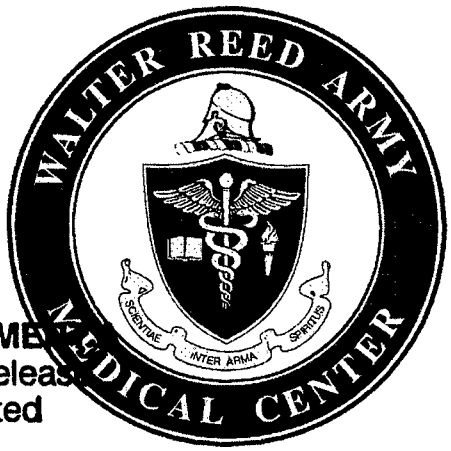
DEPARTMENT OF CLINICAL INVESTIGATION (DCI)

ANNUAL RESEARCH PROGRESS REPORT

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COL Maria H. Sjogren
Chief
Department of Clinical Investigation

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13. ABSTRACT *(Maximum 200 words)*

This Annual Progress Report documents all research protocols, both new and continuing, reviewed during FY 01 by the Clinical Investigation Committee (CIC) and the Human Use Committee/Institutional Review Board (HUC/IRB) of Walter Reed Army Medical Center (WRAMC). Continuing research review is administered by the Research Review Service (RRS), Department of Clinical Investigation (DCI), WRAMC. A detail summary sheet of each protocol giving the objective, technical approach, and progress is presented. Personnel rosters, DCI accomplishments, funding information and known publications and presentations by the WRAMC professional staff are listed for FY 01.

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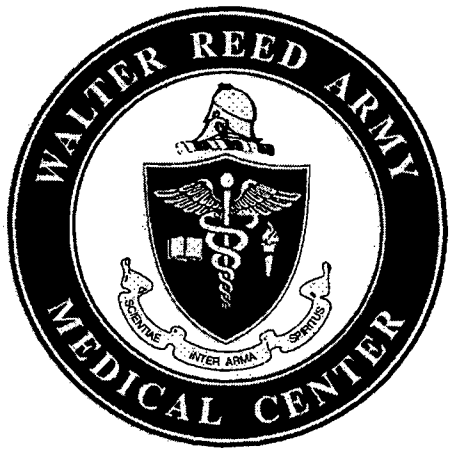
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DEPARTMENT OF CLINICAL INVESTIGATION (DCI)

ANNUAL RESEARCH PROGRESS REPORT



FY 2001 VOLUME I

WALTER REED ARMY MEDICAL CENTER, WASHINGTON, DC

A. OBJECTIVE

To implement and manage the Clinical Investigation program at Walter Reed Army Medical Center (WRAMC) by promoting, supporting, coordinating, planning, conducting, and publishing ethical, scientific inquiry into clinical health problems of beneficiaries of the military health care system, to include studies in humans and animals.

The motto of the Department of Clinical Investigation (DCI) is SHARPP: Striving to Help All Researchers from Planning to Publication.

B. TECHNICAL APPROACH

The clinical investigation program at WRAMC is conducted in accordance with the following regulations:

AR 40-7	Use of Investigational Drugs in Humans and the Use of Schedule I Controlled Drug Substances
AR 40-38	Clinical Investigation Program
AR 70-18	The Use of Animals in DOD Programs
TB MED 525	Control of Hazards to Health from Ionizing Radiation Used by the Army Medical Department
HSC 40-23	Management of Clinical Investigation Protocols and Reports
WRAMC 70-1	Clinical Investigation Program, WRAMC Research Activities
45 CFR 46	Protection of Human Subjects
32 CFR 219	Protection of Human Subjects
21 CFR 50, 56	Food and Drug Administration

NIH Guidelines For Research Involving Recombinant DNA Molecules

C. STAFFING

DESCRIPTION	GRADE	MOS	BRANCH	NAME	ACTIVITY
OFFICE OF THE CHIEF					
Chief	O6	61F8N	MC	Sjogren, MH	DCI
NCOIC	E6	91K3H	NC	Thomas, L	DCI
Secretary	07	0318	GS	Rosen, D	DCI
RESEARCH REVIEW SERVICE					
Chief	14	1530	GM	Chang, AS	DCI
IRB Admin.	13	0601	GS	Bartlett, E	DCI
Statistician	12	1530	GS	Howard, RS	DCI
Statistician	12	1530	GS	Fant, G	DCI
Clinical Nurse Spec	12	0610	GS	Porter, MD	DCI
Clinical Nurse Spec	12	0610	GS	Kessler, DD	DCI
Tech Writer-Ed Med/Sci	11	1083	GS	Miskovsky, VJ	DCI
Clinical Studies Spec	09	0301	GS	Green, IL	DCI
Clinical Studies Tech	07	0303	GS	Vacant	DCI
Editorial Asst	07	1087	GS	Muchui, MJ	DCI
Editorial Asst	07	1087	GS	Vacant	DCI
Clinical Studies Spec				Teleha, W	HMJF
Editorial Assistant				Merriwether, T	Contract
RESEARCH ADMINISTRATION SERVICE					
Chief/ Fin Prog Mgr	12	0501	GS	Word, D	DCI
Computer Spec	12	0334	GS	Rose, JG	DCI
Computer Spec	11	0334	GS	Vacant	DCI
Grant Manager	11	1101	GS	Vacant	DCI
Administrative Coord	08	0303	GS	Vacant	DCI

DESCRIPTION	GRADE	MOS	BRANCH	NAME	ACTIVITY
RESEARCH ADMINISTRATION SERVICE (continued)					
Supply Technician	07	2005	GS	Vacant	DCI
Supply Technician	06	2005	GS	Shelton, W	DCI
Office Clerk	04	2622	GS	Franklin, AF	DCI
Computer Spec				Durant, G	Contract
RESEARCH OPERATIONS SERVICE					
Clin Lab Officer	O3	71E67	MS	Vacant	DCI
Chief, Chemist	13	1320	GS	Abdel-Rahim, M	DCI
Immunologist	13	0403	GM	Vacant	DCI
Bio Lab Tech	09	0404	GS	Vacant	DCI
Bio Sci Lab NCO	E5	91K09	EN	Vacant	DCI
Bio Sci Lab Tech	05	0404	GS	Martin, JL	DCI
Biochemist	O3	71B67	MS	Capps, KB	DCI
Med Lab NCO	E5	91K09	NC	Vacant	DCI
Med Lab Sp	E4	91K10	NC	Reinhardt, B	DCI
Resch Biologist	12	0401	GS	Vacant	
Microbiologist	12	0403	GS	Vacant	DCI
Resch Physiologist	12	0413	GS	Lukes, YD	DCI
Resch Chemist	12	1320	GS	Nicholson, DE	DCI
Chemist	12	1320	GS	Lahiri, S	DCI
Resch Chemist	11	1320	GS	Bednarek, JM	DCI
Med Technologist	11	0644	GS	Kapur, JJ	DCI
Med Technologist	11	0644	GS	Morris, E	DCI
Med Technologist	11	0644	GS	Barnes, SG	DCI
Med Technologist	11	0644	GS	Anderson, JS	DCI
Med Technologist	09	0644	GS	Vacant	DCI

DESCRIPTION	GRADE	MOS	BRANCH	NAME	ACTIVITY
RESEARCH OPERATIONS SERVICE (continued)					
Bio Sci Lab Tech	09	0404	GS	Vacant	DCI
Bio Lab Tech	09	0404	GS	Jenkins, EL	DCI
CLINICAL STUDIES SERVICE					
Chief	O5	61C00	MC	Marin, R	DCI
Resch Chemist	12	1320	GS	Maydonovitch	Gastroenterology
Nurse Specialist	12	0610	GS	Parchment, VA	DCI
Nurse Specialist	12	0610	GS	Vacant	Endocrine
Nurse Specialist	12	0610	GS	Bicknell, E	DCI
Nurse Specialist	12	0610	GS	Casarena-Lepler	Gastroenterology (G)*

*(G) indicates grant-funded employee

D. FUNDING

	FY 97	FY 98	FY99	FY 00	FY 01
Appropriated Funding					
Civilian Personnel	$1,826,000	$1,681,000	$1,827,069	$2,177,569	$2,292,958
Military Personnel	$442,000	$452,000	$352,000	$418,699	$419,691
Consumable Supplies	$322,859	$303,439	$425,644	$256,972	$257,780
Civilian Contracts	$274,538	$160,000	$180,000	$319,200	$332,000
TDY	$34,210	$56,654	$45,728	$47,727	$47,000
Capital Expense Equipment Program (CEEP)	$15,600	$70,000	$126,500	$0	$0
MEDCASE	$965,000	$106,450	$0	$236,660	$0
Operations	$0	$0	$0		$589,700
Infra-Structure Program				$13,100	
Subtotal	$3,880,207	$2,829,543	$2,956,941	$3,469,927	$3,939,129
Extramural Funding					
GOG		$30,000	$0	$251,621	$8,800
CALGB		$82,700	$55,000	$99,188	$24,253
VA				$426,394	$32,214
USUHS/DoD/MRMC	$33,445	$0	$331,913	$15,330,466	$6,481,100
NIH/NCI	704,429	$1,362,000	$957,438	$755,713	$335,246
USUAMRAA				$15,426	
Partners Health Care System				$8,320	$0
Tri-Svc Nursing	$22,712	$0	$141,733	$445,781	$409,924
Travel (non-federal sources)	$21,000	$15,000	$34,508	$21,626	$38,292
Gifts (managed by DCI)	$110,614	$44,358	$252,525	$169,022	$4,200
CRDAs (managed by DCI)	$146,620	$76,059	$333,798	$277,722	$315,106
Royalty		$6,721	$91,079	$14,400	$0
TOTAL	$4,919,027	$4,446,381	$5,154,935	$21,285,606	$11,588,264

FINANCIAL REPORT ON PROTOCOLS IN FY2001
BY DEPARTMENT AND SERVICE

DEPARTMENT/ SERVICE	PROTOCOL	FY 00 Carryover Funding ($)	FY 01 Authorized Funding ($)	FY 01 Total Expenses ($)	FY 01 Carryover Funding ($)
DENTAL ACTIVITY					
	9401-99	$500	$0	$0	$500
	00-9401	$0	$1,230	$0	$0
	9400-99	$1,500	$0	$0	$1,500
DEPARTMENT	TOTAL	$2,000	$1,230	$0	$2,000
DEPARTMENT OF ALLERGY-IMMUNOLOGY					
	E00-33003	$0	$1,500	$0	$1,500
	01-33001	$0	$7,500	$7,298	$0
DEPARTMENT	TOTAL	$0	$9,000	$7,298	$1,500
DEPARTMENT OF CLINICAL INVESTIGATION					
	9224-99	$1,500	$0	$0	$1,500
	6430-99	$1,500	$0	$0	$1,500
	E00-92003	$1,500	$0	$0	$1,500
	01-9201	$0	$5,990	$2,926	$1,500
	E01-92006	$0	$1,000	$0	$1,000
DEPARTMENT	TOTAL	$4,500	$6,990	$2,926	$7,000
DEPARTMENT OF MEDICINE					
Cardiology Service					
	01-12001	$0	$1,500	$0	$1,500
	00-1201	$1,500	$0	$500	$1,000
	00-1202	$1,500	$0	$0	$1,500
	1911-99	$1,500	$0	$0	$1,500
Service	Total	$4,500	$1,500	$900	$5,500
Dermatology Service					
	01-1828	$0	$8,420	$2,934	$1,500
Service	Total	$0	$8,420	$2,934	$1,500
Endocrine-Metabolic Service					
	E44008E-99	$1,500	$0	$0	$1,500
	00-1302	$0	$1,500	$1,000	$500
	E00-13004	$1,500	$0	$214	$500
	00-1303	$0	$4,458	$3,775	$500
	1397-98	$1,500	$0	$0	$1,500
	9223-99	$1,500	$4,300	$2,149	$1,500
	E00-13003	$1,500	$0	$0	$1,500
	00-6504	$1,500	$0	$0	$1,500
	00-4404	$0	$1,500	$0	$1,500
	E01-13007	$0	$1,500	$0	$1,500
	E01-13008	$0	$1,500	$0	$1,500
	E00-13006	$0	$1,500	$844	$500
	00-1304	$1,500	$3,358	$3,106	$1,500
	00-1301	$1,500	$0	$0	$1,500
Service	Total	$12,000	$19,616	$11,088	$17,000
Gastroenterology Service					
	1453-99	$1,500	$0	$0	$1,500
	1448-98	$1,500	$0	$0	$1,500
	00-1404	$1,500	$0	$0	$1,500
	00-1406	$1,500	$0	$0	$1,500
	E01-14004	$0	$1,500	$874	$500

FINANCIAL REPORT ON PROTOCOLS IN FY2001
BY DEPARTMENT AND SERVICE

DEPARTMENT/ SERVICE	PROTOCOL	FY 00 Carryover Funding ($)	FY 01 Authorized Funding ($)	FY 01 Total Expenses ($)	FY 01 Carryover Funding ($)
	00-1403	$0	$4,749	$3,478	$500
	E01-14005	$0	$1,500	$0	$1,500
	E00-14001	$1,500	$0	$0	$1,500
	01-14001	$0	$1,700	$0	$1,500
	00-1402	$0	$3,190	$0	$1,500
Service	Total	$7,500	$12,639	$4,352	$13,000
General Medicine Service					
	00-1605	$0	$2,500	$0	$1,500
	1060-99	$1,500	$0	$0	$1,500
	00-1002	$1,500	$0	$1,000	$500
	E00-10001	$1,500	$0	$0	$1,500
	00-1001	$1,500	$0	$0	$1,500
	E00-83001	$1,500	$0	$0	$1,500
	E00-10003	$1,500	$0	$0	$1,500
	00-1003	$1,500	$0	$1,040	$500
	E01-10004	$0	$1,500	$0	$1,500
	1059-99	$1,500	$0	$0	$1,500
Service	Total	$12,000	$4,000	$2,040	$13,000
Hematology-Oncology Service					
	01-16002	$0	$1,500	$0	$1,500
Service	Total	$0	$1,500	$0	$1,500
Infectious Disease Service					
	1909-99	$0	$3,900	$0	$0
Service	Total	$0	$3,900	$0	$0
Nephrology Service					
	E00-11011	$0	$1,500	$0	$1,500
	00-1102	$0	$1,480	$1,480	$1,500
	00-1101	$0	$2,500	$0	$1,500
	1199-99	$1,500	$0	$0	$1,500
	1196-98	$0	$1,000	$0	$1,000
	E00-11010	$0	$1,500	$772	$500
	E01-11012	$0	$1,500	$866	$500
	01-11002	$0	$1,500	$0	$1,500
	00-1103	$0	$6,840	$6,741	$0
	1197-99	$1,500	$6,113	$0	$1,500
	1198-99	$1,500	$0	$0	$1,500
Service	Total	$4,500	$23,933	$9,859	$12,500
Pulmonary & Critical Care Medicine Service					
	E01-17012	$0	$1,000	$932	$0
	E00-17004	$0	$1,500	$945	$500
	E01-17010	$0	$1,500	$0	$1,500
	1706-99	$1,500	$0	$0	$1,500
	E01-17006	$0	$1,500	$0	$1,500
	E01-17008	$0	$1,500	$944	$500
	E00-17003	$0	$1,500	$1,035	$500
	1794-98	$500	$0	$0	$500
	1709-99	$1,500	$0	$0	$1,500
	01-1701	$0	$1,500	$0	$1,500
	3002-99	$1,500	$0	$0	$1,500
	E01-17009	$0	$1,500	$0	$1,500

FINANCIAL REPORT ON PROTOCOLS IN FY2001
BY DEPARTMENT AND SERVICE

DEPARTMENT/ SERVICE	PROTOCOL	FY 00 Carryover Funding ($)	FY 01 Authorized Funding ($)	FY 01 Total Expenses ($)	FY 01 Carryover Funding ($)
	E01-17007	$0	$1,500	$0	$1,500
	E00-17001	$1,500	$0	$1,004	$500
	E00-17005	$0	$1,500	$1,071	$500
	E01-17011	$0	$1,000	$0	$1,000
	1615-98	$1,500	$0	$700	$500
Service	Total	$8,000	$15,500	$6,631	$16,500
Rheumatology Service					
	00-3702	$1,500	$0	$0	$1,500
	3729-99	$1,500	$0	$1,000	$500
	00-3701	$1,500	$0	$0	$1,500
	01-37001	$0	$1,500	$0	$1,500
Service	Total	$4,500	$1,500	$1,000	$5,000
DEPARTMENT	TOTAL	$53,000	$92,508	$38,804	$85,500
DEPARTMENT OF NEUROLOGY					
	00-7104	$0	$100	$0	$0
	00-7102	$1,500	$1,029	$0	$1,500
	01-71003	$0	$7,500	$3,165	$0
	7176-99	$0	$700	$700	$0
DEPARTMENT	TOTAL	$1,500	$9,329	$3,865	$1,500
DEPARTMENT OF NURSING					
	7581-99	$1,500	$0	$0	$1,500
	01-7501	$0	$1,500	$1,000	$500
DEPARTMENT	TOTAL	$1,500	$1,500	$1,000	$2,000
DEPARTMENT OF OBSTETRICS AND GYNECOLOGY					
	E00-44010	$1,500	$0	$0	$1,500
	4413-99	$1,500	$0	$0	$1,500
	4416-99	$1,500	$0	$0	$1,500
	E00-44007	$1,500	$0	$0	$1,500
	E00-44009	$1,500	$0	$0	$1,500
	00-4406	$0	$1,500	$0	$1,500
	00-4403	$1,500	$0	$0	$1,500
	E00-44011	$1,500	$0	$0	$1,500
	E01-44016	$0	$1,500	$0	$1,500
	01-44002	$0	$1,500	$0	$1,500
	E01-44018	$0	$1,000	$0	$1,000
	01-44003	$0	$1,500	$0	$1,500
DEPARTMENT	TOTAL	$10,500	$7,000	$0	$17,500
DEPARTMENT OF PATHOLOGY AND AREA LABORATORIES					
	4837-99	$1,500	$0	$0	$1,500
	4835-99	$500	$0	$0	$500
	4836-99	$1,500	$0	$0	$1,500
	4834-99	$1,500	$0	$0	$1,500
DEPARTMENT	TOTAL	$5,000	$0	$0	$5,000
DEPARTMENT OF PEDIATRICS					
	00-6502	$500	$0	$0	$500
	6427-99	$1,500	$0	$0	$1,500
	00-6503	$1,500	$0	$0	$1,500
	00-6501	$1,300	$0	$0	$1,300
	00-9201	$1,300	$0	$0	$1,300

FINANCIAL REPORT ON PROTOCOLS IN FY2001
BY DEPARTMENT AND SERVICE

DEPARTMENT/ SERVICE	PROTOCOL	FY 00 Carryover Funding ($)	FY 01 Authorized Funding ($)	FY 01 Total Expenses ($)	FY 01 Carryover Funding ($)
	E00-64005	$1,500	$0	$0	$1,500
	E01-64007	$0	$1,500	$0	$1,500
	01-65001a	$0	$7,500	$7,440	$0
	E01-64008	$0	$1,500	$0	$1,500
DEPARTMENT	TOTAL	$7,600	$10,500	$7,440	$10,600
DEPARTMENT OF PHARMACY					
	E00-36003	$0	$1,500	$0	$1,500
	3614-99	$1,500	$0	$0	$1,500
	00-3601	$1,500	$208	$208	$1,500
DEPARTMENT	TOTAL	$3,000	$1,708	$208	$4,500
DEPARTMENT OF PHYSICAL MEDICINE & REHABILITATION					
	00-9603	$0	$1,500	$0	$1,500
	00-9604	$0	$1,500	$0	$1,500
	00-9602	$1,500	$1,377	$0	$1,500
	E00-96002	$1,500	$0	$0	$1,500
	00-9601	$1,500	$0	$0	$1,500
	E00-96003	$1,500	$0	$0	$1,500
	E01-24014	$0	$1,000	$0	$1,000
	E01-96007	$0	$1,000	$0	$1,000
DEPARTMENT	TOTAL	$6,000	$6,377	$0	$11,000
DEPARTMENT OF PSYCHIATRY					
	00-7201	$1,500	$0	$0	$1,500
	E00-72005	$1,500	$0	$0	$1,500
	7284-99	$1,500	$0	$0	$1,500
DEPARTMENT	TOTAL	$4,500	$0	$0	$4,500
DEPARTMENT OF PSYCHOLOGY					
	E01-73002	$0	$1,000	$0	$1,000
DEPARTMENT	TOTAL	$0	$1,000	$0	$1,000
DEPARTMENT OF RADIOLOGY					
Diagnostic Radiology					
	4710-99	$0	$4,875	$0	$1,500
Service	Total	$0	$4,875	$0	$1,500
Nuclear Medicine Service					
	01-4501	$0	$1,500	$0	$1,500
	00-4501	$1,500	$0	$0	$1,500
	E01-45000	$0	$1,500	$0	$1,500
Service	Total	$1,500	$3,000	$0	$4,500
Radiation Therapy					
	01-46001	$0	$1,500	$0	$1,500
Service	Total	$0	$1,500	$0	$1,500
DEPARTMENT	TOTAL	$1,500	$9,375	$0	$7,500
DEPARTMENT OF SURGERY					
Anesthesia-Operative Service					
	00-2002A	$1,500	$0	$0	$1,500
	01-2001A	$0	$3,638	$2,138	$1,500
Service	Total	$1,500	$3,638	$2,138	$3,000

FINANCIAL REPORT ON PROTOCOLS IN FY2001
BY DEPARTMENT AND SERVICE

DEPARTMENT/ SERVICE	PROTOCOL	FY 00 Carryover Funding ($)	FY 01 Authorized Funding ($)	FY 01 Total Expenses ($)	FY 01 Carryover Funding ($)
Army Audiology and Speech Center					
	01-2501	$0	$1,500	$0	$1,500
	2590-99	$0	$1,500	$0	$1,500
Service	Total	$0	$3,000	$0	$3,000
General Surgery					
	01-20005	$0	$1,200	$0	$1,000
	01-3202	$0	$1,500	$0	$1,500
	2080-99	$1,500	$0	$0	$1,500
	00-2001	$1,500	$0	$0	$1,500
	00-2002	$1,500	$3,074	$0	$1,500
	00-2003	$1,500	$4,815	$0	$1,500
	2078-99	$1,500	$3,900	$2,400	$1,500
Service	Total	$7,500	$14,489	$2,400	$10,000
Ophthalmology Service					
	2335-99	$1,500	$0	$0	$1,500
	2334-99	$1,500	$0	$0	$1,500
	00-2302	$1,500	$2,400	$2,133	$1,500
	01-23001	$0	$2,200	$0	$1,500
Service	Total	$4,500	$4,600	$2,133	$6,000
Organ Transplant Service					
	E01-26002	$0	$1,500	$0	$1,500
Service	Total	$0	$1,500	$0	$1,500
Orthopaedic Surgery Service					
	01-24003	$0	$1,500	$0	$1,500
	01-24005	$0	$1,500	$0	$1,500
	E00-24008	$1,500	$0	$378	$1,122
	2492-97	$0	$1,000	$948	$0
	01-2402	$0	$1,500	$0	$1,500
	00-2401	$1,500	$0	$1,000	$500
	2411-99	$500	$1,000	$875	$500
	00-2402	$1,500	$0	$0	$1,500
	E00-24010	$1,500	$0	$0	$1,500
	01-24004	$0	$1,500	$0	$1,500
	E00-24007	$1,500	$0	$0	$1,500
	00-2403	$1,500	$2,092	$2,092	$1,500
	00-2404	$1,500	$0	$0	$1,500
	2415-99	$1,500	$0	$956	$500
	01-24008	$0	$1,500	$0	$1,500
	E01-24015	$0	$1,000	$0	$1,000
	2410-99	$1,500	$0	$0	$1,500
	00-2406	$0	$1,000	$1,192	$500
Service	Total	$14,000	$13,592	$7,441	$20,622
Otolaryngology-Head/Neck Surgery Service					
	2592-99	$1,500	$0	$0	$1,500
	00-2508	$0	$7,820	$0	$1,500
	01-32004	$0	$1,500	$0	$1,500
	00-2504	$1,500	$0	$0	$1,500
	2572-98	$500	$0	$0	$500
	2584-99	$1,500	$0	$1,005	$500
	00-2502	$1,500	$0	$1,000	$500

FINANCIAL REPORT ON PROTOCOLS IN FY2001
BY DEPARTMENT AND SERVICE

DEPARTMENT/ SERVICE	PROTOCOL	FY 00 Carryover Funding ($)	FY 01 Authorized Funding ($)	FY 01 Total Expenses ($)	FY 01 Carryover Funding ($)
	2589-99	$1,500	$0	$0	$1,500
	00-2506	$0	$17,090	$0	$0
Service	Total	$8,000	$26,410	$2,005	$9,000
Peripheral Vascular Surgery Service					
	00-2102	$0	$5,797	$5,955	$1,500
	2130-99	$500	$0	$0	$500
	2131-99	$1,500	$0	$1,500	$0
	2132-99	$1,500	$0	$0	$1,500
	00-2101	$1,500	$0	$0	$1,500
	01-1201	$0	$6,250	$6,200	$1,500
Service	Total	$5,000	$12,047	$13,655	$6,500
Urology Service					
	E00-28004	$1,500	$0	$0	$1,500
	01-28004	$0	$1,075	$75	$1,000
	2891-99	$1,500	$0	$0	$1,500
	2894-99	$1,500	$0	$0	$1,500
	E00-28005	$500	$1,000	$1,016	$500
	2890-99	$1,500	$0	$0	$1,500
Service	Total	$6,500	$2,075	$1,091	$7,500
DEPARTMENT	TOTAL	$47,000	$81,351	$30,863	$67,122
DEPLOYMENT HEALTH CLINICAL CENTER					
	E00-89001	$1,500	$0	$0	$1,500
CENTER	TOTAL	$1,500	$0	$0	$1,500
USUHS					
	01-83001	$0	$1,500	$0	$1,500
USUHS	TOTAL	$0	$1,500	$0	$1,500
	GRAND TOTAL	**$149,100**	**$239,368**	**$92,404**	**$231,222**

E. RESEARCH ACTIVITY ACCOMPLISHED IN FY 01

With the mission to empower WRAMC researchers from planning to publication, the Department of Clinical Investigation (DCI) supported a total of 891 active protocols this year (see Table I). Two hundred twenty of these studies were newly approved during the fiscal year; the remaining 671 studies were ongoing during the fiscal year 2001.

TABLE I. WRAMC Protocol Activity

PROTOCOLS	FY97	FY98	FY99	FY00	FY01
ONGOING at beginning of FY	543*	537	621	646	671#
NEWLY APPROVED (+)	154	226	230	187	220
Full protocols	(154)	(226)	(152)	(124)	(153)
Exempt protocols			(78)	(63)	(67)
TOTAL ACTIVE During FY	697*	763	851	833♦	891
CLOSED (-)					
Full protocols	147	128	184	145	138
Exempt protocols					78
TERMINATED (-)	13*	14	21	8	6
WITHDRAWN (-)				10	5
ONGOING AT END OF FY	537*	621	646	670	664

* correction to FY 97 Publication

♦ includes one protocol with status change from FY 99 Publication

includes one protocol with status change

Of 181 new protocols submitted in FY 2001, the Human Use Committee (HUC) and/or the Clinical Investigation Committee (CIC) approved a total of 155 new protocols. The CIC reviews all protocols for scientific merit and funding with the exception of those studies being submitted for funding through an outside agency (such as National Institutes of Health or Medical Research and Materiel Command) where critical review will be provided. Some protocols are reviewed by both the HUC and the CIC; all greater than minimal risk protocols are reviewed for approval by the HUC. The procedure established for exempt category protocols

was continued, whereby research that does not fall within the purview of the Institutional Review Board (IRB) is reviewed within DCI to determine if it meets exempt criteria, continued to work well. Eighty-one new protocols were submitted under the Exempt category in FY 01 and 67 of these were granted exempt status.

In response to the emerging need to review gene therapy protocols, the Department of Clinical Investigation organized an Institutional Biosafety Committee (IBC) in 2000. This committee is comprised of WRAMC affiliated and non-affiliated members recognized as experts in their fields and qualified to critically review the issues of human gene transfer research protocols with regard to biosafety. The Institutional Biosafety Committee met twice in 2001 and provided appropriate continuing review for three approved gene therapy protocols.

In addition to administering the initial review and approval of new protocols, the continuing review of the ongoing protocols is also administrated by the Department of Clinical Investigation (DCI), Research Review Service. Continuing review of ongoing approved protocols was conducted prior to or during the anniversary month of the original approval of the protocols. In order to ensure timely completion, a request is sent to the principal investigator for submission of an annual progress report (APR) two months preceding the month the APR is actually due. The completed report consists of a detail summary sheet (DSS), a list of publications using data obtained as a result of the protocol, a copy of the approved consent form, a questionnaire regarding the maintenance of research records, and the continuing review of human subject participation or animal use. Human Use Committee/Institutional Review Board (HUC/IRB) members serve as primary reviewers for the annual progress reports throughout the year. The primary reviewers recommend approval for continuation of the study for one year, study closure, or study continuation or closure pending additional information. These recommendations are presented monthly to the HUC/IRB for their final review and vote. A total of 516 annual progress reports were reviewed and approved; the detail summary sheets of the protocols ongoing in FY 01 comprise Volume II of this document. Failure to submit an APR within 60 days after the anniversary date of the protocol results in administrative termination by the HUC, and investigators are informed that no research may be published.

The Research Review Service (RRS), under the direction of Dr. Audrey Chang, also performs and coordinates other protocol regulatory activities. A total of 217 protocol addenda were reviewed and approved

by the WRAMC HUC/IRB, and 37 internal protocol audits were conducted by the DCI this year. A total of 329 adverse events were reviewed and reported to the HUC (see Table II).

TABLE II. WRAMC FY 01 Other Research Review Activity

	FY99	FY00	FY01
Addenda Reviewed	307	266	217
Audits Conducted	17	33	37
Adverse Events Reported	893	539	329
Continuing Review and Approval of Annual Progress Reports	568	539	516

Publication and presentation productivity by WRAMC staff totaled 1,033; this included 370 publications, 564 presentations and 99 abstracts (see Table III).

TABLE III. WRAMC Publications, Abstracts and Presentations

	FY99	FY00	FY01
Publications	322	349	370
Abstracts	151	121	99
Presentations	599	584	564
TOTAL	1,072	1,054	1,033

The Research Review Service has expanded to include a new position of Institutional Review Board (IRB) Administrator. Dr. Edward Bartlett joined the DCI Research Review Service (RRS) in August 2001, to assume the responsibility for coordination of the increasing IRB oversight activities. The RRS maintained and updated the "Principal Investigator's Guide" which explains the research review process, details research resources available at WRAMC, and provides checklists, formats, and guidelines for principal investigators. The "Principal Investigator's Guide" and the routine forms and instructions necessary for preparation of a protocol application are available through the DCI website at www.wramc.amedd.army.mil/department/dci.

The Biometrics Section of the RRS continued to provide a wide range of statistical support to investigators, including research design, sample size estimation, data analysis, and general troubleshooting. Three levels of statistical courses were offered to the investigators regarding how to conduct data analyses using the SPSS program. Course contents include data coding, data entry, common statistical methods for data analysis, and non-parametric statistics. The Biometrics Section remains vital in facilitating and enhancing the functions and capabilities of research data analysis at WRAMC.

The Research Operations Service (ROS), under the direction of Mr. Maged Abdel-Rahim, continued to carry out the DCI Master Plan by initiating the renovation of Building 7. This building has been designated to house research laboratory space by the authority of the Commander and the WRAMC Space Committee. The MEDCOM has released $1.7 million for the construction phase. The ROS participated in construction meetings with the project manager from the WRAMC Department of Public Works (DPW) and a representative from the construction company, and the construction phase is underway. The completion of the renovation is scheduled for 20 August 2002. Major General Timboe has agreed to the DCI request for $95,000 to facilitate the ROS personnel and equipment relocation from Building T-2 to Building 7. The ROS Chemistry, Immunology, and Molecular Biology Sections supported a total of 37 DCI-approved protocols and 24 scientific publications. As a result of a post-wide power outage during the summer of 2001 the research samples stored in the ROS freezers and refrigerators were relocated to WRAIR for temporary storage and most of the ROS laboratory reagents and chemical supplies were destroyed. The ROS participated in a global training program for foreign students by providing training for 2 scientists (1 from Belarus and 1 from Ukraine). In the summer of 2001 a group of 3 scientists, headed by Dr. Marcos Rojkind, joined the ROS from Albert Einstein School of Medicine; their research efforts focus on alcoholism and liver fibroses.

The Research Administration Service (RAS), under the direction of Daisy Word, provided administrative support for the Department and all WRAMC investigators. Extramural funding included support from the U.S. Army Medical Research and Materiel Command, Tri Service Nursing, the National Institutes of Health, the Gynecology Oncology Group, and the Cancer and Leukemia Group B. There were also industry awards through Cooperative Research and Development Agreements (CRDA) managed through intermediary agencies including the Henry M. Jackson Foundation for the Advancement of Military Medicine

(HMJF), FACT, TRUE, and the Geneva Foundation. Extramural funding for WRAMC researchers totaled over $11,000,000 and is shown on page 5. The Computer Operations Section of RAS continued to provide comprehensive automation support and services to staff and investigators through its on-site and web resources. The major focus over the year has been to increase integration of department services, education, and information through the web interface at http://www.wramc.amedd.army.mil/departments/dci/, and to begin development of a comprehensive relational database for protocol oversight.

Under the auspices of the WRAMC Professional Education and Training Committee, DCI continued to provide training for WRAMC personnel regarding research regulations and the conduct of research at WRAMC. A total of 158 investigators participated in the FY 01 research course. A web-based version of the WRAMC research course has been developed and will become available beginning in FY 02. This on-line option will facilitate timely completion of the required course for researchers who come to WRAMC throughout the year or who are billeted at facilities other than WRAMC.

The 27th Annual Bailey K. Ashford Clinical and Laboratory Research Awards were bestowed on members of the 2001 graduating class whose research accomplishments excelled during training. The selection committee chose eight finalists from the record number of thirty nominations. The finalists presented their research results at a symposium on 3 May 2001 sponsored by Department of Clinical Investigation. The winners in the clinical and laboratory categories and the finalists along with their presentation topics appear on page 22. A poster session, the second annual such session, was held the morning of the symposium to allow the other nominees an opportunity to present their work to the WRAMC community.

