to the development of a DNCB self adherent pad which could be sent home with the patient and a report card which was mailed back. After a prolonged absence, clinical skin testing will resume where possible in all transplant recipients. A more definitive report will be possible after the next year.

We also developed an in vitro assay of lymphocyte responsiveness to DNCB, looking at lymphocytes in vitro before and after in vivo sensitization. Basically in preliminary studies, we were able to stimulate in vitro responses to DNCB in about half the patients who failed to respond in vivo. Subsequently, by preincubating macrophages with DNCB and then adding the macrophages to the patients' lymphocytes culture, we were able to produce an in vitro response without in vivo exposure. This promising work was abandoned for three reasons:

1. loss of the technical staff in Mar, 1978. One was finally replaced 15 months later.
2. loss of the laboratory facility in Dec, 1978.
3. DNCB was also sensitizing to the laboratory staff. With moving to new facilities, this work was abandoned so that other areas of immunological monitoring could be pursued with our remaining technical staff.

D. Imuran pretreatment of recipients. Based on pretreatment studies in rats, we pretreated 13 patients with Imuran for periods from 2-16 weeks, serially monitoring total monocyte counts (Wright Stain only), mitogen and MLC responses. Eleven patients were transplanted. Ten experienced rejection, but 8 have long term graft function. Monocyte counts were unpredictably decreased in 6 patients, while mitogen and MLC results were generally not affected. The clinical trial was abandoned when the effects produced were not strikingly beneficial and when repeat animal trials failed to confirm the earlier promising work. Technical support was not avaiable at the time to conduct adequate monocyte studies, thus the project was abandoned. Future studies should be performed, but will need to include a closer look at lymphocyte subpopulations and monocyte number and function.

II. Monitoring Post Transplant for Rejection

A. As mentioned earlier, post transplant mitogen and MLC tests were not helpful in detecting rejection nor in determining the adequacy of immunosuppression post transplant.

B. The previously established technology for ADCC and CDC used to detect antibody against chromium labeled frozen donor specific target cells, had to be totally revised since Jan, 1979. The technician performing these assays left in July 79 and has not been replaced. The assay is now being restandardized

C. Spontaneous Blastogenesis: This assay was established in 1977 and was performed serially post transplant until mid

1979, when the results were critically reviewed. Approximately 700 assays were performed. The assay was inconsistent and failed in all but one patient to be predictive of rejection or its resolution. The assay has been abandoned.

D. Rosettes: Active and total rosettes (24 hours) were established in 1977. Over 1400 assays were performed; 900 in FY 1979 alone. "Active" rosettes (1 hour) are supposed to decrease prior to rejection. As with spontaneous blastogenesis, the assay failed to predict graft rejection. "Stable" rosettes were examined in 10 patients. These rosettes are supposed to appear with rejection activity. They didn't. The chief utility of the rosettes in this year was for control of ALG administration. Total rosettes (o/o in 24 hours) and total circulating rosettes (WBC x percent) are monitored three times weekly and kept between 50-100/mm^3, by appropriate adjustments in ALG dose. The rosettes assay is an important part of our clinical management protocols.
Future research includes shortening the assay from 24 to 4 hours and looking at T cell subpopulations, T-gamma, T-MU, T helper, T suppressor. These assays are within our scope. A consultant specializing in these areas has planned a visit.

E. Beta$_2$ Microglobulin (B_2M) - B_2M is an immunoglobulin fragment produced by lymphocytes and has been shown to be elevated in a variety of immune disorders. B_2M is filtered by the glomerulus and secreted by the proximal tubule of the kidney. One investigator has reported elevations of B_2M preceding clinical graft rejection and normalization of B_2M after rejection reversal prior to return of normal renal function. We performed 294 assays on serial post transplant serum specimens. Due to technological and supply problems, no firm conclusions can be drawn, although the results are encouraging.

III. Post Transplant Rejection

A. Analysis of Rejected Allografts: Twenty three rejected allografts have been subjected to citric acid elution. The eluates were concentrated and analyzed for immunoglobulin by Ouchterlony immunodiffusion technique. In turn the eluate is analyzed for HLA reactivity and specificities against the lymphocyte panel. The eluate is also tested against a B cell panel and is run in ADCC and CDC against frozen donor or surrogate chromium labeled lymphocyte targets. Light, EM and immunoflorescent microscopy of the rejected kidney is being analyzed by a pathologist independently, attempting to identify T and B cells in the tissue. Although this type of analysis is potentially very important, completion of this work is regularly postponed because of more pressing clinical work. This study may be finalized this year, if personnel and funding remain constant. Several publications are possible from this work. Travel and per diem for the consultant may be necessary.

B. Analysis of post transplant rejection sera: Once the rejected kidney has been removed, there is usually an exuberant antibody response which is analyzed in a fashion similar to eluates.

Plasmapheresis may be utilized if the antibody is sufficiently specific and high-titered. The sera is followed until the responses have peaked, following which the patient may be retransplanted.

Funds Utilized, FY 79: $17,500. We had requested $50,662 and received $24,000. Due to marked personnel problems and changing lab facilities, loss of the laboratory investigator, etc. only $21,000 was spent in the entire program.

Funding Requirements, FY-80: $60,348

Publications and Abstracts:

Abstracts submitted:

1. Renal Allograft Rejection Due to HLA-B8 Antibody Following a Negative T-Cell, Positive B cell Crossmatch. Metz, S., Strong, D., Budd, J., Goldman, M., Light, J., AACHT, San Diego, May 1979.

Abstract presented:

2. Use of 2P44, 12 Heteroantiserum for Differentiation of HLA-A, B and DR reactivity in Typing and Crossmatching.
   Budd, J., Strong, D., Metz, S., et al. SEOPF Cryobiology Meeting, October 79.

Papers submitted:

1. Use of 2P44, 12 Heteroantiserum for Differentiation of HLA-A, B and DR reactivity in Typing and Crossmatching.
   Budd, J., Strong, D., Metz, S., et all. Submitted to Transplantation.
2. The Role of Histocompatibility Testing in Military Medicine; Strong, D., Metz, S., Light, J., et al. Military Medicine in press.

Other Needs: A full time investigator with immunology interests would maximize the potential presently existing in this program. A biomedical data coordinator (research assistant) would facilitate communication and data application between lab and clinical service.

Future Work: Protocols to investigate the immunological effects Thoracic Duct Drainage are being prepared. TDD, when used for a prolonged period pretransplant, appears to abrogate many of the factors which now preclude successful transplantation in the highly sensitized patient.

Type of Report: Interim

Work Unit Number: 2616

Title: Obviating the GVH Response

Investigator: Annable, C. R., LTC, MC

Objective: As above

Technical Approach: See below

Progress and Results: The primary investigator left unexpectedly in Dec, 1978, without provision for continuing work on this project.

Conclusions: None

Funds Utilized, FY 79: $895 for GVH. $3,554 were used for other animal projects (see attached list).

Funding Requirements, FY 80: None

Type of Report: Interim

GVH Work Units

Title (1): Will Pretreatment with Immunosuppressive Agents Improve Allograft Survival

Investigators: Annable, C.R., COL, MC, Wildstein, A., MAJ, MC

Technical Approach and Progress Report: Previous preliminary experiments in our laboratory using skin grafts (SG) across the major histocompatibility barrier (AGB) in rats had indicated the following:

1. Recipient pretreatment - Imuran prolonged SG survival for up to 33 days.
2. Duration of survival was proportional to duration of therapy.
3. Hematological evaluation revealed progressive depletion of the monocyte population which tended to correlate with the longer graft survival times.

On the basis of these encouraging results, additional experiments in rats, this time using a heart transplant model, were undertaken. There was no graft prolongation despite the dame AGB barrier and the same drug doses. Furthermore prolonging heart allografts is usually much easier than prolonging skin allografts, lending some doubt as to the validity of the earlier results. When the first investigator's (CRA) experimental methods were examined by a second investigator (AW) serious methodological errors were found, basically invalidating the original conclusions. Repeat skin graft studies with a standardized technique showed no prolongation. Furthermore, monocyte counts were not consistently affected. Imuran pretreatment did not prolong islet cell transplant survival either.

Publications - Abstracts: Prolonged Skin Graft Survival Following Recipient Pretreatment with Azathioprine. Academic Surgeons, 1978; American Society Transplant Surgeons, 1979.

Title (2): Is Tilorone an Effective Immunosuppressive Agent?

Investigator: Wildstein, Albert, MAJ, MC

Technical Approach and Progress Report: Tilorone, an interferon inducer, has been reported to dramatically increase heart allograft survival in the rat. Very high doses (50 mg/kg) were utilized. Tilorone was not tested at lower doses, or in the pancreatic islet cell transplant model. We tested Tilorone in both these models at 10 mg/kg without any effect. Further studies will be continued this year, pending availability of technicians, funds, and an investigator. An informal protocol has been prepared and will be submitted.

DISPOSITION FORM

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

REFERENCE OR OFFICE SYMBOL	SUBJECT
HSWP-SOT	Some perspectives in evaluating Transplant Research at WRAMC

THRU: C, Dept of Surgery FROM C, Transplant Service DATE 22 October 79 CMT 1

TO: C, Clinical Investigation

Transplantation Research was originally established in the Department of Surgery, WRAIR in accordance with AR 40-3. Eventually two laboratories were committed. Professional and technical military personnel were not replaced, however, and in 1975, transplant research was transferred to WRAMC Clinical Investigation along with 4 spaces (2 military, 2 civilian). Unfortunately one military space was not transferred, so that person could not be replaced when he was reassigned. The following chronology tends to highlight the difficulties limiting productivity from our laboratory. Had it not been for dedicated workers from the NIH contract or from USUHS, virtually no concrete work would have been performed.

Jan-Aug 1977 - Immunological monitoring begun with procedures written and standardized. Two full time technologists (NIH, Histocompatibility lab) were involved. No CIS personnel involved except Mrs. Davis working with DNCB primarily.

Aug , 1977- Two NIH personnel left. (GS-9 and GS-5). GS-9 vacant until Feb 1979. GS-5 vacant until Oct 1977. (WRAMC CW personnel) CIS Sp-5 (Dickinson) trained in new technology over next few months.

Nov, 1977 - HLA lab supervisor left (GS-11) - Not replaced for more than 12 months by WRAMC civilian personnel. Monitoring lab technologist reassigned to clinical HLA. Spec Dickinson now operating alone without supervision.

Mar, 1978 - Mrs. Davis retires (Research lab supervisor) after one year period of more than 50% absenteeism from various illnesses. Position not filled by civilian personnel for 15 months. DNCB work halted.

Jul, 1978 - WRAIR laboratory space transferred to Forest Glen. Dr. Annable and Mr. Coleman continue work on various experimental animal models. Clinically relevant research - monitoring - remains at WRAIR with one technician (Dickinson).

Sep, 1978 - USUHS supplies Med. technician (May) and 6 month training process begins in transplant immunology, providing second person in research. NIH positions still not filled. HLA lab does both clinical and NIH contract work, while we remain 4 technologists short.

Dec, 1978 - CIS monitoring laboratory moves from WRAIR to new WR. D. M. Strong, PhD., NMRI, assumes supervision of monitoring and HLA lab. Weekly conferences begun. Assessment of previous results and technology begun. COL Annable leaves on TDY. No supervisor of FG lab available.

Feb, 1979 - New NIH technologist arrives, allowing more interaction of CIS and HLA labs. Efforts by WRAIR to close FG lab begin.

Jul, 1979 - Mrs. Davis' replacement arrives. Has no immunology or transplant experience. Spec Dicinson requests and is granted transfer, as things have been going poorly with the new techniques and new personnel. Military personnel promises replacement technician in October, but person is assigned to Ft. Meade instead.

Aug, 1979 - Efforts to combine research equipment and personnel with transplant division at NMRI rebuffed. FG lab closed. CIS recalls technician, suggesting that he would be better utilized by other WRAMC services. Transplant equipment placed in storage.

HSWP-SOT 22 October 1979
SUBJECT: Some perspectives in evaluating Transplant Research at WRAMC

Summary: Research during the two years that I've been Chief of the Transplant service can be summarized as having been plagued by multiple personnel vacancies, multiple laboratory moves and failure of productive supervision by the Chief of Transplant research. Research protocols and publications have not been produced by clinical staff. Furthermore, there is no clear definition between clinical and research work in the entire transplant field, because of the experimental nature of the clinical work. Closely studying observed clinical phenomena with research tools will lead to advances in understanding of this rapidly advancing field.

For the first time in two years, our technical positions will soon be completely filled, and newly assigned physicians will allow wider participation by the entire transplant staff in CIS projects.

Other Research Activities: Facilities of the transplant service are used to support the following CIS protocols:

1. Pancreatic Islet Preservation, Study and Autotransplantation - Weber
2. Parathyroid tissue preservation in vitro study and autotransplantation - Weber
3. Rehabilitation of ESRD patients - Nash
4. Hi. compatibility Antigens in Acute Anterior Uveitis - Killian & Piana
5. B 27 HLA Typing for Rheumatology

Other protocols pending submission:

1. Adrenal gland recovery following steroid withdrawal in the failed transplant patient - Delmonico, Light, Vigersky
2. Urinary abnormalities in transplant rejection - Delmonico, Light, Nash

JIMMY A. LIGHT, MD
COL, MC
C, Transplant Service

Work Unit #2804

Title of Project: An Evaluation of the Efficacy of Tadenan in the Treatment of Benign Prostatic Hyperplasia.

Principal Investigator: Chief, Urology Service

Requested that this project be terminated. It was never initiated because of FDA regulations and criteria which we cannot meet at this time.

Work Unit No: 2805

Title of Project: Biochemical Studies of Free polyamines in Serum Specimens of Patients with Genitourinary Carcinomas

Investigators: Nesbitt D. Brown, David G. McLeod, Piyush K. Gandhi, Bhupendra P. Doctor, H. Kenneth Sleeman, and Stephen Skoog

Objectives: To develop a tumor marker procedure, using serum samples for detecting the early symptoms of genitourinary neoplastic diseases.

Technical Approach: Utilizing a highly sensitive and specific high performance liquid chromatographic method, developed for separating and quantifying polyamines in hydrolyzed urine, we plan to adapt the procedure for referencing putrescine, spermidine and spermine in deproteinized serum samples. From our previous studies (1,2), elevated levels of putrescine and spermidine were observed in urine specimens of patients with various types of genitourinary carcinomas.

Although the method is adequate for analyzing the concentration of polyamines in urine, the potential usefulness of the procedure as a cancer marker might be better realized in evaluating polyamine levels in serum.

In a series of recently published reports, it has been shown that the values of putrescine and spermidine present in serum parallel and correlate with the values of 24 hour urine samples. Other reports have suggested the use of serum as a reliable indicator of polyamine synthesis in cellular proliferation for several reasons, among them are:

1. Serum polyamine values are not influenced by diurnal variations which are seen when urine samples are analyzed.

2. Normalization of values which are required with urine samples are not required when serum samples are analyzed.

3. Fluctuation of polyamine values due to improper urine collections or changes in kidney function does not occur with serum samples.

Until recently, previous methodologies used for analyzing polyamines in serum were inadequate. A more sensitive method was required to analyze serum or plasma. Utilizing a newly developed fluorometric procedure (2), the analysis of serum polyamines can now be accomplished. The use of this new procedure may prove to be the most practical method for clinically screening patients with genitourinary carcinomas.

Sampling: To insure that the results are accurate and precise, duplicate analyses will be performed on both the normal and experimental samples. We are requesting 20 normal and 40 experimental samples, initially. We will analyzed 120 samples for the complete study. (Similar to our previous study). These dual run analyses should be completed within 12 months. A group of samples will also be analyzed as a blind study to test the validity of our method. Statistical analyses will also be done on all results.

Funds requested FY-80:

Consumable supplies:	$4,500 (Chemicals, reagents enzymes and radioisotopes)
	$5,000 (Columns and analytical small equipment)
	$500 (Attendance at meetings)

Publications:

1. Sweet, R.B., Brown, N.D., DeBarre, L., McLeod, D.G., Doctor, B.P.; and Stutzman, R.E., Biochemical Studies of Urinary polyamines in Human Genitourinary Carcinoma. Proceedings of the Kimbrough Urological Seminar: Vol. 12 (1978).

2. Brown, N.D., Sweet, R.B., Kintzios, J.A., Cox, H.D., and Doctor, B.P., Determination of 5-Dimethylaminonaphthalene 1- Sulfonyl Derivatives of Urinary polyamines by Ion-Pair High Performance Liquid Chromatography. J. Chromatog. 164, 35 (1979).

Types of Reports: Interim

Work Unit No.: 2807

Title of Project: Determination of Human Prostatic Acid Phosphatase in Both Benign and Malignant Condition by Radioimmunassay.

Principle Investigators: D.G. McLeod, M.D., R.E. Stutzman, M.D., R.A. Sepulveda, M.D., W.D. Belville, M.D.

Objectives:

1. To establish the normal range of prostatic acid phosphatase in serum and bone marrow using RIA methodology. Completed.

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. Benign group completed.

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. See publications; two year follow-up in progress.

4. To continue the support (antibody) of a project entitled "Clinicopathologic Study of Prostate Tumors".

5. To evaluate the usefulness of the methodology for the medicolegal Applicability involving rape.

6. To develop an alternate immunochemical procedure that avoids the use of radioactive pharmaceutics. (ELISA)

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. (see publication #3). The levels of prostatic acid phosphatase found in the bone marrow of patients with prostatic carcinoma are correlated with the presence of bony metastasis. (See publications 1 and 2).

Progress and Results:

1. More than 200 controls have demonstrated on upper limit of 8.1 ng/ml for serum and 12.0 ng/ml for bone marrow (97.5 percentiles).

2. We have established a consistent significant elevation of serum prostatic acid phosphatase following transurethral prostatectomy. By studying more than twenty patients all demonstrated at least a four fold elevation from the baseline during the study. Prostatic massage in benign prostatic hypertro[illegible] has had no effect on the serum level. Currently patients with prostatic carcinom are being studied. Recent literature has suggested diagnostic potential if a serum elevation is elicited.

3. Bone Marrow Results by Radioimmune Assay. To date we have determined by radioimmune assay the prostatic acid phosphatase content of more than 200 marrow aspirates obtained from patients with various stages of prostatic carcinoma. Up to ninety-six 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, 18 and 25 percent, respectively, had elevated bone marrow prostatic acid phosphatase values. We suspect that the elevations found in those patients with C and D_1 disease represent the detection of occult metastatic disease. A two year follow-up is currently being carried out to answer this question.

Conclusions: Kits are now available to determine R.I.A. At present it has become standard practice to include an R.I.A. study on patients undergoing surgery for benign prostatic hypertrophy.

Funds Utilized: None

Funding Requirements, FY-80: None

Publications: None

Type of Report: Terminated

Work Unit No.: #2809

Title of Project: Relationship of Urinary Non-Esterified Cholesterol and Prostatic Cancer in Black America

Investicators:

Principle: Harry Y. C. Wong, Ph.D.

Associate: David G. McLeod, M.D. and Eustus S. Nelson, M.D.

Objectives: To develop a new biochemical test for the early diagnosis of prostatic carcinoma.

Technical Approach: Twenty-four hour urine samples were collected from fifteen black Americans and fifty-one white American males. These were analyzed by a modification of the gas liquid chromatography method of Vela and Acevedo (Steroids 14:499, 1969).

Progress & Results: We are presently attempting to correlate the urinary NEC and alkaline phosphatase levels with the various stages of BPH and prostatic adenocarcinoma. Data from some of the patients with BPH have slightly higher NEC than our previous report. We are reviewing the patient's records to determine any endocrinopathies and/or medications, if any, they were taking when their urine samples were collected. It is known that certain diseases and drugs will produce a higher NEC level. We are in need of urine samples from "normal" healthy males, above 50 years of age for pair-matching.

Conclusions: Our preliminary findings indicate that there is an increase in the level of urinary NEC in all black patients with untreated prostatic cancer as compared to a lower concentration for subjects with benign prostatic hypertrophy. The "normal" healthy black males and most of the patients under treatment for prostatic carcinoma, with the exception of two subjects, were within normal limits. The urinary NEC levels may be useful in determining whether a patient is under control or not while being treated.

Funds Utilized, FY-79: None

Funding Requirements, FY-80:

Travel: $1,000 - To attend a meeting and presentation of paper by Dr. Nelson

Publications: None

Type of Report: Interim

Work Unit No.: 2810

Title of Project: Comparative Study of High Dose Versus Low-Dose Pre-operative Radiation to Radical Cystectomy for Control of Transitional Cell Carcinoma of the Bladder.

Investigators:

Principal: David G. McLeod, M.D.

Urology Service, WRAMC
Duke University

Objectives: The purpose of this study is to determine whether moderate dose preoperative adjunctive radiotherapy plus radical cystectomy is as effective as low dose preoperative adjunctive radiotherapy plus radical cystectomy and pelvic node dissection in enhancing survival and prolonging the disease free interval, to determine the relative rates of tumor downstaging, the relative complication rates, the relative periods of hospitalization and time lost from work, (the relative cost of treatment selection), and the impact of delayed surgical treatment on the appearance of detectable metastatic disease.

Technical Approach: Patients are randomized to receive either high dose or low dose radiation therapy prior to radical cystectomy.

Progress and Results: Six patients have been entered into the study.

Conclusions: None at present.

Funds Utilized, FY-79: None

Funding Requirements, FY-80: None

Publications: None

Type of Report: Interim

Work Unit No.: 2900

Title of Project: Efficacy of Epirizole in Eliminating or Minimizing Post-Operative Edema in Patients Undergoing Elective Plastic Surgery Procedures

Investigators: H. D. Peterson, COL, MC

Associate: F. G. Lapiana, COL, MC (for eye examinations)

Objectives: To evaluate a non-steroidal drug as to its effect in reducing post-operative edema in elective surgical procedures. This was a combined project with the Oral Surgery Svc at Brooke Army Med Ctr and 2 oral surgery services in the civilian community.

Technical Approach: A drug was given in a double blind fashion to patients having either 4 lid blepharoplasties or osteoplastic rhinoplasties on the plastic surgery svc. The drug was given 24 hours prior to surgery and for 6 days postoperatively. Edema was quantitated on a scale of 0 to 4 plus each day after the surgical procedure. There were no changes in the protocol during the study.

Progress & Results: 9 patients were evaluated, 7 blepharoplasties and 2 rhinoplasties. It was the clinical impression that there was no difference in any of the patients as far as post-operative edema. In September 1979, the drug company providing the drug requested that we not do any more cases until all of the centers had been evaluated, because it was the impression of the other centers, especially the oral surgery services where each patient was able to act as his own control, that the drug was without efficacy.

Conclusions: The final conclusion is awaiting correlation of data from the various centers. There were no serious or unexpected side effects in any of the participating patients.

Funds Utilized, FY-79: None

Funds Utilized, FY-80: None

Publications and Abstracts: As of this date, none

Estimated date of completion: The estimated date of completion will await the correlation of the data, but it is very likely that the study has been completed at this time.

Work Unit No.: 3138

Title of Project: Immunologic Mechanisms of Cutaneous Reactions to Inhalant Allergens

Investigators:

Principal: Richard D. deShazo, M.D.

Associate: H.M. Dvorak, M.D.

Objectives: To define the immunologic mechanisms responsible for untoward cutaneous reactions seen with the injection of inhalant allergens

Techinal Approach: Immediate hypersensitivity skin tests, punch skin biopsy, light and fluorescent microscopy, RAST IgE.

Progress and Results: During the last year we have been involved in a collaborative effort with investigators at FAMC in extenting our previous observations on the etiology of late cutaneous allergic reactions (LCAR). The protocol has involved the use of H_1 and H_2 antihistamines and Aspirin in attempts to block the development of LCAR. The use of these drugs was covered under FAMC protocol and parts of the study involving drug treatment were performed at FAMC. Eight patients with LCAR to ragweed were studied. H_1 blockers decreased the immediate wheal and flare (WFR) reaction but not the LCAR. H_2 blockers had no effect on either reaction. The combination of H_1 and H_2 blockers increased the inhibition of the WFR and obliterated the LCAR. Aspirin had no effect on either response. This finding implicates the involvement of the H_2 histamine receptor in the production of the LCAR for the first time. Histopathological examination of LCAR from treated patients are to be done.

In addition to these collaborative efforts, we have studied four dialysis patients for evidence of heparin induced inhibition of LCAR. To date, all have shown inhibition of LCAR with dialysis. This substantiates previous evidence for involvement of the coagulation process in the LCAR.

On-going work will further document the involvement of the H_2 receptor and the coagulation system in the LCAR. An addendum to this protocol allowing injection of H_1 agonists into human skin is planned.

Funding Requirements FY-80:

Personnel: 1 GS-07 Technician 7 weeks/year

Equipment: No additional requirements

Supplies:	$4400.00
Travel	325.00
	$4725.00

Publications:

(1) deShazo, R.D., Levinson A.I, Dvorak H.M, Davis R.W.: The late phase skin reaction. J. Immunol 122:692, 1979.

(2) Smith, J.A., Mansfield LE, deShazo, R.D, inhibition of the immediate and late cutaneous reaction to allergin. J. Allergy Clin Immunol in press.

Complications: None

Changes in Original Protocol: None

Type of Report: Interim

Work Unit No.: 3144

Title of Project: Neurophysiologic, Immunologic and Biochemical Aspects of Bronchial Asthma

Investigators:

Principal: Laurie Smith, M.D.

Associates: Richard Evans III, COL MC
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 bronchial challenge. The following tests will be performed at NIH:

1) Oral aspirin challenge
2) Eccrine sweat responses to saline mecholyl and propranolol
3) Pupillometry to measure pupil responses to Carbachol and Phenylephrine
4) Response of cyclic nucleotides to intravenous injections of very low doses of isuprel

The following tests will be performed at WRAMC Allergy Clinic:

1) Mecholyl bronchial challenge with air and He/02
2) Histamine bronchial challenge with air and He/02

Note: Certain equipment must be expanded and modified.

Progress & Results: During the previous year we expanded our study group to over 22 allergic asthmatic subjects who have undergone some or all of the above mentioned studies. We have also studied 4 intrinsic asthmatics. Further in studying an asthmatic patient with cystic fibrosis, we detected previously undescribed abnormalities of adrenergic and cholinergic sensitivity and lack of beta adrenergic sensitivity in this patient and his family. We have found the same abnormalities in cystic fibrosis patients and their parents who do not have asthma; that is, the abnormalities are present with and without asthma. We have studied 10 parents of children with cystic fibrosis and have shown definite autonomic nervous system abnormalities.

Conclusions: In summary:

1) Allergic asthmatics show increased sensitivity to alpha adrenergic and cholinergic stimulation and decreased sensitivity to beta adrenergic stimulation.

2) Intrinsic asthmatics show these defects similarly but to a greater degree.

3) Patients with cystic fibrosis and their parents, with and without asthma, also demonstrate these abnormalities.

4) These studies suggest autonomic nervous system abnormalities are not enough alone to result in bronchial asthma.

5) This project merits high priority for continued funding.

6) There have been no serious or unexpected side effects or complications in subjects participating in this study.

Funds Utilized, FY-79: None

Funding Requirements, FY-80:

Travel:		$ 600.00
Other:	Reprints and publication costs	700.00
		$1300.00

Publications and Abstracts:

1) The array of autonomic abnormalities in allergic asthmatic patients. L. J. Smith, J. R. Shelhamer, R. Evans III, D. D. Metcalfe, M. Kaliner, J. Allergy Clin Immunol 63, 141, 1979, (abstract).

2) Alpha adrenergic hyperresponsiveness in asthma: W. R. Hendersou, J. H. Shelhamer, D. B. Reingold, L. J. Smith, R. Evans III, and M. Kaliner, NEJM 300, 642, 1979.

3) An abstract: "Autonomic nervous system dysfunction in patients with cystic fibrosis: has been submitted for presentation to the American Academy of Allergy, Feb, 1980.

Type of Report: Interim

Work Unit No.: 3146

Title of Project: Immunotherapy Kit Potency Persistence

Investigators:

Principal: Richard J. Summers, M.D. LTC MC

Associates: Richard Evans III, M.D. COL MC
Michael S. Edwards, CPT MSC

Objective: The study is designed to determine the persistence of biological potency of allergy extracts during shipment and use.

Technical Approach: RAST (Radioallergosorbent Test) will be performed to determine potency persistence.

Progress & Results: The extracts have been shipped and returned. Aliquots are being taken at intervals and final results should be available in four months.

Conclusions: No conclusions can be made until all results are in.

Funds Utilized, FY-78: $500 of estimated total cost of protocol

Funds Utilized, FY-79: $1300 of estimated total cost of protocol

Funding Requirements, FY-79:

Personnel:	One GS-7 technician, currently employed, 2 weeks/year	
Equipment:	No new equipment is required	
Supplies:	Consummable - needles, syringes and RAST testing	$3700.00
Travel:	None	
	Total	$3700.00

Publications: None

Type of Report: Interim

Addendum:

Principal Investigator: Richard J. Summers, M.D. LTC MC

Associate Investigator: Richard Evans III, M.D. COL MC

Associate Investigator: Michael S. Edwards, CPT MSC

Work Unit No.: 3147

Title Of Project: Hymenoptera Venom Safety and Efficacy Evaluation as Allergen Immunotherapy in Insect Sting Allergy Patients

Investigators:

Principal: Daniel A. Ramirez, MAJ MC

Associate: Richard Evans III, COL MC

Objective: To establish the safety and effectiveness of hymenoptera venom preparations in the prevention of anaphylactic reactions following hymenoptera stings.

Technical Approach: Patients with a history of having systemic reactions following a hymenoptera sting are evaluated by skin testing using a skin test titration technique from 10^{-3} ug/ml up to 1 ug/ml. Concordant venom RAST titers are also obtained. Routine chemistries, CBC with sedimentation rate, urinalysis, C3, C4, FANA, and venom specific titers of IgE and IgG will be followed every 3 months.

Progress & Results: A total of 90 patients have been evaluated by skin testing for inclusion into the study. The lyophilized reagents used were as follows:

1. Honey Bee Venom Lot No. DA 2358
2. Polistes Wasp Venom Lot NO. DD 6555
3. Yellow Hornet Venom Lot No. DA 4877
4. Yellow Jacket Venom Lot No. DD 6377
5. White Faced Hornet Lot No. DD 6556
6. And also for treatment Mixed Vespid (White Faced Hornet, Yellow Hornet, Yellow Jacket) Lot No. DD 6379

All these allergenic extracts have expiration dates of April 1981 and are manufactured by Pharmacia Laboratories, Division of Pharmacia Inc., Piscataway, New Jersey 08854.