The Department of Clinical Investigation received the active support of many WRAMC staff members via their participation on the Human Use Committee/Institutional Review Board (HUC/IRB) {Tables IV and V}, the Clinical Investigation Committee (CIC) {Tables VI and VII}, and the Institutional Biosafety Committee (IBC) {Table VIII}. The research expertise of these individuals contributed significantly to the scientific rigor of the WRAMC clinical investigation program.

TABLE IV: Human Use Committee/Institutional Review Board Primary Members for FY 2001

Chairpersons HUC

+COL James Kikendall, MC	Gastroenterology Service DOM, Rep DCCS
+LTC Christina Yuan, MC	Nephrology Service DOM, Rep DCCS
LTC Raul Marin, MC	Co-Chairperson, HUC Assistant Chief, DCI

+Alternate chairing of the HUC meetings

WRAMC Members

Michele Sandberg, MAJ, MC	(Rep) Department of Psychiatry
Laura Brosch, LTC, AN	(Rep) Department of Nursing
Teresa Kemmer, MAJ, SP	(Rep) Chief, Nutrition Care Directorate
David Gillespie, LTC, MC	(Rep) Department of Surgery
Orman Wayne Boyd, MAJ, CH	(Rep) Chief, Dept of Ministry and Pastoral Care
Laurel Meaney, DAC	Patients' Rights Representative
Scott Murdoch, JD, DAC	(Rep) Center Judge Advocate
Verna Parchment, RN, MS	Research Review Service Department of Clinical Investigation
Vicki Miskovsky, DAC	Recorder, HUC Department of Clinical Investigation

Non-Affiliated Members

Richard Conran, COL, MC	Department of Pathology, USUHS
George C. Tsokos, LTC, MC	Chief, Physiology Service, Division of Medicine, WRAIR
Janice Agazio, DScN, DoD	Department of Nursing, USUHS
Ruth Ellen Bulger, Ph.D., DoD	Department of Anatomy, USUHS
Eric Marks, M.D., DoD	Nephrology Service, USUHS

TABLE V: Human Use Committee/Institutional Review Board Alternate Members for FY 2001

Audrey Chang, Ph.D., DAC	Chief, Research Review Service, DCI Co-Chairperson HUC
Abdull R. Muhammad, CPT, CH	(Rep) Chief, Department of Ministry & Pastoral Care
Patricia A, Patrician, LTC, AN	(Rep) Chief, Nursing Research Service
Eric Mair, MAJ, MC	Otolaryngology – Head and Neck Surgery (Rep) Department of Surgery
Dean Inouye, LTC, MC	(Rep) Chief, Department of Psychiatry
Melanie Craig, MAJ, SP	(Rep) Chief, Nutrition Care Directorate
Richard J. Relyea, DAC, JD	(Rep) Center Judge Advocate
Michelle Porter, RN, MS, DAC	Research Review Service Department of Clinical Investigation
Irone Green, DAC	Recorder Department of Clinical Investigation

TABLE VI: Clinical Investigation Committee Primary Members for FY 2001

LTC Raul Marin, MC	Chairperson, CIC Asst.Chief, Department of Clinical Investigation
Patricia A. Patrician, LTC, AN	(Rep) Chief, Nursing Research Service
Thomas Burklow, LTC, MC	(Rep) Chief, Department of Pediatrics
George Peoples, LTC, MC	(Rep) Department of Surgery
Patrick O'Malley, MAJ, MC	(Rep) Chief, Department of Medicine
Laurie Ryan, Ph.D., DAC	(Rep) Chief, Department of Neurology
Kenneth Grant, Ph.D., DAC	Army Audiology & Speech Center Rotating Senior Investigator
Scott Murdoch, JD, DAC	(Rep) Center Judge Advocate
Al Szkutnik, DAC	(Rep) Department of Pharmacy
Audrey Chang, Ph.D., DAC	Chief, Research Review Service, Department of Clinical Investigation
Daisy Word, MHSA, DAC	Chief, Research Administration Service, DCI
Vicki Miskovsky, DAC (non-voting)	Recorder, CIC

TABLE VII: Clinical Investigation Committee Alternate Members for FY 2001

Allen Taylor, LTC, MC	Acting Chairperson, CIC
Glenn Edwards, LTC, MC	(Rep) Chief, Department of Pediatrics
Laura Brosch, LTC, AN	(Rep) Chief, Nursing Research Service
Oleh Hnatiuk, LTC, MC	(Rep) Chief, Department of Medicine
Noah S. Schenkman, LTC, MC	(Rep) Chief, Department of Surgery
Andrew Eiseman, MAJ, MC	(Rep) Chief, Department of Surgery
John Choi, MAJ, MC	(Rep) Chief, Dept of Neurology
Brian Walden, Ph.D., DAC	Rotating Senior Investigator
Leonard Kessler, DAC	(Rep) Chief, Department of Pharmacy
Richard Relyea, JD, DAC	(Rep) Center Judge Advocate
Ms. Robin Howard, MS, DAC	(Rep) Chief, Research Review Service, DCI
Gregory Fant, Ph.D., DAC	(Rep) Chief, Research Review Service, DCI
* pending	Rep Chief, Research Administrations, DCI
* pending (non-voting)	Recorder, CIC

TABLE VIII: Institutional Biosafety Committee Board Members

WRAMC Affiliated Members

COL Craig D. Shriver, MC	Assistant Chair, General Surgery
LTC Thomas R. Burklow, MC	Pediatric Cardiology
LTC Raul Marin, MC	Physical Medicine & Rehab/Research Admin.
COL Bryan L. Martin, MC	Allergy/Immunology
Dr. Diarmuid Nicholson (PhD)	Biochemistry/Molecular Biology
MAJ Paula Doulaveris, MS	Pharmacology

Non-Affiliated Members

LTC Ken E. Kester, MC	Chair, Infectious Disease, WRAIR
COL Naomi E. Aronson, MC	Infectious Disease, USUHS
Dr. Kuan-Teh Jeang (MD, PhD)	Molecular Virology, NIH
Dr. Shyh-Ching Lo, (MD, PhD)	Molecular Pathobiology, AFIP
Ms. Donna J. Mateski (MS, RD)	Research Administration, Kaiser
COL Judd W. Moul, MC	Urology, USUHS

DCI Administration (non-voting)

COL Maria H. Sjogren, MC	Chief, Dept. of Clinical Investigation
Dr. Audrey Chang (PhD)	Chief, Research Review Service, DCI
CPT Ken Capps, MS	Clinical Studies Service, DCI
Ms. Deborah Kessler (RN, MSN)	Nurse Specialist
Dr. Edward Bartlett (PhD)	Asst. Chief, Research Review Service, DCI

The Bailey K. Ashford Clinical Research Awards
2001

First Place - Laboratory Award Category

Maintenance of Endothelial NOS Activity During Intestinal I/R Limits Capillary Leak
David Ward MAJ, MC
Resident, General Surgery Service

First Place - Clinical Research Category

Folic Acid Inhibits Homocysteine-Induced Proliferation of Human Arterial Smooth Muscle Cells
Brennan Carmody MAJ, MC
Resident, General Surgery Service

First Place - Laboratory Poster Award Category

Interleukin-1B, Interleukin-5, Interleukin-6, Interleukin-8, and Tumor Necrosis Factor-alpha in Chronic Sinusitis: Response to Systemic Corticosteroids
Colleen Lennard CPT, MC
Resident, Otolaryngology/Head and Neck Surgery Service

First Place - Clinical Research Poster Category

Do Different Statins Possess Different Anti-Inflammatory Effects?
Steve Kent CPT, MC
Fellow, Cardiology Service

Research Presentation Finalists

Use of Impulse Oscillometry in Adult Bronchoprovocation Testing
Alexander Niven CPT (P), MC
Fellow, Pulmonary & Critical Care Medicine Service

Serum Calcium Is Not Predictive of Ionized Calcium
Erik Rupard CPT, MC
Resident, General Medicine Service

Chronic Dialysis Patients Have High Risk for Pulmonary Embolism
Daniel Tveit LT, USNR
Fellow, Nephrology Service

Induction of Early Inflammatory Gene Expression in a Murine Model of Non-resuscitated, Fixed Volume Hemorrhage
Michael Rajnik Capt, USAF
Fellow, Pediatric Infectious Disease

III. INDEX OF PROTOCOLS BY DEPARTMENT AND SERVICE

PROTOCOL NUMBER	PRINCIPAL INVESTIGATOR, TITLE AND APPROVAL DATE	PAGE* VOL II
Aberdeen Proving Ground		
00-8601	Lopez, Mary S., LTC SP. Tele-Ergonomic Assessment Methodologies Study. (6/13/2000)	546
01-86001	Walsworth, Matt, CPT SP. Efficacy of Stretching and Mobilization with Neutral Wrist Splinting Versus Neutral Wrist Splinting Alone in Patients with Carpal Tunnel Syndrome: A Randomized Trial. (1/16/2001)	New
CHPPM		
01-90000E	Chaffin, Jeffrey, MAJ DC. Dental Mobilization of the 29th Infantry Division, Virginia National Guard. (9/5/2001)	Exempt
DENTAC		
00-9401	Taylor, Steven, LTC DE. Laryngeal Mask Airway Use in General Anesthesia for Outpatient Third Molar Surgery: Intraoperative management and Postoperative Outcomes. (8/15/2000)	579
9400	Chesla, Robert E., LTC DE. An Outcome-Based Assessment of the Sraumann ITI Dental Implant System by General Dentists. (8/27/1996)	581
9400-99	Theberge, Daniel M., COL DE. Absorption Rate a a New Bioabsorbable Membrane - A Pilot Study. (2/2/1999)	580
Department of Allergy-Immunology		
01-33001	Katial, Rohit, MAJ MC. In Vitro Gamma-Interferon Response to MTB Antigens in BCG-Vaccinated Individuals and Those with Equivocal PPD Skin Test Compared to Negative and Positive Control Subjects. (2/13/2001)	New
01-33002	Waibel, Kirk H., CPT MC. Suppression of Ragweed Wheal Response by Montelukas: A Double-blind Study. (3/20/2001)	New
3369	Kosisky, Susan, DAC. Survey of Prevalent Pollen and Fungal Aeroallergens in the Washington DC Area. (5/11/1993)	357
3372	Engler, Renata J.M., COL MC. Mosquito Hypersensitivity: Immunology and Value of Skin Testing with Whole Body Mosquito Extracts. (12/21/1993)	358
3385	Engler, Renata J.M., COL MC. Adverse Reactions with Intravenous Immunoglobulin Therapy. (12/10/1996)	359

* Page # for protocol summary in vol II. New is an FY2001 protocol which doesn't yet require an annual summary.

PROTOCOL NUMBER	PRINCIPAL INVESTIGATOR, TITLE AND APPROVAL DATE	PAGE* VOL II
3390-99	Nelson, Michael, LTC MC. A Phase 3 Study to Determine the Efficacy and Safety of C1-Inhibitor (HUMAN) Vapor Heated, Immuno in Subjects with Hereditary Angioedema (HAE). (5/25/1999)	360
Department of Clinical Investigation		
00-9201	Francis, Gary L., COL MC. Role of Focal Adhesion Kinase and E-Cadherin in Differentiated Thyroid Cancer. (10/5/1999)	560
00-9202AD	Sjogren, Maria H., COL MC. Efficacy of Therapy with Interferon (interferon alfa-2b or Pegylated Interferon alfa-2b) in Combination with Ribavirin for Chronic Hepatitis C Infections in Egypt. (1/27/2000)	Admin
01-92002	Sjogren, Maria H., COL MC. A Prospective, Randomized, Multicenter, Open-Label, Comparative Safety Study of PegasyO vs. PegasysO Plus Ribavirin Treatment vs. A Twelve-Week Treatment Delay in Patients with Chronic Hepatitis C. (1/23/2001)	New
01-92003	Sjogren, Maria H., COL MC. Hepatitis C Virus Infection: Mechanism of Disease Progression. (2/20/2001)	New
01-92004	Rojkind, Marcos, M.D.. Interleukin-6 and Tumor Necrosis Factor-Alpha Role In Alcoholic Liver Cirrhosis. (9/11/2001)	New
01-92004E	Fant, Gregory, PhD DAC. Infant Mortality Among Members of Minority People in Washington, DC.. (2/23/2001)	Exempt
01-92005	Rojkind, Marcos, M.D.. The Role of the Acute Phase Response in Alcoholic Liver Cirrhosis. (9/14/2001)	New
01-92005E	Ejnik, John W., LT MSC. Arsenic Determination by ICP-MS. (4/25/2001)	Exempt
01-92006	Rojkind, Marcos, M.D.. Alcohol-Induced Liver Fibrosis: An In Vitro Model. (9/14/2001)	New
01-92006E	Sjogren, Maria H., COL MC. Effect of Age on Disease Progression in Chronic Hepatitis C. (6/27/2001)	Exempt
01-9201	Bednarek, Jana, Ph.D. DAC. Hepatitis G Virus and Aplastic Anemia. (12/5/2000)	New
9206	Yuan, Christina M., LTC MC. Are Heat Shock Proteins Target Antigens of the Immune System in Renal Allograft Recipients?. (4/9/1996)	610
9208	Sjogren, Maria H., COL MC. Intron A + Ribavirin for Treatment of Patients with Interferon-Refractory or Interferon-Relapsed Chronic Hepatitis C. (11/26/1996)	611
9210	Sjogren, Maria H., COL MC. Hepatitis C Virus Infection: Quasispecies and Mechanisms of Disease Progression. (7/29/1997)	612

* Page # for protocol summary in vol II. New is an FY2001 protocol which doesn't yet require an annual summary.

PROTOCOL NUMBER	PRINCIPAL INVESTIGATOR, TITLE AND APPROVAL DATE	PAGE* VOL II
9211	Sjogren, Maria H., COL MC. Intron A+Ribavirin for Treatment of Patients with Chronic Hepatitis C Not Previously Treated with Interferon. (10/14/1997)	613
9212	Lukes, Yvonne D., DAC. Hormonal Regulation of the Vitamin D Receptor. (12/9/1997)	614
9213	Anderson, Jeffrey, DAC. Quantitative Measurement of Thyroglobulin mRNA Detected in Peripheral Blood Using Reverse Transcriptase Polymerase Chain Reaction. (1/13/1998)	615
9217-98	Sjogren, Maria H., COL MC. Dose Abnormal Alanine Amionotransferase Mean Hepatitis C Infection?. (4/28/1998)	619
9218-98	Morris, Elena R., M.T. DAC. ICP-MS Analysis of Depleted Uranium: A Study to Assess Uranium Levels and Isotopic Ratios in Biological Fluids. (9/15/1998)	620
9219-99	Francis, Gary L., COL MC. Molecular Marker of Radiation Induced Thyroid Disease Developing in Subjects Who lived Downwind of the Hanford Nuclear Power Plant During Childhood. (11/17/1998)	New
9220-99	Francis, Gary L., COL MC. Molecular Markers of Radiation Induced Thyroid Diseae Developing in Subjects Treated with External Beam Irradiatin for Tinea Capitus as Children. (11/17/1998)	New
9221-99	Sjogren, Maria H., COL MC. Combination of Ribavirin with Interferon Alfacon-1 or With Interferon Alfa 2b as Initial Treatment for Chronic Hepatitis C. (12/15/1998)	New
9222-99	Ramirez, Raul R., LTC MC. Role of Tyrosine Kinases in Differentiated Thyroid Cancer. (3/2/1999)	New
9223-99	Burch, Henry B., LTC MC. An Investigation of Oxidative Damage to Proteins in Thyroid Autoimmunity. (4/6/1999)	New
9224-99	Anderson, Jeffrey, DAC. Quantitative Examination of the Expression of Thyroid Hormone Responsive Mrna Species in Hyperthyroidism, Hypothyroidism, and the Polar T3 Syndrome. (4/6/1999)	New
Department of Medicine		
Cardiology Service		
00-1201	Taylor, Allen J., LTC MC. A Randomized Trial Comparing the Effects of Atorvastatin and Pravastatin on Carotid Intima-Media Thickness. (10/26/1999)	25
00-1202	Taylor, Allen J., LTC MC. SWITCH: Statins at WRAMC: Interventions for the Treatment of Cholesterol-An Observational Study of the Formulary Switch to HMG-coA Reductase Inhibitors Mandated by the Department of Defense Pharmacoeconomic Center. (11/30/1999)	26
01-12001	Gorman, Patrick, LTC MC. Acetylysteine for the Prevention of Contrast Associated Nephropathy in Diabetic Patients Undergoing Coronary Angiography. (1/23/2001)	New

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01-12003	Taylor, Allen J., LTC MC. ARBITER II: Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol - A Randomized, Placebo-controlled, Double-Blind. (7/31/2001)	New
1215	Taylor, Allen J., LTC MC. The Utility of Electron Beam Computed Tomography (EBCT) as a Screening Test for Coronary Artery Disease, and as an Intervention for Risk Factor Modification Among Over 40 Active Duty Personnel. (11/25/1997)	28
1216	Thomas, William J., MAJ MC. Coronary Stents and Abbreviated Ticlopidine. (12/16/1997)	29
1217	Taylor, Allen J., LTC MC. Use of Electron Beam Computed Tomography in the Preoperative Evaluation of Noncardiac Vascular Surgery Patients. (12/16/1997)	30
1218-98	Calagan, Jennifer L., LTC MC. Assessment of Clinical Outcome Using Prothrombin Time Patient Selft Testing (PST) to Monitor Long Term Antocoagulation Therapy. (6/16/1998)	31
1220-98	Thomas, William J., MAJ MC. Troponin I, Troponin T and T and CKMB for the Rapid Detection of Myocardial Infarction and Determination of 30-Day Prognosis. (8/4/1998)	33
1223-99	Taylor, Allen J., LTC MC. Multinational, Multi-Center, Double-Blind, Randomized, Active Controlled, Parallel Group Study Comparing the Efficacy and Safety of Long-Term Treatment with Valsartan, Captropril and Their Combination in High Risk Patients After Myocardial Infarction. (5/25/1999)	34
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00-1301	Burch, Henry B., LTC MC. The Effect of Retinols, Tamoxifen and Octreotide on Cellular Proliferation and Control of Thyroglobulin, TSH Receptor and, Sodium-Iodide Synporter mRNA Expression in Thyroid Cancer Tumor Cell Lines. (10/5/1999)	38
00-1302	Baquero, Jeannie A., CPT MC. The Effect of Omeprazole Therapy on Serum Calcitonin (CT). (2/1/2000)	39
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01-13001	Stocker, Derek J., CPT MC. A Comparison of the Effects of Rosiglitazone and Metformin on Markers of Inflammation and Carotid Plaque Burden in Patients with Type 2 Diabetes Mellitus. Cardiovascular Effects of Hypoglycemic Medications in Diabetes - CHD Study. (1/23/2001)	New
01-13002	Vigersky, Robert A., COL MC. Using Telemedicne and Wireless Technology to Improve Diabetic Outcomes in Poorly Controlled Patients. (3/20/2001)	New
01-13003	Vigersky, Robert A., COL MC. The Avandia Worldwide Awareness Registry (AWARe): Comparison of Avandia and Actos in "Real World" Medical Practice. (3/27/2001)	New
01-13004	Bernet, Victor J., LTC MC. Pilot Study: Recombinant TSH Stimulation of Radioactive Iodine Uptake in Hyperthyroidism. (5/15/2001)	New
01-13005	Langely, Roy W., MAJ MC. Determination of Thyroid Nodule Malignancy with 18F-FDG Coincidence Imaging and Tc-99m Depreotide Scintigraphy. (6/19/2001)	New
01-13005E	Langely, Roy W., MAJ MC. Thyroglobulin positive/scan negative thyroid cancer patients - the Walter Reed experience: a retrosp.. (10/2/2000)	Exempt
01-13007E	Lewi, Jack, CPT MC. A Retrospective Review of the Follow-up on Adrenal Incidentalomas at WRAMC. (1/8/2001)	Exempt
01-13008E	Mohan, Vineeth, CPT MC. A Cross-Sectional Examination of the Relationship Between Coronary Artery Calcium Scores and Serum TSH in Patients Undergoing Non-Contrast Electron Beam Computed Tomography (EBCT) at the WRAMC. (4/13/2001)	Exempt
1380-95	Francis, Gary L., COL MC. Papillary Thyroid Cancer (PTC/ret^TPC) Oncogene Activation in Neoplastic Thyroid Tissue Occurring After Exposure to a Nuclear Blast. (9/19/1995)	47
1386-96	Burch, Henry B., LTC MC. The Effect of Pretreatment with Antithyroid Drugs on the Acute Changes in Thyroid Hormone Levels Following Radioiodine Ablation for Graves' Disease: A Prospective Randomized Trial. (3/26/1996)	48
1392-98	Francis, Gary L., COL MC. Circulating Micro-Metastasis in Patients with Thyroid neoplasia. (10/28/1997)	49
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00-1402	Winters, George R. III, CPT MC. Is Schatzki's Ring Protective Against Acid Reflux?. (1/18/2000)	55
00-1403	Mulhall, Brian P., CPT MC. The Effect of Helicobacter pylori Eradication on the Severity of Gastro-esophageal Acid Reflux as Determined by 24-hours pH Measurement. (1/18/2000)	56
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00-1406	Cumings, Mark D., MAJ MC. Screening for Barrett's in Patients With and Without Heartburn. A Multi-Center Trial. (3/21/2000)	61
00-1407	Hwang, Inku, MAJ MC. Tele-Hepatitis Phase I: Vaalidation of desktop Video Teleconferencing (VTC) System at 384 kb ISDN for Evaluation of Patients with Hepatitis. (5/16/2000)	62
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01-14001	Polish, Roger D., CPT MC. Association of Helicobacter pylori Infection with Coronary Heart Disease Detected by Electron Beam CT. (1/9/2001)	New
01-14002	Baroni, Darren S., MAJ MC. An Efficacy and Safety Study of Intravenous Pantoprazole in the Prevention of Recurrent Peptic Ulcer Bleeding After Successful Hemostasis (Sponsored Stucy by Wyeth-Ayerst Research). (4/17/2001)	New
01-14003	Dunaway, Peter M., CPT MC. Effect of Complete Intraesophageal Acid Ablation Upon Cellular Markers of Proliferation, Differentiation, and Apoptosis in Long-Segment Barrett's Esophagus. (4/24/2001)	New

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01-14004	Holtzmuller, Kent, COL MC. The Timing of Liver Enzyme Elevation and Hepatitis C Seroconversion in a Cohort of United States Military Gulf War Veterans. (5/1/2001)	New
01-14004E	Dunaway, Peter M., CPT MC. The Significance of an Abnormal Number of Nonpropagated Waves on GERD, Esophageal Motility, and Dysphagia. (1/8/2001)	Exempt
01-14005	Holtzmuller, Kent, COL MC. Tele-Hepatitis Phase I: Validation of Desktop Video Teleconferencing for Evaluation of Patients with Hepatitis C. (5/29/2001)	New
01-14005E	Gorske, Andrew, CPT MC. The Correlation of Acid Reflux Symptoms with Objective Measures of Esophageal Reflux by Ambulatory pH Monitoring and Endoscopy: a Retrospective Analysis. (1/19/2001)	Exempt
01-14006	Holtzmuller, Kent, COL MC. B-Catenin Mutations and Nuclear Accumulation are Early Events in Hepatic Carcinogenesis: Role as a Marker to Determine Risk for Hepatocellular Carcinoma in Hepatitis C and Hepatitis B Patients. (6/12/2001)	New
1432	Cumings, Mark D., MAJ MC. Short Segment Barrett's Esophagus: Prevalence, Clinical Characteristics and Response to Long-Term Antisecretory Therapy. (11/29/1994)	64
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1456-99	Wong, Roy K.H., COL MC. Long-Term Prevention of Recurrent Peptic Ulcer Hemorrhage in Patients Infected with Helicobacter Pylori: A Multi-Center, NIH Funded, Prospective Randomized Double-Blind Study. (3/23/1999)	75
1457-99	Eastone, John, LCDR MC. Colorectal Neoplasia screening with Colonoscopy in Asymptomatic Women at Regional Navy/army medical centers: The CONCeRN Trial. (5/25/1999)	76
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00-1002	Helman, Donald, CPT MC. Myositis-Specific Antibodies in Subjects with Idiopathic interstital Lung Disease. (2/8/2000)	2
00-1003	Salerno, Stephen M., MAJ MC. Can Ambulatory Teaching Seminars Improve Amount and Quality of Feedback to Medical Students in the Outpatient Setting?. (2/22/2000)	3
01-10004E	Straight, Timothy M., CPT MC. Nosocomial Fever - A Pilot Study. (11/15/2000)	Exempt
01-10005E	Salerno, Stephen M., MAJ MC. Are Patients and Practice Patterns of Internists and Family Physicians Different in the Age of Managed Care. (2/12/2001)	Exempt
01-10007E	Jackson, Jeffrey L., LTC MC. Osteoporosis Risk and Management in a Primary Care Clinic. (4/20/2001)	Exempt
1044	O'Malley, Patrick, MAJ MC. Improving Teaching in the Ambulatory Setting: A Study Using Observed Teaching Sessions and Participant Evaluations. (8/2/1996)	4
1048	Kelly, William F., CPT MC. The Effect of Training and Experience on Making Do-Not-Resuscitate (DNR) Decisions. (3/11/1997)	5
1051	Shorr, Andrew F., MAJ MC. The Yield of Endobronchial Biopsy in the Diagnosis of Sarcoidosis. (4/24/1997)	6
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1054-98	Roy, Michael, MAJ MC. Retrospective Analysis of CCEP Phase II Results from the Walter Reed Gulf War Health Center, 1994-96. (5/6/1998)	8
1056-98	Dunaway, Peter M., CPT MC. Characterization of the Esophageal Striated Muscle in Patients with Achalasia: A Prospective Study. (6/16/1998)	9

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00-1504	Drabick, Joseph J., COL MC. CALGB 89803: A Phase III Intergroup Trial of Irinotecan (CPT-11) (NSC #6163480 Plus Flourouracil/Leukovorin (5-FU/LV) Versus Flourouracil/Leukovorin Alone After Curative Resection for Patients with Stage III Colon Cancer. (7/25/2000)	80
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00-1506	Flynn, Joseph M., CPT MC. CALGB 99208: Docetaxel and Estramustine Versus Mitoxantrone and Prednisone for Advanced, Hormone Refractory Prostate Cancer, Phase III. (9/19/2000)	82
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00-1603	Drabick, Joseph J., COL MC. A Multicenter Phase 2 Study of Oral N-Acetyl Dinaline (CI-994) in the Treatment of Patients with Chronic Lymphocytic Leukemia (Protocol 994-05). (12/14/1999)	86

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00-1606	Drabick, Joseph J., COL MC. A Phase II Evaluation of Rubitecan, A Novel Oral Topoisomerase I Inhibitor, in Newly Diagnosed, Recurrent and Refractory Multiple Myeloma. (2/15/2000)	88
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00-1609	Byrd, John C., MAJ MC. A Multicenter, Open Label Trial to Evaluate the Efficacy and Safety and IDEC-Y2B8 Immunotherapy of Relapsed or Refractory Low-Grade or Follicular Transformed B-Cell Non-Hodgkin's Lymphoma. (4/25/2000)	91
00-1610	Byrd, John C., MAJ MC. A Phase II, Open Label Study of HuM195 (Humanized Anti-CD33 Monoclonal Antibody) Administered to Patients with Acute Myelogenous Leukema..Failures (RF) of Control Arm of Study 195-301. (8/15/2000)	92
00-1611	Byrd, John C., MAJ MC. A Phase III, Randomized, Multicenter Study to Assess the Efficacy and Safety of HuM195 (Recombinant humanized Anti-CD33 Monoclonal Antibody) in Combination with Standarized...Chemotherapy Alone the Treatment of Patients with Refractory..Acute Myelogenous... (7/25/2000)	93
01-15005	Drabick, Joseph J., COL MC. CALGB 79804: Issues of Survivorship Among Breast Cancer Survivors. (2/27/2001)	New
01-15006	Drabick, Joseph J., COL MC. CALGB 89904: A Randomized Phase II Study of Gemcitabine/Cisplatin, Gemcitabine/Docetaxel, Gemcitabine/Irinotecan, or Fixed Dose Rate Infusion Gemcitabine in Patients with Metastatic Pancreatic Cancer. (3/20/2001)	New
01-15007	Flynn, Joseph M., CPT MC. CALGB 99903: A Phase II Study of Arsenic Trioxide (NSC #706363), IND # 57974) in Urothelial Cancer. (4/17/2001)	New
01-15008	Drabick, Joseph J., COL MC. CALGB 80001: Feasibility Study of Sentinel Lymph Node Staging for Colon Cancer. (6/26/2001)	New
01-15009	Drabick, Joseph J., COL MC. CALGB 49805: A Phase III Randomized Double Blind Study of Letrozole Versus Placebo in Women with Primary Breast Cancer Completing 5 or More Years of Adjuvant Taxmoxifen. (7/24/2001)	New
01-1501	Flynn, Joseph M., CPT MC. CALGB 99901: A Phase II Study of 9 Nitrocamptothecin (9-NC, IND # 60,162) for Hormone Refractory Prostate Cancer. (11/21/2000)	New
01-15010	Ketchum, Lloyd, CPT MC. CALGB 49801: Phase III Trial of Tamoxifen Alone Vs. Tamoxifen Plus Radiatin for Good Risk Duct Carcinoma In-Situ (DCIS) of the Female Breast. (8/31/2001)	New

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01-15012	Gorak, Edward J., MAJ MC. CALGB 509901: Phase II Study of Melanoma Vaccine (NSC #683472/675756, IND 6123) and Low-Dose, Subcutaneous Interkeukin-2 in Advanced Melanoma. (9/18/2001)	New
01-1502	Drabick, Joseph J., COL MC. CALGB 59906: A Phase II Study of Sequential Doxorubicin and Topotecan in Relapsed or Refractory Intermediated-or-High Grade Non-Hodgkin's Lymphoma. (11/21/2000)	New
01-1503	Drabick, Joseph J., COL MC. CALGB 59804: A Phase I/II Study of Gemcitabine/Vinorelbine/Liposomal Doxorubicin in Relapsed/Refractory Hodgkin's Disease. (11/30/2000)	New
01-1504	Drabick, Joseph J., COL MC. CALGB 59901: A Phase II Study of 506U78 in Patients with Previously Systemically Untreated Cutaneous T-Cell Lymphoma or With Refractory or Relapsed Non-Cutaneous Peripheral T-Cell Lymphoma. (12/12/2000)	New
01-16002	McGrail, Lisa H., CPT MC. Microarray Analysis of Breast Cancer: A Pilot Feasibility Study. (1/9/2001)	New
01-16003	Byrd, John C., MAJ MC. A Dose-Escalation/Phase II CRC Study of HMR 1275 (Flavopiridol) Administered as a 30 Minute Loading Dose Followed by a 4 Hour Infusin in Patients with Previously Treated B-Cell Chronic Lymphocytic Leukemia or Prolymphocytic Leukemia. (2/27/2001)	94
01-16004	Flynn, Joseph M., CPT MC. Expression of Human Papilloma Virus in Second Primary Malignancies Associated with Chronic Lymphocytic Leukemia. (3/13/2001)	New
01-16005	Drabick, Joseph J., COL MC. A Phase II, Open-Label, Randomized, Multicenter Trial to Evaluate the Preliminary Efficacy and Safety of Hu1D10 in Patients with Relapsed or Refractory Grades I, II, or III B-Cell Non-Hodgkin's Lymphoma (incliding follicular, small lymphocytic..... (6/19/2001)	New
01-16006	Willis, Carl R., MAJ MC. A Multicenter, Phase III Randomized Trial for Stage IIIB or IV NSCLC Comparing Weekly Taxol (Paclitaxel) and Carboplatin (Paraplatin) Regimen Versus Standard Taxol and Carboplatin Administered Every Three Weeks, Followed by Weekly Taxol. (6/26/2001)	New
01-16007	Willis, Carl R., MAJ MC. An Open-Label, Multicenter, Randomized, Phase III Study Comparing Oral Topotecan/Cisplatin Versus Etoposide/Cisplatin as Treatment for Chemotherapy-Naïve Patients with Extensive Disease-Small Cell Lung Cancer. (7/31/2001)	New
01-1601	Drabick, Joseph J., COL MC. Epstein-Barr Virus as an Etiologic Agent for Hodgkin's Disease: A Nested Case-Control Study. (12/5/2000)	New

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1501-98	Drabick, Joseph J., COL MC. CALGB 9741: A Randomized Phase III Trial of Sequential Chemotherapy Using Doxorubicin, Placlitaxel, and Cyclophosphamide or Concurrent Doxorubicin and Cyclophosphamide Followed by Paclitaxel at 14 or 21 Day Intervals in Women with Node Positive Stage II. (12/16/1997)	96
1502-98	Drabick, Joseph J., COL MC. CALGB 9762: Clinical Pharmacology of Paclitaxel in Relation to Patient Age. (1/27/1998)	97
1504-98	Byrd, John C., MAJ MC. CALGB 9763: Prospective Evaluation of Body Surface Area (BSA) as a Determinant of Paclitaxel Pharmacokinetics/Pharmacodynamics in Women with Solid Tumors. (2/24/1998)	98
1505-98	Drabick, Joseph J., COL MC. CALGB 9781: A Phase III Trial Comparing Trimodality Therapy (Cisplatin, 5-FU, Radiotheapy and Surgery) to Surgery Alone for Esophageal Cancer. (2/24/1998)	99
1506-98	Drabick, Joseph J., COL MC. CALGB 9720: Phase III Study of MDR Modulation with PSC-833 Followed by Immunotherapy with rIL-2 Vs. No Further Therapy in Previously Untreated Patients with AML > 60 Years. (3/24/1998)	100
1507-98	Drabick, Joseph J., COL MC. CALGB 9730: Single-Agent Versus Combination Chemotherapy in Advanced NSCLC: A CALGB Randomized Trial of Efficacy, Quality of Life, and Cost-Effectiveness. (3/24/1998)	101
1509	Drabick, Joseph J., COL MC. CALGB 9011 A Study of Fludarabine Vs. Chlorambucil Vs. Both Drugs for Chronic Lymphocytic Leukemia. (11/27/1990)	102
1509-98	Drabick, Joseph J., COL MC. CALGB 9793: A Phase III Trial of CHOP Versus CHOP and Chimeric Anti-CD20 Monoclonal Antibody (IDEC-C2B8) in Older Patients with Diffuse Mixed, Diffuse Large Cell and Immunoblastic Large Cell History Non-Hodgkin's Lymphoma. (3/31/1998)	103
1510-98	Drabick, Joseph J., COL MC. CALGB 9712: A Randomized Phase II Study of Concurrent Fludarabine + Chimeric Anti-CD20 Monoclonal Antibody IDEC-C2B8 (Rituximab) [NSC #687451] Induction Followed by Rituximab Consolidation Versus Fludarabine Induction Followed by Rituximab Consolidation. (4/28/1998)	104
1511-98	Drabick, Joseph J., COL MC. CALGB 9795: A Phase III Prospective Randomized Study of Adjuvant Chemotherapy with Vinorelbine and Cisplatin in Completely Resected Non-Small Cell Lung Cancer with Companion Tumor Marker Evaluation. (7/21/1998)	105
1512-98	Drabick, Joseph J., COL MC. CALGB 9732: A Randomized Phase III Study Comparing Etoposide and Cisplatin with Etoposide, Cisplatin and Paclitaxel in Patients with Extensive Small Cell Lung Cancer Includes update #1-(editorial changes). (7/28/1998)	106

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01-24005	Andersen, Romney C., MAJ MC. Prospective Cohort Analysis of Hip Arthroscopy in Young Active Adults with Two Years Follow-up. (2/6/2001)	New
01-24006	Polly, David W., COL MC. Adolescent Idiopathic Scoliosis Single Overhang Curve. (4/10/2001)	New
01-24007	Polly, David W., COL MC. A Multi-Center Study to Evaluate the Safety and Efficacy of DePuy AcroMed Titanium Surigcal Mesh and MOSS-Miami Spinal System Pedicle Screws. (4/24/2001)	New
01-24008	Taylor, Kenneth F., MAJ MC. Functional and Clinical Outcome Following Arthroscopically Assisted Anterior and Posterior Cruciate Ligament Reconstruction in a High-Demand Patient Population. (6/26/2001)	New
01-24009	Lehman, Ronald A., CPT MC. Effects of Alendronate Sodium (FOSAMAX) on Spinal Fusion in the Rabbit Model. (8/14/2001)	New
01-2401	Wallace, Roxanne, CPT MC. Quantitative Analysis of the Neovascularization of Distraction Osteogenesis from the End of Distraction to Bone Maturity Correlated with Bone Histology, Mechanical Properiteis, and Radiography. (10/3/2000)	New
01-24010	Lehman, Ronald A., CPT MC. Biomechanics of Anatomic Versus Straight Forward Technique of Thoracic Pedicle Screw Placement: A Cadaveric Study. (9/14/2001)	New

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01-24013E	Polly, David W., COL MC. Development of a Cosmesis Evaluation Tool (Questionnaire) for Idiopathic Scoliosis. (6/28/2001)	Exempt
01-24015E	Taylor, Kenneth F., MAJ MC. Congenital Hemivertebrae and Occult Intraspinal Anomolies:The Role of Routine Magnetic Resonance Imaging. (8/2/2001)	Exempt
01-24016E	Polly, David W., COL MC. Validation of Software Measurement Tool in Adolescent Scoliosis Patients. (9/28/2001)	Exempt
01-2402	Doukas, William C., LTC MC. Preoperative and Postoperative EMG Analysis of Rotator Cuff Tears: Clinical Outcome Correlation with MRI Findings, Size and Reparability. (11/30/2000)	New
2402	McHale, Kathleen A., COL MC. The Effect of Rigid Orthoses on Weight-Bearing Radiographs of the Adult Foot - A Cadaver Study. (4/8/1997)	257
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2496	Polly, David W., COL MC. PRO OSTEON Implant 500 Coralline Hydroxyapatite Bone Void Filler for Use in Filling the Iliac Crest Bone Donor Site. (10/29/1996)	262
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01-96007E	Kelly, Sean, LCDR MC. Assessment Tools Used for Resident Evaluations by Program Directors in Physical Medicine and Rehabilitation. (5/15/2001)	Exempt
01-96009E	Hommer, Dean, CPT (P) MC. The Utility of an Objective Structured Clinical Examination (OSCE) as a Component of Competency As. (9/28/2001)	Exempt
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01-48002	Myers, Cris P., COL MC. Oxidative and Nitrosative Stress in Carcinogenesis of CTCL (MF). (4/3/2001)	New
01-48003	Marrogi, Aizen J., LTC MC. Oxidative and Nitrosative Stress in Carcinogenesis of Colitis-Associated Malignancies. (5/8/2001)	New
01-48004	Turcan, William L., DoD. Extending the Expiration Date of Thawed Fresh Frozen Plasma and Plasma Frozen Within 24 Hours of Collection From 24 Hours to 48 Hours. (6/12/2001)	New
4833-98	Moul, Judd W., COL MC. Determination of Reference Values for Percent Free PSA in Patients for Prostatic Evaluation. (9/1/1998)	477
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01-64007E	Rick, James R., MAJ MC. The Role of Helicobacter pylori in Peptic Ulcer Disease Among the Pediatric Population Eligible for. (12/14/2000)	Exempt
01-64008E	Yu, Clifton E., LTC MC. A Survey of Daycare Exclusion Practices for Sick Children in the Greater Washington D.C. Area. (2/16/2001)	Exempt
01-64009E	Powers, Patricia A., COL MC. The Availability of In School Resources for Children with Diabetes while at School. (9/5/2001)	Exempt
01-65001	Francis, Gary L., COL MC. An Archival Fixed-Tissue Thyroid Tissue Bank. (4/3/2001)	New
01-65001a	Powers, Patricia A., COL MC. The Role OF Caveolin-1 in Thyroid Carcinoma. (4/10/2001)	New
01-65001b	Bauer, Andrew J., MAJ MC. Preclinical Pilot Study to Determine if the Novel Tumor-Activated Fluoropyrimidine Carbamate Capecitabine (Xeloda, Hoffman-Laroche, Inc.) could be used to Treat Thyroid Carcinoma: Are cytidine deaminase, thymidine phosphorylase, dihydropyrimidine dehydroge.... (9/14/2001)	New
01-65002	Rick, James R., MAJ MC. In situ Expression of cagA in H. pylori Infectd Children: A Case Series with Endoscopic and Histologic Correlation. (7/10/2001)	New
01-65003	Patterson, Harlan S., COL MC. Open Label Administriation of Human Botulism Immune Globulin. (7/24/2001)	New
01-65Ad-Ap	Bauer, Andrew J., MAJ MC. Resistance and Hypersensitivity to Thyroid Hormone. (11/30/2000)	Admin
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01-66001a	Edwards, E. Glenn, COL MC. POG 9904: ALinC 17 Treatment for Patients with Low Risk Acute Lymphoblastic Leukemia: A Pediatric Oncology Group Phase III Study. (4/17/2001)	New
01-66001b	Edwards, E. Glenn, COL MC. POG 9905: ALinC 17 Protocol for Patients with Standard Risk Acute Lymphoblastic Leukemia (ALL) - A Pediatric Oncology Group Phase III Study. (2/27/2001)	New

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01-66002	Edwards, E. Glenn, COL MC. ANBL00B1: Neuroblastoma Biology Studies. (4/24/2001)	New
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6181	Edwards, E. Glenn, COL MC. POG 8625/8626: Combined Therapy and Restaging in the Treatment of Stages I, IIA, IIIA1 Hodgkin's Disease in Pediatric Patients, A Phase II Study. (6/24/1986)	459
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6217	Edwards, E. Glenn, COL MC. POG 8725: Randomized Study of Intensive Chemotherapy (MOPP/ABVD Plus/Minus Low Dose Total Nodal Radiation Therapy in the Treatment of Stages IIB, IIIA2, IIIB, IV Hodgkin's Disease in Pediataric Patients, Phase III. (5/31/1988)	461
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01-36001	Rutledge, Matthew R., MAJ MS. Perceptions of Pain Control: Oncology Patients and Their Physicians. (5/29/2001)	New
3612-98	Murphy, Timothy, CPT MC. A Prospective, Randomized, Double-Blind, Placebo-Controlled Trial to Determine the Efficacy of Amiloride in Preventing Amphotericin-B Induced Hypokalemia in Neutropenic Patients. (4/28/1998)	381
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01-72006E	Black, Nancy, MAJ MC. Survey of Attitudes Towards Alternative and Complementary Medicine. (11/16/2000)	Exempt
01-7201	Black, Nancy, MAJ MC. Development of a Child and Adoleslcent Psychiatry Database. (10/17/2000)	New
7279-98	Malone, Ricky D., LTC MC. The Frequency and Nature of Forensic Issues in an Inpatient Adult General Psychiatric Population. (3/25/1998)	513
7280-98	Ritchie, Cameron E., LTC MC. Suicidal Behavior in Active Duty Patients. (4/10/1998)	514
7284-99	Black, Nancy, MAJ MC. Comparison of Parental Therapeutic Alliances Before and After Initial Psychiatric Interviews: Telepsychiatry Versus In-Person Appointments. (11/17/1998)	515
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00-7301	Kelly, Mark, Ph.D. DAC. Computerized Neuropsychological Assessment of Army Aviators (CNAAA): Development of a Digitized Database and Preliminary Investigator of the Relationship of ANAM, CogScreen and MicroCog to Aviator Trainee Checkflight Performances. (8/1/2000)	518
01-73002	James, Larry C., LTC MC. CD-ROM Technology to Increase Appropriate Self-Care and Preventive Behaviors Among Enlisted Women. (6/5/2001)	New
01-73002E	McConnell, Jill, PhD CIV. Does Depression Affect Performance on the Portland Digit Recognition Test?. (8/2/2001)	Exempt
01-7301	Baggett, Mark R., MAJ MS. Computer Automated Neuropsychological Assessment of U.S. Army Aviators. (11/30/2000)	New
7302	Jones, Alvin, Ph.D. DAC. Analysis of Component Neurocognitive Processes for the Trial Making Test: An Examination of Age Related Changes. (7/8/1997)	520
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01-47003	Brazaitis, Michael P., COL MC. Field Trial of Mobile Digital Telemammography - Phase I (Installatin and Testing). (5/22/2001)	New
01-4701	Feuerstein, Irwin M., M.D. DAC. A Prospective Study of Outcomes of Patients Examined with Electron Beam Computed Tomography of the Coronary Arteries. (11/21/2000)	New
4705	Jabbari, Bahman, COL MC. Proton Magnetic Resonance Spectroscopic Imaging in Patients with Partial Epilepsy. (4/25/1995)	446
4709	Statler, John D., MAJ MC. Utility of Electron Beam Computed Tomography in Pediatric Imaging. (10/14/1997)	447
4710-99	Feuerstein, Irwin M., M.D. DAC. Comparison of Electron Beam Computed Tomographic Virtual Colonoscopy (EBCT-VC) with Visual Colonoscopy, Using Each Patients as Their Own Control. (3/23/1999)	448
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00-4501	Stack, Aaron L., MAJ MC. Feasibility, Accuracy and Efficiency of an Internet Based Tele-Nuclear Consultation System for the Military. Phase I: Phantom Stuides. (10/12/1999)	440
00-4502	Allen, Thomas, LTC MC. Double-Blind Placebo-Controlled Study of Samarium Sm-153 Lexidronam (Quadramet) for the Treatment of Asymptomatic Skeletal Metastases in Patients with Hormone-Refractory Prostate Carcinoma. (9/19/2000)	441
01-45000E	Quang, Eiping, Ph.D.. Measurement of I-131 Thyroid Uptake Using a Gamma Camera in Comparison with a Thyroid Uptake Probe. (12/6/2000)	Exempt
01-45002	Montilla-Soler, Jaime, CPT MC. Preoperative Evaluation of Breast Carcinoma Utilizing Tc99m-Depreotide. (5/15/2001)	New
01-45003	Bridwell, Robert S., MAJ MC. An Open-Label, Multicenter, Phase 3 Trial Evaluating Ventricular Function as Assessed by Lef-Ventricular Ejection Fraction and Wall Motion using echnetium-99m Tetrofosfmin Gated SPECT Imaging. (6/19/2001)	New
01-4501	Bridwell, Robert S., MAJ MC. Intraoperative Staging of Lung Cancer Using the Gamma Probe and Tc-99m Depreotide. (12/12/2000)	New
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4601	Warlick, William B., MAJ MC. RTOG 94-08: A Phase III Trial of the Study of Endocrine-Therapy Used as a Cytoreductive and Cytostatic Agent Prior to Radiation Therapy in Good Prognosis Locally Confined Adenocarcinoma of the Prostate. (5/23/1995)	444
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01-2001A	Mongan, Paul, LTC MC. Comparison of Two Plasminogen Activators in Reducing Bleomycin Induced Pulmonary Fibrosis in the Rat. (10/3/2000)	New
01-31000E	Cohen, Steven P., LTC MC. Effects of Discogenic Pain and Radiculopathy on the Specificity of Lumbar Medial Branch Blocks. (9/28/2001)	Exempt
01-31001E	Cohen, Steven P., LTC MC. Effects of Needle Insertion Site on Discography Results. (9/28/2001)	Exempt
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01-2501	Cord, Mary T., M.A. DAC. Performance of Directional Microphone Hearing Aids in Everyday Listening Situations. (10/3/2000)	New
01-2502	Walden, Brian E., Ph.D. DAC. Perferformance of Custom-Fit Versus Fixed Format hearing Aids for Precipitously-Sloping High-Frequency Hearing Loss. (11/14/2000)	New
01-2565a	Summers, Walter Van, Ph.D. DAC. Dead Regions in the Cochlea and Their Influence on Speech Processing. (11/7/2000)	New
01-2570a	Leek, Marjorie R., PhD DAC. Spread of Masking by Harmonic Complexes in Normal-Hearing and Hearing-Impaired Listeners. (6/12/2001)	New
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01-30001	Popa, Christian, MAJ MC. Remote Consultation on the Critically Ill Patient Via Telecommunication. (6/14/2001)	New
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01-20004E	Carmody, Brennan, MAJ MC. The Learning Curve of Transrectal Ultrasound. (4/4/2001)	Exempt
01-20005	Anderson, Jimie, CPT MC. Comparison of Doppler Flow Characteristics of the Superior Mesenteric Artery to Invasive Pulmonary Artery Catheterizatin in Critically Ill Patients. (5/22/2001)	New
01-20006	Shriver, Craig D., LTC MC. Tissue and Blood Library Establishment for Molecular, Biochemical and Histoogic Study of Breast Disease. (5/22/2001)	New
01-20007	Shriver, Craig D., LTC MC. Creation of a Blood Library for the Analysis of Blood for Molecular Changes Associated with Breast Disease and Breast Cancer Development. (5/22/2001)	New
01-2001	Shriver, Craig D., LTC MC. Creation of a Database of Patients at a High Risk for Breast Cancer. (11/30/2000)	New
01-2002	Peoples, George E., LTC MC. A Prospective, Randomized, Double Blind, Multicenter Trial Assessing the Safety and Efficacy of Sequential (Intravenous/Oral) BAY 12-88093 (Moxifloxacin) 400mg Every 24 Hours Compared to Intravenous Poperacillin/Tazobactam 3.375 grams Every 6 Hours Follo. (12/12/2000)	New
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01-2335-99b	Bower, Kraig, S., LTC MC. Prospective Evaluation of Keratorefractive Surgery in Army Aviator Trainee. (9/25/2001)	New
01-2335-99c	Bower, Kraig, S., LTC MC. Operational Assessment of Refractive Surgery for Rated Army Aviators: A Prospective Evaluation. (9/25/2001)	New
2328	Ward, Thomas P., MAJ MC. The Effect of Differing Enucleation Techniques on Cure Rate and Survival Time of Patients with Uveal Malignant Melanoma: A Comparison of Standard Enucleation, "No-Touch" Enucleation, and Enucleation with Stabilization of Intraocular Pressure. (3/5/1996)	247
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01-32003	Brietzke, Scott E., CPT MC. Palatal Sclerotherapy with Sotradecol as a Treatment for Obstructive Sleep Apnea Syndrome. (2/27/2001)	New
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01-3201	McClellan, James S. Jr., CPT MC. Endoscopic Transection of the Corrugator and Procerus Muscles Through an Open Rhinoplasty Approach. (11/14/2000)	New
01-3202	Battiata, Andrew, CPT MC. Does Oral Steroid Therapy After Tonsillectomy Deceraswe Postoperative Pain and Morbidity? A Prospective, Double Blinded, Placebo Controlled Analysis. (11/30/2000)	New
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2127	Gillespie, David L., LTC MC. A Phase III, Controlled, Multi-Center, Randomized, Parallel-Group, Single-Blind Study to Compare the Safety and Hemostatic Efficcy of the Fibrin Sealant, Beriplast P, with Standard Care of Thrombin-Soaked Gelfoam in the Treatment of Bleeding Anastomosis. (11/25/1997)	239
2130-99	Gillespie, David L., LTC MC. Dose Protease Gene Expression Vary by Location in the Lower Extremity in Patients with Primary Varicose Veins or Chronic Venous Insufficiency as Compared to Controls?. (2/2/1999)	241

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01-28003	McLeod, David G., COL MC. AMS002.2: Evaluation of the Safety and Tolerability of Transurethral Dehydrated Alcohol Injection for the Treatment of Benign Prostatic Hyperplasia. (5/15/2001)	New
01-28004	Paquette, Edmond, MAJ MC. An Exploratory Comparison Between Lemonade and Potassium Citrate: The Impact on Urine pH and 24 Hour Urine Parameters. (6/26/2001)	New
01-28005	McLeod, David G., COL MC. An Open-Label, Multi-Center, Ascending, Single Dose Study Investigating the Pharmacokinetics, Pharmacodynamics and Safety of FE200486 in Prostate Cancer Patients. (8/21/2001)	New
01-28006	McLeod, David G., COL MC. An Open-Label, Multi-Center, Extension, Single Dose Study Investigating the Long-Term Safety and Tolerability of Repeat Doses of FE200486 in Prostate Cancer Patients. (8/21/2001)	New
01-28006E	Brassell, Stephen A., CPT MC. Clinical Outcomes in Stage A Prostate Cancer. (12/5/2000)	Exempt
01-28007E	Taylor, John MC, USN. Analysis of Prostate Cancer Detected With Increasing Number of Biopsy Cores Taken: Are These Tumors Clinically Significant. (4/4/2001)	Exempt
01-2801	McLeod, David G., COL MC. A Phase II, Long-Term, Open-Label Extension Study of Oral CEP-701 in Patients Previously Receivnig CEP-701 for Treatment of Prostate Cancer. (11/21/2000)	297
01-2857-98a	Moul, Judd W., COL MC. Outcome Comparison of Radical Prostaectomy Pathologic Specimens. (5/1/2001)	New

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01-2857-98c	Moul, Judd W., COL MC. Development of Internet-Accessible Prediction Models for Prostate Cancer Diagnosis, Treatment and Follow-up. (8/7/2001)	New
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2801	McLeod, David G., COL MC. Establishment of a Serum Bank for the Future Detection of New Prostate Cancer Markers in Serum of Patients with Prostate Cancer, Benign Prostate Conditions, and no Prostate Disease. (12/6/1994)	298
2802	Moul, Judd W., COL MC. Center for Prostate Disease Research Prostate Cancer Radical Prostatectomy Follow-up Questionnaire. (12/13/1994)	299
2804	Schenkman, Noah S., LTC MC. Medical Therapy in Benign Prostatic Hyperplasia: Full-Scale Trial. (1/31/1995)	300
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2837	McLeod, David G., COL MC. NPCP 2200 A Comparison of Leuprolide with Leuprolide and Flutamide in Previously Untreated Patients with Clinical Stage D2 Cancer of the Prostate. (2/26/1985)	310
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2854-98	McLeod, David G., COL MC. ECOG EST 3886 Randomized Phase III Evaluation of Hormonal Therapy Vs. Observation in Patients with Stage D1 Adenocarcinoma of the Prostate Following Pelvic Lymphadenectomy and Radical Prostatectomy. (2/5/1998)	318
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2858-98	McLeod, David G., COL MC. An Ultrasound Based System for Examinatio and Diagnosis of Prostate and Urinary Conditions - A Phase I Clinical Study. (5/26/1998)	321
2859-98	McLeod, David G., COL MC. SWOG 8894 A Comparison of Bilateral Orchiectomy with or without Flutamide for the Treatment of Patients with Histologically Confirmed Stage D2 Prostate Cancer. (2/5/1998)	322
2861-98	McLeod, David G., COL MC. ECOG P-Z887 A Phase I Study of Intravesical Tumor Necrosis Factor in the Treatment of Superficial Bladder Cancer. (2/5/1998)	323
2864-98	Moul, Judd W., COL MC. ECOG EST 9887 A Phase III Trial of Treatment of Pathologic Stage C Carcinoma of the Prostate with Adjuvant Radiotherapy. (2/5/1998)	324
2865-98	Zorn, Burkhardt H., LTC MC. Evaluation of Agents that Work Through the Cyclic GMP System on Prostatic Smooth Muscle Function. (6/16/1998)	325
2867-98	McLeod, David G., COL MC. Advanced Computer Algorithms for Assessing Prognostic and Treatment Variables in Prostate Cancer. (6/22/1998)	326
2868	McLeod, David G., COL MC. Randomized Prospective Study Comparing Radical Prostatectomy Alone Versus Radical Prostatectomy Preceded by Androgen Blockade in Clinical B2 (T2bNxMo) Prostate Cancer. (9/24/1991)	327
2871-98	McLeod, David G., COL MC. Creation of a Tissue Library for the Molecular Biologic Study of Patients with Prostate Cancer. (7/21/1998)	328
2873-98	Dean, Robert C., MAJ MC. Macroscopic and Microscopic Anatomy of the Arterial Supply to the Human Vas Deferens. (8/11/1998)	333
2877-98	Dean, Robert C., MAJ MC. Study of the Safety and Effectiveness of the Mentor Saline-Filled Testicular Prosthesis. (9/1/1998)	334
2879-99	McLeod, David G., COL MC. A Randomized Double-Blind Comparative Trial of Bicalutamide (CASODEXTM) 150mg Montherapy Versus Placebo in Patients with a Rising PSA after Radical Prostatectomy for Prostate Cancer. (10/20/1998)	335
2881-99	Moul, Judd W., COL MC. Retrospective Study of the CPDR Prostate Cancer Database to Perform Statistical Modeling Using Pre-Treatment Prognostic Variables in Predicting Disease Progress After Radiotherapy for Clinically Localized Prostate Cancer. (10/29/1998)	336
2883-99	Siegel, Timothy, MAJ MC. Cyclosporine Treatment and the Effect on Post Vasovasostomy Semen Parameters in the Lewis Rat. (11/3/1998)	337

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2886-99	Moul, Judd W., COL MC. Prostate Cancer: A Patient Education Intervention. (5/18/1999)	339
2887-99	Zorn, Burkhardt H., LTC MC. ALZA Overactive Bladder Registry Design Document. (6/8/1999)	340
2888-99	McLeod, David G., COL MC. An Open-Label, Randomized, Parallel Group Study Comparing the Perioperative Administration of Procrit (Epoetin Alfa) Plus Iron Versus Iron Alone in Patients Undergoing Radical Retropubic Prostatectomy for the Treatment of Prostate Cancer. (6/22/1999)	341
2889-99	Moul, Judd W., COL MC. Radical Prostatectomy of Prostate Cancer Patient and Circulating Cancer Cell Test (CCCT). (7/27/1999)	342
2890-99	Dean, Robert C., MAJ MC. Creation of A Prospective and Retrospective Database of Patients Evaluated and Treated for Urinary Incontinence. (8/24/1999)	343
2891-99	Schenkman, Noah S., LTC MC. Ureteral Stenting after Distal Ureteroscopy and Stone Retrieval: A Prospective Randomized Study. (8/24/1999)	344
2892-99	Moul, Judd W., COL MC. #VCL 1102-202: Phase II Study Evaluating the Safety and Efficacy of Neoadjuvant Leuvectin Immunotherapy for the Treatment of Prostate Cancer (and Amendment 1). (8/31/1999)	345
2893-99	Moul, Judd W., COL MC. #VCL 1102-203: Phase II Study Evaluating the Safety and Efficacy of Leuvectin Immunotherapy for the Treatment of Locally Recurrent Prostate Cancer Following Radiation Therapy (and Amendment 1). (8/31/1999)	347
2894-99	Schenkman, Noah S., LTC MC. Database of Urinary Stone Patients. (9/7/1999)	349
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01-89004E	Engel, Charles C., LTC MC. Are Lower Levels of Acculturation Associated with Psychological Distress Among Asian Americans Seeking Primary Care. (1/19/2001)	Exempt
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8900-99	Engel, Charles C., LTC MC. Antibiotic Treatment of Gulf War Veterans' Illnessess. (3/23/1999)	557
8901-99	Engel, Charles C., LTC MC. A Randomized, Multi-Center, Controlled Trial of Multi-Modal Therapy in Veterans with Gulf War Illnesses. (3/23/1999)	558
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01-83001	Bell, Michael, MAJ MC. Factors Related to Infant Feeding Choics. (2/13/2001)	New
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00-8101	Dunn, Sheryl L., MAJ MS. A Prospective Study to Evaluate the Testing of Individual Donor Units from Voluntary Blood Donations for the Presence of HIV-1/HCV RNA. (6/20/2000)	536
8102-98	Sisk, Rebecca J., MAJ AN. Factors Related to Medical Readiness in U.S. Military Reservists. (3/10/1998)	538
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8500-99	Spain, John, MAJ MS. An Analysis and Comparison of Pharmacy Service Provider Selection Among Military Beneficiaries for Maintenance Medication. (1/5/1999)	539
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00-8503	Schissel, Daniel, MAJ MC. Genetic Investigations of Psueofolliculitis Barbae, PFB, in United States Armed Forces. (8/15/2000)	543
00-8504	Hess, Todd D., LTC MC. Racial Differences in Central Corneal Thickness Between Caucasian and African-American Subjects. (9/19/2000)	544
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8502-99	Etzenback, John, MAJ MC. Highly Toxic Clone of Actinobacillus actinomycetemcomitans and Polymorphism in Interleukin-1 and Tumor Necrosis Factor-a Gene. (12/15/1998)	545
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8700	Schenkman, Noah S., LTC MC. Evaluation of Telesurgical/Robotic Presence. (11/25/1997)	548
8701-98	Bower, Kraig, S., LTC MC. Clinical Evaluation of a High Resolution Digitized Stero Video Slit Lamp for Use in Teleophthalmology. (7/14/1998)	549
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Moores L : Pediatric Neurotrauma. 7th Annual BAMC Trauma Symposium, San Antonio, TX, August 2001.	Presentation
Moores L : Teaching technical skills. NCCc Residency Lecture Series, Washington DC, July 2001.	Presentation
Moores L : Real life experience - Guatemala, putting it all together. Humanitarian Assistance Course for Internist, Bethesda, MD, March 2001.	Presentation
Moores L : Tumors of the pediatric central nervous system. Philadelphia, Lippincott, pp 351-360, 2001.	Publication
Moores L, Ecklund J : Penetrating Injuries of the Spine. In: Textbook of Neurological Surgery, 2001.	Publication
Moquin R : The leading edge of neurosurgical telemedicine - The military experience. Congress of Neurological Surgeons Annual Meeting, San Diego CA, September 2001.	Presentation
Moquin R : Transformental lumbar interbody fusion. Congress of Neurological Surgeons Annual Meeting, San Diego CA, September 2001.	Presentation
Moquin R : Expanding the differential diagnosis of the acute scrotum: Ventriculoperitoneal shunt herniation. Urology, 58(2): 281, 2001.	Publication

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Moquin R, Ecklund J : The 13th Annual International Spinal Workshop. Uniformed Services University of the Health Sciences, Bethesda, MD, June 2001.	Presentation
Moquin R, Ecklund J : Spinal tuberculosis. In: Textbook of Neurological Surgery, 2001.	Publication
Moquin R, Rolli M, Rosner M : Titanium mesh cages with anterior locking plate reconstruction of spinal deformities using fused deposition model. Congress of Neurological Surgeons Annual meeting, San Diego CA, September 2001.	Presentation
Moquin RR, Polly DW , Klemme WR, Monacci W : Thoracic hemivertebra excision and scoliosis deformity correction in adults via a posterior only approach. Congress of Neruological Surgeons Annual Meeting, San Diego CA, September 2001.	Presentation
Mulligan L : Pediatric tumors of the cental nervous system. New York: Thieme, 2001.	Publication
Mulligan L : Multiple subpial transections. The Yale Experience, Epilepsia, 42:226-229, 2001.	Publication
Naff J : Intraventricular thrombolysis speeds blood clot resolution. Congress of Neurological Surgeons,51st Annual Meeting, San Diego, CA, September-October 2001.	Presentation
Naff J, Rolli M, Armonda R : Three-dimensional replication of cerebral aneurysms using fused deposition modeling. The Fifth Annual Join Meeting of the American Association of Neurologic Surgeons/Congress of Neruologic Surgeons and the American Society of International and Therapeutic Neuroradiology, Hawaii, February 2001.	Presentation
Naff N : Intraventricular thrombolysis for the treatment of adult intraventricular hemorrhage. Grand Rounds, John Hopkins University School of Medicine, Division of Neurosurgery, March 2001.	Presentation
Naff N : Evaluation and management of traumatic peripheral nerve injuries. Grand Rounds, Department of Emergency Medicine, Sinai Hospital, Baltimore, MD, February 2001.	Presentation
Naff N : Evaluation and management of brachial plexus and peripheral nerve injuries. Grand Rounds, Department of Surgery, Sinai Hospital, Baltimore, MD, February 2001.	Presentation
Naff N, Ecklund J : The history of peripheral nerve technique. Neurosurgical Clinics of North America, 12(1):197-209, January 2001.	Publication
Rosner M, Ecklund J : Portable detection of brain hemorrhages. The 30th Society of Critical Care Medicine Educational and Scientific Symposium, San Francisco, CA, February 2001.	Presentation
Rosner M, Ecklund J : Intradural extrameddullary and intramedullary tumors. Chapter, Vaccaro, Master Cases in Spine Surgery, 2001.	Publication
Rosner M, Ecklund J, Ling G : Radio frequency triage system (RAFTS): A hand held tool for detecting intracranial hemorrhage and pnuemothorax. American Assoication of Neurological Surgeons 2001 Annual Meeting, Toronto, Ontario, April 2001.	Presentation
Rosner M, Mulligan L : Cervical sympathetic schwannoma: Case report. Congress of Neurological Surgeons 2001 Annual Meeting, San Diego, CA, September 2001.	Presentation
Rosner M, Rolli M, Moquin R : Single and multi-level corpectomy with fusion using titanium mesh cages and plates. Congress of Neurological Surgeons 2001 Annual Meeting, San Diego, CA, September 2001.	Presentation

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CITATION	TYPE
Ophthalmology Service	
Bauer R, Bower KS, O'Kane B, Stefanik R, Stevens R, Subramanian P, Rabin J : Physical limits on visual resolution through image intensifiers before and after PRK. Association for Research in Vision and Ophthalmology Annual Meeting, Ft. Lauderdale, Florida, May 2001.	Presentation
Bauer, R.M., Bower, K.S., O'Kane, B., Subramanian, P.S., Stefanik, R., Stevens, J., Rabin, J. : Physical limits on visual resolution through image intensifiers before and after PRK. Investigative Opthalmology and Visual Science, 42(4):S608, 2001.	Abstract
Bower KS : Pre-operative evaluation and post-operative management of refractive surgery patients. National Capital Region Army Optometry Society, Washington, DC, June 2001.	Presentation
Bower KS : Blunt anterior segment trauma. National Capital Region Federal Optometry Society, Washington, DC, September 2001.	Presentation
Bower KS : Corneal laceration repair. The Uniformed Services School of the Health Sciences Tri-Service Ocular Trauma Course, Bethesda, MD, May 2001.	Presentation
Eiseman AS : Evaluation and treatment of lid lesions. Washington Oculoplastics Lecture Series, Washington, DC, February 2001.	Presentation
Eiseman AS : Surgical anatomy of the eye, adnexa, and orbit. Uniformed Services University of the Health Sciences Head and Neck Dissection Course, Bethesda, MD, January 2001.	Presentation
Eiseman AS, Morton AD, Fante R, Kikkawa D, Mannor G : Endoscopic forehead elevation symposium. American Society of Ophthalmic Plastic and Reconstructive Surgery Meeting, Dallas, TX, October 2000.	Presentation
Fechter, H. : Refractive surgery for war fighters. Command and General Staff College, Fort Leavenworth, Kansas, February 2001.	Presentation
Fechter, H. : Refractive eye surgery. Lions Club Monthly, Fort Leavenworth, Kansas, May 2001.	Presentation
Hertle, R.W., Maybodi, M., Bauer, R.M., Walker, K. : Clinical and oculographic response to dexedrine in a patient with cone dystrophy, exotropia and congenital aperiodic alternating nystagmus. Bioncular Vision and Strabismus Quarterly, 16(4):259-264, 2001.	Publication
O'Kane B, Stefanik R, Stevens R, Subramanian P, Rabin J, Bower KS : Night vision performance and contrast sensitivity after photorefractive keratectomy. Vision Science and Its Applications 2001 Topical Meeting/ 2nd International Congress of Wavefront Sensing and Aberration-Free Refractive Correction, Monterey, California, February 2001.	Presentation
Rabin J : New tests for early detection of eye disease and refractive surgery in the military. Annual Fall USAREUR Optometry Seminal, Heidelberg, Germany (by video), 2000.	Presentation
Rabin J : Refractive surgery in the military: Past, present and future. National Capital Region Army Optometry Quarterly Meeting, WRAMC, May 2001.	Presentation
Rabin J : Multiple sclerosis: Visual methodology for early detection. Poster presentation at the Annual Meeting of the Association for Research in Vision and Opthalmology, Fort Lauderdale, May 2001.	Presentation
Rabin J : Visual methodology for early detection of multiple sclerosis and other diseases. National Capital Region Federal Optometric Society Quarterly Meeting, WRAMC, September 2001.	Presentation