No new patients have been added to this study since 30 March 1979 when the above materials were licensed for general use by the Food and Drug Administration. 24 were selected for venom immunotherapy. Nine patients have moved from the area and are no longer in the study. These patients are on clinical allergy treatment with licensed materials. 15 patients continue in the study and have reached a maintenance treatment dose of 100 ug of venom per month.

Progress & Results: (Continued) No patients have experienced a systemic reaction. No abnormalities of the laboratory parameters have thus far been detected. The specific IgE and IgG antibody titers have been performed. In approximately half of the patients, the IgE antibody titer increased with immunotherapy. In all patients, the specific IgG antibody increased with immunotherapy. Nine patients have been stung since venom therapy. None of these have had an anaphylactic reaction.

Conclusions: Hymenoptera Venom extracts have so far been shown to be safe for use in immunotherapy. Efficacy in preventing anaphylactic reactions upon subsequent stings has also been demonstrated.

This group of patients will be followed for one more year. During this time sera for specific IgE and IgG antibody will be collected at 3 month intervals. Hopefully at that time a definite statement can be made concerning the relationship of these antibody titers to risk, from subsequent insect stings.

Funds Utilized, FY-79: $7,450.80

Funding Requirements, FY-79:

Supplies:	(syringes, and radioimmunoassay materials)		
	Syringes	$ 50.00	
	Radioisotopes	1750.00	
	Rabbit antihuman IgE F(c)	1000.00	
	Goat antirabbit sera	1150.00	
	Rabbit antihuman IgG F(c)	900.00	$4850.00
Travel:	(presentation at national meeting)		500.00
			$5350.00

Type of Report: Annual Progress Report, Interim.

Publications: Ramirez, DA and Evans III, R: The diagnosis of Hymenoptera hypersensitivy, J Allergy Clin Immunol 63:136, 1979 (Abstract).

Presentations:
1. An abstract for presentation by Dr. Ramirez of part of these data regarding diagnosis has been accepted for the scientific section of the American Academy of Allergy meeting in March 1979.
2. An abstract for presention by Dr. Evans of part of these data regarding treatment has been accepted for a scientific workshop of the American Academy of Allergy meeting in March 1979.
3. Consultant Visit to Illinois Allergy Society, Chicago, Illinois, June 1979.

Addendum:

Principal Investigator: Ana A. Ortiz, MAJ MC

Associate Investigator: Richard Evans III, COL MC

Associate Investigator: Michael S. Edwards, CPT MSC

Work Unit No.: 3149

Title of Project: Investigation of Immunologic Imbalance in Atopic Dermatitis

Investigators:

Principal: Donna Lynn Schuster, MAJ MC

Associate: Richard Evans III, COL MC

Consultant: Arnold I. Levinson, MD
University of Pennsylvania
Philadelphia, Pennsylvania

Objective: The purpose of this study is to determine the presence of a possible immunologic imbalance in atopic dermatitis, particularly in regard to suppressor T cell function as well as to study the regulation of IgE in this patient population.

Technical Approach: We are currently using a standard rosetting technique to characterize lymphocyte subpopulations in patients with atopic dermatitis (AD) and elevated IgE. OXRBC sensitized with either rabbit IgM or rabbit IgG anti-OXRBC are used in a rosetting procedure to identify T mu (helper cell) or T gamma (suppressor cell) respectively. In additional experiments, these subpopulations are cultured for 1 hour, overnight with either a B adrenergic agonist (Isuprel) B adrenergic antagonist (propanolol), alpha adrenergic agonist (phenylephrine), alpha adrenergic antagonist (phentolamine) or aminophylline. In other experiments, these subpopulations are also cultured in the presence of histamine, antihistamine (H_1 benadryl) or cimetadine (H_2).

In addition, we are currently utilizing a radioimmunoassay employing both the PRIST and RAST methods to measure low level IgE found in supernatants of cocultures of lymphocyte subpopulations in our patients as well as in our controls. This method has proven to be more sensitive than the double radioimmunoassay which we were using earlier this year.

Progress & Results: To date, 12 patients with active atopic dermatitis were studied. In all 12 patients, we have found a deficiency of absolute as well as relative numbers of T gamma cells with normal numbers of total lymphocytes as well as T mu cells when compared to our control groups.

We are presently investigating whether this aberration is a marker for the elevated IgE or for the disease state itself. We are currently studying T-cell subpopulations in patients with inactive atopic dermatitis. To date, 4 patients with inactive atopic dermatitis have been found to have normal numbers of T gamma cells. We plan to continue to follow the T gamma cell numbers in our active atopic dermatitis as well as inactive atopic dermatitis patients sequentially. In addition, we are planning to study patients with elevated IgE without atopic dermatitis.

Since it has been postulated that some of the abnormalities noted in AD may be related to a B adrenergic blockade and since recent studies have demonstrated a differential sensitivity of Ig receptors on T mu and T gamma cells to agents modifying levels of cyclic nucleotides, we have begun to study the modulation of T gamma cells in AD patients when cultured in the presence of agents effecting cyclic nucleotide levels. We also are culturing these subpopulations in the presence of histamine, H_1 antagonists and H_2 antagonists to further investigate if the T gamma cell deficit may be secondary to an IgE dependent action.

To investigate the regulation of IgE directly in our patient population we have been working on a radioimmunoassay for IgE which will enable us to measure low level IgE. To date, we now are able to measure levels as low as 50 pg/ml.

Conclusions: We have found a selective deficiency of T gamma cells in patients with active AD. Preliminary studies in patients with inactive AD seem to indicate that T gamma cell deficit may correlate with the activity of the atopic dermatitis. We plan to further delineate this by studying our patient population sequentially.

Presently, we are investigating whether this T gamma cell deficit is related to a B adrenergic blockade or to an IgE dependent action. In particular, IgE directed release of vasoactive amines (i.e. histamine) which could modulate the expression of Fc receptor for IgG.

In addition, with the ability to measure low level IgE, we are planning to look directly at the modulation of IgE itself in our patient population.

Funds Utilized, FY-79: $10,000.00

Funding Requirements, FY-80:

Personnel:	20 hours of GS9 technician time per week x 52 weeks		
Equipment:	Glassware, culture plates, pipettes, plastic tubes, etc.		$ 3000.00
Supplies:	Culture media, fetal calf sera OXRBC	$5000.00	
	Radio isotopes (PRIST, RAST)	5000.00	
	Reagents for equipment (coulter counter CO2)	2000.00	
	Drugs	1000.00	13000.00
Travel:			600.00
			$16600.00

Publications & Abstracts (FY-79):

1. Schuster, D.L., Bongiovanni, B., Pierson, D. and Levinson, A.I.: Suppressor cell function in atopic dermatitis associated with elevated Immunoglobulin E., J. Allergy Clin. Immunol. 64:139, 1979.

2. Schuster, D.L., Bongiovanni, B., Pierson, D., Barbaro, J., Wong, D., and Levinson, A.I.: Deficiency of a T-cell subpopulation in Atopic Dermatitis, Clin. Res. 27:245, 1979 (abst.).

Type of Report: Interim.

Work Unit No.: 3151

Title of Project: Allergic Disease Center Study of Hymenoptera Venom as an Agent for Diagnosis

Investigators:

Principal: Daniel A. Ramirez, MAJ MC

Associate: Richard Evans III, COL MC

Objective: To establish the effectiveness of hymenoptera venoms as testing agents in making the diagnosis of insect sting allergy.

Technical Approach: Patients with a history of allergic rections to hymenoptera stings are skin tested with the commercially available whole body extracts and with insect venoms using a skin test titration of 10^{-3} ug/ml up to 1 ug/ml. Venoms from Honey Bee, Yellow Jacket, Yellow Hornet, White Faced Hornet and Wasp are provided by the NIAID, NIH. Catalog was A(63+1635)-902-585, received November 1978.

Progress & Results: 187 patients have been skin tested to date. The patients were divided into groups based upon the history of a reaction to an insect sting. The groups included: systemic reactions, large local reactions, and patients previously treated with whole body extracts (WBE). The results are as follows:

DERMAL REACTIVITY OF STUDY GROUPS

VENOM CONCENTRATION	SYSTEMIC REACTIONS n=65	LARGE LOCAL n=16	CONTROLS n=20	PREVIOUSLY ON WBE n=87
0.001ug/ml	2	0	0	2
0.01ug/ml	12	1	0	4
0.1ug/ml	26	4	0	15
1.0ug/ml	15	7	0	58
neg	10	4	20	8
% pos	84%	75%	Ø	83%

Conclusions: Direct skin stests with insect venoms clearly separate patients with a history of previous systemic reaction from the control population. Patients with a history of large local reaction to an insect sting have positive direct skin tests to venom with a surprisingly large frequency. Considerable cross reactivity or multiple sensitivity was found to the insect venoms of the vespids (yellow jacket and hornets). In the subsequent year we plan to observe the patients in the large local group for evidence of risk upon subsequent insect sting. Skin tests will be repeated in several patients. In vitro tests for IgE antibody will also be done.

Funds Utilized, FY-79: None

Funding Requirements, FY-80:

Supplies:	Syringes	$ 30.00
	Reagents for in vitro measurement of IgE (radioimmunoassay)	3000.00
Travel:	Presentation by: CPT Edwards, COL Evans and LTC Summers at the Fitzsimons Army Medical Center Pulmonary Allergy Symposium, September 1979.	600.00
		$3630.00

Type of Report: Annual Progress Report, Interim.

Addendum:

Principal Investigator: Richard Evans III, COL MC

Associate Investigator: Michael S. Edwards, CPT MSC

Work Unit No.: 3152

Title of Project: Factors Affecting Theophylline-Half-Life

Investigators:

Principal: Paul F. Walker, MAJ MC

Associates: Rodolfo Bongiovanni, CPT MSC
Richard Evans, COL MC

Objectives: Determine variations of biologic half-life of Theophylline comparing values obtained following intravenous infusion of Theophylline in normal volunteers and asthmatics under various clinical states and treatment programs.

Technical Approach: A. Population of non-asthmatic "normal" volunteers (6) will be given a single intravenous dose of aminophyllin (5 mg/kg) by rapid infusion (5 min). Blood samples will be obtained immediately prior to the infusion and at 0, 5, 10, 15, 30, 45, 60, 90, 120, 240, 360, 480 minutes following infusion of aminophyllin.

B. A population of known reversible asthmatics (15) will be studied under the conditions stated above in section A. Pulmonary function testing will also be obtained immediately prior to the infusion and at one hour following completion of the infusion, and six hours following completion of the infusion. These asthmatics will be studied under Plan A under the following conditions:

1. Acute onset dyspnea and bronchospasm, not reversible by epinephrine.

   a. Aminophylline 5 mg/kg in rapid infusion
      Solu-medrol 2 mg/kg IV Push
      Bronkosol 0.5 mg/2.5 mg NS by inhalation
   b. Blood samples obtained as in Plan A.
   c. Pulmonary functions obtained as in Section B.

2. Clinically stable, on outpatient theophylline, corticosteroids, either alupent or terbutaline orally.

3. Clinically stable on theophylline, corticosteroids

4. Clinically stable on theophylline, terbutaline/alupent.

5. Clinically stable on outpatient theophylline alone.

C. In sections 2-5, patients will be given 5 mg/kg aminophyllin in a rapid intravenous with blood samples and pulmonary function studies obtained as previously described.

Progress and Results: To date: Pharmacokinetic studies have been carried out on three normal volunteers on three separate occasions manifesting no significant difference in clearances, $T_{1/2}$ alpha and $T_{1/2}$ beta in a given individual from day to day.

Seven patients were studied under conditions of clinically stable and acute asthma with follow-up studies obtained under one of the previously-mentioned treatment programs.

In all cases so studied, there is no difference in the rate of clearance and in the $T_{1/2}$ beta.

Pharmacokinetic studies have not been completed for the other categories to date due to limitations determined by difficulties in obtaining optimal control of the disease state, and due to problems with compliance in the case of several of the participants.

Conclusions: A. There appears to be no significant effect on the clearance and $T_{1/2}$ beta of theophylline that is determined by the activity of the basic disease process.

B. There appears to be no significant difference in the clearance $T_{1/2}$ alpha and $T_{1/2}$ beta of theophylline in healthy individuals on a day-to-day basis.

C. Study should be continued to show conclusive evidence that no change on the biologic clearance and half life of theophylline is effected by the use of multiple-drug therapy.

Funds Utilized, FY-79: $3,750.00

Funding Requirements, FY-80:

Type of Report: Interim

Work Unit No.: 3154

Title of Project: Evaluation of Prostaglandin - Producing Suppressor Cells in Cancer Patients

Investigators:

Principal: Richard D. deShazo, M.D.

Associate Barbara Bongiovanni, B.S.

Objectives: To confirm the presence of previously reported prostaglandin - producing cells capable of suppressing cell mediated immunity in patients with Hodgkin's disease (HD) and establish their in vivo and in vitro sensitivity to a prostaglandin (PG) synthetase inhibitor (indomethacin).

Technical Approach: In vitro lymphocyte culture with the mitogen DHA with and without indomethacin; in vitro lymphocyte culture after oral indomethacin, serum indomethacin levels, delayed hypersensitivity skin tests.

Progress: During this FY, extensive and detailed work has been performed under this protocol. We have confirmed the existence of indomethacin sensitive mononuclear suppressor cells in 10 Hodgkin's disease patients. Furthermore, suppressor cell sensitivity to indomethacin has been extensively studied in 4 patients (in vivo) and 8 (in vitro) treated controls. This study demonstrated improvement of patient in vitro lymphocyte proliferative responses subsequent to oral treatment but failed to demonstrate changes in skin test reactivity. These findings raise the possibility that long term indomethacin therapy may result in improvement of patient lymphocyte function and alteration of the disease process it self. Ongoing research seeksto evaluate the effects of low dose (blood levels of 1 ug/ml) indomethacin therapy on skin test and lymphocyte function over a two week treatment period.

Funds Utilized FY-1979: $8,000.00

Funding Requirements, FY-80:

Personnel: 1 GS-07 Technician 30 week/year

Equipment: None

Supplies:		$8000.00
Travel:		350.00
Other:	Indomethacin levels (National Medical Laboratories)	400.00
		$8750.00

Publications: Evaluaton of Prostaglandin Secreting Suppressor Cells in Hodgkin's Disease. Clin Immunol Immunopath: in press

Estimated Date of Completion: 1981

Complications: None

Type of Report: Interim

Work Unit No.: 3155

Title of Project: Evaluation of Suppressor Regulatory Cells in the Pathogensis of Immunodeficiency Disease

Investigators:

Principal: Richard D. deShazo, M.D.

Associates: Tami Hase, B.S.
Sonnya Londono, B.S.

Objectives: To define the activity of suppressor immunoregulatory cells in immunodeficiency disease.

Technical Approach: Lymphocyte culture, ^{51}Cr chemotaxis assay

Progress: Patients with chronic mucocutaneous candidiasis (CMC) are unable to resist skin and mucous membrane colonization with Candida species. We sought to determine if this problem might be explained by an inability to generate antigen specific chemotatic lymphokine (CL), a substance thought to be capable of attracting inflammatory cells into areas of fungal colonization. Such a deficiency could be related to suppressor cell activity seen in these patients.

Seven CMC patients with positive skin tests to candida but active skin disease and eight normal vounteers with positive candida skin tests were chosen for study. Patient or control mononuclear cells (MNC) were cultured in serum-free Media 199 with penicillin, streptomycin, and 1% glutamine for 48 hours at 1×10^6 cells/ml in the presence or absence CON-A (20 ug/ml) or candida (10 ug/ml). Supernatents were harvested and frozen at -70°C until use as chemoattractant stimuli (1:2 dilution in Gey's Buffer) for ^{51}Cr labelled polymorphonuclear cells. (2.3×10^6 cells/ml) in Boyden chambers with 2-5u Sartorious filters. CL was determined as corrected counts/min (CCM) in the lower filter for CON-A or Candida generated supernatents less CCM for unstimulated cells.

All eight controls generated CL in response to both CON-A (399 ± 116) and Candida (85.9 ± 23.7) stimulation. Two of the seven patients failed to generate CL on either CON-A or candida stimulation. The remaining five generated CL to both CON-A ($448/6 \pm 102.$) and Candida (402.0 ± 326.7). This data suggests that most CMC patients with active disease and positive skin tests are capable of generating CL and that a deficit of this lymphokine is not responsible for their ongoing candidiasis. A subgroup of these patients may be unable to generate CL to multiple stimuli. Further studies of this group are underway.

Funds Utilized FY-79: $7,020.00

Funding Requirements:

Personnel:	1 GS-07 Technician 52 weeks
Equipment:	None
Supplies:	$8,600.00
Travel:	250.00
Other:	
Total	$8,850.00

Publications: Initial manuscript in progress

Estimated Date of Completion: 1981

Complications: None

Changes in Original Protocol: None

Type of Report: Ongoing

Re: Request for additional information on annual progress report for protocol #3155.

1. Regarding the question as to completion of study, this is a broad protocol allowing us to study a variety of immunodeficiency diseases as the patients become available to us.

2. The present report (FY-78) delt with evaluation of seven (7) patients with chronic mucocutaneous candidiasis. We are indeed through with studying suppressor activity in those patients as they are no longer available to us. Work on publication of this data is in progress.

3. We are presently studying a group of patients with common variable immunodeficiency disease and suppressor cells under this protocol.

4. Respectfully request that the conservative projected budget requested for this important work be funded and that the protocol be extended.

RICHARD D. DESHAZO, M.D.
MAJ, MC
Clinical Immunologist

DISPOSITION FORM

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

REFERENCE OR OFFICE SYMBOL	SUBJECT
HSWP-QAI	Protocol #3155

TO Chief, CIS FROM Richard D. deShazo, Clinical Immunologist DATE 6 Dec 79 CMT 1

Re: Request for additional information on annual progress report for protocol #3155.

1. Regarding the question as to completion of study, this is a broad protocol allowing us to study a variety of immunodeficiency diseases as the patients become available to us.

2. The present report (FY-78) delt with evaluation of seven (7) patients with chronic mucocutaneous candidiasis. We are indeed through with studying suppressor activity in those patients as they are no longer available to us. Work on publication of this data is in progress. Further studies are being carried out on serum samples obtained from these patients. We are attempting to relate their IgE production to the status of their delayed hypersensitivity (skin tests, lymphocyte proliferation) assayed at the time of the original study.

3. We are presently studying a group of patients with commmon variable immunodeficiency disease and suppressor cells under this protocol.

4. Respectfully request that the conservative projected budget requested for this important work be funded and that the protocol be extended.

Rick deS

RICHARD D. DESHAZO, M.D.
MAJ, MC
Clinical Immunologist

DA FORM 1 FEB 67 2496 REPLACES DD FORM 96, WHICH IS OBSOLETE.

Work Unit No.: 3158

Title: Evaluation of the Immune Pathologic Mechanisms Operative in Dermal Reactions to Insulin

Investigators:

Principal: Richard D. deShazo, M.D

Associates T.M. Boehm, M.D.
H.M. Dvorak, M.D.

Objectives: To define the mechanisms and develop treatment regimens for dermal reactions to insulin.

Technical Approach: Light and immunofluoresoemicroscopy of skin biopsies, radioimmunoassy of insulin antibodies, insulin skin testing.

Progress and Results: During the initial year of this study, twelve patients with serious local insulin reactions have been skin tested to standard and research insulins, their lesions biopsied and sera collected. Six of these patients were studied at Walter Reed Army Medical Center and six at the Lilly Laboratories in Indianapolis. All patients were evaluated by the principal investigators. It is anticipated that histopathological studies will allow classification of these reactions into Arthus, delayed hypersensitivity, or late cutaneous allergic responses. Treatment programs directed specifically toward these types of dermal reactions have been developed and will be explored.

At the present time, the initial biopsy specimens are in the hands of Dr. Dvorak in Boston and the insulin antibody assay is being developed. An additional set of twenty-four sera from diabetic patients has been collected for comparison study.

We plan to collect more biopsies (5) over the next year to assure that all three possible types of reactions have been studied. Futhermore, specific treatment modalities will be studied where indicated.

Funds Utilized FY-79: $400.00

Funding Requirements FY-80:

Personnel: GS-07 Technician 6 hours/week for 80 weeks

Equipment: No Additional requirements

Supplies: $2675.00

Travel: 600.00

Type of Report: Interim

1. Work Unit No: 3159-R

2. Title of Project: In Vivo Removal of Circulating Antibodies and Immune Complexes by Immunoadsorbents.

3. Principal Investigator: Bernard H. Berne, M.D., Ph.D.

4. Objectives:

   a. To develop systems containing immunoadsorbents capable of removing proteins from the blood of rabbits by extracorporeal circulation.

   b. To remove circulating antibodies and immune complexes (IC) from rabbits and to determine their clearance and reappearance rates during and after their removal.

   c. To develop a procedure for removing circulating antibodies and IC that is devoid of adverse clinical and hematological effects and which can serve as a prototype for human use.

5. Technical Approach:

Phase I - Initial experiments will test the albumin-anti-albumin system, since this has been extensively investigated already by others. We will immunize rabbits with a subcutaneous and an intramuscular injection of 5 mg of bovine serum albumin (BSA) in complete Freund's adjuvant. Antibodies to BSA should develop within two weeks; their appearance will be ascertained by radioimmunoassay. Following the appearance of antibodies, a dose of BSA will be given intravenously. This should result in the formation of immune complexes between the BSA and the anti-BSA. These will be detected by an assay for IC that we have already developed.

The amount of BSA to be injected intravenously for IC induction will have to be determined empirically, and will probably differ for each animal since each will most likely develop different antibody levels. The radioimmunoassay for anti-BSA antibodies will provide the titer of antibodies in each animal. By adding BSA to the antibody in vitro, we will be able to determine the amount of BSA necessary to form soluble complexes detectable by the immune complex assay. Taking into account the blood volume of the rabbit, we will then calculate the amount of BSA to be injected to form soluble immune complexes in vivo. We will then inject this amount of BSA into the rabbits and determine whether the in vivo formation of complexes requires the same or a different antigen/antibody ratio as compared to the in vitro model. If the in vivo formation of IC requires a different ratio, this will be used in future trials.

Other: Patient payment for skin biopsies (AR 7-25, US Statute 31, US Code 665) $1000.00

Publications: None to date

Complications: None

Type of Report: Interim

Technical Approach Continuation:

Five adult male rabbits housed at WRAIR will initially be immunized with BSA. The appearance of antibodies will be monitored by bleeding from an ear vein once every three days. After the intravenous injection of antigen, the animals will be bled daily until it is ascertained that the induced immune complexes have been cleared from the circulation. The animals will then be sacrificed and autopsied. Histological examination of the kidneys will be performed with the assistance of the Veterinary Pathology Division of WRAIR. Personnel of this division will perform autopsies on all animals that are sacrificed or die during the experiments.

Gross pathological examinations of all organs and hemotoxylin-eosin staining of rabbit kidneys will be performed, and the pathological findings will be interpreted in light of the experiments performed. Antigen, antibody and IC deposition in the kidneys will be detected by immunofluorescent microscopy for the presence of albumin, IgG, IgM, C3 and C4. Kidney slices will be incubated at low pH to elute complexes which can be detected in radioimmunoassays for albumin, anti-albumin, and IC.

With each group of five animals tested in the study, 2-5 rabbits will be set aside as untreated controls. These will be sacrificed after 4 weeks and autopsied for evidence of renal immune complexes deposited as a result of infectious processes. Complement fixation assays for agents (primarily protozoal) causing such deposits will be performed on sera from all animals in the test and control groups, and only

rabbits that appear free from these agents will be used in the studies.

If none of the original five rabbits develope detectable immune complexes after the intravenous injection of BSA, these animals will be sacrificed and a dose of BSA three times as high will be injected into a second group of five immunized rabbits. Although unlikely, it is possible that we will not succeed in inducing IC formation in either of the first two test groups. If no complexes form after ten animals have been tested, we will inject complexes formed in vitro into five unimmunized rabbits and will study the kinetics of their disappearance in these animals, as well as the pathological sequelae of the injection.

As a part of Phase 1, several radioimmunoassays will be developed. We will design an assay for BSA and for anti-BSA using a double antibody technique. BSA will be labelled with 125-I by the Chloramine T or the Bolton-Hunter method, depending upon reagent availability and labelling efficiency. A commercial rabbit antiserum to BSA will be reacted with this, and a goat antiserum to rabbit immunoglobulin will be used as a second antibody. In the test for BSA as an antigen, the BSA circulating in rabbits and present in serum will act as an unlabelled inhibitor of the precipitation of labelled BSA. In the test for antibodies to BSA, rabbit serum suspected of containing anti-BSA will be substituted for the commercial antiserum to BSA; the amount of labelled BSA precipitated will increase as the titer of anti-BSA antibody rises.

We have already developed an assay for monitoring immune complex levels based on the binding of IC by iodinated C1q and the precipitation of the bound C1q by 25g/L of polyethylene glycol (MW 6000). This assay will be applied to the measurement of IC in tested and control rabbits.

Some IC may not be detectable by the C1q binding assay, although this is one of the more sensitive tests for these. If the assay detects no IC in any rabbits which develop circulating antibodies, we will develop an IC assay based on precipitation with monoclonal rheumatoid factor or bovine conglutinin.

Phase 2 - After we establish a method for monitoring the development and persistence of anti-BSA antibodies and IC, we will begin the second phase of the study. We estimate that this will start four months after the beginning of the project. In this phase, we will establish a method for attaching BSA to immunoadsorbent columns and for monitoring the effluent from these columns.

In the initial studies of this phase, BSA will be attached covalently to Sepharose beads with cyanogen bromide. After the BSA is attached

and the beads are rinsed, serum containing antibodies to BSA will be passed through the column. The antibodies to BSA will be adsorbed by the column, and will be eluted at pH 3.0. These purified antibodies will then be labelled with 125-I. The labelled antibodies will then be used to determine the adsorptive capacity of this and other columns. Labelled antibodies will be passed through the column, and the amount eluted before and after treatment of the column with a buffer at pH 3.0. Measurement of the labelled antibodies will be performed with a gamma scintillation counter.

Columns containing bound BSA will be tested for antigen leakage by binding 125-I labelled BSA to the Sepharose. After the adsorbent has been thoroughly rinsed with buffer, it will be poured through a column and normal rabbit serum will be passed through it. The amount of radioactivity escaping from the immunoadsorbent will be monitored and will determine the leakage rate of the adsorbent in the presence of rabbit serum. Similar studies will be performed with columns containing bound human C1q which will be designed to remove IC from serum.

Phase 3 - In this phase, we will study the effects of removing circulating antibodies to BSA and IC from the sera of rabbits as part of an extracorporeal circulation system. These studies should begin six to nine months after the start of the project and are dependent upon the successful completion of the first two phases.

Eight rabbits will be injected with BSA as in Phase 1. All eight will be treated by extracorporeal circulation. Five of these will be connected to an immunoadsorbent column containing BSA linked to Sepharose beads and their blood will be perfused through the column. The remaining three will act as controls and will be connected to a column containing rabbit serum albumin linked to the beads. It is expected that the column containing BSA will remove circulating anti-BSA antibodies, while the column containing rabbit serum albumin will not.

The amount of albumin on the columns will be determined by the studies done previously in Phase 2. Columns will be enlarged if there is little antibody removal in the first perfusion studies.

Since these experiments will be directed primarily toward testing the perfusion apparatus, rather than toward the permanent alteration of the immune response, each rabbit will undergo only a single perfusion. The perfusion will be timed to occur when a high level of anti-BSA antibodies are detectable in the serum. BSA, anti-BSA and IC levels will be monitored immediately before and after the perfusion, and every three days thereafter for a period of two weeks. Rabbits will then be sacrificed and autopsied.

Phase 4 - This phase will begin after the conclusion of the previous studies, probably 9-12 months after the start of the project. Studies in this phase will be similar to those in Phase 3, except that immune complexes will be removed, rather than antibodies.

In eight rabbits, IC will either be induced or injected, as determined by the earlier Phase 1 studies. Blood from five of the eight rabbits will be perfused through a column containing human C1q bound to Sepharose beads, while blood from the remaining three will be perfused through a column containing only Sepharose beads. As in the Phase 3 studies, BSA, anti-BSA and IC levels will be measured before and after the perfusions, and the animals will be sacrificed and autopsied two weeks after the perfusions.

Animal Treatments: All rabbits will be fed and watered ad libidum and will be treated in a humane manner designed to minimize pain and discomfort. Before perfusion studies, rabbits will be premedicated by injections of atropine (2 mg) and heparin (1000 U/kg) intravenously into an ear vein. Thirty minutes later, they will be anaesthetized by a slow intravenous injection of sodium pentobarbital (30 mg/kg), which will be repeated if the animals appear to regain consciousness or show discomfort.

Bleeding of rabbits for routine testing will be performed by incising a peripheral ear vein with a scalpel after a local application of xylene to induce vasodilation. Animals will be sacrificed by an overdose of Somethal injected intravenously.

Immunoadsorption and Perfusion Techniques: We have arranged a collaborative investigation with Dr. Franco Castino of the American Red Cross Blood Research Laboratory in Bethesda, Maryland for our extracorporeal perfusion studies. Dr. Castino has developed a plasmapheresis system which filters plasma proteins through a membrane with 0.6 micron pores. Filtration of plasma through this membrane is said to be less destructive of platelets than is plasmapheresis with a centrifugal cell separator. A small model of the apparatus is available for our use in rabbit experiments.

Dr. Castino is currently isolating Factor VIII from plasma using an immunoadsorbent containing antibodies to the factor that are bound covalently to Sepharose CL beads with cyanogen bromide. Purified Factor VIII is removed from the immunoadsorbent by 1 M nACl or 0.25 M $CaCl_2$. We shall use these techniques, with appropriate modifications, for binding and eluting BSA from the immunoadsorbent.

We plan to routinely house our rabbits at WRAIR, which will allow us to observe and study them near our laboratory. We will transport the rabbits to the American Red Cross laboratory for each perfusion and will return them to WRAIR after treatment.

The rabbits will be anticoagulated and anaesthesized at the Red Cross

laboratory in most instances, although in some cases the rabbits may be premedicated at WRAIR before transportation to save time during the preinduction phase of anaesthesia. After the rabbits are fully anaesthetized, a femoral artery and vein will be cannulated and connected to the plasmapheresis system. Assisted by a peristaltic pump, blood will flow through the perfusion system and plasma will pass through the pores in the system's membrane. The separated plasma will then pass through an on-line immunoadsorbent column containing a specific protein bound covalently to Sepharose beads. Antibodies to BSA will be removed by binding BSA to the beads, as outlined above. It is expected that IC will be removed by both the columns containing BSA and those containing Clq, and we will determine which of the two methods is more efficient for this either in the studies described above or in later ones.

After the plasma has passed through the immunoadsorbent, it will then be returned to the rabbit together with the cells, which will have bypassed the loop containing the adsorbent. This bypass will spare the cells any possible trauma or removal which might occur if they were allowed to come into contact with the adsorbent.

After the perfusion is completed, the cannulas will be removed and the rounds will be repared. Rabbits will be allowed to recover from their anaesthesia and will be returned to WRAIR for studies of their post-operative clinical state. The immunoadsorbent will be recycled by removing bound antibodies and immune complexes with high molarity salt solution and buffers with low pH. The perfusion system will be cleaned, sterilized, and used in later studies.

Several investigators have previously perfused rabbits with extracorporeal immunoadsorption devices. Rabbits were anticoagulated with doses of heparin similar to those that we will use. It did not appear necessary to neutralize the anticoagulant after treatment. In our inital studies, we will not attempt to neutralize the anticoagulant and will rely on meticulous surgery to prevent post-operative bleeding from the wound. If excessive bleeding does occur, we will neutralize the heparin with protamine, but it seems likely that this will not be necessary as rabbits tend to be hypercoagulable. Prothrombin times will be monitored to follow the effects of the anticoagulant and any added protamine. Because the apparatus is specifically designed to minimize platelet loss, we expect to have few bleeding problems referable to this, particularly since the rabbits will only be perfused on one occasion.

Leakage of Sepharose beads from the apparatus will be prevented by inserting a nitrocellulose filter with 0.6 micron pores into the effluent line. This filter will allow proteins to pass through it, but will retain the beads and any other particles that might cause embolization.

Because this is only a preliminary study, and future perfusion apparatus will likely have a different design, we will not routinely test the column effluent for pyrogenicity or sterility, although all apparatus will be sterilized by heat, ethylene oxide and/or merthiolate prior to use. Should a problem develope in the studies that are referable to a failure in sterility or to pyrogenicity, appropriate studies will then be conducted. In such a case, sterility would be determined by taking samples for bacterial cultures and pyrogenicity would be measured by the Limulus amebacyte lysate test.

Post-operative Studies: In addition to measuring antigen, antibody and immune complex levels after the perfusion, other studies relating to the clinical status of the animals will be performed. During the perfusion and immediately after it, animals will be closely observed for signs of shock. They will be bled once every three days, or more often if necessary, for measurements of the leukocyte and platelet counts using a hemocytometer and for the determination of the hematocrit. Twice a week, they will be placed in a metabolic cage and their 24 hour urine output will be measured, as will their urinary sediment and protein (sulfasalicylic acid test). All of these measurements will be compared to similar ones made on the same animal before the perfusion, and any untoward effects will be noted. If renal damage appears to occur in either perfused or control animals, the BUN will be monitored. As noted above, all animals will be sacrificed and autopsied two weeks after perfusion, and specific studies will be conducted on the kidneys to determine the effects of possible immune complex deposition or other pathological changes.

7. Conclusions: Phase I studies were completed on schedule. The anti BSA assay and the IC assay proved reliable for use in rabbits. We were able to measure changes in IC and antibodies in all rabbits, and all six rabbits showed similar responses. We thus will not be overly concerned with the chance of individual variations among rabbits in the future, as this now seems small.

Since the IC levels changes suggest that mycobacteria, rather than BSA, induce most of the ICs detected, we must confirm this before embarking on Phase II. We must perform additional experiments to learn which type of complex must be removed to reduce IC levels before we actually attempt such removal.

We therefore plan to alter the original plan. Three additional rabbits will be injected with complete Freund's adjuvant containing mycobacteria and two will be injected with incomplete adjuvant without mycobacteria. No BSA will be used. We will then attempt to detect IC in the serum before and after a booster with the appropriate adjuvant.

These additional studies will not increase the cost of the project but will prolong it for 4 months. They are necessary to confirm our unexpected findings, however, and may explain their cause. In addition to providing a basis for later studies in this project, they will contribute to our understanding of this previously unexplored area and should be of great interest to the scientific community.

8. Side Effects: There have been no unexpected side effects or complications on the rabbits studied, although the immune complex response was not the same as we expected.

9. Funds Utilized FY 79:

Peristaltic Pump:	$ 700.00
Consumable Supplies:	3,250.00

10. Funding Requested, FY 80:

Consumable Supplies:

Metabolic animal cages	500.00
Radioisotopes for immunoassays (125I-Bolton-Hunter Reagent; 5 orders per year at $200.00 per order)	1,000.00
Chemicals (Cyanogen bromide-activated Sepharose, antisera, anaesthetics, buffers, antigens, others)	2,000.00
Chromatography columns	500.00
Glassware, Plasticware and pipette tips for immunoassays (1000) and general use	1,500.00
Miscellaneous Supplies	1,000.00
CONSUMABLE SUPPLIES TOTAL	6,500.00

6. Progress and Results: For Phase I studies, six rabbits were immunized with BSA in complete Freund's adjuvant. Three of these received a booster with BSA in incomplete Freund's adjuvant two months later. (Incomplete Freund's adjuvant contains no mycobacteria, in contrast to complete adjuvant).

A double antibody radioimmunoassay for anti-BSA antibodies was developed. BSA was iodinated by the chloramine T method. This was found to be stable for at least 6 months if free iodine was removed before a run. The labeled BSA was then incubated with a rabbit antiserum to BSA, which was developed by one of the six rabbits. A goat antirabbit IgG, which had previously been developed, was then added. This precipitated all BSA-anti BSA, but not BSA alone. It could thus detect and measure anti-BSA by the amount of BSA precipitated under standard conditions.

The anti-BSA RIA was able to detect the precipitation of BSA in the nanogram range. With sensitized rabbits, less than 1 microliter of serum was necessary to measure detectable antibody.

The 125I-CIQ binding assay previously developed for measuring immune complexes in humans was applied to rabbit serum. Although human CIQ was used as the binder, the test worked well on rabbits. It was able to accurately detect even small changes in immune complex circulating in rabbit serum.

The experiments demonstrated that antibody and immune complexes could first be demonstrated in rabbits 3-5 days after immunization with BSA in complete Freund's adjuvant. Both the antibodies and the IC appeared at the same time.

The IC response and antibody response differs with the passage of time. Antibody rose rapidly at first, and then more slowly for a period of 5 months. In the 3 rabbits boosted with BSA, there was an additional small rise in antibody, followed by a small decrease. In all six rabbits antibodies were still highly elevated 5 months after the primary immunization.

IC were detected first at 3 days and then rose rapidly. By 14 days they reached a peak. They did not significantly change after that, but maintained the same levels. The three rabbits which had been boosted showed no change after the booster injection.

The IC response was unexpected. Although never studied before in rabbits immunized with Freund's adjuvant, there was no reason to suspect that a constant level of IC would be maintained for 5 months regardless of a booster injection. It is possible that the IC contain antibodies and antigens concerned with constituents of Freund's adjuvant, particularly the mycobacteria; the contribution of anti-BSA antibodies may not be large, since the booster with BSA changed antibody but not IC levels.

Pathology studies of tissues from sacrificed animals revealed lymphocytic infiltrates in lungs and kidneys. These were not intense, however, and were suggestive of a chronic protozoal infection. This had been anticipated, since many rabbits in the WRAIR colony show similar lesions. No severe signs of serum sickness appeared in the rabbits.

10. Continuation:

Travel to Meetings		400.00
Publication Costs		400.00
Rabbits - Purchase:	30 rabbits @ $25.00	750.00
Boarding:	1000 rabbit days @ $0.55	550.00
	TOTAL	$8,600.00

11. Personnel: With the completion of Phase 1, an additional person is needed to complete later phases. This person would spend 50% of time on this protocol, as follows:

Rabbit bleeding and serum shortage	5 hrs/wk
Preparing immunosorbents	5 hrs/wk
Performing radioimmunoassays	10 hrs/wk
TOTAL TIME	20 hrs/wk

One additional person was authorized by the most recent manpower survey for the Rheumatology Service, through the Clinical Investigation Service. This person has not yet been assigned to the Rheumatology Service. If this assignment is not made, this project will be delayed past the expected completion date. There is no technical person assigned to this protocol, aside from the Principal Investigator. Assignment of the additional person is thus urgently needed at this time.

12. Publications: None

13. Type of Report: Interim

14. Estimated Date of Completion: 1 Feb 1983

a) Work Unit #3160-R

b) Title: Study of rheumatoid arthritis and Sjogren's syndrome precipitins in rheumatic diseases.

c) Principal Investigator: Joseph T. Tesar, M.D. Staff Rheumatologist

Associate Investigator: Allen Wehrle, M.D. and Oliver Lawless, M.D. Section of Rheumatology

d) Objectives: The study was designed to evaluate:

I: The diagnostic value of rheumatoid arthritis precipitin (RAP) and autoantibodies found in sera of patients with Sjogren's syndrome (SS-A and SS-B precipitin).

II. The biological role of RAP and Sjogren's syndrome precipitins. In addition, a correlation is to be sought between the disease activity and the titer of autoantibodies mentioned.

e) Technical Approach: Reference antisera with known precipitating antibodies to RAP and SS-A/B antigens are used for the identification of precipitin lines present in sera of patients with rheumatic diseases. The antigen used is a thymus or B-lymphocyte (tissue culture line) extract. No modification of protocol has been introduced.

f) Progress & Results: The study was started approximately 4 months ago (see notification of approval by Clinical Investigation Svc). Since test time we have examined approximately 60 patients with RA, SLE, Sjogren"s syndrome and other rheumatic diseases in accordance with protocol. We have obtained reference antisera for identification of SS-A/B and RAP antiautoantibodies from Dr. J. Vaughan's laboratory in Scripps Clinic, La Jolla. We are now in process of obtaining the necessary antigens. In addition, we have collected so far about 180 serum specimens from

patients with the relevant rheumatic diseases.

g) No conclusions have been reached yet at this early stage of study.

h) There were no side effects or complications in subjects participating since the study is a principally in vitro immunochemical study.

i) Funds Utilized: $1450 since the initiation of study 4 months ago.

j) Funds Requested for Fy 80: $7,900 (Total)

Consumable Supplies	$6,000
Research Equipment	990
Scientific Publications	500
Scientific Meetings	410

k) Publications: Fy 1978/1979
by Dr. J. Tesar

M. Floyd and J.T. Tesar. The role of IgM rheumatoid factor in experimental immune vasculitis. Clin. Exp. Immunol 36:165, 1979.

Pending Publications (1979)

J.T. Tesar and F.R. Schmid: Association of avidity of IgM rheumatoid facotr with complement fixation. Clin. Exp. Immunol.

Type of Report: Interim

Work Unit No.: 3161

Title of Project: Evaluation of Immediate Hypersensitivity Skin Tests in Uremic Patients

Investigators:

Principal: Robert W. Sigler, M.D., LTC USAF, MC

Associates: Mark R. Stein, M.D., LTC USA MC
Kenneth R. Bergman, M.D., LTC USA MC
Chris W. Old, M.D., MAJ USA MC

Objectives: To determine whether immediate hypersensitivity as assessed by wheal and flare skin testing, is a reliable method of determining potential IgE mediated allergic reactions in patients who are uremic.

Progress & Results: Patients from renal clinic are being identified and contacted to participate in the study. Final results should be available within twelve months.

Conclusions: No conclusions can be made until all results are in.

Funds Utilized, FY-79: None

Funding Requirements, FY-80:

Supplies: (consumable)		$ 750.00
Travel: (and reprints)		500.00
	Total	$1250.00

Publications: None

Type of Report: Interim

Addendum:

Principal Investigator: Kenneth R. Bergman, M.D., LTC USA MC

Associate Investigators: Robert W. Sigler, M.D., LTC USAF, MC
Ray Pratt, M.D., CPT USA MC

Work Unit No.: 4113

Title of Project: Cooperative Gynecologic-Oncology Group

Investigators:

Principal: Robert C. Park, COL, MC

Associate: Roger B. Lee, LTC, MC; Paul B. Heller, LTC, MC; William Neglia, MAJ, MC; Geoffrey Weisbaum, MAJ, MC

Objectives: The Walter Reed section of Gynecologic Oncology is involved with the nationally organized Gynecologic Oncology Group, which contains 33 of the major medical centers in the country who are interested in the area of Gynecologic tumor treatment. The GOG is recognized and funded through the National Cancer Institute.

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 762 patients have been registered in this group from WRAMC, and 238 have been placed in specific protocol studies.

Funding Requirements: No local funding is requested as this group is supported by a grant from the National Cancer Institute.

Type of Report: Interim

Work Unit No: 4116 Interim Report

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:

Principal: James B. Haddock, LTC, MC

Associates: Helen S. Powell, R.N.

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 and Results: Fifty-seven patients were studied in whom fetal distress was noted both by abnormal fetal heart rate patterns and Ph below 7.20. Again, the wide normal variance of the PEP was noted and there were differences noted in the asphyxiated vs. the non-asphysiated group. The normal range of the PEP (60 - 80) was reported in the AFD-ACOG meeting in New Orleans, October 1977.

Conclusions: The variation from the mean of the fetal systolic time interval is large and by our study a separation of the normal versus the asphyxiated group is poor. The measurement of asphyxia by intermittent scalp Ph however is crude and may well not be very relevent to cardiac or cerebral function. We hope to develop a better measurement of fetal asphyxia by power spectral analysis of heart rate variability. If this is successful, we intend to compare the technique to fetal systolic time intervals.

Funding: No funds were used for FY 79 and none are anticipated for 1980 pending development of other techniques.

Work Unit No: 4124 Interim Report

Title of Project: Fetal Intensive Care Monitoring In a Long-Range Continuing Project:

Investigators:

Principal: James Haddock, LTC, MC

Associates: Norman Neches, LTC, MC
Henry Klapholz, MD

Objectives: The objective of this reasarch is to evaluate the usefulness of fetal monitoring and labor in detecting early fetal distress and abnormal fetal heart rate patterns. Beginning 1 July 74 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 & Results: (New development) The Hewlett Packard 5600-A OB-GYN Research Computer is being installed. A new protocol has been submitted requesting funding to develop an automated system using our high speed digital computer with analogue to digital converter that will:

1. detect abnormalities of fetal heart rate
2. Quantify them and
3. Provide a summary at the completion of the labor.

The criteria of what constitutes fetal distress and an algorithm to optimally summarize such large quantities of data to be developed.

It appears that we will not need to hire a programmer at this time as we may be able to accomplish this with native talent. The necessity of a Clinical Research Secretary is still not clear

Installation of the 5600-A high speed digital computer will soon be complete and the position for a biomedical engineer to implement technical aspects of this project is near consumation.

Work Unit No: 4129 Interim Report

Title of Project: Antepartum Fetal Evaluation of Noise Evoked Fetal Heart Rate Response as an Indicator of Fetal Well Being.

Investigators:

Principal: James Haddock, LTC, MC

Associates: Helen S. Powell, R.N., Thomas Frank, Ph D, Andrew Prysbileck,

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 are 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 have 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. It is anticipated that fetal heart rate variability will be subject to analysis in the future. A protocol is being submitted for the development of the techniques for this. When this is developed, in cases where variability is poor suggesting compromise, it is a reasonable postulate that stimulus of the fetus through these noise

arousal techniques will correct poor variability associated with fetal sleep and not that associated with compromise. This is to be tested. It is planned to look at this in conjunction with analysis of FHR variability from abdominally derived fetal EKG signals which will begin later this fiscal year.

Funding: $2,300.00 is requested for low noise high gain amplifiers and special EKG leads necessary for this project.

Presentations:

(1) Armed Forces District Meeting of the American College of OB-GYN, Las Vegas, Nevada, Sep 1796.

(2) Published AJOB-GYN March 1978.

Work Unit No.: 4134

Title of Project: Treatment of Women With Cervical Cancer Stage IIB, IIIB, IVA, and or Periaortic Nodes with Radiotherapy Alone Versus Radiotherapy Plus Immunotherapy (Intravenous C-Parvum) Phase III

Investigators:

Principal: Robert C. Park, COL, MC

Associates: Roger Lee, LTC, MC; Paul B. Heller, LTC, MC; William Neglia, 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 to one of the two treatment regimens; 1) radiotherapy alone, or 2) radiotherapy plus C-Parvum.

Progress & Results: To date, 160 patients have been entered in this GOG protocol; five from Walter Reed.

Conclusions: No conclusions can be reached at this time, however, some moderate adverse reactions have been found in the combination treatment arm. No deaths considered treatment related have occurred at this time.

Funding Requirements: No local funds are necessary as this is a GOG funded protocol.

Type of Report: Interim

Work Unit No.: 4135

Title of Project: A Randomized Comparison of Melphalan Alone Versus Adriamycin and Cyclophosphamide Versus Hexamethylmelamine and Melphalan in Patients With Ovarian Adenocarcinoma: Suboptimal Stage III, Stage IV, and Recurrent Equivalent to Stage III and IV (Phase 3)

Investigators:

Principal: Robert C. Park, COL, MC

Associate: Roger Lee, LTC, MC; Paul B. Heller, LTC, MC; Jeffrey Weisbaum, MAJ, MC

Objectives: Single alkylating chemotherapy agents produce a 30% response rate in patients with epithelial ovarian cancer. The objective of this study is to determine if adding Adriamycin or Hexamethylmelamine will enhance the response rate.

Technical Approach: Patients are randomized to one of the three treatment arms. 1) Alkeran; 2) Alkeran plus Hexamethylmelamine; 3) Cytoxan plus Adriamycin.

Progress and Results: A total of 403 patients have been entered into this protocol from the entire GOG; 21 from Walter Reed. It is too early for specific statistical analysis; however, at the present time, there is no difference in overall response rate, but there is a marked difference in complete response for both combination arms. Hexamethylmelamine is an investigational drug - to date there have been no adverse reactions observed in any of the Walter Reed patients.

Conclusions: None

Funding Requirements: No local funds are required in this protocol since it is funded through GOG.

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: Roger Lee, LTC, MC; Paul B. Heller, LTC, MC

Objectives: Melphalan alone produces a 30% response rate in patients with epithelial cancer. The objectives of this study is to determine if the additional of immunotherapy will enhance the response rate.

Technical Approach: Patients with optimal Stage III epithelial ovarian carcinoma are randomized to one of two treatment regimens. Regimen #1 is Melphalan alone and Regimen #2 is Melphalan plus C-Parvum.

Progress & Results: To date, 69 patients have been entered in this GOG protocol; one has been entered from Walter Reed. To date, no statistical differences have been drawn from these regimens. No severe reactions have been noted in either treatment arms.

Conclusions: None

Funding Requirements: No local funds are required in this protocol since it is funded through the GOG.

Type of Report: Interim

Work Unit No.: 4137

Title or 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: Roger Lee, LTC, MC; Paul B. Heller, LTC, MC; William Neglia, MAJ, MC

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 to one of three treatment arms after a total abdominal hysterectomy and bilateral salpingo-oophorectomy plus evaluations of the endocervix of the diaphragm plus iliac and peri-aortic node biopsy, patients are randomized to 1) either pelvic irradiation or abdominal radiation, 2) pelvic irradiation plus Melphalan, or 3) Melphalan alone.

Progress and Results: This protocol accrues patients from GOG, RTOG, and ECOG. Because of the slow accrual, GOG has voted to discontinue participation in this study.

Conclusions: None at present.

Fudning Requirements: No local funds are necessary since this is a GOG funded protocol.

Type of Report: Interim

Work Unit No. 4138

Title of Project: Diagnosis and Treatment of Intrauterine Abnormalities Using the Hysteroscope

Investigator: Thomas A. Klein, LTC, MC

Objectives: To evaluate the feasibility of using the hysteroscope in in-patients and out-patients to establish a valid diagnosis in cases of abnormal uterine bleeding and habitual abortion.

Technical Approach: Hysteroscopy was to accompany all cases requiring diagnostic D&C in patients under 40 years of age. Results of hysteroscopically obtained biopsy were to be compared to results of conventional curettage. Logistics and patient acceptance of outpatient hysteroscopy were to be evaluated by questionnaire.

Progress and Results: The protocol has not been activated because of logistical problems and lack of sufficient time for the principal investigator to conduct the project.

Conclusions: It is requested that this protocol be terminated.

Funds Utilized, FY 79: None

Funding Requirements, FY 80: None

Type of Report: Final

Work Unit No.: 4139

Title or Project: A Randomized Comparison of Melphalan, 5FU and Megace Versus Adriamycin, Cytoxan, 5FU and Megace in the Treatment of Patients with Primary Stage III, Primary Stage IV, Recurrent or Residual Endometrial Carcinoma (Phase III)

Investigators:

Principal: Robert C. Park, COL, MC

Associate: Roger Lee, LTC, MC; Paul B. Heller, LTC, MC

Objectives: To determine the efficacy of multi-drug preparations in the treatment of high-risk endometrial carcinoma and to see if one of two programs previously shown by pilot studies, is superior.

Technical Approach: Patients with advanced or recurrent endometrial carcinoma are randomized to one of two treatment regimens: 1) Melphalan, 5FU, and Megace, and 2) Adriamycin and Cytoxan, 5FU, and Megace.

Progress and Results: To date, 288 patients have been entered into this GOG protocol; two from Walter Reed.

Conclusions: The trend suggests to better response combination chemotherapy in patients with poor prognostic features as compared to response to single agents in GOG's previous studies.

Funding Requirements: No local funds are required in this protocol since it is GOG sponsored.

Type of Report: Interim

Work Unit No.: 4140

Title of Project: A Clinical-Pathologic Study of Stage I and II Carcinoma of the Endometrium

Investigators:

Principal: Robert C. Park, COL, MC

Associate: Roger B. Lee, LTC, MC; Paul B. Heller, LTC, MC; Geoffrey Weisbaum, MAJ, MC

Objectives: The standard treatment for patients with Stage I and Stage II endometrial carcinoma has been external or internal radiation or a combination of both plus total abdominal hysterectomy and bilateral salpingo-oophorectomy. This protocol is to determine the incidence of pelvic and aortic lymph node metastasis and the relationship of these known metastasis to other important prognostic factors.

Technical Approach: Patients are selected for total abdominal hysterectomy, bilateral salpingo-oophorectomy, and pelvic and peri-aortic and lymphadenectomies.

Progress and Results: This protocol has accrued 425 entries: 38 from Walter Reed. Preliminary evaluation would indicate that pelvic and peri-aortic node sampling in this procedure is helpful in determining future treatment.

Conclusions: None at present.

Funding Requirements: No local funds are necessary since this is a GOG funded protocol.

Type of Report: Interim

Work Unit No.: 4141

Title of Project: A Randomized Study of Adriamycin as an Adjuvant After Surgery and Radiation Therapy in Patients with High Risk Endometrial Carcinoma, Stage I and Occult Stage II

Investigators:

Principal: Robert C. Park, COL, MC

Associate: Roger B. Lee, LTC, MC; Paul B. Heller, LTC, MC; William Neglia, MAJ, MC; Geoffrey Weisbaum, MAJ, MC

Objectives: To study the differences in morbidity in patient survival as functions of various tumor growth patterns in patient with poor-risk endometrial carcinoma.

Technical Approach: Patients are selected for this protocol by extent of disease determined at surgery. Those who have a greater than 1/2 myometrial invasion or pelvic or peri-aortic node involvement or microscopic evidence of cervical involvement will receive radiation therapy. Following this, there will be a randomization to Adriamycin or no further treatment.

Progress & Results: To date, 41 patients have been entered into this GOG Study; three from Walter Reed. It is too early to give any statistical analysis.

Conclusions: None

Fudning Requirements: No local funds are required in this protocol since it is funded through GOG.

Type of Report: Interim

Work Unit No.: 4142

Title of Project: A Phase II Trial of ICRF in Patients with Advanced Pelvic Malignancies.

Investigators:

Principal: Robert C. Park, COL, MC

Associate: Roger Lee, LTC, MC; Paul B. Heller, LTC, MC

Objectives: To determine the efficacy of ICRF-159 in the treatment of advanced pelvic malignancies.

Technical Approach: Patients with histologically advanced, recurrent, persistent, metastatic, or local gynecologic cancer with documented disease progression will be entered into this treatment.

Progress & Results: To date, 45 patients have been entered into this GOG protocol; two from Walter Reed. No severe reactions have been noted in this treatment arm.

Conclusions: None

Funding Requirements: No local funds are required in this protocol since it is funded through GOG.

Type of Report: Interim.

Work Unit No.: 4143

Title of Project: A Randomized Comparison of Local Excision Versus Cryosurgery in Patients with Limited Grade 1, 2, or 3 Cervical Intraepithelial Neoplasia (CIN).

Investigators:

Principal: Robert C. Park, COL, MC

Associate: Roger Lee, LTC, MC; Paul B. Heller, LTC, MC; Geoffrey Weisbaum, MAJ, M

Objectives: To evaluate and compare the immediate and long-term effectiveness of outpatient cryosurgery and outpatient local excision in the treatment of limited cervical intraepithelial neoplasia (CIN), Grades I, II, or III are then randomized to prospective studies.

Technical Approach: Patient are randomized to one of two treatment arms; 1) outpatient cryosurgery, 2) outpatient surgical excision.

Progress & Results: This protocol has had 149 accessions through the GOG, sixteen of them have been from Walter Reed. It is too early for statistical analysis.

Conclusions: None at present.

Funding Requirements: No local funds are necessary as this is a GOG funded protocol

Type of Report: Interim

Work Unit No.: 4144

Title of Project: A Randomized Comparison of Surgical Conization Versus Cryosurgery in Patients with Extensive Grade III Cervical Intraepithelial Neoplasia (CIN).

Investigators:

Principal: Robert C. Park, COL, MC

Associate: Roger R. Lee, LTC, MC; Paul R. Heller, LTC, MC; Geoffrey Weishaum, MAJ, MC

Objectives: The standard treatment for patient with cervical intraepithelial neoplasia, Grade III, would be in-hospital surgical conization or in-hospital surgical hysterectomy. The purpose of this study is to evaluate and compare the immediate and long-term effectiveness of outpatient cryosurgery to the standard cold-knife conization in the treatment of extensive surgical intraepithelial neoplasia (CIN), Grade III, in a randomized, prospective study.

Technical Approach: Patient are randomized to one of two treatment arms; 1) outpatient cryosurgery, 2) inpatient surgical conization.

Progress and Results: The GOG has accrued 31 patients to this study; two have been entered from Walter Reed. It is too early for statistical analysis.

Conclusions: None at present.

Funding Requirements: No local funds are necessary as this is a GOG funded protocol.

Type of Report: Interim

Work Unit No.: 4146

Title of Project: A Randomized Comparison of Melphalan Versus Radioisotopes in the Treatment of Patients with No Microscopic Residual Disease Having All Stages IC and II (A, B, and C) and Selected Stages IAii and IBii Ovarian Cancer.

Investigators:

Principal: Robert C. Park, COL, MC

Associate: Roger B. Lee, LTC, MC; Paul B. Heller, LTC, MC; Geoffrey Weisbaum, MAJ, MC; William Neglia, MAJ, MC

Objectives: Series from the literature report a mean 5-year survivals of 39% with operation plus radiation compared to 24% for those treated with operation alone in Stage II and poor prognosis Stage I patients with minimal residual disease. In some successful series, 30-40% of the patients die of recurrent ovarian carcinoma despite surgery and subsequent radiotherapy. The purpose of this study is to compare the usefulness of Melphalan chemotherapy and intra-abdominal radioactive phosphorous in resectable Stage II and poor prognosis Stage I patients, and to determine if addition of pelvic radiotherapy to standard surgical and chemotherapeutic treatment of incompletely resected Stage II patients improves survival.

Technical Approach: Patients who have a staging laparotomy including total abdominal hysterectomy and bilateral salpingo-oophorectomy if there is no microscopic residual disease, randomization will be to: 1) Melphalan, or 2) radioisotope. In the case of residual disease in Stage IIB and IIC lesions, the patients will be randomized to: 1) pelvic radiotherapy and Melphalan, or 2) Melphalan alone.

Progress & Results: A total of six patients from Walter Reed have been entered into this protocol at this time. It is too early for specific statistical analysis. There have been no severe toxic reactions at this time.

Conclusions: None

Funding Requirements: No local funds are required in this protocol since it is funded through the GOG.

Type of Report: Interim

Work Unit No.: 4146

Title of Project: A Randomized Comparison of Melphalan Versus Radioisotopes in the Treatment of Patients with No Microscopic Residual Disease Having All Stages IC and II (A, B, and C) and Selected Stages IAii and IBii Ovarian Cancer.

Investigators:

Principal: Robert C. Park, COL, MC

Associate: Roger B. Lee, LTC, MC; Paul B. Heller, LTC, MC; Geoffrey Weisbaum, MAJ, MC; William Neglia, MAJ, MC

Objectives: Series from the literature report a mean 5-year survivals of 39% with operation plus radiation compared to 24% for those treated with operation alone in Stage II and poor prognosis Stage I patients with minimal residual disease. In some successful series, 30-40% of the patients die of recurrent ovarian carcinoma despite surgery and subsequent radiotherapy. The purpose of this study is to compare the usefulness of Melphalan chemotherapy and intra-abdominal radioactive phosphorous in resectable Stage II and poor prognosis Stage I patients, and to determine if addition of pelvic radiotherapy to standard surgical and chemotherapeutic treatment of incompletely resected Stage II patients improves survival.

Technical Approach: Patients who have a staging laparotomy including total abdominal hysterectomy and bilateral salpingo-oophorectomy if there is no microscopic residual disease, randomization will be to: 1) Melphalan, or 2) radioisotope. In the case of residual disease in Stage IIB and IIC lesions, the patients will be randomized to: 1) pelvic radiotherapy and Melphalan, or 2) Melphalan alone.

Progress & Results: A total of six patients from Walter Reed have been entered into this protocol at this time. It is too early for specific statistical analysis. There have been no severe toxic reactions at this time.

Conclusions: None

Funding Requirements: No local funds are required in this protocol since it is funded through the GOG.

Type of Report: Interim

Work Unit No.: 4146

Title of Project: A Randomized Comparison of Melphalan Versus Radioisotopes in the Treatment of Patients with No Microscopic Residual Disease Having All Stages IC and II (A, B, and C) and Selected Stages IAii and IBii Ovarian Cancer.

Investigators:

Principal: Robert C. Park, COL, MC

Associate: Roger B. Lee, LTC, MC; Paul B. Heller, LTC, MC; Geoffrey Weisbaum, MAJ, MC; William Neglia, MAJ, MC

Objectives: Series from the literature report a mean 5-year survivals of 39% with operation plus radiation compared to 24% for those treated with operation alone in Stage II and poor prognosis Stage I patients with minimal residual disease. In some successful series, 30-40% of the patients die of recurrent ovarian carcinoma despite surgery and subsequent radiotherapy. The purpose of this study is to compare the usefulness of Melphalan chemotherapy and intra-abdominal radioactive phosphorous in resectable Stage II and poor prognosis Stage I patients, and to determine if addition of pelvic radiotherapy to standard surgical and chemotherapeutic treatment of incompletely resected Stage II patients improves survival.