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Subramanian PS, O'Kane B, Stefanik R, Stevens J, Rabin J, Bauer RM, Bower KS : Visual acuity and night vision performance after photorefractive keratectomy for myopia. American Society for Cataract and Refractive Surgery Annual Meeting, San Diego, California, May 2001.	Presentation
Ward TP, Laver NVM, Hidayat AA, Amacher AG, Neafie RC, Simon DP, Cavallaro BE : A case of eyelid involvement in aystemic loiasis. Ophthalmic Practice: The Official Journal of the American Association of Ophthalmic Pathologists, 19:74-76, 2001.	Publication
Ward, TP : Eye care in the theater of operations: Army. Tri-Service Ocular Trauma Course, Bethesda Maryland, May 2000.	Presentation
Ward, TP : Sympathetic Ophthalmia. Tri-Service Ocular Trauma Course, Bethesda Maryland, May 2001.	Presentation
Ward, TP : Posterior segment complications following cataract surgery: Medical. Tri-Service Cataract Surgery Course, Bethesda Maryland, March 2001.	Presentation
Ward, TP : The basics of medical lasers. Lasers in Surgery Course, Walter Reed Army Medical Center, Washington, District of Columbia, May 2001.	Presentation
Ward, TP : Nonsurgical ocular trauma. Ophthalmic Pathology for Ophthalmologists, Armed Forces Institute of Pathology, Washington, District of Columbia, August 2001.	Presentation
Ward, TP : Session Chair. Annual Meeting of the American Telemedicine Association, Fort Lauderdale, Florida, June 2001.	Presentation
Ward, TP : Adult orbital xanthogranuloma associated with asthma. Combined Meeting of the Association of Ophthalmic Alumni of the Armed Forces Institute of Pathology, the Hogan Society, and the Theobald Society, Bethesda, Maryland, April 2001.	Presentation
Youssef, O : Neuromyelitis optica. Grand Rounds, Unifomed Services University, Bethesda MD, December 2000.	Presentation
Youssef, O : Optic neuritis. Grand Rounds, Uniformed Services University, Bethesda MD, February 2001.	Presentation
Organ Transplant Service	
Batty DS, Swanson SJ, Hshieh P, Cruess D, Kirk AD, Agodoa LY, Abbott KC : Recipient hepatitis C seropositivity at the time of renal tranplantation in the United States: Patient characteristics and survival. American Journal of Transplantation, 1(2):179-184, 2001.	Publication
Batty DS, Swanson SJ, Kirk AD, Ko CW, Agodoa LY, Abbott KC : Hepatitis C virus seropositivity at the time of transplantation in the United States: Associated factors and patient survival. American Journal of Transplantation, (1):179-184, 2001.	Publication
Organ Transplant Staff : Sexual dysfunction after transplantation: A viagra moment?. Advances in Transplantation, Crystal City, VA, September 2001.	Presentation
Otolaryngology-Head & Neck Surgery Service	
Battiata AP, Vander Ark W, Adair, Mair EA : Pathology forum: Quiz case. Diagnosis: Intranasal glomus tumor. Arch Otolaryngol Head and Neck Surgery, 127(3):329-30, March 2001.	Publication

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Brietzke S, Mair E : Injection Snoreplasty: Follow up and New Objective Data. American Academy of Otolaryngology, Head and Neckk Surgery, Denver, CO, September 2001.	Presentation
Brietzke S, Mair E : Injection Snoreplasty: How To Treat Snoring. Joseph H. Baugh Award Finalist, 21st Annual USU Surgical Associates Meeting, Betheasda, MD, March 2001.	Presentation
Brietzke SE, Mair EA : Laryngeal Mask versus Endotracheal Tube in a Ferret Model. Ann Otol Rhinol Laryngol, 110(9):827-33, September 2001.	Publication
Brietzke SE, Mair EA : Injection Snoreplasty: How To Treat Snoring Without all the Pain and Expense. Otolaryngology Head and Neck Surgery, 124(5):503-10, May 2001.	Publication
Cable B, Mair E : Radiofrequency Ablation for Treatment of Oral Lymphangiomas. Triologic Society Southern Sectional Meeting, Macros Island, FL, January 2001.	Presentation
Casler JD : The current role of total laryngectomy in head and neck oncology. Madigan Army Medical Center, Otolaryngology Symposium, August 2001.	Presentation
Casler JD : Are ethics out of date in 21st century otolaryngology. Brazilian Otolaryngology Society and the American Academy of Otolaryngology - Head and Neck Surgery, Denver, CO, September 2001.	Presentation
Casler JD : Neuroanatomy. Otolaryngology Basic Science Course, Armed Forces Institute of Pathology, Washington, DC, March 2001.	Presentation
Casler JD : Laryngeal Cancer. Otolaryngology Basic Science Course, Armed Forces Institute of Pathology, Washington, DC, March 2001.	Presentation
Cote C, Mair E : Bronchoscopic lung volume reduction. Charles A. Hufnagel Award Finalist, 21st Annual USU Surgical Associates Meeting, Betheasda, MD, March 2001.	Presentation
Desyatnikova S, Burkey B, Futran M, Winslow CP, Anderson P, Cohen JI, Wax MK : Massive neglected cancers of the head and neck. 55th Annual Canadian Society of Otolaryngology Meeting, Vancouver, BC, April 2001.	Presentation
Desyatnikova S, Winslow C, Cohen JI, Wax MK : Effect of anemia on the fasciocutaneous flap survival in a rat model. Laryngoscope, 111(4 pt 1) 568-571, April 2001.	Publication
Desyatnikova S, Winslow CP, Anderson P, Cohen JI, Wax MK : Anastomatic device versatility in microvascular reconstruction. 55th Annual Canadian Society of Otolaryngology Meeting, Vancouver, BC, April 2001.	Presentation
Eisenman DJ, Ashbaugh C, Zwolan T, Arts HA, Telian SA : Implantation of the malformed cochlea. Otol Neurotol, 22:834-41, 2001.	Publication
Eisenman DJ, Speers R, Telian SA : Labyrinthectomy versus vestibular neurectomy: Long-term physiologic and clinical outcomes. American Neurotology Society, Palm Desert, CA, May 2001.	Presentation
Eisenman DJ, Speers R, Telian SA : Labyrinthectomy versus vestibular neurectomy: Long-term physiologic and clinical outcomes. Otolaryngology Neurotol, 22(4):539-48, July 2001.	Publication
Faulkner JA, Mair EA : Growth and Development of Homograft Tracheal Transplants in the Piglet Model. Arch Otolaryngol Head and Neck Surgery, 127(4):426-31, April 2001.	Publication

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Mair E : New Technologies in Pediatric ENT. Bronchoesophagology Course, Wilford Hall USAF Medical Center, San Antnio, TX, April 2001.	Presentation
Mair E : Novel snoring therapies. Suburban Hospital Grand Rounds, Washington, DC, January 2001.	Presentation
Mair E : Advanced endoscopic surgery in pediatric patients. Distinguished Guest Faculty, The PENN Rhinology Course: Advances in Management of Sino-nasal Disease, Philadelphia, PA, March 2001.	Presentation
Mair E : Pediatric tracheal stents. Director, Georgetown Bronchoesophagology Course, Panel Discussant, Washington, DC, October 2000.	Presentation
Mair E : Airway stents. Otolaryngology Basic Science Course, Armed Forces Institute of Pathology, Washington, DC, March 2001.	Presentation
Mair E : Advanced Pediatric FESS. Otolaryngology Basic Science Course, Armed Forces Institute of Pathology, Washington, DC, March 2001.	Presentation
Mair E : Tracheobronchial airway stents. Bronchoesophagology Course, Wilford Hall USAF Medical Center, San Antnio, TX, April 2001.	Presentation
Mair E : Difficult Pediatric Airway Cases. Director, Georgetown Bronchoesophagology Course, Panel Discussant, Washington, DC, October 2000.	Presentation
Mair E : Foreign body olympics. Director, Georgetown Bronchoesophagology Course, Panel Discussant, Washington, DC, October 2000.	Presentation
Mair E : Surgical management of pediatric patients. Distinguished Guest Faculty, The PENN Rhinology Course: Advances in Management of Sino-nasal Disease, Philadelphia, PA, March 2001.	Presentation
Mair E, Brietzke S : A snoring odyssey. Miniseminar, American Academy of Otolaryngology, Head and Neck Surgery, Denver, CO, September 2001.	Presentation
Michaelson PG, Cable BB, Mair EA : Image-guided transphenoidal drainage of a cholestrol granuloma of the petrous apex in a child. Int J Pediatr Otorhinolaryngology, 57(2):165-9, February 2001.	Publication
Pazos G, Mair E : Topical mitomycin-C and the pediatric airway. American Academy of Otolaryngology, Head and Neck Surgery, Denver, CO, September 2001.	Presentation
Pazos G, Mair E : Complications of radiofrequency ablations. Triologic Society Southern Sectional Meeting, Macros Island, FL, January 2001.	Presentation
Pazos G, Mair E : Comparison of varioius methods of myringotomy in an animal model. American Academy of Otolaryngology, Head and Neck Surgery, Denver, CO, September 2001.	Presentation
Wax MK, Winslow C, Desyatnikova S, Anderson PE, Cohen JI : A prospective comparison of scalpel versus bipolar scissors in the elevation of radial forearm fasciocutaneous free flaps. Laryngoscope, 111(4 pt 1):568-71, 2001.	Publication
Wax MK, Winslow CP, Anderson PE, Cohen LI : Ulnar fasciocutaneous free flaps in head and neck reconstruction. 55th Annual Canadian Society of Otolaryngology Meeting, Vancouver, BC, April 2001.	Presentation
Winslow CP, Burke A, Cook T, Wax MK : Total nasal reconstruction: The utility of the radial forearm free flap. 55th Annual Canadian Society of Otolaryngology Meeting, Vancouver, BC, April 2001.	Presentation

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Winslow CP, Dichard A, McGuire KA : Osteomyelitis of the temporomandibular joint. Am J Otolaryngology, 22(2): 142-5, March-April 2001.	Publication
Winslow CP, Hansen J, Mackenzie D, Cohen JI, Wax MK : Pursestring closure of radial forearm fasciocutaneous donor sites. Laryngoscope, 110(11):1815-8, November 2000.	Publication
Winslow CP, Wang TD, Wax MK : Static reanimation of the paralyzed face with an acellular dermal allograft sling. Arch Facial Plastic Surgery, 3(1):55-7, January-March 2001.	Publication
Winslow CP, Winslow TJ, Wax MK : Dysphonia and dysphagia following the anterior approach to the cervical spine. Arch Otolaryngology Head and Neck Surgery, (1):51-5, January 2001.	Publication
Thoracic Surgery Service	
Carmody TT, Rayburn DB, Hoffstetter EA, Poropatich RK : Remote intensivist consultations to care specialist to treat critically ill and unstable patients. Telemed J, 7(2):190, 2001.	Abstract
Carmody TT, Rayburn DB, Hoffstetter EA, Poropatich RK : Remote intensivist consultations to care specialist to treat critically ill and unstable patients. American Telemedicine Association Annual Meeting, Fort Lauderdale, FL, June 2001.	Presentation
Havenstrite KA, Barry MJ, Fitzpatrick TM, O'Neil KM : Simultaneous presentation of a bronchogenic cyst and pulmonary sequestration. Chest, 118(4):298S, 2000.	Abstract
Havenstrite KA, Barry MJ, Fitzpatrick TM, O'Neil KM : Simultaneous presentation of a bronchogenic cyst and pulmonary sequestration. Chest 2000, American College of Chest Physicians, San Francisco, CA, October 2000.	Presentation
Urology Service	
Akduman B, Lisle T, Handel L, Crawford D, Ziada A, Moul J : Combination of low dose flutamide and finasteride for PSA-only recurrence after definitive therapy. AUA, Anaheim, CA, June 2001.	Presentation
Jezior JR, Rosenstein DI, Jordan GH : Urethral reconstruction using skin in balantis xerotica obliterans. AUA, Anaheim, CA, June 2001.	Presentation
Kolvenbag GJCM, Newling D, McLeod DG, Debruyne F : The current and future role of non-steroidal antiandrogens in the treatment of prostate cancer. Urol Oncol, 1:73-90, 2001.	Publication
Lance RS, Freidrichs PA, Kane C, Powell CR, Pulos E, Moul JW, McLeod DG, Cornum RL, Brantley Thrasher J : A comparison of radical retropubic with perineal prostatectomy for localized prostate cancer within the uniformed services urology research group. BJU Int, 87(1):61-65, January 2001.	Publication
McLeod DG, Iversen P : Gynecomastia in patients with prostate cancer: A review of treatment options. Urology, 56(5):713-20, November 2000.	Publication
McLeod DG, Mostofi FK, Sesterhenn I, Zhang W, Davis CJ, Gibbons M, Moul JW : Significance of seminal vesicle invasion by prostatic carcinoma. AUA, Anaheim, CA, June 2001.	Presentation
McLeod DG, See W, Iversen P, Wirth M, Beckman r, Carroll K : Tolerability of bicalutamide (Casodex) 150 mg as immediate or adjuvant therapy in 8113 men with localized or locally advanced prostate cancer. AUA, Anaheim, CA, June 2001.	Presentation

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CITATION	TYPE
Moul JW : PSA-only recurrence of prostate cancer. Boston Urological Society, May 2001.	Presentation
Moul JW : Radical prostatectomy. USUHS Emerging Surgical Technology Conference, Strausborg, France, April 2001.	Presentation
Moul JW : Take home message on localized prostate cancer. AUA Annual Convention, Anaheim, CA, June 2001.	Presentation
Moul JW : CPDR Multicenter Prostate Cancer Research Database. Prostate Cancer Congress, San Juan, Puerto Rico, June 2001.	Presentation
Moul JW : Prostate cancer update: PSA recurrence. Richmond Urological Society, April 2001.	Presentation
Moul JW : Prostate cancer research update. National Prostate Cancer Coalition Annual Meeting, April 2001.	Presentation
Moul JW : Prostate cancer in the African American community. Access Oncology Webcast and Monograph, February 2001.	Presentation
Moul JW : Prostate cancer in African African men. LSU Medical Center, March 2001.	Presentation
Moul JW : Prostate disease update - Men's health. National Defense University, February 2001.	Presentation
Moul JW : Prostate cancer update. Temple University, April 2001.	Presentation
Moul JW, Connelly RR, McLeod DG, Mooneyhan R, Bauer JJ, Frazier HA, Friedrichs P, Schenkman N, Thrasher B, Marquis T, Porter J, Kusuda L, Wilhite D, Kane C : Using the percentage of biopsy core positive, PSA, and Gleason score to predict pathologic stage at the time of radical prostatectomy. AUA 96th annual Meeting, Anaheim California, June 2001.	Presentation
Moul JW, Sun L, Kane CJ, Lance R, Kusuda L, Foley J, Herring J, Baldwin DD, Baldwin DW, Soderdahl DW, Bishoff J, McLeod DG : Epidemiologic features of 2699 radical prostatectomy cases Between 1990-2000: A review of the Department of Defense Center For Prostate Disease Research Multicenter Prostate Cancer database. AUA, Anaheim, CA, June 2001.	Presentation
Opell MB, Zeng J, Bauer JJ, Zhang W, Sesterhenn IA, Mun SK, Moul JW, Lynch JH, Connelly RR : Correlating the number of positive biopsy cores to tumor volume for prostate cancer. AUA, Anaheim, CA, June 2001.	Presentation
Paquette EL, Connelly RR, Sun L, Paquette L, Moul JW, Sesterhenn IA, Zhang W, Greenspan R, McLeod DG : Improvements in pathologic staging for African-American men undergoing radical retropubic prostatectomy during the PSA era: Implications for screening a high risk group for prostate cancer. AUA, Anaheim, CA, June 2001.	Presentation
Rosenstein D, Jezior J, McCammon KA, Miner A, Schlossberg SM, Jordan GH, Ratz PH : Dependency of detrusor contractions on calcium entry and calcium sensitization. AUA, Anaheim, CA, June 2001.	Presentation
See W, McLeod DG, Wirth M, Iversen P, Peterson B, Carroll K : Bicalutamide (Casodex) 150 mg as immediate or adjuvant therapy in 8113 men with localized or locally advanced prostate cancer. AUA, Anaheim, CA, June 2001.	Presentation

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Segawa T, Xu LL, Moul JW, Srivastava S : Molecular dissection of androgen signaling pathways in the prostate cancer cells by high-throughput analysis of the androgen regulated genes. AUA, Anaheim, CA, June 2001.	Presentation
Siegel T, Moul JW, Spevak M, Alvord WG, Costabile RA : The development of erectile dysfunction in men treated for prostate cancer. J Urol, 165(2):430-435, 2001.	Publication
Xu LL, Moul JW, Srivastava S : Quantitative evaluation of prostate specific genes by electronic subtraction of sage libraries. AUA, Anaheim, CA, June 2001.	Presentation
Xu LL, Stackhouse BG, Florence K, Shanmugam N, Sesterhenn IA, Zou Z, Srikantan V, Augustus M, Roschke V, Carter K, McLeod DG, Moul JW, Soppett D, Srivastava S : PSGR, a novel prostate specific gene with homology to a G-protein coupled receptor is overexpressed in prostate cancer. Cancer Res, 60(23):6568-72, December 2000.	Publication
Zinner N, Harris R, Tomera K, McLeod D, Gleason D, Fotheringham N, Campion M, Garnick M : More rapid reduction in serum testosterone (T) and PSA with abarelix depot (A-D), a new GNRH antagonist, compared with leuprolide acetate. AUA, Anaheim, CA, June 2001.	Presentation
Zou Z, Gao C, Moul JW, Srivastava S, Zhang W, Sesterhenn IA, Gleave M, Rennie P : Modulation of maspin expression by P53 and androgen signaling in prostate tumor cells. AUA, Anaheim, CA, June 2001.	Presentation
Vascular Surgery Service	
Cote CR, Goff JM, Barry P, Casler J : Prevalence of occult carotid artery stenosis in patients with head and neck squamos cell carcinoma.. Laryngoscope, 111:2214-7, 2001.	Publication
Gillespie D, Patel A, Fileta B, Barnes S, Chang A : Expressions of MMP-1, MMP-13.MMP and MMP-13 (latent form) is upreguated in patients with incompetent greater saphenous veins. Uniformed Services University of the Health Sciences Day, Bethesda, MD, April 2001.	Presentation
Gillespie DL : Expressions of MMP-1 (active form) and MMP-13 (latent form) varies by location in incompotent greater saphenous veins. Association for Academic Surgery, Tampa, FL, November 2000.	Presentation
Gillespie DL : Expression of MMP-1 (active form) and MMP-13 (latent form) are Upregulated with Worsening Venous Reflux in Patients with Venous Insufficiency. Research Day, Uniformed Services University, Bethesda, MD, April 2001.	Presentation
Gillespie DL : Sclerotherapy Do's and Don't's. Associcion de Cirujanos Guatemala, Guatemala City, Guatemala, May 2001.	Presentation
Gillespie DL : Management of venous trauma. Associcion de Cirujanos Guatemala, Guatemala City, Guatemala, May 2001.	Presentation
Gillespie DL : Expression of MMP-1 (active form) and MMP-13 (latent form) are Upregulated with Worsening Venous Reflux in Patients with Venous Insufficiency. Society for Investigative Dermatology, Washington, DC, May 2001.	Presentation
Gillespie DL : Femorofemoral Bypass in the 21st Century. Veterans Administration Vascular Surgery Symposium 15th annual, Washington, DC, May 01.	Presentation
Gillespie DL : Current techniques in vascular surgery. J Vascular Surgery, 34(5):953, 2001.	Publication

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Gillespie DL, Patel A, Fileta B, Chang A, Barnes S, Flagg A, O'Donnell SD, Goff JM, Villavicenencio JL, Rich NM : Gene expression of MMP-1 and MMP-13 is upregulated with worsening venous reflux in patients with venous insufficiency. Annual Meeting of Investigative Dermatology, May 2001.	Presentation
O'Donnell SD : Balloon or the blade. Washington Metro Chapter ACS Spring Meeting, Washington, DC, 2001.	Presentation
O'Donnell SD : Endovascular fem-pop bypass. Society for Military Vascular Surgeons 21st Annual Vascular Surgery Seminar and Meeting Uniformed Services University, Bethesda, MD, December 2000.	Presentation
O'Donnell SD : Aortofemoral bypass in the 21st century. Veterans Administration Vascular Surgery Symposium 15th annual, Washington, DC, May 2001.	Presentation
O'Donnell SD : Endograft AAA repair in patients with renal insufficiency. Washington Vascular Meeting, Washington, DC, 2001.	Presentation
O'Donnell SD, Hadro NC, Wakefield M, Goff JM, Gillespie DL, Rich NM : Preoperative lower extremity color flow duplex prior to limb salvage surgery. Poster presentation, Society for Clinical Vascular Surgery, April 2001.	Presentation
Rehrig ST, Goff JM, Hadro NC, Gillespie DL, O'Donnell SD, Rich NR : Repair of bilateral iliac artery aneurysms associated with a congenital pelvic kidney. , 35(6):463-7, 2001.	Publication
Rosa P, Gillespie DL : Budd-Chiari syndrome: Case report and review of the literature. Vascular Surgery, 34(6):591-5, 2000.	Publication
Scultetus AH, Villavicencio JL, Gillespie DL : The nutcracker syndrome. Its role in the pelvic venous disorders. J Vascular Surgery, 34(5):812-819, 2001.	Publication
Villavicencio JL, Gillespie DL, Kreishman P : Controlled ischemia for complex venous surgery: The treatment of choice. J Vascular Surgery, 34(5):947-951, 2001.	Publication
Woll M, Goff JM, Gillespie DL, Minken SL : Bilateral spontaneous dissection of the internal carotid arteries: A case report. Vascular Surgery, 35:221-224, 2001.	Publication
DEPLOYMENT HEALTH CLINICAL CENTER	
Bell NS, Amoroso PJ, Williams JO, Yore MM, Engel CC, Senier L, DeMattos AC, Wegman DH : Demographic, Physical and Mental Health Factors Associated with Deployment of US Army Soldiers to the Persian Gulf. Military Medicine, 165(10):762-72, 2000.	Publication
Collins TL, Engel C, Liu X, Johantgen M, Smith S : Do mental disorders matter? A study of absenteeism among care-seeking Gulf War veterans with ill-defined conditions and musculoskeletal disorders. 107th Annual Meeting, Association of Military Surgeons of the United States, Las Vegas, NV, November 2000.	Presentation
Engel CC : Real people, real concerns: Complex risk management of uncertain adverse events. 2nd Annual US Army Medical Command Primary Care Symposium, Arlington, VA, October 2000.	Presentation
Engel CC, Liu X, Miller RF, McCarty BD, Ursano RJ : Relationship of physical symptoms to post-traumatic stress disorder among veterans seeking care for Gulf War-related health concerns. Psychosomatic Medicine, 62(6):739-745, 2000.	Publication

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CITATION	TYPE
Engel CC, Williams DA, Clauw DJ, Donta SD, Guarino P, Peduzzi P, Skinner JS, Barkhuizen A, Sogg S, Kazis LE, Feussner JR : Fatigue, pain, cognitive symptoms and mental health-related functioning among Gulf vets with chronic multisymptom illnesses: Results from the VA Cooperative Study #470. Illnesses among Gulf War Veterans: A Decade of Scientific Research, Washingoto, DC, January 2001.	Presentation
Engel CC Jr. : Clinical practice guidelines. Illnesses Among Gulf War Veterans: A Decade of Scientific Research, Alexandria, VA, January 2001.	Presentation
Engel CC Jr. : Toward population-based post-deployment health care. Meeting of the Armed Forces Epidemiologic Board, Bethesda, MD, September 2001.	Presentation
Engel CC Jr. : Brief review of the VHA/DoD clinical practice guidelines for major depressive disorder in adults. Annual Meeting of the Uniformed Services Association of Family Practitioners, San Diego, CA, April 2001.	Presentation
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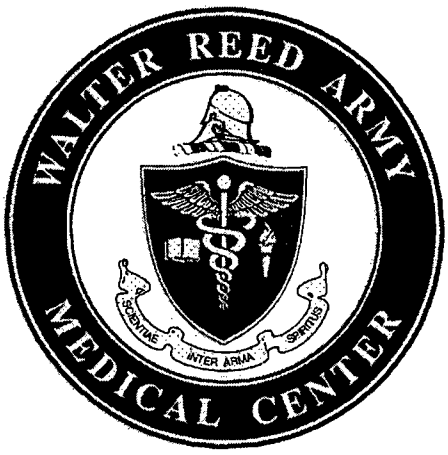
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Roesel TR : Pyridostigmine adverse reactions and self-reported sleep and memory difficutlies in active duty Gulf War veterans. Clinical Pharmacology and Therapeutics, 69:66, 2001.	Abstract
Roesel TR : Pyridostigmine adverse reactions and self-reported sleep and memory difficulties in active duty Gulf War veterans. American Society of Clinical Pharmacology and Therapeutics Annual Meeting, Orlando, FL, April 2001.	Presentation
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May JH, Vargas LG, Poropatich RK, Jacobs WG, Gilbert GR, Youngblood Sales LR, Rocca MA : Types of teleconsultations and their facilitation. Telemed J, 7(2):185, 2001.	Abstract

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CITATION	TYPE
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Poropatich RK : Potential role of telemedicine in revolutionizing management of field medical care during disasters. National Disaster Medical System Conference. Dallas, TX, April 2001.	Presentation
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Poropatich RK, Abbott K, Gadiyak G, Tomasetti S, Jacobs MC : Preventing/decreasing running injuries in a military population via a web-based tele-consult system. American Telemedicine Association Annual Meeting, Fort Lauderdale, FL, June 2001.	Presentation
Poropatich RK, Gilbert GR, Gonzalez R : NATO telemedicine interoperability and the potential for civilian transition. Telemed J, 7(2): 142, 2001.	Abstract
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DEPARTMENT OF CLINICAL INVESTIGATION (DCI)

ANNUAL RESEARCH PROGRESS REPORT



FY 2001 VOLUME II

WALTER REED ARMY MEDICAL CENTER, WASHINGTON, DC

Report Date: 10 January 2001 Work Unit # 00-1001

DETAIL SUMMARY SHEET (Human Use Protocol)

TTTLE: The Stability of Physical Symptoms and Psychiatric Illness Among Primary Care Patients

KEYWORDS:

PRINCIPAL INVESTIGATOR: Jeffrey L. Jackson
ASSOCIATES: Mark Passamonti

DEPARTMENT: Medicine
SERVICE: General Medicine

STATUS: O
INITIAL APPROVAL DATE: 01 February 2000

STUDY OBJECTIVE

1. To assess the natural history of mental disorders among primary care patients at 1 and 5 years follow-up.
2. To assess the outcome of the physical symptom for which patient initially sought medical care, 1 and 5 years later.

TECHNICAL APPROACH

Surveys conducted 1 and 5 years after initial enrollment in 2 WRAMC studies (WU 1039, WU 1057-98)

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Because of the late approval of the protocol, the opportunity to obtain 1-year follow up was lost from the smaller cohort (n=250, WU 1057-98)---the initial 2 mailings produced 105 responses (42%). A 42% response rate is not adequate and since by the end of the 2nd mailing, we were at year 2 since enrollment, no further solicitation of participation among these individuals was done. Efforts have been concentrated on obtaining follow up from the larger (n=500, WU 1039) cohort that was collected from 1995-1996. To date, follow-up has been obtained on 71% of this cohort (n=353). We are in the final phases of data collection, and anticipate completion in the next couple of months. There has been no additional recent literature since the protocol was approved. There is still no US cohort of primary care patients that have been followed more than 1 year to determine the likelihood that their mental disorder was recognized or to assess the impact of such mental disorders on symptom outcomes.

CONCLUSIONS

We have not analyzed data from this cohort, not wanting to violate principles of repeat analysis.

Report Date: 4 December 2000 Work Unit #00-1002

DETAIL SUMMARY SHEET (Human Use Protocol)

TTTLE: Myositis–Specific Antibodies in Subjects with Idiopathic Interstitial Lung Disease

KEYWORDS: myositis-specific antibody, anti-Jo-l antibody, interstitial lung disease, idiopathic pulmonary fibrosis

PRINCIPAL INVESTIGATOR: CPT Donald Helman, MC
ASSOCIATES: LTC Gregory Argyros MC; CPT Jesse Bolton MC

DEPARTMENT: Medicine
SERVICE: General Medicine

STATUS: O
INITIAL APPROVAL DATE: 08 February 2000

STUDY OBJECTIVE

- Determine the prevalence of myositis specific antibodies (MSA) in subjects with idiopathic interstitial lung disease.
- Compare clinical characteristics of those vs. those without MSA.

TECHNICAL APPROACH

- Subjects identified through pulmonary service
- Interested subjects sign consent form, undergo directed history and physical examination, have existing radiology and laboratory date reviewed, and undergo one time blood draw.
- Sera is screened for baseline chemistries, for indicators of muscle inflammation, and for the anti-Jo-l antibody.

PRIOR AND CURRENT PROGRESS

Thus far, we have enrolled 32 subjects, 20 at WRAMC and 12 at BAMC.

N	32
Male	21(63.6%)
Mean +/- STD Age	69.5 +/- 10.8 years
Biopsy Proven	18 (56.2%)
Time from Diagnosis	28.2 +/- 28.1 months
Anti-Jo-1 Antibody	0

Bernstein et al. *BMJ* 1984; 289: 151-152. 2 of 62 subjects with cryptogenic fibrosing alveolitis had anti-Jo-1 antibodies.

Targoff et al. *Semin Arthr Rheum* 1996; 26: 459-467. 2 of 26 subjects with interstitial lung disease and positive ANA had anti-Jo-1 antibodies.

CONCLUSIONS

The prevalence of anti-Jo-l antibodies in subjects with idiopathic interstitial lung disease is very low (95% CI 0-9%).

Report Date: 4 January 2001 Work Unit #00-1003

DETAIL SUMMARY SHEET (Human Use Protocol)

TTTLE: Can Ambulatory Teaching Seminars Improve Amount and Quality of Feedback to Medical Students in the Outpatient Setting?

KEYWORDS: Feedback, Ambulatory Teaching, Medical Students

PRINCIPAL INVESTIGATOR: Stephen M. Salermo MAJ MC
ASSOCIATES: Jeffrey L. Jackson LTC MC

DEPARTMENT: Medicine
SERVICE: General Medicine

STATUS: O
INITIAL APPROVAL DATE: 22 February 2000

STUDY OBJECTIVE

To determine if attending physicians in the ambulatory setting can improve the amount and quality of written and verbal feedback given to medical students after three 90-minute seminars on evaluation and feedback.

TECHNICAL APPROACH

Nine faculty members were consented and participated in a pre-post study of a faculty development program consisting of three 90-minute interactive seminars teaching evaluation, feedback, and One-Minute Preceptor micro skills. Survey and audiotapes were collected of ambulatory teachings encounters with 3rd year medical students before and after the intervention. The audiotapes were transcribed and coded by individuals blinded to the identity of the teachers and learners. Transcripts were coded using the Teacher Learner Interactive Assessment System; a qualitative tool designed to comprehensively code all utterances into mutually exclusive categories. Ten percent of audiotapes were double coded to assess inter-rater agreement. Surveys assessed learner and teacher satisfaction, perception of amount and quality of several aspects of the encounter including feedback. Finally, both learners and teachers recorded a grade for the encounter using the RIME taxonomy. All data was acquired in accordance with study protocol.

PRIOR AND CURRENT PROGRESS

Nine teachers and 64 third year medical students participated; providing 45 encounters before and 48 encounters after the seminars. 8932 utterances were coded. Coders achieved a high degree of agreement (Spearman's rho >0.8). In the baseline encounters, 17% of teacher utterances were some form of feedback, predominantly (92%) minimally positive statements such as "right" or "I agree". Only 8% of feedback utterances were specific and none were interactive. Most (91%) of the feedback was positive. After the faculty development workshops, the amount and quality of feedback increased, teachers were more likely to provide feedback (OR 1.21; 95%CI 1.07-1.36) and that feedback was nearly twice as likely (OR 2.08; 95% CI 1.45-2.99) to be specific. Both learner (p=0.82) and teacher (p=0.08) satisfaction with the amount of feedback did not change before and after the seminars. Learner perception the feedback was linked to specific behaviors did not change (p=0.80) as a result of the seminars. However teacher satisfaction that the feedback provided was specific did significantly improve after the seminars (p=0.007). The total time spent teaching during the ambulatory encounters was 14.2 ± 5.3 minutes before and 15.6 ± 6.7 minutes after the seminars, a non-significant difference (p=0.28).
The transcripts of the tapes, and the surveys are still being studied for additional information, and written feedback on the students is also being analyzed. The study has completed the audiotaping phase of the ambulatory encounters and is not enrolling new subjects. No literature addressing the specific objective of this study has been published in the 10 months between protocol approval 2/00 and present time 1/01.

CONCLUSIONS

Faculty development seminars focused on delivery of feedback can significantly improve the amount and quality of feedback delivered in the ambulatory setting without increasing the time required to teach.

Report Date: 31 July 2001 Work Unit # 1044

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: Improving Teaching in the Ambulatory Setting: A Study Using Observed Teaching Sessions and Participant Evaluations

KEYWORDS: Teaching, Ambulatory, Behaviors

PRINCIPAL INVESTIGATOR: O'Malley, Patrick MAJ MC
ASSOCIATES: Jeffrey L. Jackson, LTC MC; Steven Salerno, MAJ MC

DEPARTMENT: Medicine
SERVICE: General Medicine

STATUS: O
INITIAL APPROVAL DATE: 2 August 1996

STUDY OBJECTIVE

To study the types, frequency, and effectiveness of teaching behaviors in ambulatory teaching

TECHNICAL APPROACH

Prospective study of 103 audiotaped ambulatory encounters involving medical students and interns in the General Internal Medicine clinic at WRAMC. Patients, learners, and teachers filled out surveys before and after the encounters detailing their satisfaction with their encounters. Prospective, qualitative, collective case-study of consecutive audiotaped teaching sessions involving consenting faculty, students, interns, and 103 out of 120 eligible adult patients with acute medical problems presenting to a non-continuity walk-in clinic. Teaching encounters for each patient consisted of a case presentation by the student or intern, questions by the preceptor, focused examination of the patient, brief teaching points, and decisions regarding management and follow-up. Audiotapes were transcribed and qualitatively analyzed by 3 coders using a grounded theory approach, facilitated by NUDIST qualitative software.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Data collection completed in November 1996. Previously reported on the impact of learner involved care on patient satisfaction, and the qualitative assessment of what learners value most in ambulatory learning encounters. A coding scheme to categorize teaching behaviors, derived from the transcribed audiotapes, has been developed and inter-rater reliability assessed. We have submitted a manuscript for review (Academic Medicine) describing the tool and the prevalence of teaching behaviors. Our plan is to correlate this with learner, patient, and teacher assessment of the satisfaction with and quality of the learning encounter.