Technical Approach: Patients who have a staging laparotomy including total abdominal hysterectomy and bilateral salpingo-oophorectomy if there is no microscopic residual disease, randomization will be to: 1) Melphalan, or 2) radioisotope. In the case of residual disease in Stage IIB and IIC lesions, the patients will be randomized to: 1) pelvic radiotherapy and Melphalan, or 2) Melphalan alone.

Progress & Results: A total of six patients from Walter Reed have been entered into this protocol at this time. It is too early for specific statistical analysis. There have been no severe toxic reactions at this time.

Conclusions: None

Funding Requirements: No local funds are required in this protocol since it is funded through the GOG.

Type of Report: Interim

Work Unit No.: 4148

Title of Project: A Randomized Study of Radiation Therapy Versus Pelvic Node Resection for Patients with Invasive Squamous Cell Carcinoma of the Vulva Having Positive Groin Nodes.

Investigators:

Principal: Robert C. Park, COL, MC

Associate: Roger B. Lee, LTC, MC: Paul B. Heller, LTC, MC

Objectives: All patients with primary previously untreated histologically confirmed invasive squamous cell carcinoma of the vulva, such that radical vulvectomy suffices to remove all local lesion and whose surgery revealed nodes in the groin on one or both sides containing metastatic carcinoma. Patients will be randomized after a radical vulvectomy plus bilateral groin dissection to one of two schema. Negative nodes: the patients will be off the study. Positive nodes: the patients will be randomized to Regime I, including a pelvic node dissection, or Regime II, bilateral groin node and pelvic node radiation.

Progress & Results: To date the entire GOG has accessed 14 entries. Analysis of this study has not been carried out.

Conclusions: At this time there is no definitive conclusion as analysis has not been performed.

Funding Requirements: No local funds are required as this is a Gynecologic Oncology Group protocol.

Type of Report: Interim

Work Unit No: 4149	Interim Report
Title of Project:	Automated Detection of Fetal Heart Pattern Abnormalities
Investigators:	
Principal:	James Haddock, LTC, MC
Associates:	Helen S. Powell, R.N., Thomas Frank, Ph. D. Andrew Presbylick
Objectives:	To study the feasibility and clinical applicability of developing a computer program to recognize FHR pattern abnormalities in labor. It is anticipated that the project will have immediate applicability in our institution in recognizing abnormal patterns on a moment-to-moment basis and preventing damage to babies from delay.
Progress & Results:	Installation of a high speed digital computer necessary to the project has been nearly completed The biomedical engineering expertise will shortly be acquired to implement these projects.
Funding:	$1,500.00 is requested for travel to Case Western Reserve in Cleveland. They have been working on a similar project and Dr. Rosen has offered help in allowing us to look at what they've developed and in implementation at our institution. $4,000.00 per year has been previously approved for a biomedical engineer to develop and implement this program working on a 1/6 time basis. None of the above funds has been spent. Development and implementation of this project could greatly be facilitated through a 5-day exposure of our consultant and myself to the Case Western Reserve Group. Expenses anticipated for this year either are $333.00 per month for our consultant beginning in April as well as $1,500.00 for travel and expenses in April.

Work Unit No: 4150

Interim Report

Title of Project: On-Line Interpretation of Labor Curve Abnormalities

Investigators:

Principal: James B. Haddock, MD

Associates: Helen S. Powell, R.N., Thomas Frank, Ph. D.
Andrew Presbylick

Objectives: The purpose of this project is to develop a program for the Hewlett Packard 08 Research Computer which will identify abnormalities in the progress of labor from the input of clinical exams. This will be clinically useful in alerting personnel as to of such an event and also useful as a teaching tool as it will output likely causes of abnormality. Particularly that of feto-pelvic disproportion and list appropriate therapeutic modalities with likelihood of success of each.

Conclusion: Project has not begun.

Funding: None of the $4,000.00 per year for a biomedical engineer working on a 1/6 time basis has been utilized. It is anticipated that these funds will be needed for this fiscal year. It appears that the necessary groundwork has finally been lain in personnel for hiring the biomedical engineer for developing the necessary computer algorythm. It is anticipated that work for this will begin in January 1980 with funding at $4,000.00 per year at 1/6 time or approximately $333.00 per month beginning then.

Work Unit No: 4151

Interim Report

Title of Project: Early Reliable Detection of Fetal Heart Rate Variability by Adaptive Digital Filtering.

Investigators:

Principal: James B. Haddock, LTC, MC

Associates: Helen S. Powell, R.N., Thomas Frank, Ph. D. Andrew Presbylick.

Objectives: The objective of the project is to develop computerized methods for processing fetal EKG signals from the maternal abdomen removing maternal signals and extraneous artifact by adaptive digital filtering. The derivation of a clear fetal EKG signal by external means would allow the assessment of beat-to-beat variability by a noninvasive technology which would represent a tremendous advantage in antepartum testing.

Progress & Results: The position for a biomedical engineer consultant will be filled shortly and work may begin.

Funding: No funds have been utilized for 1979. It is anticipated that the $5,000.00 per year for a consultant to work 1/5 time on this project will be partially used in 1980. Additionally, $3,500.00 is requested to purchase 3 - 8811-A Hewlett Packard amplifiers which are compatible with our Hewlett Packard computer to amplify low amplitude fetal signals and to purchase necessary harness and electrodes.

It is anticipated that our biomedical engineer will be hired and working in Jan 1980. Therefore, the $415.00 per month for this consultant will begin approximately at this time.

It is now clear that the amplifiers mentioned above are not available within the hospital system. These will be needed almost immediately as the limitations imposed by the fetal signal must be initially known. In the mean time I would appreciate the freedom to substitute a custom made amplifier from another source if (1) cost is approximately the same (2) specifications are superior (3) safety standards can be met (4) interfacing with HP equipment can be accomplished.

Work Unit No.: 4152

Project Title: A Phase II Trial of Maytansine in Patients With Advanced Pelvic Malignancies

Investigators:

Principal: Robert C. Park, COL, MC

Associate: Roger B. Lee, LTC, MC; Paul B. Heller, LTC, MC

No patients were entered on this protocol from this institution and it is now closed to entry, for patients with squamous cell carcinoma of the cervix.

Work Unit No.: 4153

Project Title: A Phase II Trial of "Baker's Antifol" in Patients With Advanced Pelvic Malignancies.

Investigators:

Principal: Robert C. Park, COL, MC

Associate: Roger B. Lee, LTC, MC; Paul B. Heller, LTC, MC

No patients were entered on this protocol from this institution as of the present.

Work Unit No.: 4155

Title of Project: Evaluation of Adjuvant Vincristine, Dactinomycin, and Cyclophosphamide Therapy in Malignant Germ Cell Tumors of the Ovary after Resection of All Gross Tumor (Phase III).

Investigators:

Principal: Robert C. Park, COL, MC

Associate: Roger B. Lee, LTC, MC; Paul B. Heller, LTC, MC

Objectives: To evaluate the effect of combined prophylactic Vincristine, Dactinomycin, and Cyclophosphamide (VAC), chemotherapy in patients with endodermal sinus tumors, embyonal carcinoma, immature teratoma (Grade 2 and 3), choriocarcinoma, in malignant mixed germ cell tumors of the ovary, Stage I and II after total removal of all gross tumor. To evaluate the role of serum markers, especially AFP and human chorionic gonadotropin, beta HCG, these are present in predicting response and relapse. To determine the role of re-staging laparotomy in determining the response, predicting relapse, and planning further therapy.

Technical Approach: Patients who have been determined to have histologically confirmed malignant germ cell tumors of the ovary, Stage I or II, if previously untreated and completely resected, excluding patients with pure dysgerminoma unless classified as anaplastic. Patients with Grade 2 or 3 immature teratomas are eligible. Patients with early Stage III disease will be accepted if all gross tumor is resected. Patients will be treated with Vincristine, Actinomycin-D, and Cytoxan for 6 cycles. If there is progression of the disease, the patient will taken off the protocol and be placed on a more advanced protocol for this disease. If after 6 cycles, there are no positive markers and no evidence of disease, the patients will be re-staged by laparotomy. If there is no evidence of disease, the patient will receive three additional cycles of VAC chemotherapy. If there is no progression after three cycles, the VAC will be stopped. If at re-staging laparotomy, there is recurrence, the patient will be placed on a more advanced protocol.

Progress & Results: At this point, there have been six entries to this protocol. There has not been enough accrual of data to perform an analysis. This is a very rare group of ovarian tumor and will take some time to accrue sufficient data for analysis.

Conclusions: There are definitive conclusions as the analysis cannot be performed.

Funding Requirements: No local funds are required as this is a Gynecologic Oncology Group protocol.

Type of Report: Interim

Work Unit No.: 4156

Title of Project: Evaluation of Vinblastine, Bleomycin, and Cis-Platinum in Stage III and IV and Recurrent Malignant Germ Cell Tumors of the Ovary (Phase III).

Investigators:

Principal: Robert C. Park, COL, MC

Associate: Roger B. Lee, LTC, MC; Paul B. Heller, LTC, MC

Objectives: To evaluate the effect of four cycles of combined Vinblastine, Bleomycin, and Cis-platinum (DBP) chemotherapy in the management of patients with endodermal sinus tumor, emryonal carcinoma, immature teratoma (all grades), choriocarcinoma, in malignant germ cell tumors of the ovary with advanced or recurrent disease, incompletely resected. The purpose is to additionally evaluate the role of serum markers, especially alpha feta protein (AFP) and human chorionic gonadotropin (beta HCG), when these are present in predicting response and relapse. To additionally determine the role of re-staging laparotomy in patient with clinical remission, in assessing completeness of response, and implanting further therapy. To evaluate and compare the effect of Vincristine, Dactinomycin, and cyclophosphamide (VAC) chemotherapy patients found to have persistent disease at the time of re-staging laparotomy. To determine the need for maintenance of Vinblastine therapy in patients found to be free of disease at re-staging laparotomy.

Technical Approach: The DBP chemotherapy combination used effectively in advanced malignant germ tumors of the testes has been used effectively in patients with advanced and recurrent malignant germ cell tumors of the ovary, and it may prolong survival in both patients previously untreated as well as those who have failed on VAC chemotherapy. Patients who have histologically confirmed malignant germ cell tumors of the ovary with advanced stage III and IV or recurrent disease, incompletely resected, excluding patients with pure dysgerminoma all eligible. Patients with incompletely resected Stage II disease are eligible. Patients previously treated with Vincristine, Dactinomycin, and cyclophosphamide are eligible.

Progress & Results: The entire entry into this protocol is two patients. This is a rare group of tumors and accession to this protocol will be slow at best. At this time there is no analysis which has been performed.

Conclusions: At this time, there are no definitive conclusions as analysis has not been performed.

Funding Requirements: No local funds are required as this is a Gynecologic Oncology Group protocol.

Type of Report: Interim

Work Unit No.: 4159

Title of Project: Treatment of Recurrent or Advanced Uterine Sarcoma: A Randomized Comparison of Adriamycin Verses Adriamycin and Cyclophosphamide (Phase III).

Investigators:

Principal: Robert C. Park, COL, MC

Associate: Roger B. Lee, LTC, MC; Paul B. Heller, LTC, MC

Objectives: To determine if Adriamycin alone is more effective than Adriamycin and cyclophosphamide in producing responses in treatment of advanced or recurrent uterine sarcomas. To determine the duration of response for each different treatment arm.

Technical Approach: Combination chemotherapy in patients with sarcoma utilizing Adriamycin and cyclophosphamide with other agents, it has appeared the use of superior responses to either agent used alone. Patients with primary Stage III, primary Stage IV, or recurrent uterine sarcoma are eligible. Both patients with measurable and unmeasurable disease are eligible, but they will be analyzed separately. Patients with all types of uterine sarcoma are eligible. Patients previously treated with radiotherapy to the pelvic bed are eligible but they must have completed this radiation more than three months prior to entry to this study. This scheme involves exploratory laparotomy involving a total hysterectomy, bilateral salpingo-oophorectomy, and if possible an omentectomy. Patients are then stratified by having received or not received radiation and their performance of fiscal activity. Randomization involves Regimen I to Adriamycin alone versus Regimen II to Adriamycin and cyclophosphamide.

Progress & Results: At the last statistical report from GOG, eight entries were reported as being in the protocol. No analysis has been performed of this study.

Conclusions: At this time there are no definitive conclusions as analysis has not been performed.

Funding Requirements: No local funds are required as this is a Gynecologic Oncology Group protocol.

Type of Report: Interim

Work Unit No.: 4160

Title of Project: A Clinical-Pathologic Study of Stage I and II Uterine Sarcomas.

Investigators:

Principal: Robert C. Park, COL, MC

Associate: Roger B. Lee, LTC, MC; Paul B. Heller, LTC, MC

Objectives: The purpose of this study is to determine the incidence of pelvic and aortic lymph node metastasis associated with Stage I and II uterine sarcomas, the relationship of these node metastasis to other important prognostic factors, such as mitotic index of the tumor, and the complication rate of the procedures.

Technical Approach: Uterine sarcomas are a diverse group of histologic tumor types. Studies have indicated prognostic incidence of mitotic index but failed to consider the myometrial depth of invasion as related to this factor. There is no clear-cut date published regarding lymph node involvement in this disease. Patients are eligible with histologically proven uterine sarcoma, clincally Stage I and II, who are medically suitable for hysterectomy and lymphadenectomy. All histologic types of primary uterine sarcoma are eligible.

Progress & Results: Because of the rarity of the sarcomas of the uterus, there are only two entries into this protocol as of the last statistical report. Therefore, no analysis has been performed.

Conclusions: At this time there are no definitive conclusions as analysis has not been performed.

Funding Requirements: No local funds are required as this is a Gynecologic Oncology Group protocol.

Type of Report: Interim

Work Unit No.: 4163

Title of Project: A Phase II Trial of Cis-Platinum (II) Diamminedichloride in the Treatment of Advanced Gynecologic Cancer.

Investigators:

Principal: Robert C. Park, COL, MC

Associate: Roger B. Lee, LTC, MC; Paul R. Keller, LTC,

Objectives: To determine the efficacy of Cis-platinum in the treatment of advanced or recurrent gynecologic cancer.

Technical Approach: Patients who have been determined to have histologically confirmed gynecologic cancer, either recurrent or advanced on initial presentation. There is no randomization as this is a Phase II trial.

Progress & Results: One patient from Walter Reed was entered into this GOG study. The entire GOG had an entry of 129 cases. There seemed to be an indication that Cis-platinum has a marked activity as a chemotheraputic agent in certain forms of gynecologic malignancies (squamous cell carcinoma of the cervix) and it is active as a second-line chemotherapeutic in other old gynecologic malignancies (ovarian adenocarcinoma).

Conclusions: At this time, there are no definitive conclusions as analysis of endometrium in sarcoma cases is not being completed.

Funding Requirements: No local funds are required as this is a Gynecologic Oncology Group protocol.

Type of Report: Interim

Work Unit No.: 4501

Title of Project: Clinical Evaluation of Fluorescence Scanning of the Thyroid with Americium 241 Source

Investigators:

Principal: Robert J. Kaminski, LTC MC

Associate: Isamu Y. Kang, LTC MC

Progress & Results: Present research on the fluorescent imaging system is concerned with the fundamental components which affect spatial resolution. For this purpose, we have chosen a Monte Carlo approach. Using this technique, we can follow individually the passage of photons through a medium containing the element to be fluoresced. This permits us to study aspects of the imaging process not accessible by experimental means (e.g. the spatial distribution of the actual sites of x-ray stimulation within the medium). Using these methods, we can readily investigate the effect of source energy, organ depth and intrinsic spatial resolution with the goal of optimizing the design of the imaging system.

Work on this aspect of the fluorescent system is still in the organizational stage, but will be completed in the coming year.

There are two additional research projects presently in progress involving the fluorescent scanning system which are being conducted in conjunction with the Endocrinology and Metabolism Services. These are listed under Work Units 1332 and 1340. The Principal Investigator for these projects is currently on TDY in Europe and consequently, no progress report is available.

Conclusions: The fluorescent imaging system has proven to be of value in assessing thyroid status. However, there are a number of parameters and disease states that have not yet been studied and these are objects of current investigations.

Funds Utilized, FY 79: None

Funding Requirements, FY 80: $3,500.00

Publications: None

Type of Report: Interim

Work Unit No.: 4514

Title of Project: Clinical Evaluation of ^{111}Indium DTPA

Investigators:

Principal: Robert J. Kaminski, LTC MC

Associate: Isamu Y. Kang, LTC MC

Progress & Results: A total of 9 radionuclide cisternograms were performed on 9 patients during the past year. Six of the studies showed normal CSF dynamics. In the remaining three, the CSF flow pattern was abnormal.

Since the inception of this protocol, 57 patients have been studied with ^{111}Indium DTPA. Of the 64 examinations performed, 37 were abnormal, 22 were normal, 4 were unsatisfactory and one showed a questionable abnormality.

There were no known adverse reactions to the intrathecal administration of ^{111}Indium DTPA.

Conclusions: Radionuclide cisternography continues to be the study of choice for evaluating CSF dynamics.

Funds Utilized, FY 79: None

Funding Requirements, FY 80: None

Publications: None

Type of Report: Interim

Work Unit No.: 4521

Title: Technetium 99m pyridoxylideneglutamate (^{99m}Tc PG) for Diagnosis of Hepatobiliary Disease

Investigators:

Principal: Robert J. Kaminski, LTC MC

Associate: Isamu Y. Kang, LTC MC

Objective: To evaluate the clinical efficacy of Tc99m PG as a diagnostic hepatobiliary and gallbladder agent.

Technical Aporoach: The patient population will consist of personnel who have suspected acute or chronic hepatobiliary disease processes. Each patient referred to the study will fast for a 4-6 hour period when possible. Following intravenous administration of ^{99m}Tc PG, sequential scintiphotos will be obtained at 5 minute intervals for up to one hour following injection. Simultaneous computer acquisition of the data will be obtained for further analysis. Nuclear images will be made and stored on film and/or magnetic tape or data storage disks. Curve plot data can subsequently be derived from this information when appropriate.

In selected patients who have suspected gallbladder disease, delayed images may be obtained at 2-4 hours post-injection, when deemed necessary.

If gallbladder dysfunction is suspected in patients with chronic symptoms, but who have been shown not to have calculi by routine oral cholecystography, evaluation of gallbladder emptying may be obtained by intravenous injection of Kinevac. This methodology offers the advantage of a standardized, precise and reproducible quantitative assessment of gallbladder contractility. This will allow computer

analysis and printout of data for determination of a washout curve as the gallbladder empties.

Progress & Results: There were a total of 17 patients admitted to the study. Of these, 11 had abnormal hepatobiliary scans and 6 were normal. Eight of the 11 abnormals were confirmed by oral cholecystography and ultrasound, two had only the hepatobiliary scan and the remaining 1 also had an abnormal ultrasound but a normal oral cholecystogram. Of the six patients with normal hepatobiliary scans, four had confirmatory ultrasound studies and in two, ultrasound was not performed.

Five of the above six patients had an oral cholecystogram and in four of the cases, the gallbladder was not visualized.

Conclusions: In those patients where adequate clinical follow-up was available, ^{99m}Technetium Pyridoxylideneglutamate has proven to be a useful diagnostic agent in evaluating hepatobiliary disease. However, the small number of patients evaluated precludes making a positive statement of this agents value compared to other diagnostic modalities. The study is ongoing. There were no adverse reactions during this report period.

Funds Utilized, FY 79: None

Funding Requirements, FY 80:

Travel to meetings:	$400.00
Publication costs :	100.00
TOTAL	$500.00

Publications: None

Type of Report: Interim

DISPOSITION FORM

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

REFERENCE OR OFFICE SYMBOL	SUBJECT
HSWP-XR	Annual Progress report, Clinical Investigation Program Wash Unit #4601, Participation in the National Cooperative Study of Early Hodgkin's Disease

TO	FROM	DATE	CMT 1
C., Clinical Investigation Services	C., Radiation Therapy Services	25 October 79	Neglia/wbw/ 3575

1. Reference para 6 AR 40-38, Annual Progress Report of all clinical investigations specifically the National Cooperative Study of Early Hodgkin's Disease.

2. Because of inadequate staffing of the Radiation Therapy Service, it became necessary to discontinue participation in the Study.

3. Followup of remaining patients in the Study was arranged through the WRAMC principal investigator of this Study, Johannes Bloom, M.D., Chief Oncology Section. All followup and correspondence is now handled through that section. (SEE ENCLOSURE)

William J. Neglia, MD

WILLIAM J. NEGLIA, M.D.
MAJ, MC
C., Radiation Therapy Svc.

1 Incl
Ltr 13 APR 79

DA FORM 2496 REPLACES DD FORM 96, WHICH IS OBSOLETE. ☆ GPO—1975—665 422 1063

Radiation Therapy Service

April 13, 1979

Johannes Blom, M.D.
Chief Oncology Section
Hematology-Oncology Service
Department of Medicine
Walter Reed Army Medical Center

Dear Sir:

The Radiation Therapy Service at Walter Reed Army Medical Center has participated in the National Hodgkin's Study for a number of years, most patients having been treated prior to 1970. At present there are only 20 surviving patients being followed at WRAMC, most of whom we have been unable to obtain adequate follow up as they have stopped coming in for this.

The few patients who are being followed are also seen in the Hematology-Oncology clinic where tests are often ordered, but results are seldom forwarded to radiation therapy. Also over the past year it has been increasingly difficult to coordinate the patient's followup visits because of the paperwork involved, i.e., contacting the patients to schedule appointments, cutting invitational travel orders, filling out protocol forms, and trying to arrange for disbursement of funds for travel costs and reimbursement of funds from the travel center.

The Radiation Therapy Service has had no secretary since January 1979 and is currently unable to answer correspondence, cut orders and maintain the clerical end of following these patients.

I therefore request that the Radiation Therapy Service withdraw from the Hodgkin's Disease Study and that the remaining patients be followed in the Hematology-Oncology Clinic. We will be available for consultation and specific questions on any patient and will make available any radiation records on the patients treated here.

Sincerely,

William J. Peglia, M.D.
Major, M.C.
C., Rad. Therapy Svc.
Dept. of Radiology
WRAMC

cc: [illegible]

WORK UNIT NO: 5502

TITLE: A Comparison of Bovine Serum Albumin, Polymerized Bovine Serum Albumin, Low Ionic Strength Saline, and a Low Ionic Strength Additive as Potentiating Media in the enhancement of Hemagglutination Reactions in the 37°C and Anti-Human Globulin Phases of the Antigen-Antibody Reaction.

PRINCIPAL INVESTIGATOR: Major Tom Wadsworth, MSC
US Army

OBJECTIVE: The purpose of this investigation was to compare four potentiating media used to enhance the detection of unexpected antibodies normally encountered in the Blood Bank.

TECHNICAL APPROACH: Thirty specimens containing unexpected antibodies that normally react at 37°C and/or at the AHG phase were collected. Serial dilutions of each sample were prepared using inert AB serum as a diluent. The serial dilutions were cross divided into four sets, each set then being utilized for one of the four potentiating media under investigation. Reactions were read and scored at the end of a 37°C incubation and then read and scored again in the AHG phase. This procedure was repeated for each of the antibody specimens. After completion of testing, the scores were to be statistically compared.

PROGRESS AND RESULTS: The investigation has been completed. The thirty specimens obtained for testing consisted of various antibody specificities (Anti-D, -E, -K, etc.) close to a "real life" specimen as encountered in the Blood Bank. Results of the investigation indicate a decided increased enhancement of antigen-antibody detection at 37°C when utilizing the polymerized bovine serum albumin. There was a slight increased sensitivity at the AHG phase in the tests utilizing the low ionic strength additive reagent. All four of the potentiating media detected the presence of antibodies, with no failures.

CONCLUSIONS: The increased sensitivity observed when utilizing the polymerized bovine serum albumin at 37°C was statistically significant. The increased sensitivity observed at the AHG phase when using the low ionic strength additive was determined to be non-significant. There is a definite advantage in the use of polymerized bovine serum albumin as a potentiating media, especially at 37°.

FUNDS UTILIZED: FY 79; $80.00

FUNDING REQUIREMENTS, FY 80: None

PUBLICATIONS: It is intended to submit for publication to Transfusion.

TYPE OF REPORT: Completed.

WORK UNIT NO: 5503

TITLE: The Effects of Extra-Corporsal Circulation on Selected Blood Chemistry Levels Following Plateletphersis by Discontinous Flow Centrifugation

PRINCIPAL INVESTIGATION: LT Donald A. Smith
MSC, US Navy

OBJECTIVE: The purpose of this investigation was to describe the effects of plateletphersis by discontinuous-flow centrifugation on haptoglobin, total protein, and five major fractions, albumin: globulin ratio, glucose, BUN, creatinine, sodium, chloride, potassium, CO_2, uric acid, total bilirubin, alkaline phosphatase, calcuim, SGPT, SGOT, LDH, CPK, inorganic phosphorus, cholesterol and triglycerides.

TECHNICAL APPROACH: Four volunteer plateletpheresis donors screened according to selection criteria detailed in the Technical Manual of the American Association of Blood Banks, 7th Edition, were pheresed with a Haemonetics Model 30 discontinuous-flow cell separator. Specimens for study were collected prior to pheresis, after the 4th and 8th cycles and 1 hour post pheresis.

PROGRESS AND RESULTS: Four apparently healthy male donors were subjected to plateletpheresis using a Haemonetics Model 30 discontinuous-flow centrifugal cell separator. One of these donors had been pheresed thirteen times previously during the preceding two years, but the other three donors had never been pheresed before. Twenty-eight biochemical measurements were made on blood samples collected before, during, and after pheresis. BUN/creatinine ratios were used as biological markers of hemodilution, but no attempt was made to mathematically quantitate this variable. The majority of observed biochemical values fell within normal parameters. A few abnormalities were noted in the serum enzyme determinations; i.e., glutamic oxalacetic transaminase (SGOT), glutamic pyruvic transaminase (SGPT), lactate dehydrogenase (LDH), and creatine phosphokinase (CPK).

CONCLUSIONS: Since there was no particular pattern of uniformity among the observed serum enzyme abnormalities, they were probably the result of individual physiological differences among the donors, although the effects of extra-corporeal circulation cannot be ruled out with certainty.

FUNDS UTILIZED; FY79: $58.00

FUNDING REQUIREMENTS, FY80: N/A

PUBLICATIONS: It is intended to submit for publication to Transfusion.

TYPE OF REPORT: Completed

Work Unit No.: 6018

PROJECT TITLE: Newborn Host Defenses I: Developmental Aspects of Newborn Neutrophil Chemotaxis

INVESTIGATORS: Principal Alan D. Mease (until 6/79)
Paul J. Thomas (after 7/79)
Associate Doris Burgess
Frederick B. Ruymann

OBJECTIVES: This project is designed to confirm and characterize the cellular chemotactic defect of the newborn neutrophil and to correlate this decrease with gestational weight and age.

TECHNICAL APPROACH: Gallin's ^{51}Cr labelled neutrophil chemotaxis assay was modified by using an 8 micron upper and 3 micron lower filter in a modified Boyden chamber. Normal adult volunteer neutrophils and newborn (cord) neutrophils were labelled with ^{51}Cr and incubated for 3 hours in the presence of either buffer, Zymosan activated serum, or column purified C5a in the chemoattractant compartment of the Boyden chamber. The number of cells chemotaxed was determined by the number of counts per minute of the carefully washed 3 micron filters. All samples were run in quadruplicate and the mean counts per minute ± 2 standard deviations were used to compare random migration, adult neutrophil chemotaxis and newborn neutrophil chemotaxis. Analysis for significance was done by the Student t-test.
Several preliminary studies were done to study the effect of neutrophil concentration the number of neutrophils chemotaxed, the effect of vinblastin on chemotaxis, and the effect of post chemotaxis neutrophil supernatant on neutrophil chemotaxis.
Scanning electron micrographs of adult and newborn neutrophils in early chemotaxis were studied.

PROGRESS AND RESULTS: Continued experience with newborn neutrophil chemotaxis has confirmed the reproducible validity of the testing system. Statistically significant differences between newborn and adult neutrophil chemotaxis have been demonstrated in 50 newborn-adult pairs. The slow accrual of study subjects has been caused by the serendipitous nature of births occuring during the hours of 0600-1000 Monday - Friday. To date, correlations of newborn neutrophil chemotaxis with gestational age and birth weight have not been statistically significant, however, the number of preterm infants has been very small (3).

The preliminary results of the effect of concentration on neutrophil chemotaxis appeared to show a linear relationship with the slope of the adult line being greater than the slope of the newborn's line. These results are currently being further explored in "Newborn Host Defenses IV:-Study of Newborn Neutrophil-Neutrophil Interaction." (Work Unit No. 6029). Pretreatment of the adult neutrophil with vinblastine significantly decreased the neutrophil chemotaxis but had only a slight effect on the newborn neutrophil chemotaxis. Data from the preliminary study on the effect of of post-chemotaxis neutrophil supernatant on adult and newborn chemotaxis are still being evaluated for a possible further study.
Preliminary scanning electron microscope examination of adult and newborn neutrophils appear to show more "ruffling" of the neutrophil membrane of the adult neutrophil as compared to that of the newborn. Further study of the membrane surface changes by scanning EM appears to be justified by these preliminary studies.

CONCLUSIONS: Newborn neutrophils demonstrate significantly less chemotaxis tha normal adult neutrophils. The mechanism of this difference is not clear at the present time. Or research indicates that membrane interactions play a significant role in chemotaxis and that both membrane surface and intracellular factors, notably the microtubules and microfilaments, also contribute significantly to this process. Further studies of the newborn and adult neutrophil membrane interactions, mediator release, and microtubular-microfilament function as they affect chemotaxis are being pursued.

FUNDS UTILIZED FY 79	$2000
FUNDS REQUEATED FY 80	
Personnel GS 9 technician 20%	
Equipment	0
Supplies	$1500
Travel	500
Total	$2000

PUBLICATIONS AND ABSTRACTS:
Mease AD, Fischer GW, Hunter KW, Ruymann FB: Decreased phytohemagglutinin-indueced aggregation and C5a-induced chemotaxis of human newborn neutrophils. Pediatr Res, in press.

ESTIMATED DATE OF COMPLETION: 25 newborns, 6 months, Apr 80.

TYPE OF REPORT: Interim

1. Work Unit N.: 6021

2. Title of Project: The Role of Leutinizing Hormone Releasing Hormone (LHRH) in Evaluation of the Hypohalamic Pituitary Gonadal Axis in Children

3. Principal Investigator: LTC Chandra M. Tiwary, MC

4. Objective: To develop a test for assessing hypothalamic-hypophyseal gonadal axis in children which can be used on an outpatient basis.

5. Progress and Results: Thirty eight children were studies; of these 3 can not be included in the protocol because these children did not return after the first LHRH injection (the protocol requires tje LHRH injection given on 3 consecutive days). Major results are:

I. Differentiation of a female with precocious puberty. Since the prognosis and management of these two conditions are different the value of the LHRH test is obvious. The serum LH response and the ratio of the serum LH to the serum FSH following the LHRH injection is low (ie, prepubertal) in the premature adrenarche girls and high (ie, pubertal) in the precocious puberty girls. In a few cases with precocious puberty the LH response after the 3rd LHRH injection was higher than after the first injection. This was not true in any case of permature adrenarche.

The gonadotropin response in boys with premature adrenarche was variable, however very few cases (4-5) have been studied. Before a firm conclusion is drawn more cases need to be studied.

II. The pool serum LH and serum FSH value is directly correlated with the mean and the peak serum LH and FSH value. This suggests that for most clinical purposes analysis of the gonadotropin in one serum sample may be sufficient. This would reduce the cost.

III. A 5 year old girl with pseudo-precocious puberty due to estrogen producing ovarian cyst showed a prepubertal response to the LHRH. This suggests that estrogen excess in prepubertal does not change the hypothalamic pituitary response to the LHRH and may be utilized in differentiation of a girl with pseudoprecocious puberty from that with true precocious puberty.

IV. A 15 year old boy with noonan's syndrome and hypogonadism showed a prepubertal response th LHRH. This suggest that hypogonadism may be at least partially due to a hypothalamic pituitary defect. This child had not responded to a 3 week course of H.C.G. injection. Clearly more children need to be studied.

V. A 16 year old boy with prunebelly syndrome and undescended testes showed hyperresponse to the LHRH suggesting that hypogonadism in this syndrome is associated with undescended testes. The testes responded to HCG stimulation and were brought down surgically. The results signify that the abdominal testes did not respond to the normal gonadrotrcpins secretion in this boy.

6. We propose to study about 15 more children to evaluate the LHRH test in (a) males with premature adrenarche (b) Noonan syndrome children (c) children with undescended testes with and without prunebelly syndrome (d) intra cranial lesion.

7. Funds requested for FY 1980:

Cost of sample analysis	$310.00 per subject
x 15 subjects	4,650.00
Paper publication	200.00
Travel for presentation of Paper	600.00
TOTAL	$5,450.00

8. Funds requested for FY 1979: $13,350.00

Funds used	9,064.00
Funds not used	4,286.00

9. Publication: Three abstract (copies enclosed) have been published One manuscript is ready for submission for publication to Journal of Pediatrics.

10. Travel: A paper presented at the International Society of Psychoneuroendocrinology conference at UTAH 1979.

11. Type of report Interim.

Work Unit No.: 6023

TITLE OF PROJECT: Newborn Host Defenses II: Studies of the Newborn Neutrophil Membrane Using Lectins as Molecular Probes.

INVESTIGATORS: Principal: Alan D. Mease (until 6/79)
Paul J. Thomas (after 7/79)
Associate: Gerald W. Fischer
Frederick B. Ruymann
Doris Burgess

OBJECTIVE: This study is designed to study the differences between normal adult neutrophils and newborn neutrophils in their ability to form aggregates by binding plant lectins to the surface membranes. Other aggregating agents are also being investigated.

TECHNICAL APPROACH: Using standard concentrations of cells, normal adult and newborn neutrophil aggregation by Phytohemagglutinin and other agents is being studied in a Sienco dual channel platelet aggregometer. One of the other agents of special interest to us is the column purified C5a. Preincubation of the neutrophils with vinblastine (microtubule poison) and cytochalasin B (microfilament poison) prior to aggregation has also been studied in a few samples. Aggregates have been examined by standard microscopy and will be examined by scanning electron microscopy.

PROGRESS AND RESULTS: Our studies to date have demonstrated impaired newborn neutrophil PHA-induced aggregation, when compared to the adult neutrophil. Presumably, this impairment is due to a reduced number of binding sites on the newborn neutrophil membrane.
Aggregation studies with C5a (column purified) have shown that adult neutrophils have a biphasic aggregation-deaggregation curve wheras newborn neutrophils demonstrate only aggregation without deaggregation. In addition, adult neutrophils pretreated with cytochalasin B demostrate only aggregation without deaggregation. Studies by Craddock, et al, have demonstrated that, in the presence of cytochalasin B, adult neutrophils undergo complex membrane interdigitation resulting in the loss of deaggregation. We are in the process of preparing scanning and transmission EM preparations of the newborn and cytochalasin B treated adult neutrophil aggregates for comparison studies. So far 30 newborn-adult pairs have been studied. The slow accrual of samples is due to the serendipitous nature of births occuring during the 0600-1000 hour time frame

on working days.

CONCLUSIONS: Newborn neutrophils have impaired phytohemagglutinin-induced aggregation when compared to that of normal adults. The aggregation produced by the lectins appears to depend at least partly on the microtubular system since vinblastine is able to significantly impair this aggregation.
C5a aggregation of the adult neutrophil produces an aggregation-deaggregation phenomenon but produces only aggregation without deaggregation in the newborn neutrophil. Cytochalasin B (a microfilament poison) appears to eliminate the deaggregation of the adult neutrophils when aggregated with C5a.

FUNDS USED FY 79 $2500

FUNDS REQUESTED FY 80

Personnel GS 9 technician 10%	
Equipment	
Supplies	$1500
Travel	500
Total	$2000

PUBLICATIONS FY 79:
Mease AD, Fischer GW, Hunter KW, Ruymann FB: Decreased phytohemagglutinin-induced aggregation and C5a-induced chemotaxis of human newborn neutrophils. Pediatr Res (in press).

ESTIMATED DATE OF COMPLETION: 30 newborns, 8 months, June 80.

TYPE OF REPORT: Interim

Work Unit No.: 6024

TITLE OF PROJECT: Newborn Host Defenses III: Phagocytosis and killing of Group B Streptococci.

INVESTIGATORS: Prinicipal: Alan D. Mease (until 6/79)
Paul J. Thomas (after 7/79)
Associates: Gerald W. Fischer
George Lowell
Frederick B. Ruymann
James W. Bass

OBJECTIVE: The purpose of this project is to establish a reproducible bacteriocidal assay for Group B Streptococci and evaluate the ability of cord blood neutrophils to kill Group B Streptococci.

TECHNICAL APPROACH: The assay for five Group B Streptococcal strains using streptococci, specific anti-streptococcal antibody, compliment, and adult neutrophiles has been established and reported. Newborn and adult neutrophil pairs are tested for streptococcal killing and phagocytosis using this assay.

PROGRESS AND RESULTS: To date only 5 newborns have been studied by this assay because of 1) low accrual of newborn samples caused by the serendipitous nature of births between the hours of 0600-1000 on working days and 2) the change in pricipal investigator.
The results so far indicate some impairment of the newborn neutrophil to phagocitize and kill Group B Streptococci, however, the numbers are not statistically significant at this time.

CONCLUSION: A reliable neutrophil opsonophagocytic bacteriocidal assay has been worked out. More testing of the newborn neutrophils is required.

FUNDS USED FY 79 $1500

FUNDS REQUESTED FY 80

Personnel	GS 9 technician 5%	
Equipment		0
Supplies		$1000
Travel		500
Total		$1500

ESTIMATED TIME OF COMPLETION: 20 newborns, 8 months, June 80.

TYPE OF REPORT: Interim

1. Work Unit Number 6025

2. Title of the Project: Role of surface tension measurement of amniotic fluid lipid extract in pediction development of RDS in neonates.

3. Investigators:

Principal: Chandra M. Tiwary, M.D., LTC,MC
Associates: Richard D. Landes, M.D., LTC,MC
James B. Haddock, M.D., MAJ, MC
Ms. Doris Burgess, Med. Tech.

Objective: To measure surface tension of amniotic fluid lipid extract prior to and during labor, and to correlate it with the subsequent development of RDS in newborn.

Progress and Results: The surface tension measuring apparatus was receive in mid 1979. The triple distilled water or the equivalent is at present not available, I expect it to be available in the next 2-4 weeks. We shall start the work as soon as it is available. We have more than 100 amniotic fluid specimen in the freezer.

Funds Utilized for FY 1979

Personnel	Chandra M. Tiwary
Equipment	$5,385.000
Supplies	30.00
Travel	None
Other	None

Funds requested for FY 1980

Personnel	
Equipment (recorder)	2,000.00
Supplies	200.00
Travel	600.00
Publication	150.00

Date of Completion: Dec 1980 (approx 300 amniotic fluid samples)

Type of Report: Interim

1. Work Unit Number 6026

2. Title of the Project: Tracheal Aspirate surface tension as prognostic indicator in infants with Respiratory Distress Syndrome (RDS)

3. Investigators: Principal: Chandra M. Tiwary, M.D., MC, LTC
Associate: Richard D. Landes, M.D., MC, LTC
Ms. Doris Birgess, Med. Tech.

4. Objective: To measure the surface tension of the lipid extract of tracheal aspirate at various periods and to use this data in evaluating the prognosis of newborn with respiratory distress syndrome (RDS).

5. Progress and Result: The apparatus for the measurement of surface tension was received, assembled, installed, and calibrated in September 1979. The supply of triple distilled water or deionized water is expected to be available in a few weeks. We shall then start measurement of the samples.

No. of babies to be studied: 50

Funds utilized - FY 1979:

Personnel	Chandra M. Tiwary
Equipment	None
Supplies	None
Travel	None
Other	None

Funds not used

Funds requested FY 1979:

	Chandra M. Tiwary
Personnel	
Equipment	
Supplies	$650.00
Travel	600.00
Paper, Preparation, Publication and reprints	150.00
Total	1,400.00

Type of Report: Interim

Work Unit No.: 6027

Title of Project: WRAMC Protocol 7808 - Combined Modality Therapy of Brain Tumors in Childhood

Investigators:

Principal: COL Frederick B. Ruymann, MC

Associate: MAJ Paul J. Thomas, MC

Objectives: To determine if the addition of chemotherapy with corticosteroids, vincristine, high dose methotrexate, 4^{1}-demethyl-epipodo phyllotoxin 9-(4,6-O-ethyl-idene-B-D-glucopyranoside) (VP 16), 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU) and procarbazine following surgery and radiation for children with brain tumors will increase survival as compared to historical controls treated with surgery and radiation alone. To study the effect of this chemotherapy on the quality of life as measured by psychometric tests, neurologic examinations and developmental tests. Document toxicity which may arise from this treatment, especially possibly leukoencephalopathy. Examine methotrexate kinetics.

Technical Approach: See attached schema.

Progress and Results: The Pediatric Oncology Group has entered three patients. One patient with medulloblastoma is alive free of disease at 300 days on VP-16. One patient with right cerebellar medulloblastoma on VP-16 is likewise without evidence of disease on day 241. The third patient had an unresectable thalmic mass treated with high dose methotrexate and expired.

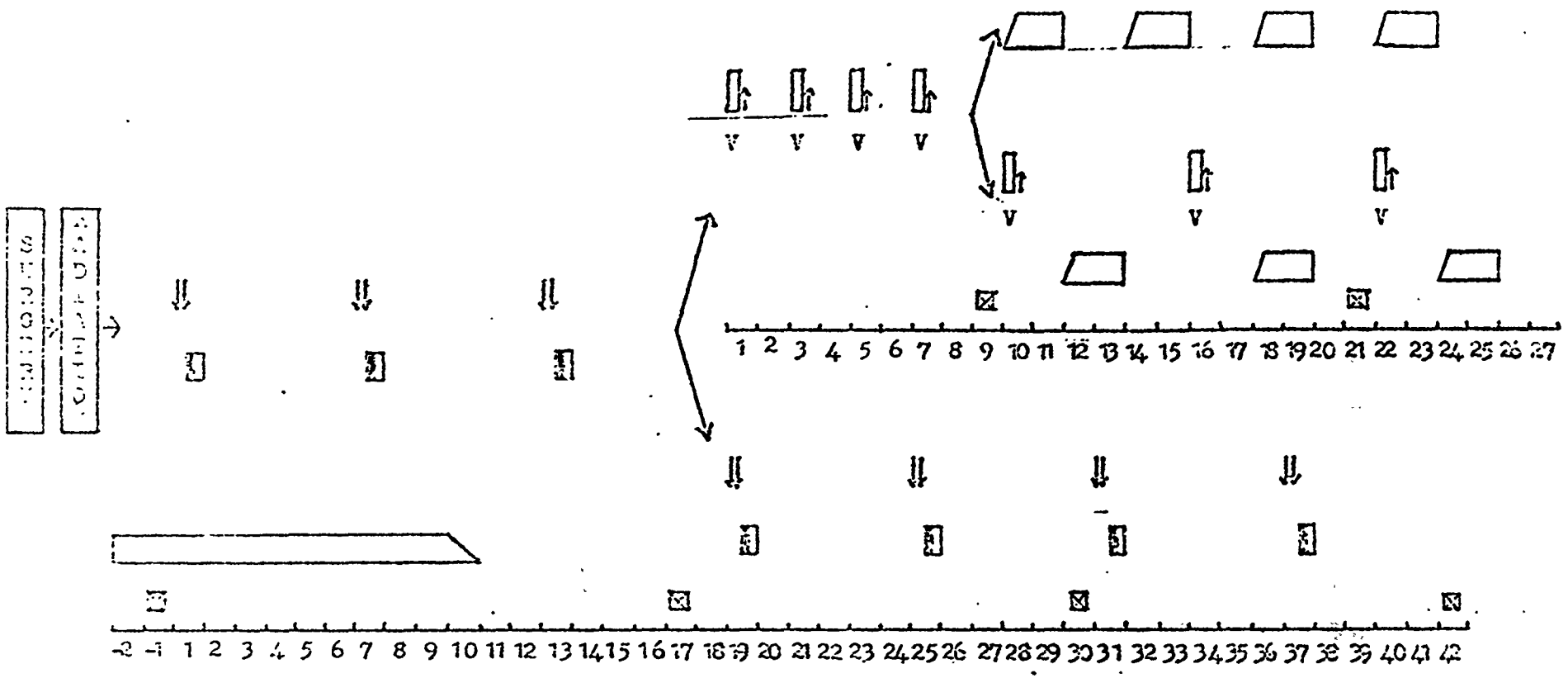
Conclusions: Too early for appropriate evaluation.

Side Effects/Complications: No unusual/unexpected side effects were encountered.

Funds Utilized FY 79/Requested FY 80: See Introductory Remarks to Annual Progress Report

Publications: None

Type of Report: Interim. This study needs a minimum of 24 patients; pending accrual rate this study may not be completed until 1984.



⊠ MRI scan every 12 weeks during maintenance and at the times noted above

Dexamethasone 1-4 mg p.o. every 6 hours for at least one week, then changing to 4-16 mg p.o. every other day weeks 1-9 with 1 week taper week 10

⇓ VP-16 60 mg/M² IV daily on the first and second days of each course

I CCNU 60 mg/M² p.o. on the third day of each course

□ CCNU 60 mg/M² p.o. on the fourth day of each course given only to patients with ependymomas who have not received spinal irradiation

V Vincristine 2 mg/M² IV push ½ hour prior to beginning the high dose methotrexate infusion

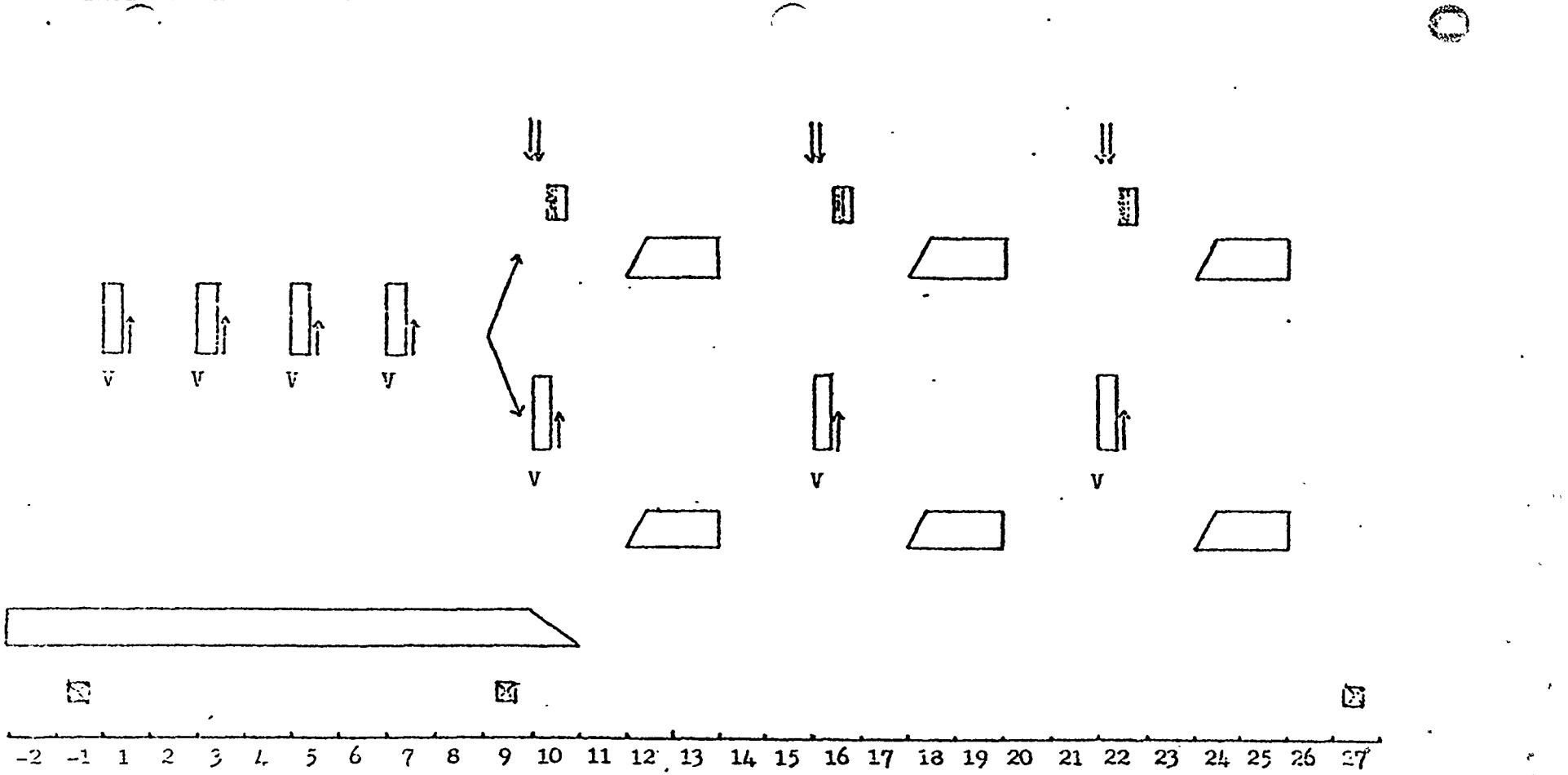
High dose methotrexate up to 500 mg/kg IV as a 6 hour infusion

† Leucovorin (citrovorum factor 15 mg/M² IV or IM every 6 hours beginning 2 hours after completion of the high dose methotrexate infusion

Procarbazine 100 mg/M² p.o. daily for 14 days (day 1- 50 mg/M²; day 2- 100 mg; days 3-14- 100 mg/M²)

INCREASED RISK TREATMENT PHASE

FIGURE II



CBC seen every 12 weeks during maintenance and at the times noted above

Dexamethasone 1-4 mg p.o. every 6 hours for at least one week, then changing to 4-16 mg p.o. every other day weeks 1-9 with 1 week taper week 10

VP-16 60 mg/M² IV daily on [illegible]

CCNU 60 mg/M² p.o. on the third day of each course

CCNU 60 mg/M² p.o. on the fourth day of each course given only to patients with ependymomas who have not received spinal irradiation

V Vincristine 2 mg/M² IV push ½ hour prior to beginning the high dose methotrexate infusion

High dose methotrexate up to 500 mg/kg IV as a 6 hour infusion

Leucovorin (citrovorum factor) 15 mg/M² IV or IM every 6 hours beginning 2 hours after completion of the high dose methotrexate infusion

Procarbazine 100 mg/M² p.o. daily for 14 days (day 1- [illegible])

WORK UNIT NUMBER - 6028

TITLE OF PROJECT: Application of Hemoglobin A_{1c} as an Indicator of Juvenile Diabetic Control

INVESTIGATOR:

Principal: Chandra M. Tiwary, M.D., LTC, MC

COINVESTIGATOR: Rodolfo Bongiovanni, CPT, MSC, Biochemist

OBJECTIVE: The purpose of this study is twofold. The first is to show a more effective means of assessing a patient's long-term Diabetes Mellitus disease state with the monitoring of glycosylated hemoglobin levels, and to determine the optimized time for obtaining blood for the Hb. A_{1c} determination. Secondly, obese patients known to have high glucose and Hb. A_{1c} levels will be studied to show if there is a correlation between Hb A_{1c} and insulin.

RESULTS AND PROGRESS: We measured Hb A_{1c} in normal control children (n=10), in obese children (n=8), and in children with diabetes (n=20). Repeat Hb A_{1c} measurement were performed at an interval of 1-12 weeks in children with diabetes. A total of 150 Hb A_{1c} measurement were performed, the results are:

1. The Hb A_{1c} in normal children varies from 5-7.5%.
2. Hb A_{1c} in obese children is not different from the controls.
3. Hb A_{1c} in obese children does not correlate with serum insulin value.
4. Following a change in the diabetic control, the trend in Hb A_{1c} change is evident in one week, however, clinically significant alteration is evident in 2 weeks. We feel that for clinical purposes a measurement of Hb A_{1c} at about 2-4 weeks interval in a newly diagnosed diabetes and between 4-12 weeks in other diabetics should be adequate.

However the last conclusion is only tentative because repeated measurements at 1-2 weeks intervals were performed only a few childrens (n=5). More children need to be studied at frequent intervals for a firm conclusion.

Funds Utilized, FY 1979	$2,200.00
Funds requested, FY 1980	
1. Mission travel to present results at a National meeting and publication	800.00
2. Hemoglobin A_{1c} Assay/supplies	2,200.00
3. Technician Time *10 hours/week)	
TOTAL	$3,000.00

Publications and Abstracts, FY 1979 None

Estimated time of completion 2 years

Type of Report: Interim

Work Unit No.: 7111

Title: Interruption of Maintenance Neuroleptic Therapy

Investigators: R. Harlan Bridenbaugh, LTC, MC
Robert L. Bank, MAJ, MC

Objectives: (1) To determine the immediate and long-term results of interrupting maintenance neuroleptic therapy, (2) to compare three and twelve week schedules for tapering neuroleptic therapy, and (3) to determine the relationship between serum prolactin and clinical status during reduction of neuroleptic therapy.

Technical Approach: Systematic evaluation of patient's mental status and psychological functioning by standardized rating scales. Monitoring of serum prolactin levels during tapering and after discontinuance of maintenance neuroleptic therapy.

Progress and Results: Three (3) patients have been entered in the project and have completed the required series of blood tests and psychosocial evaluations. Serum prolactin levels were performed on blood samples that had been kept frozen at -70° C. All values obtained were within the normal range. During FY79 no new patient entries were made due to loss of co-investigator. With the presence of a research fellow (new co-investigator) this year, we expect to obtain 15-20 patient entries between January and June 1980.

Conclusions: Patients entered into the project thus far have apparently been on maintenance neuroleptic medication in doses that are too low to raise serum prolactin levels. Clinical implications at this point cannot be made because only a small number of patients have been studied. Many factors have made it difficult to obtain patient entry thus far. It is expected that one more year will be required to obtain adequate patient material.

Funds Utilized, FY79: None.

Funding Requested, FY80:

(a) Serum prolactin assays, 100 @ $4.00 ea =	$400
(b) Travel to present results	500
	$900

Publications: None

Type of Report: Interim

Work Unit No.: 7214

Title: Pre- and Post-Discharge Assessment of Psychiatric Patients

Investigators: Donald W. Morgan, COL, MC
R. Harlan Bridenbaugh, LTC, MC
Emmanuel G. Cassimatis, MAJ, MC
Charles R. Privitera, MAJ, MC

Objective: To establish, within the Department of Psychiatry, WRAMC, a structured method of assessing pre- and post-discharge levels of psychosocial function of psychiatric patients seen by a Medical Evaluation Board (MEB); to compare pre-discharge morbidity with post-discharge function of psychiatric patients seen by an MEB; and to systematize the MEB procedure in order that training and education goals can be met.

Technical Approach: From Jan 77 to Aug 77, 200 consecutive patients seen by an MEB were entered into the study. Baseline psychological and demographic data were obtained while still on an inpatient status. Patients have been followed every three months by mailed questionnaires to monitor emotional and social-vocational functioning.

Progress and Results: The return rate for the questionnaire has been approixmately 85%. Three patients have committed suicide. A wide range of outcomes are thus far apparent with about one-third of the group experiencing rehospitalization thus far. We have completed the operational phase at this point and will discontinue periodic mailing of questionnaires. We will now begin examination of the information obtained. More detailed assessment of data already collected will be carried out in the next 6-9 months.

Conclusions: It is feasible to follow patients by mail questionnaire. More specific information concerning outcome will be available when the questionnaires are systematically assessed.

Funds Utilized, FY79: None.

Funding Requested, FY80: Travel to present results - $500.00

Publications: None

Type of Report: Interim

Work Unit No.: 7217

Title: Management of Impairment of Accommodation Secondary to Psychotropic Medication

Investigators: R. Harlan Bridenbaugh, LTC, MC
Richard J. Sapolis, MAJ, ANC
Daniel L. LaDuke, CPT, ANC
Mary Barbara Papineau, CPT, ANC

Objective: To determine the incidence of impairment of accommodation secondary to the anticholinergic action of neuroleptics, tricyclic antidepressants, and anti-Parkinson agents; to evaluate the effectiveness of optical management of such impairment secondary to the above psychotropic agents; and to examine the relationship between dosage of medication and degree of impairment of accommodation.

Technical Approach: Patients who where receiving psychotropic agents that have anticholinergic action were evaluated by means of a near vision reading card. If blurring of vision was noted at a normal reading distance (16" to 20"), then patient was tried on + diopter eyeglasses in increasing increments of +0.5 diopter. Final strength of glasses dispensed was determined by patient choice alone. Level of medication was recorded and monitored and patients were re-evaluated at weekly intervals.

Progress and Results: Nineteen (19) patients were formally entered into the project in 1978 and a large number of patients, over 30, were issued eyeglasses but not entered into the study. Screening was completed in June 1978 on Ward 108 on all patients receiving psychotropics with anticholinergic effect. Two-thirds of all patients showed evidence of impairment of accommodation. Due to numerous administrative problems, we have not been able to obtain eyeglasses for ward use. The final phase of this project will be the "clinical" application phase. When approximately 50 pairs of eyeglasses become available (in various diopter strengths of +0.5 to +2.5), we will implement their use as a patient care item. From the clinical application phase of this project, we will easily be able to obtain more information concerning severity and prevalence of impaired accommodation which can then complement the data obtained thus far. A final paper is expected to be written by April 1980.

Conclusions: Blurring of vision from the anticholinergic action of certain psychotropic agents is very prevalent on an acute treatment psychiatric ward. The immediate maangement is the same as for presbyopia, i.e., the application of + diopter reading glasses.

Funds Utilized, FY79: None

Funds Requested, FY80: Travel to present results - $500.00

Publications: None

Type of Report: Interim

Work Unit No.: 7218

Title: Physostigmine Infusion and Lithium Responsivity

Investigators: Paul Newhouse, CPT, MC
R. Harlan Bridenbaugh, LTC, MC

Objective: To examine the mental status changes induced by physostigmine infusion and to determine if lithium responsivity is related to such mental status changes.

Technical Approach: Patients who are going to begin lithium therapy are observed for 48 hours with no neuroleptic medication. Patient then receives two infusions (one placebo, one physostigmine - 4 mg.) on two separate days utilizing a randomized, double-blind, crossover design. Systematized ratings of mental status are made while undergoing the infusions and while on lithium therapy.

Progress and Results: No patients thus far have been entered into this study.

Conclusions: None

Funds Utilized, FY79: None.

Funds Requested, FY80: Travel to present results - $500.00

Publications: None

Type of Report: Interim

DISPOSITION FORM

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

REFERENCE OR OFFICE SYMBOL	SUBJECT
HSWP-RR	Reply to Reviewer of Work Unit #7218

TO C, Clin Invest Svc

FROM Investigators, Work Unit #7218

DATE 6 Dec 79

CMT 1

(RHBridenbaugh/b··/61778)

1. In reply to the reviewer's comments concerning the Annual Progress report on Work Unit #7218, the following is submitted:

a. We anticipate beginning our protocol in Feb 1980 and hope to study 4-8 patients in CY 1980.

b. Many factors have impeded progress on the protocol, but the main issue is the fact that the investigators have been deliberating on changes to the protocol as originally approved. Along with a number of other minor changes, we are considering changing the rate of infusion of physostigmine (4 mg. in increments of 0.5 mg. q. 60 sec.) in addition to changing the placebo infusion to "active placebo" (i.e., neostigmine--a cholinesterase inhibitor that doesn't cross the blood brain barrier). We are in the process of further survey of literature and will obtain consultation from the Anesthesiology Service and expect to submit an Addendum for review by the Clinical Investigation Committee and Human Use Committee at the Jan 1980 meeting.

c. It is acknowledged that the above <u>should</u> have been included in our original Annual Progress report.

R. Harlan Bridenbaugh

PAUL NEWHOUSE, MD
CPT, MC
Co-Investigator, Work Unit #7218

R. Harlan Bridenbaugh

R. HARLAN BRIDENBAUGH, MD
LTC, MC
Co-Investigator, Work Unit #7218

DA FORM 1 FEB 62 2496 REPLACES DD FORM 96, WHICH IS OBSOLETE.

☆GPO-1975-665-422/1063

Work Unit No.: 7300

Title of Project: LSD Follow-Up Study (Establishment of Normal Controls for Neuropsychological Examination)

Investigators: David A. McFarling, MAJ, MC
Francis J. Fishburne, LTC, MSC

Objectives: To obtain base rate values of a neurologically screened normal adult population with respect to the Halstead-Reitan neuropsychological battery.

Technical Approach: Volunteer subjects are first screened using a clinical neurological examination, electroencephalography, and computerized axial tomography (CAT scan). Subjects who are normal on all screening procedures are then administered the Halstead-Reitan neuropsychological battery.

Progress and Results: Twenty-seven (27) subjects have been evaluated to date.

Conclusions: Deferred.

Funds Utilized: None.