The number of subjects enrolled to the study since last APR at WRAMC is _0_ and the total enrolled to date at WRAMC is _103___. The total number enrolled study-wide is __NA___, if multi-site study.

CONCLUSIONS

Qualitative analysis of transcribed audiotapes is still in progress. A teacher and learner interactive analysis system (TELIAS) has been developed and a report of this tool has been submitted for publication

Report Date: 03 January 2001 Work Unit # 1048

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: The Effect of Training and Experience on Making Do-Not-Resuscitate (DNR) Decisions

KEYWORDS:

PRINCIPAL INVESTIGATOR: William F. Kelly CPT MC
ASSOCIATES: COL Arn Eliasson MC, CPT Derek Stocker MC, LTC Oleh Hnatiuk MC

DEPARTMENT: Medicine
SERVICE: General Medicine

STATUS: C
INITIAL APPROVAL DATE: 12 March 1996

STUDY OBJECTIVE

To determine the impact of subspecialty training and experience on patterns of Do-Not-Resuscitate (DNR) decision-making

TECHNICAL APPROACH

Practitioners from several different internal medicine specialities and levels of training are asked to complete a survey to determine what differences, if any, exist between the various groups in their patterns of DNR ordering. This may help target certain physician groups for further training in DNR ordering, ethical issues and informed consent.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Results: 114 of 162 (70%) of physicians responded to the survey. Pulmonary and CCM physicians (DNR score 158+/-22) were more likely to recommend DNR orders than cardiologists (123+/-31; p=0.006) or housestaff (132+/-24; p=0.010). The differences between PCCM physicians and general internists (130+/-30) approached statistical significance (p=0.054). There were no differences between PCCM physicians and hematologist/oncologists, infectious disease and gastroenterology. Among housestaff the likelihood of recommending a DNR order increased with years of experience (r=0.45; p=0.002). The opposite trend was true for staff groups. No significant differences in opinion by gender, religion or personal experiences were found. The project was well received when presented in poster form at the ATS meeting in October, San Francisco. We are in the process of manuscript revision and submission for publication.
The number of subjects enrolled to the study since the last APR at WRAMC is 162 and the total enrolled to date at WRAMC is 162. The total number enrolled study-wide is 162, if a multi-site study.

CONCLUSIONS

Project completed. Manuscript being written and submitted for publication.

Report Date: 14 February 2001 Work Unit #1051

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: The Yield of Endobronchial Biopsy in the Diagnosis of Sarcoidosis

KEYWORDS: sarcoidosis, biopsy

PRINCIPAL INVESTIGATOR: Shorr, Andrew F. MAJ MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: General Medicine

STATUS: O
INITIAL APPROVAL DATE: 24 April 1997

STUDY OBJECTIVE

To determine the yield of endobronchial biopsy in the diagnosis of sarcoidosis and to determine the relationship between endobronchial disease and other aspects of sarcoidosis (i.e. airway hyper reactivity, ACE level, D-dimer status).

TECHNICAL APPROACH

Patients have a series of breathing tests and blood tests and the result of these are correlated with the results from endobronchial biopsy done during bronchoscopy for the diagnosis of suspected sarcoidosis. No modifications have been made to the protocol.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

The number of subjects enrolled to the study since last APR at WRAMC is 12 and the total enrolled to date at WRAMC is 46. There have been no adverse events. Similarly, there have been no new publications or development in this area of research in the last year. Our data does show that endobronchial biopsy increases the yield of bronchoscopy by about 20% and we are still collecting and analyzing the data regarding airway hyperreactivity.

CONCLUSIONS

1) EBBX increases the yield of FOB for suspected sarcoidosis
2) Endobronchial involvement is likely a risk factor for airway hyperreactivity (AHR) in sarcoidosis
3) Other correlates of endobronchial involvement and AHR in sarcoidosis remain to be elucidated.

Report Date: 23 January 2001

Work Unit # 1053

DETAIL SUMMARY SHEET

TITLE: Adrenal Suppression Following Short-Term Use of Corticosteroids: Results of a Prospective Study

KEYWORDS: Corticosteroids, adrenal suppression, low-dose ACTH stimulation test

PRINCIPAL INVESTIGATOR: O'Malley, Patrick MAJ MC
ASSOCIATES: Torrens, Javier MAJ MC; Sachar, David CPT MC

DEPARTMENT: Medicine
SERVICE: General Medicine

STATUS: O
INITIAL APPROVAL DATE: 05 November 1997

STUDY OBJECTIVE

To determine the presence and duration of measurable adrenal suppression following short-term, high dose prednisone therapy.

TECHNICAL APPROACH

Prospective study of a convenience sample of patients being treated with short-term, high dose corticosteroid therapy. Participants will be tested for adrenal suppression using a low-dose ACTH stimulation test, at 1 week, and 12 weeks after completion of therapy.

PRIOR AND CURRENT PROGRESS

30 patients (mean age: 56.3 years; range 21-85 yrs; 76% female) were enrolled. 56% were prescribed oral steroids for respiratory disease.

One week after completion of steroid therapy, 92% of participants had competent adrenal responses, while 96% were adrenally competent at four weeks. The single patient with an inadequate response at 4 weeks had an adequate response at 1 week.

CONCLUSIONS

Adrenal suppression after short course pulse steroids is probably short-lived and clinically insignificant beyond a few weeks.

Report Date: 02 April 2001 Work Unit # 1054-98

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: Retrospective Analysis of CCEP Phase II Results from the Walter Reed Gulf War Health Center, 1994-96

KEYWORDS: Gulf War, symptoms, somatization, depression

PRINCIPAL INVESTIGATOR: Roy, Michael MAJ MC
ASSOCIATES:

DEPARTMENT: Medicine STATUS: O
SERVICE: General Medicine INITIAL APPROVAL DATE: 06 May 1998

STUDY OBJECTIVE

The object of this protocol is to perform descriptive analysis of Gulf War veterans evaluated in the Comprehensive Clinical Evaluation Program, and compare them with patients seen at other sites within the CCEP, as well as with all Gulf War veterans; in particular, to examine ill-defined conditions and psychological diagnoses.

TECHNICAL APPROACH

Comparisons between groups performed primarily by descriptive analysis due to large sample sizes. Data has been extracted from mental health reports by two independent chart abstractors after ensuring that abstraction was reliable by determination of kappa scores for inter-observer variability. The abstracted data is in the process of being analyzed by multivariate linear regression to attempt to identify predictors of psychological conditions.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 651.

CONCLUSIONS

Unfortunately, no work has been done on this protocol since the last APR, April 2000. However, I am hiring a research assistant and do expect to complete data analysis and interpretation in the coming year.

Report Date: 30 March 2001

Work Unit # 1056-98

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: Characterization of the Esophageal Striated Muscle in Patients with Achalasia: A Prospective Study (6/98)

KEYWORDS: achalasia-striated muscle, manometry

PRINCIPAL INVESTIGATOR: Dunaway, Peter CPT MC
ASSOCIATES: Maydonivitch, Corinne; Wong, Roy COL MC

DEPARTMENT: Medicine
SERVICE: General Medicine

STATUS: O
INITIAL APPROVAL DATE: 16 June 1998

STUDY OBJECTIVE:
To prospectively compare the esophageal striated muscle manometric characteristics between achalasia patients and age matched controls.

TECHNICAL APPROACH:
Use standard esophageal manometer to measure individual striated muscle contractions. No modifications from the original protocol have been made.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE:
There are no significant produced thus far with this study or in the literature. No adverse events have occurred.

CONCLUSIONS:
Research ongoing. No significant conclusions to report at this time.

Report Date: 15 December 2000

Work Unit # 1059-99

DETAIL SUMMARY SHEET

TITLE: Disordered Sleep and Depression as Predictors of the Effectiveness of Low-Dose Nortriptyline in Chronic Headache Prophylaxis

KEYWORDS: Sleep, Depression, Nortriptyline, Headaches

PRINCIPAL INVESTIGATOR: LTC Robert J. Labutta, MC
ASSOCIATES: MAJ Jeffrey Jackson, MC

DEPARTMENT: Medicine
SERVICE: General Medicine

STATUS: C
INITIAL APPROVAL DATE: 05 January 1999

STUDY OBJECTIVE:
The objectives of the study are to: 1) determine if a relationship exists between the efficacy of low dose nortriptyline in prophylaxing chronic headache and the pre-treatment clinical indices of depression and disordered sleep and 2) determine of improvement in headache is associated with improvement in depressive symptoms or sleep indices.

TECHNICAL APPROACH:
Prospective cohort design. Questionnaires at entry, one month into stable dose of nortriptyline, and at three months into stable dose of nortriptyline.

PRIOR AND CURRENT PROGRESS
A total of three (3) patients have been entered into the study. No patients have been enrolled into the study in the past year. No adverse events or reactions. No patients have been withdrawn from the study.

CONCLUSIONS
Since no patients have been enrolled in the study in the past year, the study will be terminated.

Report Date: 30 November 2000 Work Unit # 1060-99

DETAIL SUMMARY SHEET

TITLE: Diagnostic Accuracy of Pleural Fluid Cholesterol and Lactate Dehydrogenase in Identifying Exudates vs. Transudates

KEYWORDS: pleural effusions, pleural cholesterol, pleural lactate dehydrogenase, exudates, transudates

PRINCIPAL INVESTIGATOR: Jasmine T. Daniels MD
ASSOCIATES: Colin Daniels MD, William Kelly MD, Audrey Chang PhD, Lisa Moores MD

DEPARTMENT: Medicine
SERVICE: General Medicine

STATUS: O
INITIAL APPROVAL DATE: 12 January 1999

STUDY OBJECTIVE:

1. To validate the results of Costa et al and evaluate the accuracy of Light's criteria in our population of patients.
2. To determine if measurement of pleural fluid cholesterol in combination (paired or triple) with other pleural fluid measurement (LDH and protein) will provide us with similar or better sensitivity and/or specificity than Light's criteria (which uses serum and pleural fluid measurements) in differentiating exudative and transudative pleural effusions.

TECHNICAL APPROACH:

As per the recommendations from the CIC during the initial review of our protocol, we have been performing follow-up only at 6 months after diagnosis, rather than at 3 and 6 months as initially stated in our protocol.

PRIOR AND CURRENT PROGRESS

Have enrolled 107 patients to date with a goal sample size of 230. Initial data analysis was performed after 100 patients had been enrolled. There have been no adverse events related to this protocol

CONCLUSIONS

Initial data analysis suggests that the diagnostic accuracy of pleural fluid measures of cholesterol and LDH alone are approaching that of Light's criteria and may ultimately be used in differentiating exudates and transudates, however, ongoing data collection continues.

Report Date: 16 February 2001 Work Unit # 1061-99

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: Mental Disorders in a Neurology Clinic Setting

KEYWORDS:

PRINCIPAL INVESTIGATOR: Ekstrand, John MAJ MC
ASSOCIATES:

DEPARTMENT: Medicine STATUS: C
SERVICE: General Medicine INITIAL APPROVAL DATE: 9 March 1999

STUDY OBJECTIVE

1. Determine the prevalence of common psychiatric disorders among patients during their first visit to a neurology clinic.
2. Determine the likelihood of establishing a neurologic diagnosis if a psychiatric disorder is present.

TECHNICAL APPROACH

No modifications to original

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

The number of subjects enrolled to the study since last APR at WRAMC is 10 and the total enrolled to date at WRAMC is 234. The total number enrolled study-wide is _____, if multi-site study.

CONCLUSIONS

Results – Psychiatric disorders were detected in 41% of patients. The most common diagnoses were depression syndromes (30%) and somatoform disorder (23%) (some patients had multiple disorders). A neurologic diagnosis was made in 89% of cases, 77% of which were felt to be primarily organic and 21% both organic and psychiatric. No primarily psychiatric disorder diagnosis was made. The diagnosis of somatoform disorder was significantly associated with the lack of a neurologic diagnosis (OR: 0.26, 95% CI: 0.09 – 0.74). No other psychiatric diagnosis was associated with the absence of diagnosable neurologic disease.

Conclusions – Forty one percent of new patients seen in a general neurology clinic had a psychiatric disorder, much higher than the rate found in primary care (20 – 29%). The presence of a somatoform disorder reduces the likelihood that an organic cause would be found for the patient's symptoms. Prospective studies are needed to determine if screening for psychiatric disease prior to referring patients with unexplained neurologic complaints would reduce costs or improve recognition of potentially treatable psychiatric disorders.

Report Date: 22 November 2000

Work Unit # 00-1101

DETAIL SUMMARY SHEET(Animal Protocol)

TITLE: The Effect of Enalapril and Myccophenolate Mofetil in PAN-Induced FSGS in the Rat

KEYWORDS: enalapril, focal and segmental sclerosis, kidney, mycophenolate mofetil

PRINCIPAL INVESTIGATOR: Christina M. Yuan, LTC MC
ASSOCIATES: Dr. Sharda Sabnis (AFIP), Mrs. Luana Kiandoli

DEPARTMENT: Medicine
SERVICE: Nephrology

STATUS: O
INITIAL APPROVAL DATE: 2 November 1999

STUDY OBJECTIVE:
In a rat model of focal and segmental sclerosis (FSGS), does treatment with mycophenolate mofetil (MMF) PO in addition to the PO ACEI, enalapril, given at 3 and 12 weeks after initiation of the disease, result in amelioration of the histologic changes seen in untreated rats.

TECHNICAL APPROACH:
66 male Sprague Dawley rats were divided into 6 groups. Negative controls (normal); positive controls (with PAN induced FSGS); and animals with PAN induced FSGS treated with a) enalapril beginning 3 weeks after initiating FSGS with PAN; b) enalapril and MMF beginning at 3 weeks; c) enalapril beginning at 12 weeks after initiating FSGS; and d) enalapril and MMF beginning at 12 weeks. The 3 week time point was chosen because the earliest renal histologic change is seen at that time point. The 12 week time point was chosen because the animals are nephrotic at that time (and the disease is thus "clincally evident"). At 3, 12, and 18 weeks animals were placed in metabolic cages, and 24-hour urine collected for protein and creatinine. At 18 weeks, after metabolic cage work was completed, all animals were euthanized under anesthesia (ketamine/telazol), and blood and kidneys removed for determination of serum creatinine and renal histology. Euthanasia was accomplished by exsangination, followed opening the chest and ventricular cavity.

PRIOR AND CURRENT PROGRESS:
66 animals have been used, and all are now either euthanized or died during the course of the experiment. 9 animals died prematurely between 12 and 18 weeks, 3 of these were sacrificed because of weight loss. 6 others were found dead in the cage. All of these animals were in the enalapril-treated groups. Enalapril is known to inhibit weight gain in rats, and makes animals with renal failure (as these all had) susceptible to fatal hyperkalemia. There was no evidence of infection on autopsy. The animals did not appear to be in pain or distress the day before they were found dead. Previously we have used enalapril only from time 0, i.e., concurrent with initiation of PAN-induced FSGS. Its use appears associated with toxicity at later time points, at least in the dose used in this model (100 mg/L drinking water).
Analysis of tissue and blood/urine studies is ongoing.

CONCLUSIONS:
See progress above.

Report Date: 5 April 2001

Work Unit # 00-1102

DETAIL SUMMARY SHEET (Animal Protocol)

TITLE: Tacrolimus and Distal Renal Tubular Acidosis in the Rat.

KEYWORDS: tacrolimus, renal tubular acidosis, rats

PRINCIPAL INVESTIGATOR: CPT DeGaetano, Michael V
ASSOCIATES: CM Yuan, LTC MC; Luana Kiandoli

DEPARTMENT: Medicine
SERVICE: Nephrology

STATUS: O
INITIAL APPROVAL DATE: 2 May 2000

STUDY OBJECTIVE:
To develop a rat model of renal tubular (non-anion gap) acidosis due to tacrolimus administration. This syndrome is frequently observed in humans receiving the drug in immunosuppressive doses, but has not been described in rats.

TECHNICAL APPROACH:
41 rats (12 controls, 20 receiving 1 mg/kg/day tacrolimus (low dose), and 9 receiving 3 mg/kg/day tacrolimus (high dose)) will be randomly entered. They will receive daily either tacrolimus PO in cherry syrup on a whole wheat biscuit, or cherry syrup alone (controls) for up to 8 weeks. Tail blood will be drawn at 4, 6, and 8 weeks to determine presence of acidosis (defined as serum bicarbonate >3 meq/liter lower than control animals), and tacrolimus level. Upon development of acidosis or at 8 weeks of treatment, animals will be placed in metabolic cages, and urine collected to determine urine anion gap and creatinine clearance. Animals will be anesthetized, aortic blood collected for blood gas determination, electrolytes, and BUN/creatinine. They will then be euthanized, and kidneys harvested for histopathologic evaluation. Up to 2 rats from each group will also undergo bicarbonate loading (per protocol) while anesthetized, to demonstrate the tubular site of acidosis.

PRIOR AND CURRENT PROGRESS:
41 rats have been entered into the protocol. 21 are completing the 5th week of tacrolimus treatment, and 20 are completing the 4th week of treatment. Of the first group, there were no acidotic rats in either the high or low dose groups at 4 weeks. Controls had mean serum bicarbonate of 32 meq/L; low dose rats of 31 meq/L, and high dose rats 33 meq/L. There have been no adverse events, and no unexpected deaths among the animals. All are gaining weight normally, and show no evidence of pain or distress. We expect to conclude the part of the study involving animals by the second week of May 2001.

CONCLUSIONS:
None able to be drawn at present.

Report Date: 8 July 2001

Work Unit # 00-1103

DETAIL SUMMARY SHEET (Animal Protocol)

TITLE: Measurement of Electrolytes in Microdialysis Samples by Mass Spectometry

KEYWORDS: electrolytes, microdialysis, inductively-coupled plasma mass spectrometry

PRINCIPAL INVESTIGATOR: Yuan, Christina LTC MC
ASSOCIATES: Oliver, III James D. MAJ MC; Atkins, James L. COL MC; Abdel-Rahim, Maged M. MS; Morris, Elena R.; Pamnani, Motilal B. MBBS, PhD

DEPARTMENT: Medicine
SERVICE: Nephrology

STATUS: O
INITIAL APPROVAL DATE: 01 August 2000

STUDY OBJECTIVE

To measure potassium, calcium, and magnesium concentrations in microliter-volume samples obtained by the insertion of microdialysis probes in rat tissues (obtained under active animal use protocol USUHS #G176HX; administered and performed at USUHS).

TECHNICAL APPROACH

No addenda to current protocol. We are submitting an application for extension of the current protocol to include additional samples. This is an experimental laboratory protocol using existing samples obtained during the performance of an animal use protocol (USUHS #G176HX). 28 samples are tested on samples from each animal. There are 20 animals approved for use in USUHS #G176HX. Interstitial electrolytes are measured using 15 ul samples using inductively coupled plasma-mass spectrometry (ICP-MS) with internal standards as follow: Rb for K; ^{44}Ca for Ca, and ^{26}Mg for Mg. Only the potassium measurements have been done thus far.

PRIOR AND CURRENT PROGRESS

To date we have analyzed specimens from 20 animals. We have performed analysis of $[K^+]$ and $[Rb^+]$ exchange in microdialysis probes using ICP and ICP-MS. These results suggest that 1) $[K^+]$ obtained from intravascular microdialysis probes are in near-equilibrium (>90%) with venous concentrations, and 2) $[K^+]$ obtained from interstitial microdialysis probes only ~30% those of the surrounding tissue.
The current equipment at DCI is not sensitive enough to perform analysis of Ca vs. ^{44}Ca and Mg vs. ^{26}Mg, and thus we have not been able to perform the corresponding equilibrium calibrations for calcium and magnesium. A new-generation ICP-MS machine is being set up at AFIP, which should enable this. We plan to expand our studies using this new equipment when it becomes available.

CONCLUSIONS

Microdialysis sampling in conjunction with ICP-MS technology provide a unique method of analyzing tissue electrolytes from microliter samples. It is necessary to use a Rb^+ internal standard for potassium measurements because the degree of equilibrium achieved by the probes varies with the tissue used. It will be necessary to use next-generation equipment to characterize Ca^{++} and Mg^{++} concentrations.

Report Date: 26 January 2001

Work Unit # 1182

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: Methicillin-Resistant Staphylococcus aureus (MRSA) Nasal Carriage Rates in End-Stage Renal Disease Patients and Staff at WRAMC

KEYWORDS: MRSA nasal discharge, chronic dialysis

PRINCIPAL INVESTIGATOR: Welch, Paul LTC MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Nephrology

STATUS: C
INITIAL APPROVAL DATE: 12 March 1996

STUDY OBJECTIVE

To estimate: 1) the methicillin-resistant Staphylococcus aureus nasal carriage rate in ESRD patients receiving chronic dialysis care at WRAMC; 2) the MRSA nasal carriage rate in staff caring for these patients; and 3) the MRSA nasal carriage in dialysis patients receiving care chronically outside of WRAMC and temporarily dialysis at WRAMC.

TECHNICAL APPROACH

Three nasal swabs will be taken over 6 months from WRAMC chronic dialysis patients and staff. Single nasal swab will be taken on dialysis patients temporarily dialyzed at WRAMC.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

No action on this project has occurred since the last APR including new subjects enrolled, data analyzed, or publications submitted. No new significant findings related to this subject have been published. We do not plan to do any more work on this protocol.

CONCLUSIONS

Since no further work or publications are planned with this protocol, we request that the protocol be closed. If additional work is contemplated, we will submit a new protocol.

Report Date: 5 April 2001

Work Unit # 1186

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: The Clinical Efficacy of Transjugular Renal Biopsy: A Pilot Study

KEYWORDS: kidney biopsy, transjugular approach, fluoroscopy

PRINCIPAL INVESTIGATOR: Yuan, Christina LTC MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Nephrology

STATUS: O
INITIAL APPROVAL DATE: 6 May 1997

STUDY OBJECTIVE

The main purpose of the study is to describe the diagnostic utility and morbidity associated with transjugular renal biopsy performed at Walter Reed Army Medical Center.

TECHNICAL APPROACH

The study is a descriptive analysis of the tissue obtained by the transjugular route. Patients will consist of male and female adults for whom percutaneous renal biopsy would be contraindicated. Information to be described includes indications, adequacy of the tissue obtained, the ability of the pathologist to render a histologic diagnosis, and post-procedure complications.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Mal et al in France have reported large series (>200) cases of transjugular renal biopsy. More recently an even larger series (400 cases) was also reported from France. However, the vast majority of these cases have used the Colapinto needles (which use aspiration), as opposed the automated side-cut Quick Core needles, which have been used at WRAMC. We have been informed that a relatively large series (25 cases) will be reported in the June issue of the Am J Kidney Disease, and based on our prior review, we have been asked to write an editorial on this article. We have recruited no subjects in 2000, and thus have no new findings or adverse events to report since the last APR.

The number of subjects enrolled to the study since last APR at WRAMC is _0___ and the total enrolled to date at WRAMC is ___9____. The total number enrolled study-wide is __NA_____, if multi-site study.

CONCLUSIONS

Transjugular biopsy can achieve safe and adequate results in patients considered high risk for conventional renal biopsy. Patients particularly who may benefit from this approach are those with combined liver and kidney disease, and those with uncorrectable coagulopathy or needing permanent anticoagulation.

Report Date: 18 September 2000 Work Unit # 1189

DETAIL SUMMARY SHEET(Animal Protocol)

TITLE: Is HSP 70 Expression Upregulated in the MRL/lpr Mouse Model of Lupus Nephritis and Is This Upregulation Immunogenic?

KEYWORDS: heat shock proteins, lupus, glomerulonephritis

PRINCIPAL INVESTIGATOR: Yuan, Christina LTC MC
ASSOCIATES: Christopher LeBrun, CPT(P) MC

DEPARTMENT: Medicine
SERVICE: Nephrology

STATUS: C
INITIAL APPROVAL DATE: 14 October 1997

STUDY OBJECTIVE

Hsp90 and Hsp70 antigen and antibody expression has been shown to be increased in both human lupus and in animal models of the disease, and may correlate with severity of disease. In the MrL/MpJ-lpr/lpr mouse (a murine model of human lupus), the renal histopathologic changes of nephritis will be described overtime (5, 8 and 14 weeks), and Hsp90 and 70 antigen expression in the kidney will be followed, as well as the time course of antibody expression to these Hsp's.

TECHNICAL APPROACH

MrL/MpJ—lpr/lpr mice will be euthanized at 5, 6 and 14 weeks of life, and the light microscopic histopathology of the kidneys assessed vs. the MrL/MpJ--+/+ mouse controls. Immunostaining of renal tissue for Hsp90 and 70 will also be performed at these time points, as will ELISAs for Hsp70 and 90 IgG in mouse serum.

PRIOR AND CURRENT PROGRESS

66 mice were used, as outlined in the protocol. There were no unexpected deaths or adverse events. We have completed the animal studies, and have shown that the animals develop a mesangial proliferative glomerulonephritis by week 14 vs. controls, with no significant differences in Hsp70 or 90 antigen expression in the kidney at any time point vs. controls. Hsp90 antibody production is significantly increased in the lupus mice at week 5 vs. controls and increases thereafter. Hsp70 antibody production is significantly and markedly increased only at week 14 (concurrent with the appearance of histopathologic change. Publication is pending. We plan to used the money budgeted for publication, but no further funds.

CONCLUSIONS

Hsp90 antibodies are expressed prior to the development of immune-complex glomerulonephritis, while Hsp70 antibody levels increase concurrent with the development of the glomerular disease. However the antigenic source does not appear to be within the kidney, based on immunostaining studies.

Report Date: 22 November 2000 Work Unit # 1190

DETAIL SUMMARY SHEET

TITLE: Is HSP Expression Upregulation in Human Lupus Nephritis, and Is This Upregulation Immunogenic? A Pilot Study

KEYWORDS: lupus nephritis, heat shock protein, immune response

PRINCIPAL INVESTIGATOR: Yuan, Christina LTC MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Nephrology

STATUS: C
INITIAL APPROVAL DATE: 12 November 1997

STUDY OBJECTIVE

It has been shown in patients with systemic lupus erythematosis that serum antibodies for Hsp70 and 90 are present, and appears to correlate with the severity of disease (i.e., presence of nephritis). We propose to explore whether Hsp70 and/or 90 antigens are increased in histopathologic renal tissue from patients with lupus nephritis and to preliminarily relate the presence of these antigens with the WHO nephropathology classification of lupus.

TECHNICAL APPROACH

Retrospective review from tissue of stored blocks from past biospies of patients with known lupus obtained from the AFIP. Five blocks will be randomly selected from each category (I-V) and immunostained for Hsp70 and 90. Staining will be assessed in a semiquantitative, blinded manner by the nephropathologist (Dr. Sabnis).

PRIOR AND CURRENT PROGRESS

We have validated our tissue staining for Hsp70 and 90 using mouse kidney (WU 1189), as well as our semiquantitative grading system. Tissue has been identified by Dr. Sabnis, but is not yet stained.due to findings in the mouse study, which showed no Hsp 70 or 90 staining in the MRL/lpr model of lupus nephritis.

CONCLUSIONS

We have stained for HSP47 successfully in another model (i.e., PAN-induced FSGS), and had considered applying this stain to the tissue of lupus patients. It seems unlikely staining for Hsp 70 or 90 will yield positive results in view of the findings of the mouse study. It is unlikely that we will be able to undertake the present study due to lack of personnel time, and other commitments on the part of our renal pathologist. We are thus requesting closure of this study. No human tissue was ever pulled from archive or stained.

Report Date: 5 April 2001

Work Unit # 1194-98

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: Improving Rates of Acute Renal Allograft Rejection with a Regimen of Cyclosporin, Mycophenolate Mofetial and Prednisone

KEYWORDS: kidney transplantation, allograft rejection, allograft failure, cyclosporin, mycophenolate mofetil

PRINCIPAL INVESTIGATOR: Oliver, James MAJ MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Nephrology

STATUS: O
INITIAL APPROVAL DATE: 29 May 1998

STUDY OBJECTIVE

To describe the rates of rejection, graft and patient survival achieved in the WRAMC Renal Organ Transplant program as compared to national averages.

TECHNICAL APPROACH

A retrospective review of transplant data from the WRAMC Organ Transplant database, from inpatient and outpatient charts being conducted in parallel with querying of the United States Renal Database System (USRDS). Rejection rates as a function of patient characteristics and of immunosuppressive regimen are being compared.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Since the study is retrospective reporting of adverse events is also retrospective. Our primary outcomes were graft survival and rejection rates. The results of this project were published as an abstract in J Am Soc Nephrol 1999;10:741A, Abstract A3750, and presented as a poster at the 32nd Annual American Society of Nephrology meeting, 1999. Several other abstracts have reported similar single center findings, but none has yet been published.

The number of subjects enrolled to the study since last APR at WRAMC is __132__ and the total enrolled to date at WRAMC is __132_____. The total number enrolled study-wide is ____NA___, if multi-site study.

CONCLUSIONS

Socioeconomic status and the ability to pay for medications may be more important than recipient race in renal transplant outcomes.

Report Date: 18 September 2000 Work Unit # 1196-99

DETAIL SUMMARY SHEET (Animal Protocol)

TITLE: Is HSP47 Expression Upregulated in PAN-Induced FSGS in the Rat, and Does Pirfenidone Affect this Upregulation?

KEYWORDS: Heat shock proteins, pirfenidone, focal and segmental glomerulosclerosis (FSGS)

PRINCIPAL INVESTIGATOR: Yuan, Christina M. LTC MC
ASSOCIATES: Kevin P. Stiles, CPT (P) MC

DEPARTMENT: Medicine
SERVICE: Nephrology

STATUS: O
INITIAL APPROVAL DATE: 13 October 1998

STUDY OBJECTIVE

PAN-induced FSGS in the rat is a model for FSGS in the human, and will be used in this study to investigate the effects of Pirfenidone, an antifibrotic agent, with and without an ACE inhibitor and an HMG-CoA reductase inhibitor on renal histology and renal function over time. The role of Hsp47 (a collagen chaperone, and a marker of fibrosis) will also be investigated.

TECHNICAL APPROACH

Sprague Dawley rats will have FSGS induced with serial sq injections of PAN, and treated with either vehicle, oral enalapril and sq lovastatin; oral pirfendione; or pirfenidone/enalapril/lovastatin. A group of normal control animals receiving vehicle alone will also be studied. Animals will be euthanized at 3; 12; and 18 weeks post PAN-induction, and the light microscopic histopathology of the kidneys assessed. Immunostaining of renal tissue for Hsp47 will also be performed at these time points, as will ELISAs for Hsp47 and TGF-beta in rat serum. 24-hour urine studies, and terminal serum studies for renal function will also be performed.

PRIOR AND CURRENT PROGRESS

We have completed the animal studies (150 animals), and have shown that at 18 weeks the Pirfenidone/enalapril/lovastatin treated animals are indistinguishable from normal controls with regard to renal function, proteinuria, and renal histology. The enalapril/lovastatin treated animals have intermediate histology, and pirfenidone-treated animals alone are not distinguishable from FSGS control animals. Histologic readings for Hsp 47 stained tissue at 18 weeks remains to be done, as is the 12 and 18 week TGF-Beta assays. All necessary supplies are in hand.

CONCLUSIONS

The combination of Pirfenidone/enalapril/lovastatin in PAN-induced FSGS appears to inhibit renal function loss as well as chronic histologic change. All animals (150) approved for the study have been entered, and have been euthanized. One died unexpectedly in an accident, after leaping from a table during an injection.

Report Date: 16 December 2000

Work Unit # 1197-99

DETAIL SUMMARY SHEET

TITLE: The Impact of Therapeutic Plasma Exchange on the Medications Used in Transplantation

KEYWORDS: Plasmapheresis; Immunosuppression; Pharmacokinetics

PRINCIPAL INVESTIGATOR: Stiles, Kevin CPT MC
ASSOCIATES: Yuan, Christina M LTC, MC; Viola, Rebecca MPh

DEPARTMENT: Medicine
SERVICE: Nephrology

STATUS: O
INITIAL APPROVAL DATE: 19 January 1999

STUDY OBJECTIVE:

Prospective, descriptive study to document the clearance of various immunosuppressive drugs used in renal transplantation by plasmapheresis (TPE). Clearance of one of the following drugs will be assessed using pheresed plasma levels and plasma volume and patient plasma levels: daclizumab; mycophenolate mofetil; ganciclovir; cyclophosphamide; OKT3, and cytomegalovirus hyperimmune globulin.

TECHNICAL APPROACH:

Patients ≥ 18 years old undergoing plasmapheresis for various medical indications, and receiving any of the above medications will be asked to participate. Drug levels will be drawn peripherally prior to TPE, immediately post TPE, and at 2 and 4 hours post TPE. Levels will also be determined in the plasma effluent, and the volume of the effluent will be used to determine total clearance of drug. Levels will be determined at various laboratories. All data regarding clearance will be provided to the patient's physician, so that drug dosing and re-dosing may be done in accordance with the clearance data. 5 patients will be entered, as opportunity presents itself. The diseases for which TPE is performed are rare, and the use of these drugs concurrently is also rare.

PRIOR AND CURRENT PROGRESS

No patients have been entered into the study in the past year. None have presented that met the inclusion criteria.

CONCLUSIONS

None yet available.

Report Date: 16 December 2000 Work Unit # 1198-99

DETAIL SUMMARY SHEET

TITLE: Na+, K+-ATPase Inhibitor in the Mechanism of Hypertension in Diabetes Mellitus

KEYWORDS: diabetes; sodium pump inhibitor, ouabain

PRINCIPAL INVESTIGATOR: Yuan, Christina LTC MC
ASSOCIATES: Victor Bernet MAJ MC; Kevin Abbott LTC MC

DEPARTMENT: Medicine
SERVICE: Nephrology

STATUS: O
INITIAL APPROVAL DATE: 19 January 1999

STUDY OBJECTIVE

To determine whether the presence of elevated levels of ouabain-like factor (OLF) is associated with diabetic nephropathy in Type I and Type II diabetics vs. diabetic patients without nephropathy.

TECHNICAL APPROACH

Patients seen in the endocrine and nephrology clinics, with type I or type II diabetes, with or without nephropathy (as defined by presence of fixed proteinuria/albuminuria and hypertension) will be invited to participate in the study. A one time 10 cc sample of plasma and RBCs will be collected from a peripheral vein for determination of OLF levels. Levels will be measured in a blinded fashion. BP, weight, urine protein, serum creatinine, and glycosylated hemoglobin will also be determined. Patients must be $\geq$ 18 years or $\leq$ 75 years of age, not pregnant, not s/p kidney transplant, and with a serum creatinine of 1.5 mg% or less to be in the study.