Funding Requirements, FY-80: None.

Publications: None.

Type of Report: Interim.

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
LTC John A. Kark, M.D., MC

Associate: Johannes Blom, M.D.
LTC Jeffrey R. Berenberg, M.D., MC
MAJ Salvatore Scialla, M.D., MC
COL Robert W. Muir, M.D., MC

Objectives: B6 and glycogen metabolism are being investigated 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.

During the past three years, we have concentrated almost entirely on the B6 metabolism aspects of this study, and are particularly interested in what controls plasma B6 levels in these patients.

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 three 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).

During the past year, we have concentrated primarily on isolating subpopulations of blood cell precursors from the bone marrow. The technique which appears to suit our needs most satisfactorily so far uses velocity sedimentation at unit velocity.[1,2] In this technique, bone marrow cells (or cells from another tissue, such as spleen, tonsil, or lymph node) are disaggregated, washed, and centrifuged at less than 4000 x g for 10 minutes, and resuspended in phosphate buffered saline (PBS) with 0.3% bovine serum albumin (BSA). Cell counts are adjusted to 5 x 10^6/ml in order to prevent streaming on the separation column. A Sta-Put Cell Separator (Johns Scientific, Toronto) is employed, with its gradient generator system loaded with 600 ml Minimal Essential Medium (MEM) and 1% BSA in Bottle A, and 600 ml MEM with 2% BSA in Bottle B. The top layer of 50 ml PBS with

0.3% BSA is first loaded into the column, followed by the previously prepared cell charge. A buffer gradient of 0.5% BSA in MEM is then introduced. After all air bubbles are removed, all clamps from the gradient generator bottles are opened, and the separator chamber is allowed to fill, lifting the cell layer off the bottom. After all the BSA solutions are instilled, sedimentation is permitted to continue for an additional 3.5 to 4 hours. The column is then drained, discarding the cone volume, in fractions of 30 ml. Each fraction or pair of fractions is pooled, and then each pooled fraction is centrifuged and resuspended in a total volume of 500 µl fetal calf serum and plated on slides for later histologic studies. The remainder of each pooled fraction is lysed with ultrasound, and biochemical studies are performed on the lysate.

Other separation techniques, particularly elutriation, centrifugation with PVP beads, and fluorescent activated cell sorting, will also be examined and compared to velocity sedimentation. Centrifugation with a Ficoll-Hypaque density gradient was shown not to be adequate for separation of bone marrow precursors, in a series of studies in our laboratory last year.

Progress and Results: none

Conclusions: none

Subject side effects/complications: No patients were studied in FY 79

Funds Utilized, FY 79: none

Funds Requested, FY 80: none

Publications and Abstracts, FY 79: none

Estimated Date of Completion and/or Number of Subjects to be Studied Before Completion: Owing to loss of the persons carrying out these studies, and the lack of available time for their pursuit by the remaining investigator, this study is terminated.

Work Unit No.: 9010

Title of Project: Vitamin B6 Metabolism in the Hematopoietic System of Patients Receiving Isoniazid and Patients with Sideroblastic Anemia

Investigators:

Principal: John A. Kark, M.D., LTC, MC

Associate: Cecil U. Hicks, Medical Technologist
Harold L. Williams, Chemist

Objectives: To improve the management of isoniazid therapy. To identify biochemical indicators for B6-responsive sideroblastic anemia.

Technical Approach: Further investigation of INH inhibition of PLK will be carried out on purified erythrocyte PLK. The methods to be used have been described by Chern and Beutler, and in Methods in Enzymology. Following the completion of kinetic studies on purified enzyme, work will be carried out to establish a fluorometric assay for erthrocyte pyridoxal-isoniazid hydrazone, using normal hemolyzates.

Attempts will be made to accomplish enrichment of bone marrow aspirates with erythroblasts, in order to obtain a population of nucleated red cells for study of heme synthesis and B6 metabolism in erythroblasts of patients with refractory anemia, especially sideroblastic anemia.

Studies will focus on the comparison of defects in ALA-synthetase activity with defects in heme synthetase activity of erythroblasts, using a new, greatly improved assay for heme synthetase (Williams, Harold L. et al. An Improved Radiochemical Method for Measuring Ferrochetalase Activity. Clin. Chem., in press,. Assay of vitamin B6 metabolism on bone marrow erythroblasts will include those cells which do not reproduce mature circulating red cells, and might provide a picture of metabolic defects, much less apparent in the surviving cohort of cells.

Progress and Results: INH: no clinical studies were carried out in FY 79. Plans were drawn up for completion of these experiments by clarifying the mechanism of inhibition of PLK by PL-INH using purified enzyme.

Sideroblastic anemias: data was collected from previous clinical observations, and a manuscript is in preparation. No clinical studies were performed in FY 79.

Conclusions: INH: no new conclusions were drawn.

Sideroblastic anemia: no new conclusions, see the report for FY 78.

Subject side effects/complications: No clinical studies were carried out in FY 79.

Funds Utilized, FY 80: none

Funds Requested, FY 80: none

Publications and Abstracts, FY 79: Manuscripts are in preparation.

Estimated Date of Completion and/or Number of Subjects to be Studied Before Completion: Both studies are in an interim state. We estimate that about 25 patients and controls will be studied, and that this protocol will be completed in FY 81.

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 System

Investigators:

Principal: MAJ August J. Salvado, M.D, MC

Associate: MAJ William M. Butler, M.D. MC
LTC Jeffrey Berenberg, M.D. MC
Nancy Josza

Objectives: To determine whether the hepatitis virus injures erythroid progenitors (CFU-E and BFU-E) in the bone marrow and to clarify the mechanisms of this injury.

Technical Approach: The plasma clot culture technique for erythroid progenitors is used to determine colony growth of CFU-E and BFU-E from marrow of patients with acute hepatitis. Normal control marrow is obtained as an extra aspirate from patients having marrows done as part of a staging work-up for malignancy.

Progress and Results: The plasma clot system is fully developed and results from controls compare favorably with the current literature. One patient with hepatitis has been studied and demonstrated normal marrow erythroid progenitors, however, his plasma did not augment the number of progenitors in either patient or control marrow. Control serum did augment control and patient marrow progenitors. Significant delay in patient accrual continues to be a problem and a shortage of erythropoietin which developed this year has also delayed this project.

Conclusions: Not applicable

Funds Utilized FY 79/ Requested FY 80: None

Publications: None

Estimated Completion: Ten patients with hepatitis are to be studied. This project should be completed within two years.

Type of Report: Interim

Work Unit No.: 9013

Title of Project: The Carbohydrate Dependence of Platelet Surface Interactions in Hypercoagulable States

Investigators:

Principal: MAJ Salvatore Scialla, M.D., MC

Associate: LTC Michael J. Haut, M.D., MC
MAJ Grant Taylor
LTC Jeffrey Berenberg, M.D., MC

Objectives: To examine platelets and plasma from selected individuals with hypercoagulable states to determine if altered carbohydrate and carbohydrate synthesizing capacity is present.

Technical Approach:

1. Platelets and plasma are separated from blood drawn from controls and cancer patients.

2. Coagulation profiles are performed on the plasma sample which includes a detailed analysis of Factor VIII complex.

3. Detailed analysis of the Factor VIII complex includes a separation procedure by chromatography using agarose. Sialic Acid content of Factor VIII is determined by the Warren Method.

4. Platelet surface sialyltransferase is determined by a C^{14} Sialic Acid incorporation assay with platelets as the enzyme source.

5. Platelet surface sialic acid is determined by incubation with neuriminidase and subsequently the sialic acid assay by Warren.

6. The above studies are correlated with platelet aggregation photometric method.

Progress and Results: The mechanism of sialyltransferase activity (STA) and platelet function is being clarified. An inhibitor of the platelet release reaction (Prostaglandin E_1) does not inhibit collagen stimulated STA. The work this year is to clarify the interaction of Factor VIII, STA, and sialic acid.

Conclusions: Sialyltransferase Activity may be involved with the initial phase of platelet surface changes.

Funds Utilized, FY 79: none

Funds Requested, FY 80: none

Publications and Abstracts, FY 79:

Scialla, S.J., Speckart, S., and Kimball, D.B. Alterations in Platelet Surface Sialyltransferase Activity and Platelet Aggregation in a Group of Cancer Patients with a High Incidence of Thrombosis. Cancer Research 39:2031 (1979).

Scialla, S.J., Speckart, S.F., and Kimball, D.B. Aspirin Effects on Platelet Aggregation and Platelet Surface Sialyltransferase Activity. Clinical Research, April, 1978.

Scialla, S.J., and Berenberg, J.L. The Relationship Between Stimulated Sialyltransferase Activity, Release Reaction, an Aggregation in Washed Platelets Using Prostaglandin E_1 Inhibition. Submitted to American Foundation of Clinical Research-Eastern Regional Section - October, 1979.

Estimated Date of Completion and/or Number of Subjects to be Studied Before Completion: Interim

40 patients to be studied

This project should end in FY-80.

Work Unit No.: 9014

Title of Project: Dengue Fever Virus and Human Monocyte Interactions

Investigators:

Principal: MAJ Carlos C. Daughaday

Associate: Walter Brandt, Ph.D.

Objectives: To determine mechanisms which make monocytes permissive to Dengue virus replication.

Technical Approach: Human monocytes were purified from the blood of normal volunteers by gradient centrifugation and plastic adherence techniques. Dengue fever virus was added to monocyte cultures *in vitro* in the presence of serum and immunoglobulin fractions. Intracellular infection of the cells was then determined by measuring plaque formation in cultures. (Blood samples will be taken from 23 normal volunteers.)

Progress and Results:

1. The ability of Dengue virus to replicate in adherent mononuclear cells *in vitro* was confirmed.

2. Virus will not grow in adherent mononuclear cells, however, after the cells have been exposed to trypsin (0.075%).

3. Specific antibody when combined with virus permits virus infection of trypsinized monocytes.

4. Preparation of specific F(ab) fragments from immune sera to Dengue was accomplished. Virus and specific F(ab) did not overcome inability of virus to infect trypsinized monocytes, as did virus and intact specific immunoglobulin.

Funds Utilized, FY79: none

Funds Requested, FY80: none

Estimated completion: Completed with departure of Dr. Daughaday from WRAIR

Type of report: Final

Work Unit No.: 9015

Title of Project: The Effect of Pyridoxine on Red Cell Metabolism of B6 and on the Oxygen-Affinity of Hemoglobin

Investigators:

Principal: LTC John A. Kark, M.D., MC

Associate: LTC Michael J. Haut, M.D., MC

Objectives: To determine changes in plasma and red cell vitamin B6 metabolism and in the oxygen-affinity of hemoglobin in normal subjects who take pharmacologic doses of pyridoxine.

Technical Approach: Measurements will be made of plasma and erythrocyte levels of B6 compounds, activities of erythrocyte enzymes involved in B6 metabolism, and oxygen-dissociation curves for intact erythrocytes, as outlined in the original application.

Progress and Results: No volunteers were obtained.

Conclusions: No conclusions could be drawn.

Subject side effects/complications: No subjects participated.

Funds Utilized, FY 79: none

Funds Requested, FY 80: none

Publications and Abstracts, FY 79: none

Estimated Date of Completion and/or Number of Subjects to be Studied Before Completion: Owing to inability to obtain subjects at this time, the project is terminated.

Work Unit No.: 9016

Title of Project: Investigation of Pyridoxine as a Treatment for Sickle Hemoglobinopathies

Investigators:

Principal: LTC John A. Kark, M.D., MC

Associate: Cecil U. Hicks, Medical Technologist
Lawrence S. Lessin, M.D., Professor of Medicine
George Washington University School of Medicine
Washington, DC

Objectives: To determine how incubation of sickle erythrocytes with pyridoxine reduces the extent of sickling under low PO_2.

To determine whether treatment with pyridoxine could reduce the clinical complications of the sickle hemoglobinopathies and provide protection for individuals with sickle trait.

Technical Approach: In the original experiments, inhibitory effects of pyridoxine only occurred under special circumstances, including the use of hypertonic solutions and higher PO_2. For isotonic suspending media or isotonic whole blood at PO_2 levels from 15 to 40 mm Hg, no antisickling effects were observed. These results, and the absence of chromatographic, isoelectric focussing, or oxygen affinity changes imply that pyridoxine does not exert antisickling effects by reaction with hemoglobin. The effect of pyridoxine on the red cell water content will be examined by observing the effect of incubation with pyridoxine on the red cell volume distribution, using a Coulter Counter Channellyzer. The effect of pyridoxine on the red cell membrane will be studied by use of an ultrafiltration apparatus, and localization of 14-C-pyridoxine on fractionated erythrocytes.

In the original experiments, pyridoxal was found to react extensively with intracellular hemoglobin, producing a marked right shift of the oxygen dissociation curve of whole blood. This reaction occurred with the same kinetics using sickle erythrocytes. As a result of the increase in percent oxy-hemoglobin, sickling was greatly inhibited. A modified technique of high pressure liquid chromatography, which permitted rapid assay of the glycosylated hemoglobins at moderate pressure (about 150 lb/sq. inch), was used to assay pyridoxal-modified hemoglobin. The rate and extent of reaction could be determined with 5% accuracy using this method.

Progress and Results: A report was prepared for studies completed in February through June, 1978; and was accepted for publication. These experiments were reviewed prior to publication in the FY 78 Annual Report. Briefly, we found that incubation of whole blood with pyridoxal, but not pyridoxine, resulted in modification of intracellular

hemoglobin, such that oxygen affinity was greatly increased. Incubation with sickle erythrocytes protected those cells from sickling when exposed to low oxygen, as demonstrated by cell shape and by the absence of hemoglobin S fibers.

Using the high pressure liquid chromatography ion-exchange assay, we have begun to characterize the extent of reaction under different conditions, using small blood samples from five normal volunteers. Hemoglobin could be modified 75% by 30 to 60 minute incubations at 37 degrees C, and pH 7.4. Use of 25 degree or 4 degree incubations resulted in much slower reaction, so that only 10% or 5% modification was observed over 12 hours.

Conclusions: Pyridoxal is a potent antisickling agent in vitro. It can be used to modify intracellular hemoglobin by incubation or exposure of cells for periods of 15 to 60 minutes at body temperature. This effect is probably due to binding at the alpha-NH_2 termini of hemoglobin, with increased stabliziation of the oxy or R-state. The antisickling effects of pyridoxine occurred at 100-fold lower concentrations, are much less dramatic, and do not involve inhibition of polymerization of hemoglobins.

Subject side effects/complications: Subjects only donated small amounts of blood. No side effects or complications were noted.

Funds Utilized, FY 79: none

Funds Requested, FY 80: none

Publications and Abstracts, FY 79:

Kark, J.A., Kale, M.P., Tarassoff, P.G., Woods, M., and Lessin, L.S. Inhibition of Erythrocyte Sickling in vitro by pyridoxal. Journal of Clinical Investigation 62: 888-891 (October, 1978).

Estimated Date of Completion and/or Number of Subjects to be Studied Before Completion: Very encouraging results were found for compounds closely related to pyridoxine, especially pyridoxal. Investigation of this lead will be carried out through another protocol.

Studies of the milder antisickling activity of pyridoxine will continue for another year, and will require small blood samples from about 10 normal subjects and 10 patients with sickle cell anemia.

Number of patients: 10 patients with sickle hemoglobinopathies were studied
10 healthy controls were studied

Type of Report: Interim

Work Unit No.: 9017

Title of Project: Treatment of Sickle Cell Anemia with Pyridoxine

Investigators:

Principal: LTC John A. Kark, M.D., MC

Associate: LTC Milton P. Kale, M.D., MC
Lawrence S. Lessin, M.D.
Professor of Medicine
George Washington University School of Medicine
Washington, DC

Objectives: To determine whether ingestion of pyridoxine can reduce signs of *in vivo* sickling of erythrocytes in patients with sickle cell anemia.

Technical Approach: Levels of plasma and erythrocyte PLP, blood ISC's, rate of *in vitro* sickling under standard conditions, and the mean red cell life span will be measured before, during, and after administration of pyridoxine.

Progress and Results: Since the nature of the *in vitro* antisickling effects of pyridoxine remains poorly defined at present, it would be preferable to put this study aside until the mechanism, and hence the expected degree of response and optimum pattern of dosage with pyridoxine, is known. No patients have been studied.

Conclusions: Initiation of these studies will await elucidation of the mechanism of *in vitro* antisickling effects of pyridoxine.

Subject side effects/complications: There were no participants.

Funds Utilized, FY 79: none

Funds Requested, FY 80: none

Publications and Abstracts, FY 79: none

Estimated Date of Completion and/or Number of Subjects to be Studied Before Completion: This project is terminated.

Work Unit No.: 9018

Title of Project: De Novo Synthesis of Purine Nucleotides in Human Erythrocyte Precursors

Investigators: LTC Michael J. Haut, M.D., MC
John Prichard, M.S. (GS-11)
LTC Robert H. Prall, M.D., MC
MAJ August J. Salvado, M.D., MC
CPT H. Kyle Webster, Ph.D., MSC

Type of Report: Terminated. The investigators have departed and no continuation of this project will be involved.

Work Unit: 9025

Title: Functional Characterization of Human Intestinal Lymphocytes in Gastrointestinal Disorders

Investigators:

Principal investigator: Robert H. Reid, M.D.
LTC, MC

Objective: To determine the Lamina Propria mononuclear cells' (lymphocyte, monocyte, and macrophage) cytotoxicity effector function in normal and Inflammatory Bowel Disease Mucosa.

Technical Approach: Lamina propria mononuclear cells are isolated from human intestinal tissue using a sequential dithiothreitol-EDTA-Collagenase technique. The cells are studied for effector function in various antibody dependent cellular cytotoxicity (ADCC), spontaneous cell-mediated cytotoxicity (SCMC), and lectin-induced cellular cytotoxicity (LICC) assays.

Progress and Results: No patient tissue has been studied during FY 79. The results to date are the following: 1) Fc-receptor bearing lymphocytes as well as T&B cells and macrophages are present in normal and IBD human intestinal mucosa. 2) Lymphocytes from both normal and IBD human intestinal mucosa mediate ADCC and LICC with red cells as targets. 3) Intestinal mononuclear cells occassionally mediate ADCC and SCMC with cell lines as targets. 4) No major difference in cytotoxic capabilities or surface characteristics between normal and IBD intestinal lymphocytes has been observed.

Conclusions: Not applicable

Funding Utilized, FY 79: None

Funding Requested, FY 80: None

Publications: R.P. MacDermott, G.O. Franklin, K.M. Jenkins, I.J. Koduer, G.S. Nash, I.J. Weinrieb; Human Intestinal mononuclear cells I. Investigation of Antibody-Dependent, Lectin-Induced, and Spontaneous Cell-Mediated Cytotoxic Capabilities. Gastroenterology 78: 47-56, 1980.

Type of Report: Interim

Work Unit No.: 9030

Title of Project: Circulating Serum Isoenzymes in Mesenteric Infarction

Investigators:

Principal: Geoffrey M. Graeber, MAJ, MC
John W. Harmon, MAJ, MC
Patrick J. Cafferty, PFC, USA
Division of Surgery, WRAIR
Michael J. Reardon, DVM PhD, MAJ VC
Div of Pathology WRAIR

Objectives:

1. Evaluate the anticipated elevations of total serum CPK and LDH in patients suffering from abdominal catastrophes.
2. Study the anticipated changes in the isoenzyme patterns of serum CPK and LDH in patients suffering from abdominal catastrophes.
3. Determine the diagnostic value of such tests in helping to distinguish mesenteric infarction from other acute intraabdominal problems.

Technical Approach: Patients who are seen by the General Surgery Service for acute abdominal emergencies have been entered into the protocol as soon as their consent has been obtained. Blood samples have been drawn before surgery, in the recovery room, and for up to seven days after surgery. The samples are analyzed for total and respective isoenzyme concentrations of creatine phosphokinase (CPK) and lactic dehydrogenase (LDH). Two distinct groups of patients can be delineated: those who had mesenteric infarctions and those who suffered other acute conditions.

Patients who are undergoing routine intraabdominal procedures have served as control groups. Their serum CPK and LDH values have been determined on a similar basis to provide a control group.

Progress & Results: As noted in the original protocol, the study will need to be run over 18 months to gain adequate numbers. (Our preliminary findings are based on data obtained over a three month period). A total of 69 patients have been entered into the study. No changes or modifications in the protocol have been made.

Initial results show that patients who have suffered mesenteric infarctions will exhibit CPK-MB bands in their sera. We have also seen minimal rises in the serum of the CPK-BB isoenzyme which was, theoretically, the most promising indicator.

Progress & Results: The results from the study of the LDH isoenzyme system shows that any elevations after routine surgery are due to LDH_5, the predominant enzyme in liver and skeletal muscle. When patients have suffered a mesenteric infarction, the LDH isoenzyme patterns show definite increases in LDH_3 and LDH_4. These findings are different from the changes seen in myocardial infarction when LDH_1, becomes the predominant serum isoenzyme.

Review of the control group values shows that CPK-MB and CPK-BB do not elevate after routine surgery. LDH elevations are only those compatible with skeletal muscle injury.

Conclusions:

1. There have been no serious or unexpected side effects or complications in subjects participating in the project.
2. The CPK and LDH isoenzymes systems appear to be valid markers for mesenteric necrosis.
3. The serum changes in the CPK and LDH isoenzyme systems seen after surgery are compatible with skeletal muscle injury. No myocardial isoenzyme rises have been detected.

Funds Utilized, FY-79:

Personnel: None

Equipment:	Rental fee for electrophoresis equipment in approved budget	$4,001.40
	Funds used FY-79	2,232.20
	Funds requested FY-80	$1,769.20
Supplies:	Consumable supplies (alcohol wipes, syringes, needles, vacutainer tubes) Budgeted in original request	$1,700.00
	Funds used in FY-79	610.00
	Funds requested in FY-80	$1,090.00
Travel:	Budgeted for presentation of paper	$600.00
	Funds used FY-79	0.00
		$600.00
Reprints:	Budget allocation	$250.00
	Funds used FY-79	0.00
		$250.00

Funds Requested, FY-80:

Equipment:	For continued rental	$1,769.00
Supplies:	Consumable	1,090.00
Travel:	Meeting for presentation	600.00
Reprints:		250.00
		$3,709.20

Publications: None. The study has been in progress for a period of time which is too short to yield significant patient numbers.

Type of Report: Interim

PROJECT NUMBER: 9032

PRINCIPAL INVESTIGATOR: Paul B. Sullivan, 2nd LT, USAFR
CO-Investigator: Dr. Dennis Donohue, MAJ ANC

THE RELATIONSHIP BETWEEN THE DEGREE AND CONTENT OF SELF-DISCLOSURE A MALE WITH A MYOCARDIAL INFARCTION WOULD DISCLOSE TO A MALE NURSE AND FEMALE NURSE.

The problem investigated in this study was to ascertain if there was a relationship between the degree and content of self-disclosure a male with a myocardial infarction would disclose to a male nurse and female nurse.

The following research hypotheses and their null correlaries were developed to describe the questions investigated: (1) There will be a/no significantly higher amount of disclosure in all aspects of self to a male nurse than to a female nurse. (2) There will be a/no significantly higher amount of disclosure in the Body aspect of self to a male nurse than to a female nurse. (3) There will be a/no significantly higher amount of disclosure in the Work aspect of self to a male nurse than to a female nurse. (4) There will be a/no significantly higher amount of disclosure in the Money aspect of self to a male nurse than to a female nurse. (5) There will be a/no significantly higher amount of disclosure in the Personality aspect of self to a male nurse than to a female nurse. (6) There will be a/no significantly higher amount of disclosure in the Tastes and Interests aspect of self to a male nurse than to a female nurse. (7) There will be a/no significantly higher amount of disclosure in the Attitudes and Opinions aspect of self to a male nurse than to a female nurse.

This study was limited to seventeen males, twelve or 71% were white and five or 29% were black. The mean age was 54.6 years with a range from forty-two to sixty-nine years. Sixteen or 95% were married and one or 5% were single. Pathologically, five anatomical sites of infarction were determined by electrocardiographic analysis. The mode for the sample was the inferior MI which occurred in ten or 58.8%.

Data for self-disclosure was obtained through the administration of Jourard's Self-disclosure Inventory (SDI). An analysis of variance was computed to test the relationship between the total amount of self-disclosure (H_1) and the Least Significance Difference measure was used to determine the relationship between the individual aspects of disclosure to the male nurse target versus female nurse target (H_2-H_7).

Analysis of the data led to the acceptance of all seven null hypotheses. Significant findings ($p<.05$, two tailed analysis) were found between the aspects of self Money and Personality and the remaining aspects of self Work, Body, Tastes and Interests and Attitudes and Opinions.

Based on the findings of this investigation, the following conclusions were made:

1. There is no significant relationship between the degree and content of self-disclosure a male with a myocardial infarction would disclose of himself when the targets for disclosure was the nursing staff, whether male or female.

2. There is a significant difference in the degree a male

with a myocardial infarction would disclose of himself in the aspects of self Money and Personality and the remaining aspects of self Work, Body, Tastes and Interests and Attitudes and Opinions when the targets for disclosure was the nursing staff, whether male or female.

The following recommendations were made:

1. The descriptive design be repeated using Jourard's 40 item self-disclosure questionaire.

2. An experimental design be employed using control groups, the SDI and a liking scale.

3. An investigation which identifies the components of the nurse-patient relationship which the myocardial infarction patient considers therapeutic would be of benefit for nursing practice and add to the theory base of nursing.

4. Studies of the application of the self-disclosure and/or interpersonal constructs of the nurse-patient relationship in other clinical areas would be helpful in determining parameters of a therapeutic relationship.

TYPE OF REPORT: Completed

Work Unit Number: 9033

Title: Role Performance Expected of Primary Care Nurse Practitioners

Investigator: MAJ Janet R. Southby, ANC
C, Nursing Research Service
Walter Reed Army Medical Center
(Nee: Janet S. Rexrode)

Objective, Approach, Results and Conclusions: See Abstract (Enclosure 1).

Funds Utilized FY-79: None requested.

Publications:

Rexrode, J.S. Expectations and perceptions for the role of primary care nurse practitioners within the Army health care system. Unpublished doctoral dissertation, The Catholic University of America, 1979.

Southby, J.R. Primary Care Nurse Practitioners Within the Army Health Care System. Military Medicine, in press, (See Enclosure 2).

Date of Completion: May 1979

Type of Report: Completed

Work Unit #: 9034

Title of Project: The Effects of the Relaxation Response on Psychological Anxiety and Physiological Cardiovascular Function in Acute Post

Principal Investigator: Stephen J. Boccuzzi, RN, MSN

Implications

Implications from this study for nursing include the following:

1. Acute post myocardial infarcted Type A personalities may derive benefits from the relaxation response especially in terms of controlling anxiety in the acute stage and long term chronic rehabilitation stage.

2. Relaxation may effectively decrease anxiety to enhance education and counseling toward promotion of a better lifestyle and prevention of future coronary episodes.

3. Relaxation may enhance physiological rest in the acute stage by lowering cardiovascular parameters and decreasing oxygen requirements and expenditure of energy.

4. Those who practice relaxation over a short period may not have mastery over the technique to produce any dramatic effects physiologically especially after an infarct.

5. Of the seven individuals in the study, six were Type A indicating that a large percentage of individuals afflicted with coronary heart disease are of the coronary prone personality type, indicating the need to better control the malignant behaviors and thought processes of this personality type.

6. There are great implications for future study with a larger sample size and possibility of using other psychological and physiological parameters to strengthen the results.

Type of Report: Interim

Work Unit No.: 9035

Title of Project: Effects of Altitude, Mood and Dietary Habits on Performance of a Choice-Reaction Time Task.

Principal Investigator: James P. Dixon, Capt, USAF, BSC
C, Aerospace Physiological Rsch
Division of Aerospace Pathology
Armed Forces Institute of Pathology

Objectives: To evaluate the subtle influence of mood, altitude, dietary habits and other stresses on performance and to relate these decrements to the job performance of service personnel.

Technical Approach: By means of a choice-reaction time task, efficiency (number of correct divided by total time) will guage performance. This will be related to the physiological parameters of arterial oxygen saturation, respiration and heart rates at various altitudes.

Progress & Results: When the first set of control runs (100% 0_2 were compared to the experimental runs (compressed air at an altitude unknown to the subject), extreme decrements were found. In fact, a greater decrement in performance occurred with the mask and compressed air than occurred without a mask at the same altitude. This problem has not been resolved, but the appearance of hypoxia symptoms has implicated the bottled gas. Oxygen saturation is now measured using a Hewlett-Packard ear oximeter. The test protocol now employs a nasal cannula instead of a mask and the experiment has been started again. It is our observation that the cannula can probably provide sufficient oxygenation up to 25,000 with the proper flow rate. Subjects have expressed approval of the cannula during their first several runs. We have not yet analysed these data, therefore no results can be stated.

Funds: None requested at this time.

Interim Report: Please note that there has been some minor changes in the experiment. Specifically, they are as follows:

1. Nasal cannula replaces the mask.
2. Number of trials in the choice-reaction time task has been increased.
3. Flights may include rapid decompressions to no more that FL450, with subjects closely monitored using an oximeter (0_2 saturation, heart rate, respiration rate measured) such that physiological parameters are not allowed above an equivalent 25,000 feet.
4. Since altitude is presently the primary variable, other stresses will be studied in subsequent experiments after baseline values on performance have been established in these subjects.

DISPOSITION FORM

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

REFERENCE OR OFFICE SYMBOL	SUBJECT
AFIP-CPL-A	Reply to Reviewer (Work Unit #9035)

TO	FROM	DATE	CMT 1
C, Clin Invest SVC	Chief, Aerospace Physiological Research	6 December 79 JPD/hg/62868	

1. I am not concerned with knowing the exact FI_{O_2} obtained when delivering oxygen with the nasal cannula. What I am concerned with is the arterial oxygen saturation, which I am measuring continuously with an H-P Ear Oximeter.

2. The nasal cannula can provide high concentrations of oxygen. Insufficient arterial oxygenation will only result if the flow rate is not high enough (less than 2.5 LPM NTPD).

James P Dixon

JAMES P. DIXON
Capt, USAF, BSC

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

WORK UNIT #9036

TITLE OF PROJECT: Urease and Deaminases in Chemistry and Medicine (NIH Grant)

SUBJECT: Clinical Investigation of Patients with Myo-Adenylate Deaminase Deficiency

PRINCIPAL INVESTIGATOR: William N. Fishbein, M.D., Ph.D.

DATE OF APPROVAL AT WRAMC: 28 June 1977

ANNUAL PROGRESS REPORT 10/1/78 - 9/30/79:

As before we have used antecubital venipuncture for all cases, and have encountered no side effects. Seven patients have now been tested for their lactate/ammonia exercise response. No drugs have been used, and no WRAMC funds.

Type of Report: Interim

Work Unit Number: 9036A

Title: The Educational and Psychological Needs Specific to Human Sexuality of Middle-Aged Males Post Uncomplicated Myocardial Infarction

Principal Investigator: Patricia J. Baldwin, R.N., D.N.Sc., Howard University, School of Nursing, Washington, DC

Liaison Officer: MAJ J.R. Southby, ANC
C, Nursing Research Service
Walter Reed Army Medical Center

Objective: To describe the educational and psychological needs specific to human sexuality of middle-aged males post uncomplicated myocardial infarction.

Technical Approach: A descriptive survey using a valid and reliable questionnaire, the Sexual Needs Questionnaire, developed by Huffman (1977), is being conducted. Subjects who meet the following criteria are contacted on the 6, 7, or 8 day post M.I. and the study is explained and written consent obtained:

1. Hospitalized American males, 40-60 years of age.
2. Patients having sustained an uncomplicated M.I.
3. The M.I. will be the patient's first known incidence.
4. Patient's relationship with mate will be of at least three month's duration.
5. Approval of primary physician.

Progress and Results: The above technical approach has been followed and, to date, only two subjects have been obtained for the study at WRAMC.

Conclusions: Due to lack of substantial patient follow-up by data collectors, the expected subject number (20) has not been obtained at WRAMC. The project will be re-evaluated and appropriate measures will be taken.

Funds Utilized, FY-78: None

Funds Requested, FY-80: None

Publications: None

Estimated Date of Completion: September 1980

Type of Report: Interim

Work Unit Number: 9039

Title: Nurse Controlled Factors That Influence the Development of Diarrhea in Tube-Fed Patients.

Investigator: MAJ Reuben B. Bowie, ANC

Objective: Primary - To ascertain whether a regime which increases the frequency of changing the nasogastric tube and/or the feeding bag leads to decreased incidence of diarrhea in tube-fed patients as compared to current standard procedure. Secondary - To describe gross changes of the nose and throat mucosa in response to increased frequency of changing the nasogastric tube.

Technical Approach: A predetermined random order is used to assign patients to each of three study groups if the following criteria for selection are met: 1) neurosurgical diagnosis without complicating gastro intestinal disease; 2) assigned to neurosurgical service; 3) orders are written for tube feeding; 4) patient has initially demonstrated a tolerance for formula and method of feeding defined in the protocol; 5) physician concurrance for participation; and 6) appropriate signed consent. Study controls include: size 12 Salem-sump nasogastric tube will be used for insertion via the Hansen method; 1500 ml of Ensure Plus/24 hrs are given in 250 ml boluses q4h; served at room temperature from individual "pop open" serving cans which have been cleaned of obvious debris. Each formula feeding is followed by 200 ml of water. Medications are given separately with no more than 50 ml of water so that total volume per feeding does not exceed 500 ml. Flow rate for feedings is approximately 130 gtts/minute. Feedings are administered with the patient in semi-fowler's position. Each subject is studied for 7 days unless diarrhea develops prior to that time. Daily exam of the nose and throat mucosa is performed by the investigator. All tube changes (days 1 & 7, study groups 1 & 2; days 1 - 7, study group 3) are accomplished by the investigator; bag changes (qd for study group 1; q feeding for study groups 2 & 3) are accomplished by the nursing staff. All stools are recorded by the nursing staff according to Hansen's scale. This approach represents no change from the original protocol.

Progress and Results: After gaining initial approval, study was suspended due to a formal inquiry. Investigator response to clarify methodology and review by Clinical Investigation and Human Use Committees resulted in approval being reinstated on 26 June 1979. The 1st patient was entered in the study on 20 July 1979. To date, a total of four (4) patients have completed the study. Availability of subjects

has been less than initially anticipated. The reasons for the decrease in population are unclear at this time, but consultation with the statistician is planned to evaluate the feasibility of reducing the sample size. Some initial data analysis will be attempted when N=6.

Conclusions: With so few study subjects, it is not yet feasible to predict a trend in the relationship of tube and bag changes to the development of diarrhea. However, due to meticulous attention to controlled variables, the study has apparently had a positive affect on nursing practice. No side affects or complications which could be attributable to the protocol have been noted in study subjects.

Funds Used FY-79: $43.50 for Salem Sump Tubes. Gavage containers and Telfa pads requested through CIS have been unavailable. Those required for subjects already studied were obtained through unit supply channels and have not been excessive.

Funding Requirement FY-80:

Equipment:

feeding bags	-	$ 922.50	
Salem sump tubes	-	87.00	
Telfa pads	-	44.40	
Data processing	-	300.00	
Presentation and reprints	-	500.00	
TOTAL		$1984.40	Less if total number subjects is decreased.

Publications: None

Type of report: Annual Progress 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: E. Mendoza, M.D., MAJ, MC
F. Flynn, M.D., CPT, 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: Group I subjects were selected by the pulmonary section on the basis of a history compatible with COPD, an FEV_1 of less than 50%, and the absence of conditions known to be associated with neuropathy. These subjects were evaluated by standard neurological and electrophysiologic examination. The latter included sensory and motor conduction velocities as well as sample EMG's when indicated. Group II subjects had minimal COPD as evidenced by an FEV_1 of 70%-90%. Other requirements and evaluation were identical to those for Group I subjects. Group III subjects were chosen from the neurology staff and served as normal controls.

Progress and Results: 23 Group I subjects have been studied; 20 showed electrophysiologic evidence of neuropathy. Abnormalities were noted most commonly in the sensory nerves including the sural (20 subjects); ulnar (12 subjects), radial (9 subjects), and median (7 subjects). The peroneal (6 subjects) and median (5 subjects) were the most commonly affected motor nerves. Seven subjects demonstrated electromyographic evidence of denervation and re-inervation in the lower extremities. Four subjects exhibited clinical signs suggestive of peripheral neuropathy.

Four of 10 subjects studied in Group II had borderline sensory studies. None had abnormal motor nerve conduction or abnormal EMG's and all had normal clinical examinations. Ten subjects comprised Group III and were tested to establish normal values for our laboratory. These normal values compared very well with published data from other laboratories.

Conclusions: These findings indicate that subclinical sensory or sensorimotor neuropathy commonly occurs with COPD. The fact that abnormalities occur more commonly in the longest sensory and motor nerves of subjects with more severe pulmonary disease suggests a metabolic axonal-type polyneuropathy. The high incidence of neuropathy noted with COPD and the frequency of COPD in the population indicates that our findings are of considerable epidemiologic significance.

Funds Utilized: None

Funding Requirements: None

Publications: Neurology 29:596, 1979 (Abstract).

Type of Report: Final

Work Unit # 9080

Title of Project: Coronary Artery Disease and Coronary-Prone Behavior.

Investigators:

Principal: David S. Krantz, Ph.D., Assistant Professor of Medical Psychology, U.S.U.H.S

Co-Investigator: James Davia, M.D., Chief, Cardiology, WRAMC

Objectives, Methods, and Progress:

1. A first line of research concerns associations between aspects of behavior and presence of coronary disease. Approximately 115 consecutive patients of WRAMC who were awaiting cardiac catheterization completed the Jenkins Activity Survey and were given the Rosenman diagnostic interview to measure Type A behavior. We have been investigating the possible relationship of various components of Type A (e.g., hostility, competitiveness, time urgency, speech patterns, etc.) to presence of coronary artery disease. It remains unclear from previous research whether the intensity of various components of Type A behavior is associated with greater risk of disease. While, strictly speaking, this question can only be answered by prospective study, tape recorded interviews of cardiac catheterized patients are being broken down and analyzed item-by-item. We will examine the relationship of Type A components to angiographic results of cardiac catheterization and other standard risk factors obtained from WRAMC medical records. Angiographic data have been obtained for each patient

2. The second line of research being investigated in this project concerns possible physiologic mechanisms linking behavior processes with coronary artery disease. Research by Dembroski, Manuck and others has demonstrated that type A subjects when presented with challenging tasks and situations. Dembroski and McDougall have recently presented some suggestive evidence that patients with a history of ischemic heart disease show a trend toward similar enhanced cardiovascular responsiveness. Since January 1979, we have been measuring cardiovascular reactivity (blood pressure and heart rate) in consecutive patients the day before cardiac catheterization. We are interested in determining how heart rate and blood pressure responsiveness vary in these patients as a function of a) magnitude of coronary artery disease b) magnitude of Type A behavior c) presence of established or labile hypertension and d) family history of cardiovascular disease. An association between cardiovascular responsiveness and coronary artery disease would lend credence to the notion that this responsiveness (or other physiologic correlates of this responsiveness) play a role in the pathogenesis of coronary disease. It is also not known how various processes which have been shown to be related to elevated pressor response (e.g., Type A; family history of disease) are themselves related to each other. 115 patients have been tested so far in this study.

and these data await analysis.

Research Goals for the Upcoming Year

We plan to complete data analysis for the present studies and then to collect data for a second study outlined in the original approved protocol. This second study will look at (non-invasively measured) cardiovascular responses as a function of magnitude of angiographically-documented coronary artery disease.

Conclusions: Await results of data analysis. There have been no unexpected side effects/complications associated with this research project.

Funds Utilized: The study is funded by grants from NIH and U.S.U.H.S.

No additional funding is required from WRAMC.

Publications: Krantz, D.S., Sanmarco, M.E., Selvester, R. & Matthews, K.A. Psychological correlates of progression of atherosclerosis in men. Psychosomatic Medicine, in press.

Krantz, D.S. Cognitive processes and recovery from heart attack: A review and theoretical analysis. Journal of Human Stress, in press.

Type of Report: Interim: Approval for continuation of project requested for FY-80.

a. Work Unit Number: 9081.

b. Title: Preventive Intervention in Basic Combat Training.

c. Investigators:

(1) Principal: James M. Georgoulakis.

(2) Associate: Robert L. Bank; John A. Jenkins.

d. Objectives: To evaluate the effects of early counseling on identified vulnerable basic combat trainees.

e. Technical Approach: There were no modifications to the original protocol.

f. Progress and Results:

(1) The number of patients studied was 269.

(2) The project is completed.

(3) The results are as follows:

(a) A positive correlation (significance = .001) exists between the counseling of vulnerable trainees and the successful completion of basic training.

(b) Early intervention did not foster a dependency on the counselor. Nor did the number of visits to the CMHA increase in a manner that would hinder, prevent, or reduce training time (significance = 0.6104).

(c) No significant relationship exists between the variables counselor gender and graduation from basic combat training.

g. Conclusions: Early intervention (counseling) has a positive effect on the completion of basic combat training.

h. There were no serious or unexpected side effects/ complications in participating subjects.

i. Funds Utilized, FY 79: $5,800.

j. Funds Requested, FY 80:

Personnel: None.
Equipment: None.
Supplies: None.
Travel: $400. To enable the principal investigator to present findings for the Training Command at Ft. Knox, KY.

k. Publications and Abstracts, FY 79.

(1) Social Factors and Perceived Problems as Indicators of Success in Basic Combat Training, Part I and II, Military Medicine, September, October 1979.

ℓ. Estimated Date of Completion: Final briefing to the Training Command at Ft. Knox, KY, will be conducted NLT April 1980.

Type of Report: Completed

Work Unit No.: 9082

Title of Project: Treatment and Rehabilitation of Knee Injuries at the United States Military Academy, West Point, NY 10996

Investigators:

Principal: LTC Walton W. Curl

Associate: LTC Keith L. Markey

Objectives: To develop predictive parameters and programs to lower the knee injury rate of cadets at the United States Military Academy. It is also the objective to analyze and develop better treatment modalities for those injuries which do occur.

Technical Approach: Cadets who are participating in the intramural and intercollegiate football, wrestling, and lacrosse programs are being screened as part of the pre-season physical examination for multiple parameters which might effect knee injury rate. These parameters include: joint laxity, height, weight, body type, etc. This data and following the individuals through the sport season, determine what types of injuries they incur and it is hoped that a statistical correlation can be performed to relate these various parameters to knee injuries.

The treatment phase deals with the diagnosis and treatment of essentially isolated tears of the anterior cruciate ligament. Those who have a proven torn anterior cruciate ligament then undergo an acute repair and reconstruction of the torn anterior cruciate ligament utilizing the medial third of the patellar tendon. They are then casted with a long-leg cast with the bent knee at 60° for six weeks and then a cast-brace at 30-60° for six weeks.They are then started on a knee rehabilitation program. These patients are then followed at 3 and 6 months, 1 year, 2 year and 5 year. and 10 year intervals for long term sequelae.

Progress and Results: Preventive phase: 200 intramural football players were examined and evaluated utilizing the Cybex examination as well as a physical examination and questionnaire at the start of the intramural football season. Analysis of their injuries is still in progress.

Treatment phase: Twelve isolated anterior cruciate ligament injuries have been identified utilizing arthroscopy. All of these have been treated using the medial third of the patellar tendon to augment the repair of the anterior cruciate ligament and they are currently either in the cast-brace or have been taken out of the cast-brace and started on physical therapy program and are being followed. The protocol has been modified in that no anterior cruciate ligaments have been identified that have not been operated on. This is primarily due to patient's desiring an operation if they are to be casted for a twelve week period. Therefore, discussion is to be opened as to possibly doing a combined study with the United Stated Naval Academy and utilizing their anterior cruciate ligaments as controls in that they no longer have an operative facility. This will be discussed at Walter Reed Army Medical Center with our Orthopaedic Consultant after the start of the year.

Conclusions: The study is still on-going. There have been no unexpected side effects or complications in the individuals participating in this project. No conclusions can be made at this time as to the efficacy of the treatment phase nor can conclusions be drawn at this time as to specific parameters which may lead to a knee injury.

Funds Utilized, FY-79: The research secretary who was funded for a three month part time basis for the end of FY-79. No other funds were utilized out of the clinical research investigation project.

Funding Requirements, FY-80:

Personnel: Judy Iten, GS3 - 1/2 time basis for full FY-80

Equipment: Lenox Hill braces for bracing anterior cruciate ligaments - $285.00 ea, estimated number required - 40.

Supplies: None

Travel: $1,000.00 for TDY for the purpose of presenting results as well as visiting other Medical Centers to discuss the role of the anterior cruciate ligament.

Other: None

Publications: None

Type of Report: Interim

Work Unit No.: 9038

Title of Dissertation: JOB STRESS AND ITS CONSEQUENCES ON A GROUP OF INTENSIVE CARE AND NON-INTENSIVE CARE NURSES

Joseph P. Maloney, Doctor of Philosophy, 1979

Dissertation directed by: Dr. Frank Milhollan
Associate Professor
Department of Human Development

The focus of this study was to examine job-related stress levels between two groups of nurses: intensive care nurses and non-intensive care nurses. The researcher was interested in determining which environment was most stressful and if the nurses working in the more stressful environment would exhibit an unusual amount of anxiety, psychosomatic problems, personal-family problems, and job dissatisfaction as a result of job stress.

This study involved the administration of five questionnaires to sixty nurses. All the subjects were female, registered professional nurses. The two groups of nurses completed the Spielberger State-Trait Anxiety Inventory, the Somatic Complaint Index the Job Satisfaction Index, the Personal-Family Problem Index, and the Demographic Questionnaire.

The literature provides considerable support that nursing is a very stressful occupation, but to date there have been no attempts at determining the effects of this stress on the individual, the individual's family or the organization.

6. There were significant differences between the scores of the intensive care nurses and the non-intensive care nurses in the area of personal-family problems. The non-intensive care nurses had significantly higher personal-family problems scores.

The findings of this study apply to a specific population of nurses. It is suggested that this study be replicated using different instruments, larger samples, different groups of nurses, various settings, and that a longitidinal study be carried out.

Based on the outcomes of this study, it was deduced that perhaps the current literature has been overly dramatic in their description of the stressfulness of intensive care nursing. Comparisons between the two groups of nurses indicated that non-intensive care nurses experience significantly higher levels of both state and trait anxiety. They also reported significantly higher scores of somatic complaints, workload dissatisfaction and personal-family problems. Based on these findings, organizations should make an effort to identify the sources of stress and take measures to eliminate or reduce these stresses in the non-intensive care environment. These goals can be achieved. Proper selection and placement of nurses, reduction of environmental stress in the job, and the use of supportive techniques to reduce job stress are among the means available.

Type of Report: Completed

DEPARTMENT OF THE ARMY
UNITED STATES ARMY INSTITUTE OF DENTAL RESEARCH
WASHINGTON, D.C. 20012

IN REPLY REFER TO:
SGRD-UDZ

31 October 1979

SUBJECT: Annual Progress Report - Clinical Investigation Program. Work Unit #9094 - Utilization of Biodegradable Copolymers of Polylactic and Polyglycollic Acid - Present status - Terminated - Not approved at Federal Drug Administration

Timothy M. Boehm, MAJ, MC
Chief, Clinical Investigation Service
Walter Reed Army Medical Center
ATTN: HSWP-QCR
Washington, D.C. 20012

Dear Dr. Boehm:

Unfortunately I must report that this protocol was never approved at the Federal Drug Administration level and therefore for the present time it must be terminated.

Thanks to you and your staff for the efforts put forth on behalf of this project.

Sincerely,

DUANE E. CUTRIGHT
COL, DC
Commanding

*WR 70-1

DEPARTMENT OF THE ARMY
HEADQUARTERS WALTER REED ARMY MEDICAL CENTER
Washington, D.C. 20012

WRAMC Regulation
70-1

8 January 1979

Clinical Investigation Program

WRAMC RESEARCH ACTIVITIES

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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.

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*This Regulation supersedes WR 70-1, dated 1 April 1973

e. The studies are performed in a considered, coordinated, and professional manner.

f. Whenever feasible, studies should be initially performed in animal models.

g. The rights, well-being, and dignity of human subjects are maintained in accordance with the principles of the Declaration of Helsinki of the World Medical Association, and that written consent is obtained when indicated.

h. Any research involving animals will conform with AR 70-18 and the Laboratory Animal Welfare Act (Public Law 89-544; 7 USC 2131 et seq).

i. Assure compliance with existent military regulations to include AR 40-7, Use of Investigational Drugs in Humans; AR 40-37, Radioisotope License Program (Human Use); AR 70-25, Use of Volunteers as Subjects of Research; and WRAMC Reg 40-10, Health Physics Regulation; AR 40-38, Medical Services Clinical Investigation Program.

j. The voluntary consent of each adult human subject is essential. Each individual who initiates or directs the clinical investigation has a personal duty and responsibility for ascertaining the quality of the subject's consent. Before the acceptance of the subject, he must be given adequate explanation. He must be informed of the nature, duration and purpose of the study; the methods and means by which it is to be conducted; all inconveniences and means by which it is to be conducted; all inconveniences and hazards reasonably to be expected; and the effects upon his health or person which may possibly come from his participation in the study. He should be informed of any benefits he may acquire from participation in the study, and if there should be no benefits, the participant should be so informed. The process of obtaining voluntary consent must be witnessed by an observer who is not a coinvestigator on the research protocol. Written consent will be obtained in accordance with the format outlined in the appendix and will be in nonmedical language that is easily understood by the subject. The investigator will be required to maintain copies of the written voluntary consent for five years following completion of the study. Copies of the consent forms for all protocols must be forwarded to Chief, Clinical Investigation Service, within one month of entry of the patient onto study. The consent form must include the patient's printed or typed name, address, and social security number.

k) Children older than age seven, unless incapacitated, must assent (See definition section for definiton of assent.) to participation in studies. Additionally, the written consent of the parent or

guardian must be secured and properly witnessed. An effort should be made to secure the written consent of the child utilizing a consent form written at his age level. In addition, "instructions to guardian" may need to be prepared that is written at an adult level. Both the processes of assent and securing written consent should be directed toward providing the patient and parent (guardian) the information given to adult volunteers, i.e., the nature, duration and purpose of the study, the methods and means by which it is to be conducted, etc.

3. DEFINITIONS.

a. Clinical investigation under this program consists of the organized scientific inquiry, both in humans and by directly related laboratory work, into clinical problems of significant concern in the necessary health care of members of the military community, including active duty personnel, dependents, and retirees. Clinical investigation at WRAMC shall include projects involving WRAMC patients, investigators, or facilities.

b. Subjects are any persons who may be at risk because of participation as an object of clinical investigation by members of the AMEDD or their appointed representatives. These may include inpatients, outpatients, organ donors, informants, or normal individuals who participate in studies of medical, physiological, sociological, or psychological orientation. Selection of subjects must be equitable.

c. At risk: A person is "at risk" if he/she may be exposed to the possibility of harm (physical, psychological, or sociological) as a consequence of activity which extends beyond use of established and accepted methods necessary to meet his/her needs. Determination of nature and extent of "at risk" is a matter of common sense and professional judgment. In most cases, utilization of someone's time (inconvenience) will constitute "risk" since the activity is not an accepted method to meet the person's needs. Responsibility for this determination resides at all levels of institutional and departmental review.

d. Children: Persons who have not attained the legal age of consent to general medical care as determined under the law of the jurisdiction in which the research is to be conducted (DC - age 18).

e. Research: A formal investigation designed to develop or contribute to generalizable knowledge. This may involve dietary manipulations, alteration of daily routine or environment, questionnaires, record review.

f. Minimal Risk in Children: The probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical or psychological examination of healthy children. Examples include immunization, modest changes in diet or schedule, obtaining blood and urine specimens, and most behavioral research.

g. Assent: A child's affirmative agreement to participate in research which can only be given following an explanation appropriate to the level of understanding of the child. It is recognized that "assent" may have no legal status and may be difficult to obtain in young children; nevertheless, some sort of opportunity should be offered the child to agree to participate. (Ref Federal Register 43:2084-2114, Jan 13, 1978, and 43:31786-31794, Jul 21, 1978.)

4. COMMITTEES: The following committees will be appointed. At the option of the Chairman, the Clinical Investigation Committee and the Human Use Committee will meet either separately or simultaneously.

a. Clinical Investigation Committee: To review all clinical investigation proposals for scientific adequacy and to establish priorities for support. For the purpose of recommending new drugs which have not been released by the Food and Drug Administration, the Committee will serve also as the Therapeutic Agents Board (para 126, AR 40-2). This committee will be composed of a representative from each of the following:

Director, Medical Education (Chairman)
Chief, Clinical Investigation Service (Secretary)
Chief, Department of Medicine
Rotating Service Chief from Department of Medicine
Chief, Department of Surgery
Rotating Service Chief from Department of Surgery
Chief, Department of Pathology
Chief, Department of Radiology
Chief, Department of Pediatrics
Chief, Department of Psychiatry
Chief, Department of Obstetrics and Gynecology
Commander, USA Dental Activities (DENTAC)
Director, WRAIR
Chief, Nuclear Medicine Service
Chief, Health Physics
Chief, Pharmacy Service
Director, Patient Administration Directorate
Chief, Nursing Research Service
Assistant Chief, Clinical Investigation Service
A rotating senior clinical investigator (list to be established by Chief, Clinical Investigation Service)
Representative (USCHS)

The attendance of each member will be recorded in the minutes.

b. Human Use Committee: To review for medical safety and suitability all clinical investigation protocols involving the use of human subjects. This committee will be composed of a representative from each of the following:

Director, Medical Education (Chairman)
Chief, Clinical Investigation Service (Secretary)
Chief, Department of Clinical Pastoral Service
A Legal Counsel
Chief, Department of Nursing
Chief, Department of Psychiatry
Chief, Department of Obstetrics and Gynecology
Chief, Nuclear Medicine Service
Command Sergeant Major
Director, Human Resources Directorate
CDR, USA Dental Activities (DENTAC)
Clinical Pharmacist, Hematology-Oncology Service
Assistant Chief, Clinical Investigation Service
Patients' rights representative
Representative (USUHS)
Director, Patient Administration Directorate
A rotating senior clinical investigator (list to be established by Chief, Clinical Investigation Service)

The Attendance of each member will be recorded in the minutes.

c. Radioactive Drug Research Committee (RDRC): To review all research protocols using radioactive drugs in human subjects, and to insure that such protocols are in compliance with the Code of Federal Regulations, Title 21, Chp 1, Part 361. All protocols utilizing radioactive drugs will include radiologic assessment data, as an appendix to the protocol, including name of the radionuclide, presence of any contaminants, maximum dose to be administered, radiation absorbed doses to whole body and other organs accumulating the isotope, dosage from any X-ray procedures that are part of the research study, and any limitation regarding patient population due to sex and age. A report will be made by the RDRC to the Clinical Investigation Committee regarding each radioactive drug protocol in humans. In addition, the Committee will be responsible for preparing the annual report on research use of a radioactive drug to the FDA. This Committee will be composed of at least five individuals, including Chief, Nuclear Medicine Service; Chief, Health Physics; Chief, Clinical Investigation Service; Nuclear Medicine Service Pharmacist; and Chief, Radiation Therapy Service.

The RDRC will select a chairman, who will sign all applications, minutes, and reports of the Committee as well as a secretary. The RDRC will meet at least quarterly. A quorum consisting of a majority of the membership must be present, with attendance of at least individuals who are specialists in nuclear medicine, radioactive drug formulation, and radiation safety and dosimetry. Minutes will be kept, including numerical results on voting. No member shall vote on a protocol in which he is an investigator. The RDRC will submit an annual report to the FDA prior to 31 January of each year.

The investigator must submit a report (Appendix C) and a copy of the signed consent form to the RDRC within 15 days from the date of administration of the isotope.

d. Functions of the Committees: Either the Clinical Investigation Committee or Human Use Committee can terminate any investigation or place restrictions on a study at any time the Committees become concerned about the scientific merit of the study or adequacy of protection of human subjects. The Chief, Clinical Investigation Service can order a cessation of activity in any study pending an evaluation of the circumstances.

5. CLINICAL INVESTIGATION COMMITTEE: The Clinical Investigation Committee will meet once monthly, usually on the fourth Tuesday at 1400 hours. Special meetings can be called at any time, either upon request of the Commander, Chief, Clinical Investigation Service, or by written request of three Committee members. The Committee will review all new research proposals, either involving WRAMC patients, investigators, or facilities. Their review of proposals will address in particular scientific design, merit and funding. Departmental chairman will not vote on protocols from their own department, nor will any member vote on any protocol in which he is a coinvestigator. Periodically, the Committee will review approved and ongoing research. Each project will be reviewed at least once yearly, at the termination of the research and whenever there is a change either in the goals or the procedures or drugs used in human subjects, or deviation from the approved protocol. Adverse reactions to investigational drugs or procedures will be promptly reported to the Committee. The Committee will make recommendations to the Commander. Two-thirds of the membership in attendance will constitute a majority. A majority is necessary for protocol approval. A majority of the Committee will constitute a quorum and will include at least three physicians and three nonphysicians. There will be no proxy voting. Investigators will be informed within one week of the meeting in writing of the approval disapproval of the project and reasons for so doing. A disapproved protocol must be resubmitted for approval. The Committee

may elect to approve a study with the addition of certain minor restraints/modifications. The Commander will have the right to disapprove any protocol on the grounds of being unsuitable for implementation at WRAMC but cannot overrule the disapproval of the Committee. Appendix D outlines the administrative methods by which primary and secondary review of protocols and review of annual progress reports will be achieved.

6. HUMAN USE COMMITTEE: The Human Use Committee will meet once monthly, usually on the fourth Tuesday either concurrently or with the Clinical Investigation Committee following the Clinical Investigation Committee meeting. Special meetings can be called at any time, either upon request of the Commander, Chief, Clinical Investigation Service, or by written request of three Committee members. The Committee will review all new research proposals in which human subjects are used. Their review of proposals will address in particular, the protection of human research subjects. Periodically, at least once yearly, the Committee will review approved and ongoing investigational studies in which humans are used. Each project will be reviewed at least once yearly and whenever there is a change in the goals or the procedures or drugs used in human subjects. The Committee will make recommendations to the Commander. Two thirds of the membership in attendance will constitute a majority. A majority is necessary for protocol approval. A majority of the Committee will constitute a quorum and will include at least three physicians and three nonphysicians. The Commander will have the right to disapprove any protocol on the grounds of being unsuitable for implementation at WRAMC but cannot overrule the disapproval of the Committee. There will be no proxy voting.

7. CHIEF, CLINICAL INVESTIGATION SERVICE.

a. Shall function as secretary/recorder at meetings. He will summarize the discussion on issues. Records of institutional review board's activities will be retained indefinitely.

b. Can terminate any project at any time pending Clinical Investigation Committee and Human Use Committee review.

c. Will be the contact with the Commander to assesss availability of resources to support projects and will manage those resources with guidance from Committees and Commander.

d. Will keep the Commander and Committees informed of the continuing changes in FDA/NIH requirements.

e. Will supervise under the guidance of the Clinical Investigation Committee and Human Use Committee, the secretarial/administrative support staff to support clinical research and insure compliance with regulations.

f. Will advise the Clinical Investigation Committee regarding alternatives if priorities for support need to be established.

8. RECORDS AND REPORTS.

a. Initial Protocol. Requests for initiating research projects will be submitted in one copy to the Commander, Walter Reed Army Medical Center, ATTN: Chief, Clinical Investigation Service. This will be submitted by the principal investigator through the chief of the respective service and department, and prepared as described in Appendix A. Protocols which do not conform to Appendix A will not be accepted by the Chief, Clinical Investigation Service. Frequent deficiencies in protocols include omission of an impact statement, failure to state the time required to complete the project, failure to include budget information, and failure to include signatures of the respective chief of service and department. When radiological, laboratory, or nursing support is required, the principal investigator should have obtained the concurrence of the appropriate chief of service prior to submission to the Clinical Investigation Committee. The chief of the department proposing the study will provide an indorsement that the proposal conforms to the criteria described in paragraph 2 above. To be placed on the agenda for the monthly committee meeting, the research protocol must be received by the 25th of the month preceding the meeting. Protocols will be distributed to the Committee members at least one week prior to the meeting, with appropriate agenda. Under no circumstances will a project require greater than three years to complete. If more than three years are needed, submission of a new protocol will be required.

b. Addenda to Initial Protocols. Whenever there is a change either in the goals or the procedures or drugs used in human subjects, the investigator will submit an addendum to the Commander thru the chief of the respective service and department, and Chief, Clinical Investigation Service. If necessary, the Committee will review this addendum as a new research proposal.

c. Annual Progress Reports: Annual progress reports will be prepared for each approved project as prescribed by AR 40-38, Clinical Investigation Program and will be submitted to Clinical Investigation Service prior to 15 August of each year until the investigation is completed. See Appendix B. Accurate preparation of budgetary data and/or documentation of abstracts or publications is essential. Failure to submit an annual progress report will result in termination of the project and withdrawal of the principal investigator's privilege to function as a principal investigator in any project.

d. Interim Reports. Interim reports must be submitted at any time when important development, adversities or other circumstances occur which should be brought to the attention of higher headquarters. In particular, interim reports must be submitted when unexpected deaths or harmful side effects occur during the course of an investigation. Interim reports are required within three working days of the

development. They will be considered by the Chief, Clinical Investigation Service, who may elect to suspend work on the investigation until the Committee has an opportunity to meet.

e. Final Reports. Final reports are required upon completion or termination of a specific research effort. The report will include a summary of all work performed, results obtained, together with copies of all publications, whether printed, in press or submitted for publication. Inclusion of references to previous progress reports is optional. If the project is terminated prior to completion, the reasons for termination should be reported. Report is due within 30 days following completion or termination of effort.

f. Special Therapeutic or Diagnostic Procedures. Any special therapeutic or diagnostic procedures or any new, hazardous, or otherwise noteworthy therapeutic or diagnostic measures will be recorded in Space 24 of DA Form 8-274, Clinical Record Cover Sheet for Inpatients.

g. All reports will be forwarded to the Clinical Investigation Service following review by the appropriate chief of service and department. The Clinical Investigation Service will schedule presentations to the appropriate hospital review committees. Following review by the Commander of committee reports the Clinical Investigation Service will insure that reports are forwarded to the Surgeon General as required by AR 40-38.

h. Radioactive Drug Protocols Involving Administration of Radioactive Drugs to Humans. The investigator must submit a report (Appendix C) and a copy of the signed consent form to the Radioactive Drug Research Committee (RDRC) within 15 days from administration of the isotope.

i. Volunteer Agreements. Copies of volunteer agreements for all protocols must be forwarded to Chief, Clinical Investigation Service, within one month of entry of the patient onto study. The consent form must include the patient's printed or typed name, address, and social security number (see Appendix A).