PRIOR AND CURRENT PROGRESS

16 patients have been entered into the study. 2 have refused entry. There have been 4 quality control samples submitted (to which the Pamnani laboratory is blinded.) Therefore, there have been 20 specimens submitted for analysis. There have been no adverse outcomes. All 16 patients have had complete baseline evaluations as outlined in the protocol, and experimental assays are ongoing. No preliminary data is yet available. In June 2000, we submitted an addendum to allow continued recruitment of patients through June 2001; begin advertising in the nephrology and endocrine clinics; and increase the upper limit of age to 75. Accrual rate increased to 7 patients in the last 3 months; only 9 patients had been recruited in the previous year.

CONCLUSIONS

None yet available.

Report Date: 24 November 2000

Work Unit # 1199-99

DETAIL SUMMARY SHEET

TITLE: Patterns of Protein Size- and Charge-Selectivity in Clinical Kidney Disease

KEYWORDS: glomerulonephritis, proteinura, permselectivity

PRINCIPAL INVESTIGATOR: James D. Oliver MAJ MC
ASSOCIATES: Christina Yuan LTC MC; Paul Welch LTC MC; Sharda Sabnis MD; Maged Abdel-Rahim MS

DEPARTMENT: Medicine
SERVICE: Nephrology

STATUS: O
INITIAL APPROVAL DATE: 26 January 1999

STUDY OBJECTIVE

To determine the fractional excretion of specific proteins in renal disease and controls, and to examine whether the patterns of proteinuria correlate with histological characteristics demonstrated on renal biopsy.

TECHNICAL APPROACH

Patients seen in the nephrology clinic with kidney disease who are being referred for renal biopsy will have blood and urine samples drawn to measure the fractional excretions of various proteins: β-2 microglobulin, retinal binding protein, transferring, pancreatic and total amylase, IgG and IgG4, and albumin polymers. These will be compared to values obtained from a matched set of health control volunteers. From the biopsy specimens, the essential diagnostic category and grading of the severity of disease will be determined in a blinded fashion. The fractional excretions will be correlated to the histological changes. Patients must be over 18 years of age and not s/p kidney transplant to be eligible.

PRIOR AND CURRENT PROGRESS

Because of unavailability of some assays, we have had to look into some alternative ELISA methods. These are expected to be completed in the spring, at which point patient enrollment will begin. At present, there have been no patients enrolled in the study.

CONCLUSIONS

None at this time.

Report Date: 9 August 2000

Work Unit # 00-1201

DETAIL SUMMARY SHEET

TITLE: A Randomized Trial Comparing the Effects of Atorvastatin and Pravastatin on Cartoid Intima-Media Thickness

KEYWORDS: Randomized Trial, atherosclerosis, HMG-CoA reductase inhibitor

PRINCIPAL INVESTIGATOR: Allen J. Taylor MD LTC MC
ASSOCIATES: Louis Coyle DO, Patrick Flaherty Do, Thor Markwood MD, Steve Kent MD, Patrick G. O'Malley MD, MPH

DEPARTMENT: Medicine
SERVICE: Cardiology

STATUS: O
INITIAL APPROVAL DATE: 26 October 1999

STUDY OBJECTIVE

To evaluate the relative effects of two different HMG-CoA reductase inhibitors on cartoid atherosclerosis regression.

TECHNICAL APPROACH

This study is a randomized study comparing the efficacy of atorvastatin and pravastatin on cartoid atherosclerosis (carotid intima-media thickness). Patients beginning cholesterol lowering therapy who have a baseline serum cholesterol of 160mg/dL or greater and who are not currently on cholesterol lowering medication are randomized to one of 2 open-label treatment arms: pravastin 40mg qd, or atorvastatin 80 mg qd. The primary endpoint is the change in carotid intima-media thickness over 12 months. Lab monitoring is performed at baseline, 3 and 12 months. The sample size for statistical significance is 132 patients. The protocol is approved for a maximum of 200 patients.

PRIOR AND CURRENT PROGRESS

As of 14 August 2000, 111 patients have been enrolled in the study. Nine patients have withdrawn from the study: drug intolerance (4), patient request (4) and a new diagnosis of liver cancer (1). The enrollment pace is approximately 15-20 patients a month.

CONCLUSIONS

The ARBITER study is well underway towards our target sample size of approximately 150-160 subjects. Preliminary and final results will be available in late 2000 through 2001.

Report Date: 2 October 2000

Work Unit # 00-1202

DETAIL SUMMARY SHEET

TITLE: SWITCH: Statins at WRAMC: Interventions for the Treatment of Cholesterol-An Observed Study of the Formulary Switch to HMG-coA Reductase Inhibitors Mandated by the Department of the Defense Pharmacoeconomic Center

KEYWORDS: HMG-CoA reductase inhibitors, therapeutic interchange

PRINCIPAL INVESTIGATOR: Allen J. Taylor MD LTC MC
ASSOCIATES: David L. Jones MD MPH; Karen Grace Pharm D; Jennifer Swiecki Pharm D; Richard Hyatt M.S.; Rebecca Viola R.Ph.

DEPARTMENT: Medicine
SERVICE: Cardiology

STATUS: O
INITIAL APPROVAL DATE: 30 November 1999

STUDY OBJECTIVE: To monitor the safety and efficacy of HMG-coA reductase ("statin") therapy in outpatients being switched to agents mandated by the Department of Defense (DOD) Pharmacoeconomic Center (PEC).

TECHNICAL APPROACH: Prospective, observational study using FDA-recommended monitoring of statin therapy.
Methodology: This is an 18-week observational study evaluating the safety and efficacy of the algorithm-based conversion to cerivastatin or simvastatin. Patients presenting to the WRAMC pharmacy to obtain refills of their currently prescribed statin medication between January and April 2000 were referred to the lipid clinic where received their new medication with drug-information counseling and drug-interaction screening by a pharmacist. The specific agent (i.e., cerivastatin or simvastatin) was determined according to an algorithm based on a statin equivalency chart. After this, they were offered enrollment in the SWITCH protocol.

Patients consenting to participate in SWITCH will underwent the following procedures:

- ☐ **STEP I:**
- ☐ Collection of baseline demographic data to determine NCEP II goals (see data collection form [only form to be used]) and current dietary fat intake.
- ☐ Baseline serum lipid panel and LAE's prior to beginning the new agent. All unused serum was discarded. Patients received an informational sheet detailing the study procedures and known drug interactions with simvastatin and cerivastatin.
- ☐ Patients with LAE's > 3X the upper laboratory reference value on baseline laboratories underwent no further trial procedures and were referred back to their prescribing health care provider.
- ☐ Follow-up lipid panel and LAE testing at 6 weeks:
- ☐ Comparison of LDL to NCEP II goal.
- ☐ Patients with LAE's > 3X the upper laboratory reference value on baseline laboratories underwent no further trial procedures and were referred back to their prescribing health care provider.
- ☐ Telephone contact at 6 weeks to provide lipid panel results and screen for drug intolerance/side effects. Patients that achieved their NCEP II goal were finished with the study procedures, and were mailed a refill prescription, and referred back to their primary care provider for continuing care.
- ☐ **STEP II:** Patients not achieving their NCEP II lipid goals at 6 weeks:
- ☐ An upward dose-titration or medication change was made by telephone (6-week telephone call). This new medication dose or new medication was mailed to the patient, or picked-up by the patient at the WRAMC pharmacy.
- ☐ Follow-up lipid panel and LAE testing at 12 weeks. All unused serum was discarded.
- ☐ Telephone contact to provide lipid panel results and screen for drug intolerance/side effects. Patients that achieved their NCEP II goal were finished with the study procedures, and were mailed a refill prescription, and referred back to their primary care provider for continuing care.
- ☐ **STEP III:** Patients not achieving their NCEP II lipid goal after 12 weeks on the new statin were mailed a prescription for Simvastatin 80 mg qd (90 days plus refills) followed by a repeat lipid panel and LAE testing 4-6 weeks later. All unused serum was discarded. At this point, their involvement in the trial was complete and they were referred to their primary care provider for continued care.

e. Schedule of data collection:

SWITCH	Intake	6 weeks	12 weeks*	18 weeks**
NCEP II baseline demographics	X			
Lipid panel, LAE's	X	X	X	X
Telephone screening		X	X	X

* Only for patients not at NCEP II goal at 6 weeks
** Only for patients not at NCEP II goal at 12 weeks

PRIOR AND CURRENT PROGRESS

Between 3 January and 30 April 2000, 1359 eligible patients presented for conversion of their statin. Of these, 980 (72.1%) consented to participate in the study. Renal insufficiency (serum creatinine > 2.0 mg/dL) was subsequently detected in 38 patients, leaving 942 subjects in the study cohort. Reasons cited for refusal (n=376) included patient preference (n=134, 35.6%), request to be followed by their primary care provider (n=106, 28.2%), inconvenience (time or distance) (n=71, 18.9%), patient unavailable for follow-up procedures (n=37; 9.8%), or miscellaneous (n=28, 7.4%).

The mean age of the 942 study participants was 68 ± 10; 59.2% were men. There was a high prevalence of secondary prevention treatment indications including known coronary artery disease (46.9%) and diabetes mellitus (23.8%). Pravastatin (42.0%) and atorvastatin (44.1%) were the most commonly prescribed statins prior to the conversion. Following the conversion, the majority of patients were treated with cerivastatin 0.4 mg/d (82.4%) or 0.8 mg/d (13.3%). A total of 894 patients (94.9%) returned for their 6-week lab follow-up examination.

Lipid Results

At baseline, the mean LDL cholesterol was 115 ± 29 mg/dL, and 64.8% of LDL values were at or below the NCEP goal value. Six weeks after the statin conversion, the mean LDL cholesterol fell to 106 ± 25 mg/dL (P<.001). This reduction in the LDL cholesterol was the result of conversion of lower potency and lower dose statins to cerivastatin 0.4 mg. Consequently, the proportion of patients at NCEP goal post-statin conversion increased to 74.5%. HDL cholesterol also significantly increased from 50 ± 14 mg/dL to 51 ± 14 mg/dL (P < .001). Similar effects for changes in serum lipid measurements and NCEP goal adherence were obtained in subgroups of patients treated for secondary and primary coronary heart disease prevention indications. Each of the 3 statin conversions (cerivastatin 0.4 and 0.8 mg/d and simvastatin 80 mg/d) resulted in improved or neutral effects on lipid values.

Side Effects

Side effects resulting in drug discontinuation occurred in 28 of 942 (3.0%) patients. Overall, side effects reported as adverse drug effects or considered to be minor, coincidental complaints with continuation of the prescribed statin were unrelated to the pre-conversion statin. The incidence of side effects tended to be less common with cerivastatin 0.4 mg/d than either cerivastatin 0.8 mg/d or simvastatin 80 mg/d, but the difference was not statistically significant. Myalgias were the most common symptoms, reported in 19 (2.0%) patients. Among these, 5 patients, all previously treated with atorvastatin 20-40 mg/d, had definite myositis (cerivastatin 0.8 mg/d, n=4; simvastastin 80 mg/d, n=1). Two patients required hospitalization with severe muscle weakness and CK elevations (>30,000 U/dL). All 5 patients reported compliance with the 72-hour washout period for conversion from atorvastatin. Two of these patients also had potential drug interactions with other CYP3A4 inhibitors (grapefruit juice, n=1, and verapamil, n=1). Mean values for liver-associated enzymes were unchanged following the statin conversion; one patient (0.1%) had an increase above 3 times the upper laboratory reference value.

Costs and Satisfaction

There is a marked difference in the DOD contract price for cerivastatin ($.31/0.4mg tablet) and simvastastin ($0.99/day). Thus, the distribution of cerivastatin vs. simvastatin use was vital to achieve the economic goal of the formulary conversion. Walter Reed's statin conversion program converted 92.4% of the eligible population to cerivastatin, far exceeding the DOD PEC benchmark goal of 65% (required to meet the DOD PEC goal for cost-avoidance). Projected Walter Reed pharmacy cost savings for this conversion were $203 per patient treatment year. Satisfaction with the conversion process was very high; 93.6% of patients indicated they were either extremely (81.7%) or very (11.9%) satisfied with the program.

CONCLUSIONS

The empiric DOD PEC statin formulary conversion resulted in greater efficacy of cholesterol reduction at reduced cost. Uncommon, but serious, adverse effects can occur, even in patients formerly tolerant of a statin medication. The WRAMC statin formulary conversion program was an innovative approach to the problems within therapeutic interchange. This program maximized the safety and cost-savings of the formulary change, while achieving high levels of patient satisfaction and critical improvements in therapeutic benchmarks of lipid-lowering therapy. Through teamwork in a multidisciplinary environment enhanced by media outreach and industry collaboration, the program has demonstrated that therapeutic interchange can be a win-win situation for both patients and the healthcare system.

Report Date: 2 October 2000

Work Unit # 1215

DETAIL SUMMARY SHEET

TITLE: The Utility of Electron Beam Computed Tomography (EBCT) as a Screening Test for Coronary Artery Disease and as an Intervention for Risk Factor Modification Among Over 40 Active Duty Personnel

KEYWORDS: Coronary artery disease, risk factors, prognosis, computed tomography

PRINCIPAL INVESTIGATOR: Taylor, Allen LTC MC
ASSOCIATES: O'Malley, Patrick MAJ MC; Jones David LTC MC; Vernalis, Marina COL MC; Feuerstein, I; Brazaitis, M COL MC

DEPARTMENT: Medicine
SERVICE: Cardiology

STATUS: O
INITIAL APPROVAL DATE: 25 November 1997

STUDY OBJECTIVE: To evaluate the prevalence, relationship to coronary risk factors, management impact and prognosis of coronary calcium detected using electron beam computed tomography in active duty Army personnel.

TECHNICAL APPROACH: A. 2000 consecutive, over age 40 active duty Army personnel from the National Capital Area will be screened for conventional coronary risk factors and electron beam computed tomography. This cohort will be followed annually for the occurrence of cardiovascular events. 440 of the participants will be enrolled in a randomized controlled trial (2x2 factorial design) comparing immediate vs. deferred EBCT results and standard care vs. case management risk factor modification.

PRIOR AND CURRENT PROGRESS: As of Sept 29, 2000, 1069 patients have been enrolled in the cohort study. 389 of these patients have also consented to participate in the randomized controlled trial portion of PACC. The consent rate for the cohort study is 89%. The phase I results (Aim 1) are completed, comprising reporting on the risk factors and prevalence of coronary calcium in the first 630 enrollees.
The prevalence of coronary artery calcification is 20.6% in men and 4.3% in women.
The contract to SAR Inc. (employees handle data collection and management for the study) was renewed as of August 2000 for the coming year, at a budgeted amount (WRAMC budget) of $640K.
The following ammendments to the protocol have been completed in the past year:
A. 17 Feb 00: The purpose of this amendment was to request a change in the inclusion criteria to speed enrollment in the cohort study. Initially, we were enrolling only active duty army personnel, 40-45 years old who are undergoing a mandatory Army physical examination. This amendment:

1. Removes the requirement of patients enrolling in the project as part of an Army physical examination. The inclusion criteria were thus relaxed to allow open enrollment of any Army active duty personnel. Open enrollment in the environment of a clinical trial is appropriate. Coronary risk factors will be compared in the initial (first 1000) and open-enrollment (second 1000) cohorts to evaluate for systematic differences suggesting referral bias.
2. Expands the eligible age range from 40-45 to 40-50. The purpose of this is to enrich the cohort with coronary calcification, because coronary artery calcification is very age-dependent. Increasing the age limit should slightly increase the prevalence of coronary artery calcification by approximately 5%.

B. 16 Mar 00: The purpose of this addendum was to further explore the factors that may predict the development of subclinical atherosclerosis indicated by coronary calcium. These studies are utilizing banked serum stored since the intake evaluation for subjects enrolled between January 1999 (when serum banking began) and March 2000. Specifically, we are examining 2 separate risk factors in relation to coronary calcium: A. lipid subfractions, and B. high sensitive C-reactive protein (hs-CRP). The substudies utilize a case-control study design.

C. 17 Mar 00: A new study advertisement was approved to incorporate the changes listed under "A" above.
D. 3 Apr 00: Laboratory measurements were revised with the deletion of thiocyanate, and the addition of hs-CRP within the cohort study (with the aim of studying the long-term prognosis associated with coronary artery calcification) of PACC.
E. 1 June 00: The purpose of this amendment was to modify the entry questionnaire by adding 2 short questionnaires to assess for anger and its expression.

CONCLUSIONS: The initial aim of PACC (to define the prevalence of coronary artery calcification in the Army over-40 physical population) is complete. Enrollment in the cohort study is over half complete, and enrollment in the randomized trial is almost complete. Continued subgroup analyses on questions of interest within the approved dataset are continuing.

Report Date: 2 January 2001

Work Unit # 1216

DETAIL SUMMARY SHEET

TITLE: Coronary Stents and Abbreviated Ticlopidine

KEYWORDS:

PRINCIPAL INVESTIGATOR: Thomas, William MAJ MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Cardiology

STATUS: C
INITIAL APPROVAL DATE: 16 December 1997

STUDY OBJECTIVE
To compare events between two and four weeks of Ticlopidine post coronary stenting.

TECHNICAL APPROACH
Same as the original protocol. Randomized to two or four weeks of drug treatment.

PRIOR AND CURRENT PROGRESS
Approximately 100 pts randomized, few events. No difference in endpoints between groups.

CONCLUSIONS
In this small study, no difference in event rates found between two and four weeks of ticlid post stenting.

Report Date: 2 October 2000 Work Unit # 1217

DETAIL SUMMARY SHEET

TITLE: Use of Electron Beam Computed Tomography in the Preoperative Evaluation of Noncardiac Vascular Surgery Patients

KEYWORDS: Electron beam computed tomography; preoperative cardiac evaluation

PRINCIPAL INVESTIGATOR: Allen J. Taylor MD LTC MC
ASSOCIATES:

DEPARTMENT: Medicine STATUS: O
SERVICE: Cardiology INITIAL APPROVAL DATE: 16 December 1997

STUDY OBJECTIVE
To determine the utility of preoperative EBCT in predicting immediate and short-term outcomes among arterial surgical patients operated at WRAMC.

TECHNICAL APPROACH:
Subjects are recruited from the Vascular Surgery Clinic during their preoperative evaluation. EBCT is obtained prior to, or shortly after, admission. Follow-up blood tests and ECGs are obtained for up to 72 hours postoperatively. Follow-up telephone contacts are made over the ensuing 12 months.

PRIOR AND CURRENT PROGRESS
As of July 2000, 77 patients had been enrolled, and 46 patients completed the study procedures. Enrollment has been slower than anticipated for a number of reasons: lower than expected surgical volume, exclusion criteria, inconsistent availability of staff to recruit patients. Because of this, a decision was made to stop enrollment in July 2000 and to analyze the data collected to date. These data have been analyzed, and will be published as a pilot study. It is anticipated that additional patients will not be recruited.

CONCLUSIONS
Enrollment in this study has been terminated by the investigators. The patient's enrolled to date will provide data for a manuscript describing this pilot effort. The data is currently being analyzed.

Report Date: 1 May 2001

Work Unit # 1218-98

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: Assessment of Clinical Outcome Using Prothrombin Time Patient Self Testing (PST) to Monitor Long Term Anticoagulation Therapy

KEYWORDS:

PRINCIPAL INVESTIGATOR: Calagan, Jennifer L. LTC MC
ASSOCIATES: Mamo, Sewnet-DPH candidate: John, Cheryl RN; Vernalis, Marina COL MC

DEPARTMENT: Medicine
SERVICE: Cardiology

STATUS: O
INITIAL APPROVAL DATE: 16 June 1998

STUDY OBJECTIVE

To assess the use of Patient Self-Testing (PST) to monitor the effect of Coumadin® therapy for effectiveness, safety and convenience/compliance. To assess the use of HealthBuddy® telephone/internet communication device to monitor further complications, status and Coumadin® use in WRAMC Coumadin® Clinic patients. Additionally, to compare the use of PST and HealthBuddy® to standard/traditional in-hospital monitoring of effects of Coumadin® therapy.

TECHNICAL APPROACH

PST has been conducted using the ProTime® Microcoagulation System (ITC, Edison, NJ). An initial group of patients was advised of the protocol, trained in the use of the system, and then randomized to either standard monitoring or the PST arm. The member of the second group was further trained on the use of the system, given supplies and tracking forms, and issued a home unit. Patients in the first/control group will remain under the standard clinic protocol for monitoring of PT/INR, but will be also trained in and given report and tracking forms. The outcomes studied will be percentage of time within therapeutic range, precision in dose adjustment, patient compliance, complications and patient satisfaction. After this study was started, funding and the technology to monitor patient health status, Coumadin® use, potential complications and other relevant changes to medical regimen became available in the form of the HealthBuddy®, a device which allows two-way non-simultaneous exchange of information between Coumadin® Clinic and the patient at home. The device plugs into an existing phone line and is programmed to communicate via the internet with a server which can post the responses to a secure, passworded web site. This should allow patients and Coumadin® Clinic to exchanges questions and information without a patient visit on-site or a series of phone calls. This device has been used with other medical conditions (e.g. diabetes) but never tested for use in a high volume clinic with military population on fairly high-risk therapy. The need for prompt detection of aberrancies in INR, patient's medical condition, new or deleted medications and suggest that such a device might improve efficacy of therapy while reducing potential for complications or earlier detection of complications. The protocol was amended to now include four arms: the original two (control and PST) plus a HealthBuddy® arm and an arm with both devices. It will also include subgroups of "new" patients.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

The study has been amended as described above and now contains 4 arms of up to 105 patients each: Control (In-hospital INR testing and phone or in-person (standard) monitoring of health status: Group 2, PST Protime® device with standard monitoring; Group 3, in-hospital testing with HealthBuddy® monitoring of health status; and Group 4, patients with both devices. Neither technology has been used for military patients using Coumadin®, although the VA has used HealthBuddy® for diabetic patients. Preliminary studies have shown improved time in range for INR with PST, although complication rates and adverse outcomes were not discussed. This protocol does not include patient self-management, although it will be looked for as a "complication". The study below accepted only established patients.

Watzke HH, Forberg E, Svolba G, Jimenez-Boj E, Krinninger B. A prospective controlled trial comparing weekly self-testing and self-dosing with the conventional management of patients on oral anticoagulant therapy. Thromb. Haemost 1999; 82 (suppl. 8): 219)
While Health Hero Network has conducted patient satisfaction surveys, no outcome data was found on search of the literature. The HealthBuddy has been used in a number of health conditions.

No subjects have been enrolled, none have withdrawn, and there have been no adverse events reported since the last APR (2000). Enrollment was suspended while the protocol was being reviewed. Current participants will be offered continuation in the revised study in their original groups of assignment.
The number of subjects enrolled to the study since last APR at WRAMC is __0__ and the total enrolled to date at WRAMC is ___2____. The total number enrolled study-wide is __NA_____, if multi-site study.

CONCLUSIONS

This protocol has now been amended and expanded to 4 groups totaling 400-420 patients as described above. It will now also include approximately 48 patients newly beginning on Coumadin® therapy and as such requiring frequent testing in a group unfamiliar with Coumadin® usage before education. Interim data have not been analyzed as only 2 patients had been enrolled prior to amendment. Approval to enroll for the revised study was granted on 13 March 2001. The consent form was revised and given a DCI stamp with the original protocol approval date of 6/16/98 and consent form approval date of 7/18/00: a copy of this form is at DCI. Health Hero Network has agreed to provide up to 200 HealthBuddies® with support at no charge to the government and ITC has agree to increase its number of loaned ProTime® PST units with support again at no charge to the government. A database of active, long-term established Coumadin® Clinic patients was generated and eligible patients randomized. Enrollment is projected to resume May 2001

Report Date: 20 October 2000

Work Unit #1220-98

DETAIL SUMMARY SHEET

TITLE: Troponin I, Troponin T and T and CKMB for the Rapid Detection of Myocardial Infarction and Determination of 30-Day Prognosis

PRINCIPAL INVESTIGATOR: Thomas, William MAJ MC
ASSOCIATES: Jeschke, Robert CPT MC

DEPARTMENT: Medicine
SERVICE: Cardiology

STATUS: T*
INITIAL APPROVAL DATE: 04 August 1998

STUDY OBJECTIVE

To determine whether Troponin I or Troponin T will detect myocardial infraction earlier than CKMB. To determine whether Troponin I, Troponin T, or CKMB has greater sensitivity and specificity for 30 days cardiac events in patients with admitted chest pain.

TECHNICAL APPROACH

No change from protocol approved 04 August 1998. Specifically, this is a prospective observational study evaluating predetermined clinical endpoints and their association with values obtained from a prospectively collected database of serum troponins and CKMB levels. Patients who were admitted, during the studies enrollment period, to WRAMC intensive care units for evaluation for an AMI and whose serum troponin and CKMB levels were entered in the original pathology database were eligible for enrollment. Inclusion criteria were as follows: (1) Consecutive patients willing to have one clinical follow-up by telephone at 1 to 6 months after admission to the ICU for evaluation of an AMI; (2) Patients who had serum troponin 1, troponin T, and CKMB (plus total CPK) levels measured at presentation, 4hrs and 8hrs, in addition to CKMB and total CPK measured at 12 or 24hrs, with results available in the hospital database. The hospital laboratory database was queried and analyzed for troponins and CKMB's comparing categorical variables (positive or negative) at 4 and 8hrs from presentation and continuous variables being time (hrs) to first positive level. The reference standard (gold standard) used for the diagnosis of an AMI will be the presence of index symptoms (chest pain) plus: (1) a positive CKMB at <24 hrs, or (2) new diagnostic Q-waves on EKG.
A negative Troponin 1 will be defined as a level less than 0.4 ng/ml (Abbott assay)
A negative troponin T will be defined as a level less than 0.1 ng/ml (Boehringer assay)
A negative CKMD will be defined as CKMB units <8 ng/ml (Abbott assay)
The clinical database will be analyzed comparing positive serum cardiac markers with major adverse cardiac eventsat 30 days (MACE – death, re-infraction, or urgent revascularization)

PRIOR AND CURRENT PROGRESS

The original pilot database made available from previous principle and associate investigators has been analyzed for suitability for inclusion in the study. This includes a total of 65 patients. Chart review of 30 of those 65 patients has been conducted. An ongoing effort is being made to obtain the full database of those patients enrolled during the data collection period of the study (unsuccessful to date) from the original investigators. Will plan to update the Department of Clinical Investigation within a 2-month time period as to the status of this effort.

CONCLUSIONS

Further data analysis and data review is pending retrieval of the full database. Update to the success of data retrieval will be made to DCI within a 2-month time period.

*On 24 April 2001, the Human Use Committee voted to administratively terminate research protocol Work Unit #1220-98. No further research may be conducted on this protocol. This action was taken because the Committee noted that this protocol had previously been in abeyance due to failure to submit a completed Annual Progress Report, as required by Title 21, Code of Federal Regulations, Part 312.33, and by Army regulations. An APR was later received, reviewed, and a stipulation for approval was that an audit be performed for this study. A change of PI has not been received by DCI. An audit conducted revealed that the intended new PI (Dr. Robert Jerschke) could not locate the existing data for this protocol. The Human Use Committee requires that the Chief, Cardiology Service, be responsible to make every effort to locate the missing research data and, if found, to destroy the information, and provide evidence to DCI of destruction of the information.

Report Date: 13 March 2001

Work Unit # 1223-99

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: Multinational, Multi-center Double-Blind Randomized Active Controlled Parallel Group Study Comparing the Efficacy and Safety of Long-Term Treatment with Valsartan, Captopril, and Their Combination in High Risk Patients After Myocardial Infarction

KEYWORDS: Myocardial infarction, Angiotensin, Congestive heart failure

PRINCIPAL INVESTIGATOR: Allen J. Taylor LTC MC
ASSOCIATES: Thomas Ostronic LTC MC

DEPARTMENT: Medicine
SERVICE: Cardiology

STATUS: O
INITIAL APPROVAL DATE: 25 May 1998

STUDY OBJECTIVE

The primary objective of this study is to compare captopril, valsartan, or their combination in patients with reduced ejection fraction on the prevention of mortality after myocardial infarction.

TECHNICAL APPROACH

After informed consent is obtained, patients are randomized in a double blind, allocation concealed fashion to 1 of the 3 experimental arms. Scheduled dose titration ensues, and patients are tracked for recurrent cardiovascular events.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

The principal aim of this study is to compare the effects of captopril, valsartan or their combination on post myocardial infarction mortality. As of 13 March 2001, this question remains unanswered by the available literature. The results of VAL-HEFT were reported in November 2000 at the Annual Scientific Sessions of the American Heart Association. This study failed to find any mortality benefit of adding valsartan to an ACE-inhibitor for patients with class 2 and 3 heart failure. The post-MI population of VALIANT is an important, high-risk population for which data on the comparison of ACEI vs. ARB is needed.

We began active recruitment 3 April 00. Two WRAMC patients have been enrolled to date (Overall study enrollment worldwide exceeds 10,000). One of these patients died of out-of-hospital sudden cardiac death. Up until the time of death, she had tolerated the study medication during an in-hospital titration phase. She was known to have congestive heart failure with multi-vessel, extensive coronary artery disease that was not amenable to revascularization. In many randomized trials, ACE inhibitors and angiotensin-receptor blockers have been shown to be protective from sudden cardiac death. Thus, her death was attributed to cardiac causes, determined not related to study drug.

The number of subjects enrolled to the study since last APR at WRAMC is 2 and the total enrolled to date at WRAMC is 2. The total number enrolled study-wide is 10,000.

CONCLUSIONS

Enrollment is ongoing at WRAMC. The target enrollment of approximately 14,000 patients will likely be completed within the next 12 months.

Report Date: 3 August 2001

Work Unit # 1224-99

DETAIL SUMMARY SHEET

TITLE: Non-Invasive Coronary Artery Disease Reversal

KEYWORDS: Heart Disease Reversal; Lifestyle Modification; Coronary Artery Disease

PRINCIPAL INVESTIGATOR: Vernalis, Marina COL MC
ASSOCIATES: Ocuin, Esther LTC MC

DEPARTMENT: Medicine
SERVICE: Cardiology

STATUS: O
INITIAL APPROVAL DATE: 21 September 1999

STUDY OBJECTIVE

The overall purpose of this study is to determine if comprehensive lifestyle changes (low-fat vegan diet supplemented with soy and antioxidants, moderate aerobic exercise, stress management, and group support) can slow, stop or reverse the progressive of coronary artery disease. Specific objectives are as follows:

1. To investigate the efficacy of intensive lifestyle modification in improving the clinical status of patients with moderate to severe coronary artery disease (CAD) measured by a 50% reduction in angina frequency. Secondary endpoints to this objective will measure New York Heart Association (NYHA) class and exercise time.
2. To investigate the effect of intensive lifestyle modification on levels of CAD associated "markers" (such as lipids, homocysteine, C-reactive protein and fibrinogen) via development and analysis of study data banks.
3. To investigate the effect of intensive lifestyle modification on measurements of established CAD (such as exercise tolerance, NYHA functional class, angina, blood pressure and weight).
4. To determine if a disciplined military active duty and retired patient population can achieve and adhere to the goals of this lifestyle change program in a non-residential, outpatient setting. This will be determined using patient questionnaires addressing degrees of observance of the program's components.
5. To determine the potential effects of the program on DoD healthcare expenditures for CAD treatment.
6. To establish a sera bank for possible future research of markers as yet unidentified.

TECHNICAL APPROACH

A. Study Design

This ongoing study is designed as a prospective, non-randomized, single-arm (treatment), observational trial, in which each individual serves as his/her own control, comparing outcomes to baseline data.

The Non-Invasive Coronary Artery Disease Reversal protocol received final approval by the WRAMC DCI on 21 September 1999. Required revisions were received on 28 January 2000.

B. Study Addenda

On 23 May 2001, the WRAMC Human Use Committee (HUC) approved advertisement for the study. The WRAMC HUC approved an addendum, consisting of change of location for stored sera samples and modifications to the inclusion/exclusion criteria, with required revisions on 22 June 2000. This addendum requested changes in the inclusion criteria and addition of carotid ultrasound. This consent form will be instituted with recruitment of study participants for Cohort #3. Additionally, an expedited addendum was approved by DCI on 28 July 2000. No changes in the consent form were necessary. This addendum allowed for the repeat collection of labs and survey questionnaires in cases where the enrolled participant had to be delayed in initiating the program either due to a revascularization procedure or some other extenuating circumstances. This repeat data allows for a more accurate medical picture of the participant at the time of program initiation. An addendum dated 17 February 2001 was received by DCI and was approved by HUC on 27 February 2001 and 19 June 2001. Final revisions were received on 5 July 2001. This addendum requested clarifying language in consent form of approved stress testing under the protocol. Only pharmacologic or treadmill stress testing is approved, including exercise stress echocardiograms. No nuclear (thallium) stress testing, either pharmacologic or treadmill, is included in the protocol. This clarification was required after a review of our research records revealed 6 follow-up thallium stress tests conducted under the auspices of this protocol that were not clinically indicated. An approved letter has been sent to the participants involved explaining their radiation exposure.

PRIOR AND CURRENT PROGRESS

The number of subjects enrolled to the study since last APR at WRAMC is 55 and the total enrolled to date at WRAMC is 85. Beginning February 2000, the CADRe Clinical staff began enrollment of the first cohort. Currently, five cohorts are in various stages of the program.

Of the 85 participants enrolled, 74% have a documented history of hypertension; 23.5% are diabetics and 75% are currently using lipid-lowering drug therapy for hypercholesteremia.

In summary, 85 patients have enrolled in the study. There are currently 48 patients actively participating in the maintenance program; 21 have completed the program. Of these twenty-one, nineteen have completed the one-year follow-up testing. Thirteen patients (15.3% dropout rate) have either voluntarily withdrawn or have been medically withdrawn from the study. There are currently 4 enrolled patients that have been deferred to a later retreat date. Of the 85 patients enrolled, mean age is 61.66 years, 32.9% are female and 72% have documented coronary artery disease. Of the 72% that have documented coronary artery disease, 60% have had at least one revascularization procedure. Eleven of the enrolled patients are active duty, 51 are retired beneficiaries and 23 are family members. All branches of the service are also represented in this sample.

Adverse events related to subject

There has been one serious adverse event in the course of this study. Participant died as a result of a massive right hemisphere hemorrhagic CVA.

All adverse events (Death, ER visits, hospitalizations, etc) have been submitted to WRAMC Department of Clinical Investigations (DCI) for review. Based on a recent review conducted by the DCI Human Use Committee, a recommendation has been submitted to the principal investigator to amend the current consent form. The committee has suggested the following language be included "possible risk of salt overload" and "risk of coronary event and musculoskeletal injury as a result of exercising". An addendum will be submitted based on these recommendations.

Patient withdrawal from study

As previously stated, 13 participants have withdrawn from the program. One was withdrawn as a result of death, six relayed a lack of commitment to continue with the program, two could not begin the program as a result of their active duty spouses' unexpected reassignment, one disenrolled to seek other treatment options, three disenrolled after exacerbation of chronic illness and one disenrolled for cardiac instability as a result of the screening process. One participant withdrew from Cohort 3 as a result of finding out of state employment upon retirement. However, this participant re-enrolled upon return to the local area and is now participating in Cohort-4. Therefore, at the present time, there has been a 15.3% drop rate.

Preliminary results and conclusions

The retreat (Week 1) for all five cohorts has gone very well. Spouses were highly encouraged to participate in the retreat. Participant evaluations of all aspects of the weeklong retreat were highly positive and motivating.

The participants have received the Maintenance Program very well. In April 2001, CADRe spearheaded its first evening maintenance program. This has been received very positively from our working and active duty participants. An interim review of participant adherence for all cohorts has been at the 6-8 week mark into the maintenance program. This provides a "snapshot of progress" during the entry stage of their program adherence within the various modalities (i.e. stress management, diet and exercise).

In February 2001, the program provided space for the participant's "Community Day". This allocation of space was made at the recommendation of Cohort 1 participants. Upon completion of Stage 2, they wanted to continue to meet in a central location on a monthly basis and begin developing their "self-directed" community as outlined by Dr. Dean Ornish. In order to facilitate this request, the CADRe program allocated one of the multipurpose rooms for one hour the second Monday of each month. This "Day" is open to any study participant and provides the cohorts an opportunity to gather without supervision or structure from the CADRe Clinical Staff. It is clearly communicated to each cohort that this "Day" is not part of the study and they are not obligated or required to participate. However, the Clinical Psychologist supporting the program has agreed to facilitate this group. Attendance has averaged 5-10 participants per month.

In June 2001, individual final progress report sessions were held for the seven Cohort 1 participants. This session was two-fold: (1) provide the participants an opportunity to give the clinical team feedback about the program, and (2) provide the participants with a summary of their program adherence within the various modalities over the entire 52-week study period. In addition, each participant was given a summary of his or her individual study outcomes. No aggregate

data was provided to the members of this cohort. This session also provided the clinical staff an opportunity to encourage continuity of care with both primary and specialty providers.

Beginning with Cohort 4, carotid intima media thickness (CIMT) measurements were collected at baseline. These studies will be collected on each subsequent cohort at baseline and one year. Baseline testing has been done on 34 participants. There is not comparative data as yet.

CONCLUSIONS

Preliminary results in this small sample suggest this lifestyle program has a favorable short-term effect in lowering certain CAD associated risk factors (weight, body fate, blood pressure, total cholesterol, low density lipoprotein). However, no conclusions should be drawn at this time.

Additionally, samples of baseline and 3-month frozen sera on 32 of the participants were sent for analysis of lipid concentrations and apo A-I/A-II concentrations. Of these 32 participants, 84.4% (n=27) bad CAD. The remaining 5 had cardiovascular risk factors. Statin therapy (23/32 pts; 72%) was held stable during the 12 week period. Apo A-I and apo A-II concentrations were measure nephrometrically on a Cobas Fara II analyzer using turbidometric immunoassay. For these 32 patients, dietary and program compliance was high. Total, LDL, and HDL cholesterol all were significantly reduced after the 3-month dietary intervention, whereas triglycerides increased (see Table). The reduction in HDL was associated with a significant fall in apo A-I level (baseline 142 ± 5 v. 34 ± 5; P=.11). The adverse HDL and apoprotein effects were unrelated to concurrent statin therapy. In this small sample, this lifestyle program has a favorable short-term effect on LDL cholesterol. However, its effects on HDL and triglycerides are unfavorable, and include preferential reductions in the concentration of apo A-I. These data indicate that the early HDL effects on a low fat diet are not overcome by other lifestyle changes including exercise.

Report Date: 4 September 2000 Work Unit # 00-1301

DETAIL SUMMARY SHEET

TITLE: The Effect of Retinols, Tamoxifen and Octreotide on Cellular Proliferation and Control of Thyroglobulin, TSH Receptor and Sodium-Iodide Synporter mRNA Expression in Thyroid Cancer Tumor Cell Lines

KEYWORDS: Retinols, Tamoxifen, Octreotide, Cellular Proliferation, Thyroglobulin, TSH Receptor, Sodium-Iodide Symporter, Thyroid Cancer, Tumor Cell Lines

PRINCIPAL INVESTIGATOR: Burch HB
ASSOCIATES: Rhooms PK

DEPARTMENT: Medicine
SERVICE: Endocrine

STATUS: O
INITIAL APPROVAL DATE: 5 October 1999

STUDY OBJECTIVE

To assess the effect of retinols, tamoxifen, and octreotide on cellular proliferation and control of thyroglobulin, TSH receptor and sodium synporter mRNA expression in thyroid cancer tumor cell lines.

TECHNICAL APPROACH

To apply quantitative PCR to the measurement of changes in the above mRNA levels in response to the above effectors. IN addition, a cellular proliferation assay will assess the effects of these mediators on cellular proliferation.

PRIOR AND CURRENT PROGRESS

Follicular thyroid cancer cell lines sought, received, and established. Assay standardization underway.

CONCLUSIONS

Studies underway.

Report Date: 14 December 2000 Work Unit #00-1302

DETAIL SUMMARY SHEET (Human Use Protocol)

TTTLE: The Effect of Omeprazole Therapy on Serum Calcitonin (CT)

KEYWORDS:

PRINCIPAL INVESTIGATOR: CPT Jeannie Baquero MC
ASSOCIATES: MAJ Victor Barnet MC, Barbara Solomon DSNc, CPT Mark Cummings MC, COL Roy K.H Wong, MC

DEPARTMENT: Medicine
SERVICE: Endocrine

STATUS: O
INITIAL APPROVAL DATE: 1 February 2000

STUDY OBJECTIVE

Determine the effect of omeprazole therapy on serum calcitonin levels.

TECHNICAL APPROACH

The study is an observational descriptive study. Patients currently taking omeprazole will be recruited from the GI Clinic to have a single blood draw for this study. Patients eligible for the study will have a brief history and thyroid examination performed by one of the endocrinology investigators. Samples will be drawn and labeled in such a fashion that all assays are performed in a blinded manner. Blood will be batch analyzed for serum gastrin and calcitonin by Quest Diagnostics, 33608 Ortega Highway, San Juan Capistrano, CA 92690-6130. All samples will be collected and stored in the Endocrinology Clinic. The samples will be sent by the Endocrine clinic to Quest and assayed as a batch to minimize inter-assay variation. Any excess of the samples will be discarded after the results are completed. Subjects will not be informed of the experimental lab results unless calcitonin levels are elevated greater than 100pg/ml. If this occurs the subject will be referred to the Endocrinology Service for additional evaluation.
Data collected will include the omeprazole dose, time of dose, age, gender, thyroid history, and thyroid examination of participants. Serum gastrin and calcitonin will be measured at <1 month, 1-6 month, >6-12 months, >12 months after starting therapy. The data will be collected using a data collection form. Each patient will be given a unique identifier that will be used on a master list kept in the endocrinology clinic. This identifier will be used on the master data sheet to maintain patient confidentiality. For each time range (<1 month, >1-6 months, >6-12 months, >12 months) 13 patients will be included for each of the two omeprazole dose ranges (20mg or >/= 40 mg Qd). This is an addendum to previous dose ranges of </= 40 mg Qd and >40mg Qd. Twenty-six subjects will be in time range (104 patients) plus the prospective group that will be followed at two additional time points (52 additional samples). This total is 156 data points.

PRIOR AND CURRENT PROGRESS

Amendments to research include: change in the two omeprazole dose ranges to 20 mg QD and >/= 40 mg QD. Our current enrollment to date includes 74 subjects: There have been no adverse reactions from this study, and no patients have been withdrawn from this study.

CONCLUSIONS

Secondary to a large coefficient of variation, a batch analysis will be done at the conclusion of our study. No conclusions have been made to date.

Report Date: 5 January 2001 Work Unit #00-1303

DETAIL SUMMARY SHEET (Human Use Protocol)

TTTLE: Galectin-3 Levels as a Marker of Thyroid Cancer in Fine-Needle Aspiration (FNA) Samples

KEYWORDS: Thyroid Cancer, FNA

PRINCIPAL INVESTIGATOR: LTC Victor Bernet, MC
ASSOCIATES: J. Anderson, Y..Vaishnav, B. Solomon, K. Burman, M. Ringel, M. Saji, C. Adair

DEPARTMENT: Medicine
SERVICE: Endocrine

STATUS: O
INITIAL APPROVAL DATE: 8 February 2000

STUDY OBJECTIVE

- Confirm and expand the previously reported immunohistochemical findings that Galectin-3 staining us found predominantly in papillary and follicular thyroid cancer tissue in contradistinction to benign nodules and normal thyroid tissue.
- Develop a quantitative RT-PCR assay to measure levels of Galectin-3 in thyroid tissue.
- Assess the level of Galectin-3 mRNA expression in various types of benign and malignant thyroid histo-pathology samples.

TECHNICAL APPROACH

Patients undergoing thyroidectomy for standard clinical indications consented to have their removed tissues be "snap frozen" in liquid nitrogen and stored at -70° C. In total, 38 such histopathologically diagnosed frozen tissue frozen tissue specimens consisted of 7 normal (NL), 9 benign (BN), 7 papillary thyroid cancer (PTC), 9 follicular thyroid cancer (FTC) and 6 follicular adenoma (FA) were included in this study. Genomic RNA from these frozen specimens was recovered using a standard Trizol method (Tri Reagent ®, Molecular Research, Inc.) A quantitative RT-PCR was developed for Gal-3 using a sequence specific ogligonucleotide probe and forward and reverse primers. A 103 bp long Gal-3 c-DNA segment, spanning thee junction of exon 4 and 5 (GeneBank ACC# NM_002306) was amplified using the forward primer: ACGGTGAAGCCCAATGCA and reverse primer TGACTCTCTCCTGTTGTTCTCATTGAA; and antisense probe AATGATGTTGCCTTCCACTTTAAC CCAGG labeled with 5'-reporter dye (FAM) and 3'-quencher dye (TAMRA). To help validate the kinetic quantitative RT-PCR method, human thyroid m-RNA (Clontech) was utilized for the construction of standard curves and GADPH (glyceraldehydes-3-phospate dehydrogenase) m-RNA was used as an endogenous reference for Gal-3. The m-RNA templates were excluded from the negative standards. For each sample, the amount of target (Gal-3) and the endogenous reference were determined from the calibration curves. The target amount was then divided by the reference amount to obtain normalized values. Two techniques, agarose gel electrophoresis and cycle sequencing were utilized to confirm the identity of the PCR amplified 103 bp-c-DNA segment (Gal-3).

PRIOR AND CURRENT PROGRESS

We isolated total RNA from 19 "snap frozen" surgical samples including 5 papillary cancers, 2 follicular cancers, 1 follicular adenoma, 5 "benign" nodules, and 5 samples from normal thyroid tissue adjacent to the papillary cancers. Levels of Gal-m-RNA were determined by real-time quantitative RT-PCR using non-intron spanning Gal-3 primers and an internal fluorescent probe and were normalized to simultaneously measured GAPDH mRNA. Product size was confirmed by gel electrophoresis. Levels of Gal-3 mRNA were higher in papillary cancers than normal tissue (2120 vs. 348.5 pg/ng GAPDH mRNA, p=0.008). However, levels of Gal-3 mRNA were not increased in follicular carcinomas compared to normal (351.2 vs. 248.5 pg/ng GAPDH mRNA). Gal-3 mRNA was also not elevated in either benign nodules or in one benign follicular adenoma.

CONCLUSIONS

- Results indicate that Gal-3 can indeed be amplified and quantitatively measures by RT-PCR from mRNA isolated from thyroid histology samples.
- The high level of Gal-3 in the PTC samples in this study are consistent with prior immunohistochemical studies which revealed increased Gal-3 in PTC lesions, as also is the fact that benign
- However, Gal-3 levels found in FTC and FA samples were not different, being similarly higher than NL/BN samples, and less than PTC and normal thyroid tissue had only low levels of Gal-3 detected.

We are now actively working on the next portion of the study trying to isolate and amplify Gaectin-3 mRNA from selected thyroid slides as approved under an interim addendum. Once this phase is completed, we plan to progress to the prospective arm of the study as approved.

Report Date: 18 May 2001

Work Unit # 00-1304

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: Investigations of Activation of BAG-1 and p73 Genes in Thyroid Cancer in Tissue

KEYWORDS: Thyroid cancer, molecular markers, protein, immunohistochemical analysis, mRNA, RT-PCR, BAG-1, p73

PRINCIPAL INVESTIGATOR: Yashesh Vaishnav
ASSOCIATES: Victor Bernet; Henry Burch; Carol Adair; Jeffery Anderson; Brian Reinhardt

DEPARTMENT: Medicine
SERVICE: Endocrine

STATUS: O
INITIAL APPROVAL DATE: 13 June 2000

STUDY OBJECTIVE

1. To identify activation of the potential cancer genes BAG-1 and/or p73 in thyroid cancer tissue
2. To explore if we can quantitatively amplify expression levels of BAG-1 and/or p73 mRNA isolated from cancerous thyroid tissue
3. To determine whether levels of BAG-1 and/or p73 isolated from cancerous thyroid tissues can be used as markers of different subclasses of thyroid cancers.

TECHNICAL APPROACH :

Qualitative Assessment of BAG-1 and p-73 gene by Immunohistochemical Analysis: For qualitative assessment of BAG-1 and p73 in normal (5 BN) and cancerous (5 PTC, 5 FTC) tissues, paraffin-embedded thyroid tissues were obtained from WRAMC Pathology paraffin-embedded tissue archives. The immunohistochemical analysis for BAG-1 and p73 were performed. Briefly, paraffin-embedded tissues were sectioned (4-5 μM thick) and mounted on a silicon-coated glass slides in triplicates. The slides were deparaffinized in zylene and rehydrated through a series of decreasing content of ethanol solution, and finally in distilled water. Endogenous peroxide activity was quenched using 6% hydrogen peroxide in methanol for 15 minutes. Slides were then placed in a humid chamber and incubated at room temperature for 30 minutes with 10% normal goat serum (D30025, Dimension Laboratories) in phosphate buffer saline containing 0.1% Triton X-100 (Sigma Chemical Co., St. Louis, MO) to block nonspecific staining. Sections were routinely incubated overnight at 4° C with either polyclonal antibody with either BAG-1 or p73. Sections were next incubated for 30 minutes with 200x dilution of biotinylated goat antirabbit IgA (BA-1000, Vector Laboratories, Inc., Burlingam, CA). Slides were washed extensively with phosphate buffered saline between each of the above steps. Sections were then exposed to diaminobenzadine (D-5637, Sigma) peroxidase substrate solution for 5 minutes, and then washed with distilled water to stop the diaminobenzadine reaction. The sections were then rehydrated through a graded ethanol series and xylene, then coverslipped using Permount (SP153-100, Fisher Scientific Co.) For the positive control, sections known to stain positively were included in each batch; and, for the negative control, sections were prepared by replacing primary antibody with mouse or goat ascites fluid (Sigma Chemical Co.). All slides were examined by 3 investigators. The investigators were blinded to clinical and pathological information of the specimens.

Quantitative Assessment of BAG-1 from the Paraffin-embedded Tissues by Quantitative RT-PCR: Total RNA from sections (6 μM thick) from 15 Paraffin-embedded tissue samples (5 BN, 5 FTC and 5 PTC) were extracted for deparafinization with xylene and ethanol treatments and from these specimens total RNA was extracted in Trizol (Sigma). The details of the RNA recovery procedures were included in the original Protocol (WU-001304) in the technical Appendix IA and IB. These techniques have been previously used at WRAMC with very good results. The RNA recovered served as substrate for quantitative reverse transcriptase polymerase chain reaction (RT-PCR) amplification. The extracted total RNA isolated from the tissue specimens was subjected to RT-PCR in a duplicate manner using GGAGGAAATGGCGGCAG as

the forward primer and GGTCGTGCTTCTCATTGCTG as the reverse primer (PCR product size = 62 b.p.). To quantitatively amplify BAG-1 using ABI PRISM 700 Sequence Detection System with a fluorescent-labeled BAG-1 specific oligonucleotide probe CCTTCAACACCCCAGCCATGTACGTT (Taqman Probe) was utilized. To help validate the kinetic quantitative RT-PCR method, calibration curves were constructed using human thyroid mRNA (Clontech). The human thyroid mRNA was serially diluted to produced a standard curve that ranged from 8 pG - 2000 pG using 5 different concentrations. No mRNA template was used for the negative controls. β-Actin gene was used as endogenous reference BAG-1. For β-actin, GCGAGAAGATGACCCAGATCAT (forward primer) and (GGTACGGCCAGAGGCGT (reverse primer) were used; and β-actin specific probe for quantification purposes of β-actin TaqMan Probe CCTTCAACACCCCAGCCATGTACGTT. The amount of the target gene and endogenous reference for each sample was determined from the calibration curves. The target amount was divided by the reference amount to obtain the normalized target values.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Summary of Recent Literature:

Despite of recent progress in understanding cancer at the level of regulatory gene/protein expression, the diagnosis of thyroid cancer remain and ongoing problem. Thyroid nodules are very common, and have 5-20% chances of being malignant. Thyroid cancer is the most frequently occurring endocrine malignancy; however, preoperative diagnosis of some lesions, in particular with follicular histology, is difficult, and consistent number of cases assessed by cytology/FNA as 'Follicular adenoma' are surgically resected more for diagnostic than therapeutic purposes (Ref 1). Presently, there is much need in discovering a reliable molecular marker or set of markers for aiding clinicians in identifying benign from cancerous thyroid nodule.

Carcinogenesis is a multistep process characterized by multiple genetic alterations including activation of oncogenes, and inactivation of tumor suppressor genes (Ref 2). Program cell death (apoptosis) processes play important role in carcinogenesis. Apoptosis is a ubiquitous process in which a cell commits 'suicide' under certain environmental conditions. Increasing evidence suggest that apoptosis is controlled through the expression of many cellular proteins as either inducers or inhibitors of apoptosis. It has been also suggested that the qualitative and quantitative defects in apoptosis regulating genes are important in pathogenesis of human cancers (Ref 3). Several genes, Bcl-2, Bcl-X_L, Mel-1 are identified as apoptosis inhibitors, and Bax, Bcl-5, Bacl, Bak are as apoptosis inducers. More recently, potential cancer markers BAG-1 (Ref 4-6) and p-73 (Ref 7, 8) are identified as apoptosis inhibitors and inducers, respectively in a variety of cancer tissue types: although, their roles in regard to thyroid nodule or cancer have not been examined, yet. Therefore, the ability to identify and quantify the presence of BAG-1 and p73 in thyroid nodule is important and being studied in our laboratories. This novel approach could potentially be useful in the management of patients with inconclusive diagnosis.

The immunohistochemical and Western blot techniques for the assessment of BAG-1 and p-73 proteins and Northern blot procedure for the assessment of BAG-1 m-RNA utilized in the referenced articles, are qualitative or semiquantitative in nature. These procedures are limited by relatively low sensitivity and are time consuming. These qualitative and quantitative assays, although potentially useful, are not automated . In an effort to enhance the sensitivity, selectivity and specificity of these assays we are currently developing an alternative method for the quantitative assessment of BAG-1 mRNA and p-73 mRNA in normal and cancerous tissues using RT-PCR amplification of thyroid-specific mRNA (BAG-1 and p-73). This will provide a promising alternative assay system to evaluate normal versus cancerous thyroid tissues.

Study Findings Obtained Thus Far:

BAG-1 Studies: Our research group set out to determine if BAG-1, a multifunctional antiapoptotic protein previousiy identified in breast cancer, is expressed in thyroid tissue. In addition, if found to be expressed in thyroid tissue, might BAG-1 be a suitable marker for thyroid cancer. Slides prepared from 15 paraffin block specimens were examined utilizing immunohistochemical techniques with a BAG-1 specific IgG antibody. These samples included papillary thyroid cancer (PTC), n=5; follicular thyroid cancer (FTC), n=5; and normal thyroid, n=5. Slides were interpreted for the presence of BAG-1 staining by three separate reviewers who were blinded to the histological diagnosis. All three reviewers consistently noted

BAG-1 staining in the cytoplasm of all 15 specimens. The intensity of cytoplasmic staining was judged to be variable from weakly to strongly positive, but no consistent pattern of staining was found which would permit differentiation between the varying types of thyroid tissue whether cancerous or normal tissue. In an attempt to determine if quantitative RT-PCR assessment of BAG-1 expression would allow differentiation of PTC, and FTC from NL, RNA was isolated from 15 paraffin block tissue specimens (PTC, n=5), (FTC, n=5), and NL, N=5). Levels of BAG-1 mRNA were determined by real-time quantitative RT-PCR using BAG-1 specific primers with an internal fluorescent probe, with values normalized to simultaneously measured $_{\beta}$-actin. mRNA. The following levels of BAG-1 [ng BAG-1/pg $_{\beta}$-actin mRNA] expression were determined: NL 1250 ± 837, PTC 1136 ± 951, and FTC 2510 ± 1901. Statistical analysis did not reveal any significant difference between the groups, despite the trend for BAG-1 to be somewhat higher in the FTC lesions.

P73 Studies;

Similar to BAG-1, parallel studies for evaluations p73 protein are also being performed utilizing immunohistochemical staining in FTC (n=5), PTC (n=5) and NL (n=5) paraffin-embedded thyroid tissue. However, thus far we have not detected significant staining in either NL or PTC, FTC tissue specimens perhaps due to very low expression of p73 protein in both normal and cancerous thyroid tissue. At the present time, it seems to us very likely that we could iron out this problem by amplifying the signals by using higher concentration of the antibody than what we have been utilizing. We have the necessary kit (reagents) for the minor modification of our normal procedure.

Amendment or Modification to the Research Study Since the Last Review: None

Adverse Events/ and /or /Expected: None Serious AE for other Site: N.A.

Information on Patients Withdrawal from the Study: N.A. (none)

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The number of subjects enrolled to the study since last APR at WRAMC is N.A. and the total enrolled to date at WRAMC is N.A.. The total number enrolled study-wide is N.A, if multi-site study.

CONCLUSIONS

BAG-1 Studies: At the present time, the preliminary results of the BAG-1 studies do not indicate that BAG-1 expression will be useful marker for the detection of thyroid cancer. The limited number of specimens in this study may have restricted the ability to establish a difference by RT-PCR in BAG-1 expression between the groups, and consideration is being given to test a larger number of samples.

p73 Studies: p73 studies are still remain inconclusive until the amplification of immunohistochemical staining signals can be amplified. Currently work is being performed to amplify the slide staining signals.

Report Date: 12 June 2001 Work Unit # 00-1305

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: A 20 Week Multicenter, Double-Blind, Randomized Parallel-Group Fixed Dose Study to Prospectively Evaluate the Efficacy, Safety and Tolerability of Oral Nateglinide Monotherapy (120 mg), Compared to Oral Rosiglitazone Monotherapy (8mg) in Patients with Type 2 Diabetes Mellitus Inadequately Controlled With Diet and Exercise Alone

KEYWORDS: Nateglinide; Rosiglitazone; Diabetes Mellitus

PRINCIPAL INVESTIGATOR: Robert A. Vigersky COL MC
ASSOCIATES: Barbara Solomon, DNSc

DEPARTMENT: Medicine
SERVICE: Endocrine

STATUS: O
INITIAL APPROVAL DATE: 18 July 2000

STUDY OBJECTIVE:
Primary:
1. Evaluate the effect of nateglinide monotherapy compared to rosiglitazone monotherapy on glycosylated hemoglobin (HbA_{1C}) after 20 weeks of double-blind treatment in patients with Type 2 diabetes mellitus inadequately controlled by diet and exercise alone.
2. Evaluate the safety and tolerability of nateglinide monotherapy and rosiglitazone monotherapy.
Secondary:
Evaluate the effect on prandial glucose, insulin, C-peptide, fasting lipid parameters (total cholesterol, triglycerides, LDL-C, HDL-C), fasting plasma glucose (FPG) and body weight after 20 weeks of double-blind treatment of nateglinide monotherapy compared to rosiglitazone monotherapy in patients with Type 2 diabetes mellitus inadequately controlled by diet and exercise alone.

TECHNICAL APPROACH:
Investigational therapy and reference therapy:
Nateglinide tablets will contain either 120 mg (FCN 3742038.00.009C; .010C) or matching placebo (FCN 3741865.00.013H; .018H). Rosiglitazone 4 mg capsules will be purchased commercially and will be blinded to match the corresponding placebo capsules.
All labels will be in the local language and will comply with local regulations. Labels will bear a letter A (nateglinide medication tablets) or B (rosiglitazone medication capsules), the period of the study for which the contents should be used, the randomization number (where appropriate), and details about correct storage.
Period I: Single - Blind Period Dosing Instructions
The first dose of Period I medication will be administered as the first main meal dose after the completion of all procedures at the week -4 visit. The last dose of Period I medication will be the dose taken with the meal challenge at the week 0 visit. . In order to maintain the study blinding, subjects should not be informed that they are on placebo medication during the first 4 weeks of treatment.
Period II: Double - Blind Period Dosing Instructions
The first dose of nateglinide Period II medication will be the first main meal dose after the completion of all procedures at the week 0 visit. The last dose of period II medication will be the dose taken with the meal challenge at the week 20 visit.
General Dosing Instructions
Subjects must be instructed on the following points related to study medication dosing:
Take one tablet from Bottle A, 1-30 minutes before breakfast, lunch and dinner. Take two capsules from Bottle B with breakfast. If breakfast is missed, take two capsules from Bottle B with the next meal.
Plan regularly scheduled meals (breakfast, lunch, dinner), so as not to deviate from the dosing regimen.
If a meal is missed, do not take the study medication from Bottle A. Do not take the morning dose of study medication (Bottle A or Bottle B) or eat breakfast on the day of a scheduled study visit. After each study

visit, the first dose of study medication (Bottle A and Bottle B) should be taken before their next main meal.

Treatment assignment

After satisfying the Week -4 inclusion/exclusion criteria, each patient will receive a unique subject identification number. After meeting the Week 0 inclusion/exclusion criteria, each patient will be randomized to one of the treatment groups.

Blinding

The double dummy blinding of the study will be maintained by the use of identical placebo and active tablets/capsules for each study drug.

Concomitant therapy

The use of the following medications may interfere with the study evaluations and interpretation of study results and therefore is not permitted. Any antidiabetic agent other than those permitted by the protocol. This includes all sulfonylureas within 5 months prior to week -4, and all other oral antidiabetic agents (biguanides, repaglinide, α-glucosidase inhibitors and thiazolidinediones) within 4 weeks prior to week -4 and during the full course of the study. For those patients taken off oral anti-diabetic medication with the intent to enter the patient in the study, written informed consent will be obtained at the time of discontinuation of medication. It is the physician's responsibility to monitor the patient during this period. Corticosteroids except those taken by inhalation or by topical application. Change in dosage of thyroid supplement within 3 months prior to Week –4 or during the study. All other prior non-study medication(s) will be allowed, provided the need for such medication(s) is a continuation of a need that existed prior to entry into the study and the manner with which these medication(s) will be used remains essentially unchanged. Sugar-containing (syrups) and sympathomimetic (e.g., Sudafed®) preparations should be avoided. If any medication other than those being taken at Week -4 is required during the study, the reason will be reported on the Past History or Adverse Event CRF as appropriate and the medication will be reported on the Concomitant Medications or Significant Non-Drug Therapies CRF.

Treatment compliance

Patients will be instructed to return medication bottles to the study site at each visit.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE:

There have been 3 Amendments to the Protocol:

Amendment 1 changes the sulfonylurea treatment period from with 5 months of week –4 to within 2 months of week –4. Amendment 2 changes the inclusion criteria for Period I from a medical history of Type 2 diabetes mellitus of ≥ 3 months and ≤ 5 years to only ≥ 3 months. In addition, the exclusion criteria for Period I is raised from 200 mg% to 240 mg%. Amendment 3 reduces the inclusion criteria of HbA1c in Period II from 7.5% to 7.0%.

Enrollment for this multicentered study through May 2001 is 138 patients out of 345 screened. Enrollment has been extended a third time to 30 June 2001.

One each of the following adverse events have been reported none of which were judged to be related to the drug: Ischemic entercolitis, aplastic anemia, hepatic encephalopathy, sudden death, hypoglycemic coma, elevated CRP, hypotension, asthma, hyperglycemia with sudden death, acute elevation in liver function tests, and interstitial pneumonia. All these cases occurred in Japanese centers. Two rashes have been reported – one in the US and one in Japan.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 0. The total number enrolled study-wide is 138, if multi-site study.

CONCLUSIONS:

Due to the strict criteria for enrollment (despite the loosening of the inclusion criteria), no patients have been enrolled in this study to date. It is unlikely that with the upcoming deadline for closure of the enrollment period (unless is it further extended) that there will be any WRAMC patients who participate in this study. Since approval of this protocol, nateglinide has been approved by the FDA for general use under the tradename Starlix.

Report Date: 8 August 2001

Work Unit # 1380-95

DETAIL SUMMARY SHEET

TITLE: Papillary Thyroid Cancer (PTC/ret TPC) Oncogene Activation in Neoplastic Thyroid Tissue Occurring After Exposure to a Nuclear Blast

KEYWORDS: oncogene, radiation, thyroid

PRINCIPAL INVESTIGATOR: Francis, Gary COL MC
ASSOCIATES: Djuh, Yin-Ying MS; Anderson, Jeff; Galvin, Margaret

DEPARTMENT: Medicine
SERVICE: Endocrine

STATUS: C
INITIAL APPROVAL DATE: 19 September 1995

STUDY OBJECTIVE

To determine the frequency of ret proto-oncogene activation in radiation-associated thyroid neoplasia.

TECHNICAL APPROACH

Samples of neoplastic thyroid tissue from fine-needle aspirations and fresh frozen thyroid tissue obtained in the Marshall Islands serve as substrates for the following studies: 1) RT-PCR is used to amplify each of the three described mutational forms of the PTC/ret oncogene; and 2) Presence of the activated mutation is documented by the presence of the chimerical mRNA amplification product of the appropriate size on agarose gel electrophoresis.

PRIOR AND CURRENT PROGRESS

The number of subjects enrolled to the study since last APR at WRAMC is__0__and the total enrolled to date at WRAMC is_80_. The total number enrolled study-wide is__80__, if multi-site study.
A total of 80 samples of thyroid tissue from patients exposed to, radiation have been examined for the presence of ret/PTC mutations. Additional tumors are being extracted for analysis depending on the quality of the DNA, which can be extracted.
From these samples, we have found that ret/PTC mutations are detected in 24% of samples (3 ret/PTC-1 and 2 ret/PTC-3). Additional dosimetry data is being collected to correlate the presence of ret/PTC mutations with the individual radiation exposure.

CONCLUSIONS

This study has progressed well with successful DNA extractions from radiation-induced tumors. The presence of ret/IPTC mutations has been shown, and correlation with absorbed radiation dose is still forthcoming. At this time, we anticipate no additional patient samples will be analyzed. Only data analysis is continuing at this time.

Report Date: 09 February 2001 Work Unit # 1386-96

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: The Effect of Pretreatment With Antithyroid Drugs on the Acute Changes in Thyroid Hormone Levels Following Radioiodine Ablation for Graves' Disease: A Prospective Randomized Trial

KEYWORDS: Graves' disease, Clinical practice, radioiodine

PRINCIPAL INVESTIGATOR: Burch, Henry B LTC MC
ASSOCIATES: Solomon, Barbara RN, Ph.D.

DEPARTMENT: Medicine
SERVICE: Endocrine

STATUS: C
INITIAL APPROVAL DATE: 12 March 1996

STUDY OBJECTIVE

To compare the acute changes in thyroid hormone levels following I-131 therapy for Graves' disease in patients randomized into pretreatment with antithyroid drugs and no pretreatment groups.

TECHNICAL APPROACH

Patients meeting eligibility criteria are randomized into the two arms of the protocol. Baseline serum and serial collection over a period of 2 weeks following I-131 are performed. Serum is placed in labeled tubes and frozen for batch processing.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Study completed. Manuscript is in preparation. No new patients entered since last APR. No active amendments. No adverse events related to protocol.
The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 31. The total number enrolled study-wide is 45, if multi-site study.

CONCLUSIONS

Antithyroid drug pretreatment before I-131 ablation has no effect on the acute changes in thyroid hormone levels following ablation therapy. Long-term effects of pretreatment on cure rate are being assessed as per recent addendum

Report Date: 29 August 2000 Work Unit # 1392-98

DETAIL SUMMARY SHEET

TITLE: Circulating Micro-Metastasis in Patients with Thyroid Neoplasia

KEYWORDS:

PRINCIPAL INVESTIGATOR: Fenton, Cydney L., CPT MC
ASSOCIATES: Gary L Francis, COL USA; Yvonne Lukes DCI

DEPARTMENT: Medicine
SERVICE: Endocrine

STATUS: O
INITIAL APPROVAL DATE: 28 October 1999

STUDY OBJECTIVE

1) Do patients with thyroid cancer have detectable thyroid cells in the peripheral circulation as determined by RT-PCR for Tg-mRNA? 2) Does the presence of Tg-mRNA correlate with clinical staging of thyroid cancer and clinical outcome; 3) Does the presence of Tg-mRNA correlate with expression HGF/cMET or P53; 4) Does the level of Tg-mRNA vary in normal individuals after thyroid palpitation; 5) Can the level of Tg-mRNA be used in conjunction with FNA in the detection of thyroid cancer.