8. REPORTS TO PHARMACEUTICAL COMPANIES. For procurement of investigational drugs which have not yet been released by the Food and Drug Administration, detailed reports to the drug company are required by FDA (Form FD 1573). The reports are the responsibility of the principal investigator, and are a matter of direct communication between him/her and the drug company.

9. REQUEST FOR FUNDS. Requests for funds to support the clinical investigation program are presented to the Center Command annually during the month of March.

a. Projects requiring refunding in the amount of $1,000 or more are submitted each year prior to 1 March in the format of Appendix A for consideration. Projects requiring substantial increases (> 20% increase) in funding must undergo review by the Committee before funding will be approved.

b. New proposals which require funds may be submitted at any time. Approval of funding is dependent upon availability of local, Health Services Command or Surgeon General resources. Format Appendix A.

10. INFORMED CONSENT.

a. Patient Consent. The utilization of drugs or procedures which have not yet been accepted or established by common use require the patient's consent. The patient must be informed, i.e., his/her consent must be based upon his/her having knowledge of the experimental nature, purpose, and possible hazards. The consent should be in writing, except as provided in paragraph 7b, AR 40-7, or if the patient is a child (see 11). The consent form must be witnessed by someone other than an investigator on the project. Copies of the written voluntary consent will be maintained by the principal investigator for five years after termination of the study and will be forwarded to the Chief, Clinical Investigation Service, within 30 days of entry of the patient onto study.

b. Human Volunteer. Investigative studies in which drugs are employed are subject to, and must comply with AR 40-7, Use of Investigational Drugs and/or AR 70-25, Use of Volunteers as Subjects of Research in addition to AR 40-38.

11. RESEARCH INVOLVING CHILDREN.

a. In general, research in children will not be undertaken unless appropriate studies have first been undertaken in animals, adults, or older children. If the project is minimal risk, it may be undertaken if the Clinical Investigation Committee and Human Use Committee have approved the protocol, the assent of the child capable of understanding is obtained (possibly in writing), and written permission of the parent or guardian is secured.

b. If the project is more than minimal risk, research that has potential direct benefit to the child, may be undertaken if the Clinical Investigation Committee, Human Use Committee, and the Office of the Surgeon General have approved the protocol, considering that the risk is justified by the anticipated benefit, that the risk benefit ratio is at least as favorable as that presented by alternative approaches, the assent of the child capable of understanding is obtained (possibly in writing), and written permission of the parent or guardian is secured.

c. If the project is more than minimal risk and of no direct benefit for subjects, the research may be undertaken if the Clinical Investigation Committee, Human Use Committee, and the Office of the Surgeon General have approved the protocol, that the procedure presents experiences commensurate with those inherent in their actual medical situation and is likely to yield generalizable knowledge about the subject's condition, the knowledge is of vital importance, the assent of the child capable of understanding (possibly in writing) is obtained, and written permission of the parent or guardian is secured.

d. Appendix A includes the appropriate volunteer agreement for protocols involving research in children. On the opposite side must be "instructions to guardian" and if the project is directed at children capable of understanding written instructions, there must be "instructions to patient" written at a level comprehensible by the average aged participant in the project.

e. The Human Use Committee will periodically monitor the process of assent and permission in research involving children.

12. LOW RISK PROTOCOLS IN ADULTS. A protocol in which there is a minimum possibility of injury to the subject's health or rights as a result of the study. The study may not involve an investigational drug or device and may involve only human subjects who have given fully informed consent. That is, the study may not involve subjects who are minors, prisoners, institutionalized mentally infirmed or mentally disabled. The study also may not include subjects temporarily mentally disturbed by reasons of unconsciousness or coma. Low risk protocols may be undertaken after local approval by the Clinical Investigation Committee and Human Use Committee. These protocols will continue to be forwarded to the Human Use Review Office, who will notify the Chief, Clinical Investigation Service, immediately if there is any difficulty with either the protocol or the assessment of level of risk. The following types of procedures are examples of low risk studies:

a) Collection and analysis of additional small amounts of cerebrospinal fluid, amniotic fluid and venous or arterial blood when taken in conjunction with specimens of these fluids which are to be drawn for accepted clinical indications and do not require another puncture to obtain the additional amounts of these fluids for investigational purposes.

b) Analysis of hair and nail clippings collected in a nondisfiguring manner and the analysis of deciduous teeth.

c) Collection for analysis of excreta and external secretions including feces, urine, sweat, saliva, cerumen and tears or swab culture specimens of body orifices, placenta expelled at delivery, umbilical cord blood after the cord is clamped at delivery, and amniotic fluid at the time of artificial rupture of the membranes prior to or during delivery.

d) Recording of data by physical sensors applied either superficially or at a distance and which do not involve significant input of energy into the subject. Such procedures include, but are not necessarily limited to weighing, electrocardiography, electromyography and detection of naturally occurring radioactivity, electroencephalogram, thermography, diagnostic echography and electroretinography, caliper measure of anthropomorphic characteristics and detection of naturally occurring radioactivity.

e) Blood drawing of quantities of blood less than 20 cc/6 weeks from adult subjects in whom their underlying medical condition is not known to be associated with anemia. These patients need not have a hematocrit done before obtaining the blood specimens.

f) Blood drawing of quantities of blood less than 450 cc/6 weeks or 12% of the estimated blood volume, 7% of the body weight, whichever is lesser, from subjects who are not anemic. (Anemia is defined as a hematocrit < 40 for males, < 35 for female and a reticulocyte count $> 1.5\%$). If quantities of blood > 20 cc/6 weeks are to be obtained, the protocol must state that a hematocrit and reticulocyte count be obtained in patients prior to entry onto study and be not anemic.

g) Studies involving generally accepted, medically indicated diagnostic or therapeutic procedures or comparisons of two or more generally accepted alternative procedures.

h) Nonroutine or additional analysis of anatomical or biopsy specimens removed as the sole consequence of a widely accepted surgical indication.

i) Collection of both supra- and subgingival plaque, provided the procedure is no more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques.

j) Voice recordings made for research purposes such as investigations or speech deficits.

k) Moderate exercise by healthy volunteers.

l) The use of survey research instruments (interviews or questionnaires) and psychological tests, interviews and procedures that are part of the standard battery of assessments used by psychologists in diagnostic studies and in the evaluation of judgmental, perceptual, learning and psychomotor processes, provided that the subjects are normal volunteers and that the data will be gathered anonymously or that confidentiality will be protected by procedures appropriate to the sensitivity of the data.

m) Program evaluation projects that make no extra requirements on the subjects participating in the program and that will not benefit the subjects in the program.

n) Noninvasive pulmonary function testing such as (but not limited to) spirometry and plethysmography.

o) Collection and analysis of small amounts of internal secretions such as gastric contents and pulmonary aspirates when collection of these secretions does not involve the placement of either a nasogastric tube or endotracheal suction tube solely for obtaining specimens for research purposes.

p) Diary recordings of dietary intake, symptoms, physical activities and the like, whether the diarist remains anonymous or not.

13. Research in Pregnant Women Fetuses -- shall conform to the requirements of CFR 46.205 - 46.208.

A. General limitations.

1. No activity to which this subpart is applicable may be undertaken unless:

a) Appropriate studies on animals and nonpregnant individuals have been completed;

b) Except where the purpose of the activity is to meet the health needs of the mother or the particular fetus, the risk to the fetus is minimal and, in all cases, is the least possible risk for achieving the objectives of the activity.

c) Individuals engaged in the activity will have no part in: (i) Any decisions as to the timing, method, and procedures used to terminate the pregnancy, and (ii) determining the viability of the fetus at the termination of the pregnancy; and

d) No procedural changes which may cause greater than minimal risk to the fetus or the pregnant woman will be introduced into the procedure for terminating the pregnancy solely in the interest of the activity.

2. No inducements, monetary or otherwise, may be offered to terminate pregnancy for purposes of the activity.

B. Activities directed toward pregnant women as subjects.

a) No pregnant women may be involved as a subject in an activity covered by this subpart unless: (1) The purpose of the activity is to meet the health needs of the mother and the fetus will be placed at risk only to the minimum extent necessary to meet such needs, or (2) the risk to the fetus is minimal.

b) An activity permitted under paragraph (a) of this section may be conducted only if the mother and father are legally competent and have given their informed consent after having been fully informed regarding possible impact on the fetus, except that the father's informed consent need not be secured if:

1) The purpose of the activity is to meet the health needs of the mother;

2) His identity or whereabouts cannot reasonably be ascertained;

3) He is not reasonably available;

4) The pregnancy resulted from rape.

C. Activities directed toward fetuses in utero as subjects.

1. No fetus in utero may be involved as a subject in any activity covered by this subpart unless:

a) The purpose of the activity is to meet the health needs of the particular fetus and the fetus will be placed at risk only to the minimum extent necessary to meet such needs, or

b) The risk to the fetus imposed by the research is minimal and the purpose of the activity is the development of important biomedical knowledge which cannot be obtained by other means.

2. An activity permitted under paragraph (1) of this section may be conducted only if the mother and father are legally competent and have given their informed consent, except that the father's consent need not be secured if:

a) His identity or whereabouts cannot reasonably be ascertained,

b) He is not reasonably available, or

c) The pregnancy resulted from rape.

D. Activities directed toward fetuses ex utero, including nonviable fetuses, as subjects.

1. Until it has been ascertained whether or not a fetus ex utero is viable, a fetus ex utero may not be involved as a subject in an activity covered by this subpart unless:

a) There will be no added risk to the fetus resulting from the activity, and the purpose of the activity is the development of important biomedical knowledge which cannot be obtained by other means, or

b) The purpose of the activity is to enhance the possibility of survival of the particular fetus to the point of viability.

(c) No nonviable fetus may be involved as a subject in an activity covered by this subpart unless:

(1) Vital functions of the fetus will not be artificially maintained,

(2) Experimental activities which of themselves would terminate the heartbeat or respiration of the fetus will not be employed, and

(3) The purpose of the activity is the development of important biomedical knowledge which cannot be obtained by other means.

a) In the event the fetus ex utero is found to be viable, it may be included as a subject in the activity only to the extent permitted by and in accordance with the requirements of other subparts of this part.

b) An activity permitted under paragraph (1) or (2) of this section may be conducted only if the mother and father are legally competent and have given their informed consent, except that the father's informed consent need not be secured if: (1) his identity or whereabouts cannot reasonably be ascertained, (2) he is not reasonably available, or (3) the pregnancy resulted from rape.

14. RESEARCH, MENTALLY INFIRMED. An appropriate addendum to these regulations will be published when the federal regulations regarding research in the mentally infirmed are promulgated.

HSWP-QCR

FOR THE COMMANDER:

FRANKLIN J. GORZUP
MAJ, MSC
ADJUTANT

DISTRIBUTION:

I plus 100 copies to
Clinical Investigation Svc

APPENDIX A

APPLICATION FOR CLINICAL INVESTIGATION PROJECT
(New protocols must conform to this format and be complete.)

1. PRINCIPAL INVESTIGATOR:

2. PROJECT TITLE: (Enter short project title.)

3. OBJECTIVE: (Brief but specific statement of the objective of the project.)

4. MEDICAL APPLICATION: (Explain briefly the medical importance and possible usefulness of the project.)

5. STATUS: (What has been accomplished or published in the proposed area of study and in what manner will the project relate to or differ from that which has been accomplished. If references or personal communication with other Army medical facilities are involved, so indicate.)

6. PLAN: (Outline exactly what is proposed to be accomplished in sufficient detail to indicate a clear course of action. Technological validity of procedures and chronological steps should be shown.) (NOTE: The Surgeon General and the local Commander must have a very clear picture of how the investigation will proceed to meet the objective of the project. This paragraph frequently furnishes the basis for approval or disapproval of the project.)

7. BIBLIOGRAPHY: (List source of information.)

8. FACILITIES TO BE USED: (Such as laboratory, ward or clinic.)

9. TIME REQUIRED TO COMPLETE: (Give month and year of expected start and anticipated completion. Under no circumstances will projects be funded for longer than three years without submission of a new protocol).

10. PERSONNEL TO CONDUCT PROJECT: (List names and positions of persons to be directly involved in project work. Attach short biographical sketch, including resume of education, research training, and list of publications, for each person named.)

11. FUNDING IMPLICATIONS: (List total budget for the protocol, as well as the budget for the FY in which the protocol is approved.)

	FY-78	Total for the Protocol
a. Personnel: (itemize and explain need)	$____	$____
b. Equipment: (itemize and explain need)	____	____
c. Consumable Supplies: (itemize)	____	____
d. Travel: (itemize and explain need)	____	____
e. Modification of Facilities: (explain)	____	____
f. Other (explain)	____	____
TOTAL	____	____

12. DATE PREPARED: (give day, month and year of preparation)

_____
(Signature of Principal Investigator)

_____
(Signature of Department Chief)

_____
(Enter title and mailing address of Principal Investigator)

APPENDIX A

IMPACT STATEMENT

(Must be attached to each protocol enumerating impact considered to be beyond good patient care.)

Patients:

Bed Occupancy:

Laboratory:

Radiology:

Pharmacy:

Nursing Service:

Registrar:

Other:

Approvals	Chief of Service	Chief of Dept	For Hosp Comm
Date:			
Signature:			
Name:			
Grade:			
Position:			

(This is a format. It will not be used as a form.)

APPENDIX A

VOLUNTEER AGREEMENT

Work Unit #_____

I,_____, having attained my eighteenth (18th) birthday, and otherwise having full capacity to consent, do hereby volunteer to participate in an investigational study entitled:

_____ under the direction of_____ _____of the Department/Service/Institute of _____, Walter Reed Army Medical Center, Washington, D.C.

The implications of my voluntary participation; the nature, duration and purpose of the study; the methods and means by which the study is to be conducted; and the known inconveniences and hazards have been thoroughly explained to me by the principal investigator or by one of the coinvestigators and such inconveniences and hazards are set forth in detail on the attached page of this Agreement, along with my initials or signature. I have been given an opportunity to ask questions concerning this investigational study and my participation in the study, and any such questions have been answered to my full and complete satisfaction.

During the course of my treatment as a patient at Walter Reed Army Medical Center, I have been provided with a copy of a Privacy Act statement (DD Form 2005) which has made me aware of the safeguards available to me because of the Privacy Act of 1974. I have been given the opportunity to review the DD Form 2005, ask questions and to retain a personal copy. I have been made aware that the information gained about me, because of my participation in this investigational study, may be publicized in medical literature, discussed as an educational model, and used generally in the furtherance of medical science. I freely consent to provide such personal information as is requested of me for this investigational study and freely consent to the disclosure of pertinent personal information derived from my participation in this investigational study for reasons of publication in medical literature, discussion as an educational model and for those additional reasons which specifically relate to the furtherance of medical science.

I understand that in the event of physical injury resulting from the research procedures, medical treatment for injuries or illness is available and that compensation may be available through judicial avenues.

WR 70-1 8 January 1979

I am aware that at any time during the course of this investigational study I may revoke my consent and withdraw from this study, without prejudice; however, I may be requested for medical reasons to undergo further examinations if in the opinion of my attending physician such examinations are necessary for my health or well being.

If there is any portion of this explanation that you don't understand, ask your doctor before signing.

Signature	Date
Printed Name	Social Security Number
Address	

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

HSWP-QCR 22 January 1980
SUBJECT: Minutes of the Clinical Investigation and Human Use Committee Meeting.

c) The Committee concurred with Mr. Bosworth's recommendation that signature lines for the Investigators and Witnesses be added to the WRAMC Volunteer Agreement and the Patient Consent Explanation Sheet to provide future legal protection. Also, it was decided that the patient would initial each page of the Consent Form. This will be added to WRAMC Regulation 70-1.

On this page of the Volunteer Agreement, the principal investigator should set forth full details concerning the investigational study, insofar as such would affect or influence the tentative subject in any way. This explanation should be worded so that it can be clearly understood by the subject. The subject should place his initials at the end of the last line of explanation.

A proper explanation should, at a minimum, provide the answers to the following questions in lay language:

1. What will be administered or done to the subject?
2. How long will the subject's participation last?
3. To what tests or examinations will the subjects be required to submit?
4. Why is the investigation being conducted?
5. Has this particular study been done previously, and, if so, with what results?
6. What inconveniences or discomforts is the subject likely to experience?
7. What risks or hazards can be reasonably anticipated?
8. What steps will be taken to prevent or minimize these risks or hazards?
9. If blood is being drawn in the study, the total amount of blood should be accurately quantitated in both cc's and ounces.
10. The volunteer should be offered the opportunity to ask questions.
11. Alternatives to participation in the study should be identified. It Should be emphasized that participation in the study is entirely optional.
12. An instruction that the subject is free to decline participation or terminate participation at any time without prejudice.
13. Can the patient expect to accrue any benefit from participation in the study; if none, so state.
14. A statement informing the volunteer of available opportunities for compensation for any injury incurred during the study.
15. Exculpatory language should not be used.
16. For Oncology protocols, a statement that "there is no guarantee that the proposed chemotherapy program is better than a standard program".

APPENDIX A

VOLUNTEER AGREEMENT
(Children Under Legal Age of Consent or Adults Not Competent to Give Informed Consent)

I/We _____ having fully capacity to consent for my/our _____ (Relationship), _____ (Name of Participant), to participate in an investigational study entitled: _____ _____, under the direction of _____. The implications of his/her participation; the nature, duration and purpose; the methods and means by which it is to be conducted; and the inconveniences and hazards which may reasonably be expected have been explained to me/us by _____, and are set forth on the reverse side of this Agreement, which I/we have initialed. I/we have been given an opportunity to ask questions concerning this investigational study, and any such questions have been answered to my/our full and complete satisfaction.

I/we understand that I/we may at any time during the course of the investigational study revoke my/our consent, and withdraw the above named participant from the study without prejudice; however, he/she may be requested to undergo certain further examinations, if in the opinion of the attending physician, such examinations are necessary for his/her health or well being.

Signature	Relationship	Date

Signature	Relationship	Date

I was present during the explanation referred to above, as well as the parent's/guardian's opportunity for questions, and hereby witness their signature.

Witness' Signature	Date

APPENDIX B

Annual Progress Report FY

Work Unit No.:

Title of Project:

Investigators:

Principal: (senior investigator responsible for project)

Associate: (coinvestigators)

Objectives: (goal of research)

Technical Approach: (method of attaining objectives)

Progress and Results: (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. The number of patients studied must be precisely delineated.)

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 or abstracts from your service which are related to the research described in this report. Failure to enumerate publications or abstracts may compromise funding of the protocol.)

Type of Report: (completed, terminated, interim)

(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 report.)

DISPOSITION FORM

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

REFERENCE OR OFFICE SYMBOL	SUBJECT
HSWP-QCR	Radioactive Drug Research Report

TO Secretary, RDRC#23
Bldg 188, FGS
WRAMC

FROM

DATE

CMT 1

1. Work Unit #: _____

2. Work Unit Title: _____

_____

_____

3. Patient Information:

   a. Identification Code: _____ (This number must allow for referencing back to a specific patient)

   b. Age: _____

   c. Sex: _____

   d. Weight: _____

4. Pharmacological Dose Information:

   a. Active Ingredients: _____

   b. Maximum Amount Administered per Subject: _____

5. Radionuclide Information:

   a. Radionuclide Used (Include any significant contaminants): _____

   b. Activity of Radionuclide Used: _____

   c. Date Radionuclide Administered: _____

6. Were X-ray procedures utilized in conjunction with this research protocol? YES _____ NO _____

7. Has any subject used in this study participated in other radioactive drug research studies? YES _____ NO _____

_____
SIGNATURE OF RESPONSIBLE INVESTIGATOR

DA FORM 2496 REPLACES DD FORM 98, WHICH IS OBSOLETE.

☆GPO-1979-666-422/1063

APPENDIX D

I. Implementation of the System of Protocol Review (including the System of Primary and Secondary Reviewers).

A. Protocols must be received by the 25th of the preceding month (or next working day if the 25th is a weekend day or holiday) in order to be considered at the next meeting, usually the fourth Tuesday of each month. Protocols not approved by the Department and Service Chief would not be accepted. The investigator would be expected to provide Clinical Investigation Service with several key references from the bibliography of the protocol.

B. Upon receipt of the protocol by Clinical Investigation Service, an administrative review and evaluation of the consent form would be undertaken. (See Incl #1 explanation and review sheet.) Any protocol with deficiencies would not proceed further in the review process until the deficiencies were resolved. Minor deficiencies in the consent form would be corrected by the editorial staff in the Clinical Investigation Service office. The investigator would receive a revised consent form and an explanation for revisions.

C. Protocols would then be read and reviewed by Chief and Asst Chief, Clinical Investigation Service, who would evaluate them primarily for adequacy of experimental design. The Chief and Asst Chief might elect to have an outside consultant review some protocols.

D. These protocols judged to be of reasonably sound design would be forwarded on about the first of the month to two (2) primary reviewers and two (2) secondary reviewers. The primary and secondary reviewers would be members of the Committee. Any of the primary and secondary reviewers could utilize additional consultation. An attempt would be made to select primary reviewers from the Committee on the basis of knowledge/expertise allied with the area under investigation in the project. An exception would be Oncology protocols, which would be distributed to the Committee on a rotational basis. Primary reviewers would attempt to assess scientific merit, experimental design, and give some priority for funding. They would be provided the key references submitted by the principal investigator. Each primary reviewer would submit a written report to Clinical Investigation Service of his assessment of the protocol by the 15th of the month (see Incl #2). At his discretion, he could consult with the investigator, and/or another consultant reviewer and suggest modifications or simply submit a written report to Clinical Investigation Service.

The secondary reviewers would also be selected from the Committee, except that they would not have expertise or knowledge allied with the area under investigation. They would be selected on a rotational basis, would submit the same written reports as first reviewers, and would be especially expected to provide some degree of more remote perspective regarding the merit of a project.

E. The entire Committee would be provided copies of the protocol, primary review and secondary review. Attendance of the investigator at the meeting would be optional but he would be provided with a copy of the minutes which would contain the reasons for approval/disapproval. The written protocol would be expected to be sufficiently explanatory that only adjunctive information would be the only input requested of the investigator at the meeting. The entire Committee would consider the protocol and reviewer's comments and vote for approval/disapproval. The numerical estimation of scientific merit and priority for funding from the reviewers would be recorded in the minutes. The entire Committee would have an opportunity to revise the numerical estimate of scientific merit and priority for funding.

F. A list of volunteer consultants and their areas of expertise would be compiled from USUHS, AFIP, WRAIR and NNMC.

II. Annual Review of Protocols

A. Henceforth, the Service will issue investigators lab notebooks, which will be available for inspection upon 24 hour notice and will be returned to Clinical Investigation Service upon completion of the project or the investigator's departure from WRAMC, at the discretion of the Chief, Clinical Investigation Service. For certain types of projects, a study record could suffice in lieu of a lab notebook.

B. Funded protocols which have been approved more than three years before must be resubmitted to the Committee for approval. Cooperative group protocols not requiring funding will be exempted from the three year limit. After three years, they are automatically considered terminated. Notice will be given to the principal investigator of these protocols three months prior to termination.

C. On a random basis, periodic inspections will be made of the data books, consent forms, and general status of individual work units. Written recommendations will be made to the Committee based on the basis of these inspections. At least one week notice will be afforded investigators. The Committee may elect to terminate a project or give the investigator time to correct deficiencies prior to a reinspection.

D. This year's Annual Progress Report will be divided into equal packages for each member of the Committee (see Incl #3) who can:

1) Certify that the Annual Progress Report is adequate and the project merits continuation.

2) Request additional data from the principal investigator.

3) Recommend the entire Committee closely scrutinize the project and decide whether or not continuation is warranted.

Administrative Checklist for Evaluation of Protocols
(available for distribution to principal investigators)

	YES	NO
1. Administrative inadequacies:		
Is the format inappropriate?		
Has the protocol been signed off by the Chief of Service and Chief of Department?		
Is there an impact statement?		
Is the impact statement signed off by the involved Services?		
Is the budgetary information sufficiently explicit? The exact type of supplies should be enumerated.		
Is there a justification for major equipment purchases?		
2. Adequacies of consent forms:		
A. Does the consent form contain:		
1) An explanation of the purpose of the study		
2) The duration of the study		
3) A full explanation of what is going to happen to the patient		
4) A description of all discomforts and risks related to the research		
5) A disclosure of an alternative to participation in the study. It should be emphasized that participation in the study is entirely optional.		
6) A description of any benefits to be expected from participation in the study		
7) An offer to answer any questions concerning the study		
8) An instruction that the subject is free to decline participation or terminate participation at any time without prejudice.		

Sheet #1

	YES	NO
9) A statement informing the volunteer of available opportunities for compensation for any injury incurred during the study.		
10) For Oncology protocols, a statement that "there is no guarantee that the proposed chemotherapy program is better than a standard program"		
B. Is the language used in the consent form comprehensible by lay patients?		
C. Is there exculpatory language in the protocol?		

Signature_____

Date_____

Form for Primary and Secondary Review of Protocols

Protocol Title: _____

_____

Reviewer: _____

Recommendations to the Committee:

☐ approval ☐ disapproval ☐ provisional approval with stipulation

Narrative justification for recommendations:

Prioritization (Assign a number between 1 and 5, with 1.0 being outstanding, 3.0 average, and 5.0 disapproval.)

Scientific merit _____ (Assign a number)

Priority for funding _____

Is the budget realistic and adequately justified?

Circle #2

Dear Professional Committee Member of Clinical Investigation Committee:

Enclosed is the FY-1978 Annual Progress Report (APR) for Work Unit #

It is requested that you represent the Clinical Investigation Committee by reviewing the APR for the enclosed protocol. Upon request, we will provide you with the original protocol, or you may come to the Clinical Investigation Service office during duty hours. The following questions are offered to you as guidelines to assist you in your review.

1) Is progress being made on the protocol?

2) Does the progress report indicate substantial deviation from the original protocol?

3) Is there any evidence of either unexpected side effects or an increased incidence of expected untoward side effects?

4) Is the request for funding appropriate? (One should consider here the merit of the project, previous budget, previous progress as documented by abstracts or publications, and justification for funding in the APR.)

Comments:

Recommendations: (please check in box)

☐ 1) That the APR and request for funding be approved by the Committee.

☐ 2) That the following additional information/clarification be furnished by the principal investigator.

☐ 3) That the entire Committee closely scrutinize this APR and examine the following specific aspects of the APR.

_____ Signature

_____ Date

Encl 3

Work Unit No.: 1647

Title of Project: Inhibition of Red Cell Pyridoxal Kinase by the Carbonyl Reagents, Isoniazid and Hydralazine.

Investigators:

Principal Investigator: LTC John A. Kark, MC

Associate Investigator: LTC Michael J. Haut, MC

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: Pyridoxal-isoniazid hydrazone (PL-INH) could be detected by fluorescence in hemolysates, but the amount of fluorescence varied as the log of concentration. On-going work concerns obtaining conditions for lineal assay of PL-INH concentration.

Conclusions: PL-INH can be detected in hemolysates. Further work is needed to obtain a quantitative measurement of red cell levels.

Funding Requirements: None

Publications: None

Type of Report: Terminated because of priorities and limited technical help. No patients were studied this past fiscal year.

Work Unit No.: 1307-79

Title: Effects of High Dose Dexamethasone on Subhuman Primates

Investigators: Ira Menlman, M.D., MAJ, Robert Smallridge, M.D., LTC, Harold Williams, Ph.D.

Objectives: See previous protocol.

Technical Approach Modification: Along with the proposed approach in the initial protocol we have also looked at the levels of thyroid hormone in blood, the response to TRH of TSH in the animals, and the conversion by liver of T_4 to T_3. We have also measured ALA synthetase activity in the liver of the animals.

Progress and Results: The protocol was carried out as planned, and the animals sacrificed. Data thus far revealed marked Cushingoid changes in 4 of the 6 treated animals with marked mesenteric saponification. The other 2 treated animals were clinically mildly cushingoid. No changes were distinquishable in serum amylase or lipase. Measurement of coagulation factors reveal increased factor VIII antigen which is being further evaluated. We are surprised to find no differences between treated and control animals in basal TSH or TSH in response to TRH, and T_4 to T_3 conversion is also surprisingly increased. Liver ALA synthetase is markedly decreased in treated animals, but muscle levels were not significantly different. Thus far, in two treated and two control animals, no difference nas been noted histologically by light microscopy. Pancreatic tissue does reveal subtle changes which are being pursued. Other aspects remain to be evaluated.

Conclusions: There have been no complications to/or of this study, and it has progressed nicely. Thus far, interesting and important data have been found with respect to thyroid function in hypercortisol states. Chronic steroids in primates appear not to decrease TSH or its response to TRH, and do not decrease T_4 to T_3 conversion. Abnormal coagulation factors are seen, and are being further evaluated. Thus far, further definition of the myopathy has not been forthcoming, but only preliminary studies are completed. Unsuspected liver enzyme changes i.e, decreased ALA synthetase in dexamethasone treated animals, has been noted and may be very important.

Funding Requirements:

Supplies	1000.
Audio-Visual	400.
Xerox,misc	100.
Travel	600.
Total	2100.

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