TECHNICAL APPROACH

1) Evaluation of Tg-mRNA levels in normal subjects before and after thyroid palpitation.
2) Evaluation of serum VEGF levels by ELISA patients with benign and malignant thyroid disease/

PRIOR AND CURRENT PROGRESS

Sera have been extracted for determination of Tg-mRNA in a total of 38 patients with benign and malignant thyroid diseases. Tg-mRNA levels are of similar magnitude to those previously found in adults and appear to distinguish disease-free states from persistent thyroid cancer. Tg-mRNA levels in patients with thyroid cancer correlate with total body tumor burden as shown by Tg levels and 131-iodine uptake.

CONCLUSIONS

This study is critically important for our understanding of the biological behavior of thyroid cancers. We have found that Tg-mRNA levels correlate with disease burden and therefore, could be of use in following disease status in patients who have interfering Tg antibodies.

Report Date: 7 March 2001 Work Unit #1395-98

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: Establishment of a Thyroid Patient Serum Bank

KEYWORDS:

PRINCIPAL INVESTIGATOR: Burch, Henry LTC MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Endocrine

STATUS: O
INITIAL APPROVAL DATE: 21 April 1998

STUDY OBJECTIVE
To collect serum from a variety of patients with endocrine disorders to facilitate future research requiring serum.

TECHNICAL APPROACH
Obtain informed consent. Perform standard phlebotomy, centrifuge and store specimens at -70C.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
No patients have requested that their serum sample be removed from the serum bank.
The number of subjects enrolled to the study since last APR at WRAMC is 61 and the total enrolled to date at WRAMC is 158. The total number enrolled study-wide is N/A . No adverse effects have been experienced.

CONCLUSIONS
Serum banking will be used to support other DCI approved protocols.

Report Date: 7 March 2001

Work Unit # 1396-98

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: Establishment of a Thyroid Tissue Bank

KEYWORDS:

PRINCIPAL INVESTIGATOR: Burch, Henry LTC MC.
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Endocrine

STATUS: O
INITIAL APPROVAL DATE: 21 April 1998

STUDY OBJECTIVE

To create and maintain a tissue and fine needle aspiration bank from patients with a variety of thyroid disorders, in order to facilitate future research projects requiring thyroid tissue.

TECHNICAL APPROACH

After obtaining informed consent, a small piece of tissue being removed for clinical indications is snap frozen in liquid nitrogen and stored in a -70 C freezer.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

The number of subjects enrolled to the study since last APR at WRAMC is 26 and the total enrolled to date at WRAMC is 78. The total number enrolled study-wide is NA. No adverse effects have occurred from study involvement.

CONCLUSIONS

Tissue samples to be used in future DCI approved protocols.

Report Date: 17 July 2001

Work Unit # 1398-98

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: Quantitative PCR for the Analysis of TSH-R Gene Expression on the Retroocular Fibroblast

KEYWORDS:

PRINCIPAL INVESTIGATOR: Burch, Henry LTC MC
ASSOCIATES: Anderson, J., Oliver, T., Rhooms P., Lukes Y.

DEPARTMENT: Medicine
SERVICE: Endocrine

STATUS: C
INITIAL APPROVAL DATE: 19 September 1995

STUDY OBJECTIVE

To quantitate extrathyroidal expression of the gene for the TSH-receptor.

TECHNICAL APPROACH

To apply quantitative PCR to the estimation of basal and stimulated expression of the TSH-receptor gene in retroocular fibroblasts.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Primers and probe were designed. A standard curve was generated and the technique applied to successfully quantitate TSH-R gene expression in retroocular fibroblasts. Stimulation studies have been performed using T3 and TSH. Total RNA was extracted from stimulated retroocular fibroblasts from 2 Graves' ophthalmopathy patients and two non-Graves' ophthalmopathy eye surgery patients (all samples previously obtained from Mayo Clinic—no new patients have been enrolled). Fibroblasts used were obtained from immortal cell lines received previously from the Mayo Clinic, according to DCI-approved protocols.

The number of subjects enrolled to the study since last APR at WRAMC is _0_ and the total enrolled to date at WRAMC is _0___. The total number enrolled study-wide is __0__, if multi-site study.

CONCLUSIONS

Quantitiative PCR is a useful mechanism for determining TSH-R expression in retroocular fibroblasts.

Report Date: 05 January 2001

Work Unit # 1399-99

DETAIL SUMMARY SHEET (Human Use Protocol)

TTTLE: The Effect of Retinoic Acid on Sodium-Iodide Symporter mRNA Expression in Thyrocytes Circulating in the Blood Stream – A Pilot Study

KEYWORDS:

PRINCIPAL INVESTIGATOR: Bernet, Victor J. LTC MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Endocrine

STATUS: O
INITIAL APPROVAL DATE: 16 February 1999

STUDY OBJECTIVE

To determine the effects of 13-cis-retinoic acid on the quantity of sodium-iodide symporter (NIS) messenger RNA in peripheral blood.

TECHNICAL APPROACH

To begin to evaluate the function of the circulating cells, we sought to determine whether oral 13-cis-retinoic acid administrations would be associated with an increase in NIS mRNA expression in peripheral blood of subjects with no known thyroid disease. Total RNA was extracted from whole blood (Ultraspec RNA isolation system) obtained from 9 subjects (mean age +/- SD: 24 +/- 11 years, 44% female) taking oral 13-cis-retinoic acid for acne (Accutane, mean dose +/- SD 71 mg +/-20, duration of therapy mean +/- SD 11 +/- 8 wks) and from 5 normal subjects. All participants had normal thyroid physical examinations. In addition to serum Tg immunoassay, NIS and Tg mRNA expression was determined by quantitative RT-PCR (ABI PRISM 7700 sequence detection system).

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Serum Tg, free T4, and TSH concentrations were normal for each subject. Thyroglobulin mRNA was detected in each sample (mean +/- SE, subjects 32 +/- 20 pg Eq/ug RNA, normal controls 8.5 +/- 2, $p = 0.41$). NIS mRNA expression was detectable in none of the 5 normal controls, and only 1/9 subjects on 13-cis retinoic acid (mean value +/- SE 525 +/- 75 ng Eq/ug RNA). In summary, using the present amplification protocol, NIS mRNA is detected less frequently than Tg mRNA in the peripheral circulation of subjects with no known thyroid disease. Furthermore, oral administration of 13-cis-retinoic acid in doses commonly used to treat acne was not associated with measureable changes in peripheral blood NIS or Tg mRNA expression.

CONCLUSIONS

Although no statistical difference in NIS mRNA could be detected to this point, the results are limited secondary to the limited number of samples tested to date. The notable variation in NIS mRNA levels between subject's leads us to believe it is worth proceeding with the next portion of the study. We are interested in proceeding with the second portion of the study, which allows for a prospective, longitudinal study of NIS mRNA response which may yield differences that would not be detected by a cross-sectional study. We request an extension of one year in order to progress with the next part of this protocol.

Report Date: 02 November 2000 Work Unit # 00-1401

DETAIL SUMMARY SHEET

TITLE: Exploration Of Genome-Wide Expression Profiles In Subtypes Of Colorectal Neoplasia

KEYWORDS: Colon Cancer, genetics

PRINCIPAL INVESTIGATOR: James Walter Kikendall COL MC
ASSOCIATES: Eugenia Rued-Pedraza COL MC

DEPARTMENT: Medicine
SERVICE: Gastroenterology

STATUS: O
INTIAL APPROVAL DATE: 14 December 1999

STUDY OBJECTIVE:
To explore the differential patterns of gene expression in normal, adenomatous polyp and cancer tissues in the colon using micro-array technology.

TECHNICAL APPROACH:
In the feasibility study now underway, we will enroll up to 40 subjects scheduled for colonoscopy because of certain specific criteria. Participants will complete a data form. Tissue will be collected during the clinically indicated colonoscopy if the patient has a neoplastic lesion of appropriate size. Data forms and tissue will be anonymized prior to transfer to NCI for genetic analysis by micro-array. If this study demonstrates feasibility we will develop and submit plans for funding the full study involving tissue from up to 300 subjects.

PRIOR AND CURRENT PROGRESS:
Because of lack of personnel and overly restrictive entry criteria for the initially approved feasibility study, only two subjects have entered the study. An addendum relaxing the entry criteria was recently approved, and a nurse may soon be available from NCI for support of the project.

CONCLUSIONS:
None at this time.

Report Date: 01 June 2001

Work Unit # 00-1402

DETAIL SUMMARY SHEET

TITLE: Is Schatzki's Ring Protective Against Acid Reflux?

KEYWORDS: Schatzki's Ring, GERD (GastroEsophageal Reflux Disease)

PRINCIPAL INVESTIGATOR: MAJ George Winters, III MD
ASSOCIATES: COL Roy Wong MD, CL Maydonovitch

DEPARTMENT: Medicine
SERVICE: Gastroenterology

STATUS: C
INITIAL APPROVAL DATE: 18 January 2000

STUDY OBJECTIVE

To determine the effect of dilation Schatzki's Rings on the presence and severity of acid reflux, and to help determine the role of Schatzki's Rings in reflux disease.

TECHNICAL APPROACH

Methodology per approved protocol. No addenda have been submitted.

PRIOR AND CURRENT PROGRESS

The number of subjects enrolled to the study since last APR at WRAMC is 9 and the total enrolled to date at WRAMC is 21.

CONCLUSIONS

We found a trend toward improvement in J/D score and percent supine reflux after dilation of the Schatzki's Ring. This suggests that the intact ring may act as a barrier to esophageal acid clearance, especially when supine, and actually worsen esophageal acid exposure. This is the opposite of what we expected to find, but represents a novel concept in our thinking about Schatki's Rings.

Report Date: 07 December 2000

Work Unit # 00-1403

DETAIL SUMMARY SHEET

TITLE: The Effect of *Helicobacter pylori* eradication on the severity of Gastro-esophageal Acid Reflux as Determined by 24-hr pH Measurement

KEYWORDS: *H. pylori*, Gastroesophageal Reflux

PRINCIPAL INVESTIGATOR: Roger Keith Flincher CPT MC
ASSOCIATES: Roy Wong COL MC, Corinne Maydonovitch, Allan Andrews CPT MC

DEPARTMENT: Medicine
SERVICE: Gastroenterology

STATUS: O
INITIAL APPROVAL DATE: 18 January 2000

STUDY OBJECTIVE

To assess the effect of *H. pylori* eradication on gastro-esophageal reflux and whether the pattern of the gastritis from *H. pylori* infection plays any role in potential changes in gastric acidity and associated gastro-esophageal reflux.

TECHNICAL APPROACH

We plan to enroll 250 patients, with a goal of 80 patients completing the study after several exclusionary steps. All adult patients presenting with gastro-esophageal reflux disease (GERD) symptoms will be offered participation. Serology for *H. pylori* IgG antibody will be performed to screen for *H. pylori* infection. Seropositive patients will undergo ^{13}C-urea breath testing (UBT), to document active *H. pylori* infection and 24-hr esophageal pH testing and manometry to establish the presence and severity of GERD. A symptom questionnaire will also be completed. Patients with active *H. pylori* infection will undergo upper endoscopy and gastric biopsies. Histology will be used to determine the presence and pattern of gastritis and *H. pylori*. Four biopsies will be frozen for subsequent PCR analysis of the H. pylori genome to assess for virulence factors. Cag-A serology will be attained to assess its prevalence and relation to GERD severity. Patients will receive antibiotic therapy to eradicate *H. pylori* infection, and UBT will be repeated 10 weeks later to confirm eradication. Patients then will have repeat 24-hr esophageal pH testing and symptom questionnaire to determine post-eradication GERD severity compared to pre-eradication status. The presence of antibodies to Cag-A will be compared to histological gastritis, GERD severity, and to post-eradication symptom changes. This study will provide a better understanding of the role of *H. pylori* and its eradication in GERD, and may have important implications in the management of GERD and *H. pylori* infections. Protocol Addendum- Urea breathing testing was added to the initial evaluation to document active *H. pylori* infection instead of waiting until endoscopy. This was done to lessen the potential risks to the study patients and lessen endoscopy by preventing endoscopy on *H. pylori* negative patients.

PRIOR AND CURRENT PROGRESS

The study was progressing slower than anticipated due to slow enrollment and the possible loss of the $^{13}CO_2$ analyzer used to process the results of the urea breath test. The company who loaned USUHS the machine considered having the machine returned, but we have secured further use of the device. Recently the enrollment of patients has improved by the addition of Dr. Andrews to the study. He is assisting in initial enrollment and has recruited several current patients. We have currently enrolled 65 patients, with 23 being *H. pylori* serology positive. To date, 17 enrolled subjects have been documented by ^{13}C urea breath testing (UBT) to have active *H. pylori* infection. Of these, 12 subjects have completed the baseline/pre-*H. pylori* eradication 24-hr pH test, 8 have undergone upper endoscopy, and 3 have completed the study (post-eradication UBT negative and post-eradication pH testing completed). The data presented is preliminary.

The demographic data of the 12 subjects are as follows: mean age-51.5 yo $\pm$ 15.5 yrs; %female-30%; race-46% African-American, 38% Caucasian; GERD duration-mean 7.5 yrs; PPI use-53%. Using non-parametric testing, our preliminary testing shows that cardia inflammation severity (using the updated Sydney System) is inversely associated with % total time pH<4 (r=-0.75 : p=0.030) and % upright time pH<4 (r=-0.75; p=0.030) on the baseline 24-hour pH test, Body inflammation appears to be directly correlated with % total time pH<4 (r=0.764; p=0.027). Antrum inflammation is not significantly correlated to reflux severity (% total time pH<4) in patients with endoscopically apparent non-antral predominant gastritis (p=0.11). The three patients completing the study have shown a decrease in their % total time pH<4 (mean 7.9% → 5.8%; p=0.18) and Johnson/Demeester scores (mean 48.1→22.1; p=0.10), but statistical significance is not yet achieved due to the small sample size.
If these data continue the current trends, severe cardia inflammation may be associated with less severe reflux disease in H. pylori infected patients. Whether *H. pylori* in the cardia plays a role in this effect is unclear. The downward trend in pH results after H. pylori eradication is also intriguing. Further patient enrollment will be needed to see if this is a real effect and to compare the findings to the histologic pattern of gastritis.

CONCLUSIONS

This study is already showing interesting data regarding the relationship between gastritis and GERD severity. We hope to clarify the role of *H. pylori* in GERD (i.e., the possible role of virulence factors in H. pylori's effect on gastritis and GERD, and the effect of *H. pylori* eradication on the severity of GERD). This study could be a decisive and important addition to the knowledge of *H. pylori* and GERD and may alter the current therapy for GERD patients.

Report Date: 2 February 2001 Work Unit # 00-1404

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: A Comparison of Pediatric and Adult Colonoscopes in Adult Patients Presenting for Routine Colonoscopy

KEYWORDS:

PRINCIPAL INVESTIGATOR: Cumings, Mark D. MAJ MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Gastroenterology

STATUS: O
INITIAL APPROVAL DATE: 21 March 2000

STUDY OBJECTIVE

To evaluate use of a pediatric colonoscope with an adult colonoscope by comparing a) total procedure time, b) time to reach cecum, and c) rate at which the endoscopist reaches the cecum.

TECHNICAL APPROACH

Adult patients presenting to our clinic for colonoscopy will be assessed for entry in the study by the primary investigator prior to the date of the colonoscopy. Patients will be recruited by the primary investigator, gastroenterology fellows, and staff at the time of initial patient interview with the physician. Prior to the initiation of the study, a randomization schedule will be used to assign subjects to either the pediatric or adult colonoscope study groups. The primary investigator will contact patients prior to their scheduled colonoscopy to inquire about study participation. Those patients wishing to participate will then be evaluated for exclusion criteria. On the day of the procedure the patient will be consented by either the endoscopist or primary investigator. The GI staff will be aware of the assigned scope, but the patient will not know which scope is assigned. A gastroenterology staff physician will perform all endoscopies. Patients will undergo standard bowel preparation using Go-Lytely. All patients will receive the standard pre-procedure care: brief history by the nurse, insertion of a peripheral IV, recording of demographic data, and recording of initial vital signs. Premenopausal women will be required to undergo pregnancy testing with a qualitative urine pregnancy test prior to colonoscopy. During the procedure vital signs will be monitored every 5 minutes and recorded every 15 minutes. Patients will be provided sedation (opioids and benzodiazepines) prior to and during the procedure as deemed necessary by the endoscopist. The amount of time for each procedure will be recorded. Procedure start time will be the time the colonoscope is inserted into the anal canal. Procedure end time will be when the scope is removed from the patient. Time will be recorded in minutes and seconds. Both the total time it takes to reach the cecum (TTC) and total time for procedure (TTP) will be recorded. TTC is the length of time from insertion to visualization of cecal landmarks, to include ileocecal valve. TTP is the length of time from insertion to removal of scope from the patient. Prior to the start of the study, baseline times will be established for each staff by taking the average times of 10 procedures each using the pediatric scope and adult scope. Following the procedure the patient will be recovered for approximately one hour in the GI recovery area. Once recovered and prior to departing the clinic, the endoscopy nurse will obtain pain and satisfaction scores from the patient using a visual analogue scale. The pain and satisfaction assessment will be repeated approximately 24 hours after the procedure.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

We currently have not enrolled any patients. During the time my protocol was undergoing review for approval by DCI a study was published similar to the study I was proposing. Usefulness of a pediatric colonoscopy for colonoscopy in adults. Tahira Saifuddin, et al. Gastrointest Endosc 2000;51:314-7. They concluded that the peds colonoscope is suitable for routine colonoscopy in adults. It is also useful in pts in whom colonoscopy with the adult colonoscope is unsuccessful in reaching the cecum (particularly in

women). They plan on conducting another study to see if the peds colonoscope is superior to adult colonoscope in women with prior hysterectomy. Following publication of this article I felt as though I should change my protocol to study just pts with a low BMI to see if the peds scope was superior to the adult scope. Even though my protocol was approved 31 Aug 2000, I received an email from Dr. Chang 15 Dec 00 stating that the protocol had been forwarded to CIRO and that they were requesting some revisions be made. The revision that I have a problem with is the one requesting the category of risk be changed from "minimal" to "greater than minimal" because, according to JM Lamiell, "those randomized to pediatric C-scope will not receive standard of care...Pediatric C-scope may be inaccurate, e.g., false negative peds scope procedure that misses malignancy." So, back to step one. Approval of this protocol has been much more complicated and time-consuming than I ever imagined and I'm still on the fence in terms of how much more time I should invest in this.
The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 0.

CONCLUSIONS
Please see above. No data collected yet. Currently in process of making an addendum to the original protocol.

Report Date: 15 February 2001 Work Unit #00-1405

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: Phase II Study of Long Term PEG Intron for Patients Who Have Failed to Respond to Rebetron/Interferon with Advanced Fibrosis and Cirrhosis Secondary to Hepatitis C

KEYWORDS: Hepatitis C, Cirrhosis, Interferon

PRINCIPAL INVESTIGATOR: Holtzmuller, Kent COL MC
ASSOCIATES:

DEPARTMENT: Medicine STATUS: O
SERVICE: Gastroenterology INITIAL APPROVAL DATE: 21 March 2000

STUDY OBJECTIVE
The specific aims of this proposal are to evaluate the role of long term PEG-Intron therapy on the natural history of patients with advanced chronic HCV infection with a primary focus on prevention of hepatic decompensation, progression of fibrosis and hepatoma development. Viral clearance is not an endpoint, although viral levels will be obtained annually.

TECHNICAL APPROACH
Randomized trial of PEG-Intron 0.5mcg per kg weekly clochine 0.6 mg bid in prior non-responders to interferon/REBETRON with advanced fibrosis/cirrhosis (Ishak stage 4-6). The length of therapy is four years. After the first six months of therapy, the study subjects will be seen quarterly for clinical evaluation for decompensation of liver function, clinical screening for development of hepatocellular cancer and liver biopsies for determination of progression of liver fibrosis every two years.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
PEG-Intron was approved by the FDA in Jan 2001 for use in Hepatitis C patients. Published reports are now available to show that PEG-Intron is superior to Intron and is as safe as Intron in the treatment of hepatitis C and in patients with cirrhosis (1,2)

References:

1. Heathcote EJ, Shiffman ML, Cooksley GE, Dusheiko GM, et al. Peginterferon alfa-2a in patients with chronic hepatitis C and cirrhosis. N Engl J Med 2000; 343:1673-1680

2. Glue P, Rouzier-Panis R, Raffanel C et al. A dose-ranging study of pegylated interferon alfa-2b and ribavirin in chronic hepatitis C. The Hepatitis C Intervention Group. Hepatology 2000; 32:647-653

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 0. The total number enrolled study-wide is 119, if multi-site study.

CONCLUSIONS
It is too early in the study to come to any conclusions.

Report Date: 2 February 2001

Work Unit # 00-1406

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: Screening for Barrett's in Patients With and Without Heartburn. A Multi-Center Trial

PRINCIPAL INVESTIGATOR: Cumings, Mark D. CPT MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Gastroenterology

STATUS: O
INITIAL APPROVAL DATE: 21 March 2000

STUDY OBJECTIVE: To determine the relative prevalence of Barrett's esophagus in persons with and without symptoms of gastro esophageal reflux disease. To also determine the relative prevalence of Barrett's esophagus in males vs. females, and whites vs. blacks.

TECHNICAL APPROACH: Patients who are age 40 or older, have had no previous EGD, and are planning to receive sedation for their colonoscopy will be assessed for entry in the study. The primary investigator will contact patients prior to their scheduled colonoscopy to inquire about study participation. Those patients wishing to participate will then be evaluated for exclusion criteria. On the day of the procedure the patient will be consented by either the endoscopist or primary investigator. The primary investigator, or designee, will have the patient complete two questionnaires prior to the procedure. Gastroenterology fellows and gastroenterology staff physicians will perform colonoscopies and upper endoscopies. Patients will undergo standard bowel preparation using either Go-Lytely or oral fleet phospho-soda. All patients will receive the standard pre-procedure care: brief history by the nurse, insertion of a peripheral IV, recording of demographic data, and recording of initial vital signs. Premenopausal women will be required to undergo pregnancy testing with a qualitative urine pregnancy test prior to the procedure. During the procedure vital signs will be monitored every 5 minutes and recorded every 15 minutes. Patients will be provided sedation (opioids and benzodiazepines) prior to and during the procedure as deemed necessary by the endoscopist. After receiving sedation the patient will undergo upper endoscopy first, followed by colonoscopy. The patients who refuse will be excluded but their refusal will be recorded. Following the procedure the patient will be recovered for approximately one hour in the GI recovery area. Tissue samples will be taken, shipped, and stored for the duration of the trial (approximately three years). Once the study is over the tissue will be destroyed. No genetic research will be conducted. All patient identification information will be maintained at WRAMC by the primary investigator; we will code the samples and data sheets and maintain code at WRAMC.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE: A total of 650 pts have been endoscoped so far. On the multivariate analysis, age, H.pylori negative status, and the presence of esophageal erosions were predictors of Barrett's. Race was not a significant predictor but we have under-recruited in this regard and currently have only about 95 African Americans in the study. However, the initial results suggest that race is an indirect measure of H. pylori status. Heartburn predicted circumferential Barrett's but not short segment (tongues). A proposal to increase the number of patients in the study from 500 to 1,000 was approved 17 Aug 00. There is no change in the number of pts WRAMC is recruiting, previously approved for 100. There was a minor revision to question number 3 on the DHSI reflux scale that was also approved on 17 Aug 00. We have not encountered any adverse events to date. The number of subjects enrolled to the study since last APR at WRAMC is 60 and the total enrolled to date at WRAMC is 60. The total number enrolled study-wide is 650.

CONCLUSIONS: On the multivariate analysis, age, H.pylori negative status, and the presence of esophageal erosions were predictors of Barrett's. Race was not a significant predictor but we have under-recruited in this regard and currently have only about 95 African Americans in the study. However, the initial results suggest that race is an indirect measure of H. pylori status. Heartburn predicted circumferential Barrett's but not short segment (tongues).

Report Date: 28 February 2001 Work Unit # 00-1407

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: Tele-Hepatitis Phase I: Validation of Desktop Video Teleconferencing (VTC) System at 384 kb ISDN for Evaluation of Patients with Hepatitis.

KEYWORDS: Telemedicine, VTC, hepatitis, ISDN

PRINCIPAL INVESTIGATOR: MAJ Inku Hwang
ASSOCIATES: COL Kent C. Holtzmuller, COL Michael A. Dunn, COL Maria H. Sjogren, COL Roy H. Wong, COL Ronald K. Poropatich

DEPARTMENT: Medicine
SERVICE: Gastroenterology

STATUS: O
INITIAL APPROVAL DATE: 16 May 2000

STUDY OBJECTIVE

1. Determine the diagnostic concordance of visual physical exam findings in patients with chronic hepatitis using in person vs. desktop VTC at 128kb connection.
2. Determine the patient satisfaction of using VTC consultation system.
3. Determine physician satisfaction of using VTC consultation system.
4. Estimate cost savings of using VTC consultation system in place of traditional face-to-face consultation for follow-ups.

TECHNICAL APPROACH

We hope to validate the use of inexpensive desktop VTC system connected at 128 kb ISDN line to visually diagnose patients with findings from chronic hepatitis. Diagnostic concordance between in person evaluation vs. those performed using the VTC will be compared. Also, both patients and physicians will be surveyed for both level of experience with VTC and computer systems and satisfaction of such a system. Finally, for those patients on TDY from distant sites, we will collect monetary and time cost data for their visit to Walter Reed. There have been no modifications in methodology from the initial approved protocol.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

There have been no updates in the literature on the use of telemedicine in hepatitis. We are still in the process of installing the network, hardware and software to make the VTC possible, and have not yet enrolled any patients for this protocol. We have thus had no adverse events, and no patients have withdrawn from our study.

CONCLUSIONS

No conclusions can be drawn from our study thus far given lack of patient enrollment.

Report Date: 31 May 2001 Work Unit # 00-1408

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: A Randomized Multicenter Trial Comparing Induction PEG Intron-A Plus Ribavirin Versus PEG-Intron A in Patients Who Have Previously Not Responded or Have Relapsed Following Intron-A Based Therapy for Chronic Hepatitis C, With Maintenance Therapy for Patients Who Continue to Remain Non-Responsive

KEYWORDS: Hepatitis C, Interferon, Ribavirin

PRINCIPAL INVESTIGATOR: Holtzmuller, Kent COL MC
ASSOCIATES:

DEPARTMENT: Medicine STATUS: O
SERVICE: Gastroenterology INITIAL APPROVAL DATE: 18 July 2000

STUDY OBJECTIVE: The primary objective of this study is to evaluate the efficacy of pegylated interferon alfa- 2b and ribavirin in patients with hepatitis C who have previously failed an interferon based protocol.

TECHNICAL APPROACH: There have been no modifications to the protocol design. The number of patients that WRAMC is allowed to enter the study has been increased by 20 patients to a total of 40. This is an open label trial where HCV patients who have previously been treated with interferon based anti-viral therapy are treated with pegylated interferon alfa-2b and ribavirin for 48 weeks. The patients are randomized to pegylated interferon alfa-2b 1.5 mcg/kg/week + ribavirin 1000-1200 mg/day for 12 weeks followed by pegylated interferon alfa-2b 1.0 mcg/kg + ribavirin 800 mg/day for 36 weeks or pegylated interferon alfa-2b 1.0 mcg/kg + ribavirin 800 mg/day for 48 weeks.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE: Pegylated interferon alfa-2b was approved by the FDA on 31 Jan 2001 as once-weekly monotherapy for the treatment of chronic hepatitis C in patients not previously treated with alpha interferon who have compensated liver disease and are at least 18 years of age. The combination of pegylated interferon alfa-2b and ribavirin has been approved by the European Commission of the European Union for the treatment of naive and relapsed (previously treated) adult patients with histologically proven hepatitis C. The combination of pegylated interferon alfa-2b and ribavirin has been shown to be safe and effective (1). Twenty patients have been enrolled at WRAMC to date. An addendum was submitted to the HUC to increase WRAMC enrollment to 40 patients. This request was reviewed by the HUC on 8 May 2001 and approved pending changes in the consent form to reflect that pegylated interferon alfa-2b is no longer an IND drug. The revised consent form has been submitted to DCI for review. Nine of the twenty patients have reached 24 weeks of therapy. The HCV RNA clearance at week 24 is 33%. The medications have been discontinued on two patients at WRAMC. Both patients were biochemical and virologic nonresponders to the pegylated interferon alfa-2b and ribavirin therapy at 12 and 24 weeks and were experiencing significant fatigue. Attached is the Annual Report from Dr. Lawitz (primary investigator for the multi-center trial).

Reference:
1. Glue P, Rouzier-Panis R, Raffanel C, et al. A dose ranging study of pegylated interferon alfa-2b and ribavirin in chronic hepatitis C. The Hepatitis C Intervention Therapy Group. Hepatology 2000;32:647-653.

The number of subjects enrolled to the study since last APR at WRAMC is 20 and the total enrolled to date at WRAMC is 20. The total number enrolled study-wide is 510, if multi-site study.

CONCLUSIONS: This study is ongoing. The medications are tolerated well. The HCV RNA clearance for the nine patients at WRAMC who have achieved week 24 is 33%.

Report Date: 30 August 2000 Work Unit # 1432

DETAIL SUMMARY SHEET

TITLE: Short Segment Barrett's Esophagus: Prevalence, Clinical Characteristics, and Responses to Long-Term Antisecretory Therapy

KEYWORDS: short segment, Barrett's Esophagus, Prilosec

PRINCIPAL INVESTIGATOR: Horwhat, David MAJ MC
ASSOCIATES: Wong, R. COL MC; Frishberg, D. MAJ MC; Maydonovitch, C. DAC; Tang, D. CIV

DEPARTMENT: Medicine
SERVICE: Gastroenterology

STATUS: O
INITIAL APPROVAL DATE: 29 November 1994

STUDY OBJECTIVE

To determine: 1) the prevalence of Short-Segment Barrett's Esophagus (SSBE) in patients undergoing upper endoscopy in WRAMC's Gastroenterology Clinic; and 2) the response of SSBE to maximal antireflux therapy with Prilosec; and 3) the incidence of specialized intestinal metaplasia of the esophagus in a cohort of patients originally identified in part I; and 4) the 24hr pH and esophageal manometry characteristics of patients with specialized intestinal metaplasia of the gastroesophageal junction (EGJSIM).

TECHNICAL APPROACH

This has been two-part study with several addenda to allow further study. In Part I, patients complete a questionnaire prior to endoscopy (EGD). During the patient's routine EGD, photographs and four biopsies of the distal esophagus will be obtained to evaluate the presence of SSBE. In Part II, patients found to have SSBE undergo repeat EGD with biopsy, manometry, and 24-hour pH prior to treatment with Prilosec and are then followed at 3-month intervals for 2 years. In the follow-up phase to Part I, 151 patients found to have specialized intestinal metaplasia (SIM) of the esophagus (at the EGJ, SSBE and LSBE) in part I are asked to return for repeat surveillance biopsies to assess the incidence of SIM in this cohort. In a recently approved addendum, we have been given permission to perform 24hr pH analysis and esophageal motility/manometry on our cohort of 45 patients that have been demonstrated to have EGJSIM.

PRIOR AND CURRENT PROGRESS

Of the original cohort of 151 Barrett's patients identified in the original screening phase of the study, 101 patients were enrolled in the follow-up phase and underwent repeat EGD with biopsy to assess for regression or progression of Barrett's esophagus. Thirty-six of 101 patients were enrolled and studied this reporting period. There were no adverse events. A manuscript is in progress to report the follow-up data.

CONCLUSIONS

This study has generated one of the largest databases on Barrett's esophagus in the country. Analysis of the recent follow-up study indicates that EGJSIM patients who have specialized intestinal metaplasia just at the GE junction are most likely to have complete normalization of SIM at follow up. In contrast, no patients with long segment Barrett's esophagus (>3cm) showed complete normalization of their Barrett's esophagus.

Report Date: 20 June 2001

Work Unit # 1438

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: Use of Lectin Binding as a Probe for Colonic Neoplasms: A Pilot Study

KEYWORDS: colonic neoplasms, lectins, colonocyte

PRINCIPAL INVESTIGATOR: Gorske, Andrew CPT MC
ASSOCIATES: Kikendall, JW COL MC; Wong, RKH COL MC; Maydonovitch, C DAC

DEPARTMENT: Medicine
SERVICE: Gastroenterology

STATUS: C
INITIAL APPROVAL DATE: 10 September 1996

STUDY OBJECTIVE

To determine whether binding by various fluorescence-tagged lectins to exfoliated colonic mucosal cells shows promise as a rapid, non-invasive means of screening for colonic neoplasms.

TECHNICAL APPROACH

Exfoliated colonic mucosal cells (colonocytes) are harvested from the stool by a centrifugal elutriation process developed by PP Nair et al. Stool specimens are collected from three patient groups; controls, patients with adenomatous polyps and patients with colon cancer. The colonocytes are incubated with a panel of selected lectins with specificity for different antigens and the amount of lectin binding is assayed by fluorescence flow cytometry. Differences in lectin-binding patterns are then compared between the groups to determine if they are distinguishable from each other by this test.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

To date, 107 patients have been prospectively enrolled in the colonocyte study (Table 1). Desilets enrolled 34 patients from October 1996 through June 1997. These patients constituted the pilot study group. Daniels enrolled 20 patients from July 1998 through June 1999, and the final 53 patients were enrolled from July 1999 through March 2000. Of the enrolled patients, 79 returned a stool specimen to the Gastroenterology clinic. Lectin binding was determined for 62 of the 79 samples. There were 17 specimens, which were discarded because of improper collection, availability of lab personnel or equipment malfunction. Two patients did not have a colonoscopy. There have been no additional patients enrolled since the last APR. These data are summarized below.

Table 1.

Investigator	Enrolled	Returned	Processed	Not Processed
Desilets	34	34	31	3
Daniels	20	11	7	4
Gorske	53	34	24	10
	107	79 (74%)	62 (58%)	17 (16%)

The colonoscopy results for those patients who returned a stool sample are summarized below.

Investigator	Normal	Polyps	Cancer	Total
Desilets	10	11	10	31
Daniels	4	3	-	7
Gorske	13	7	4	24
	27 (44%)	21 (34%)	14 (22%)	62

There have been no adverse events during the duration of this study. No patients have been withdrawn from the study. There have been no modifications to the study since the last APR.

CONCLUSIONS

The lectin data, for patients enrolled by Daniels and Gorske, has been inconsistent with data reported in the pilot study, who were enrolled by Desilets. Initially, this was felt to be due to the small number of patients analyzed. Additional patients were enrolled over the next 9 months and their lectin binding data was reviewed. These data were also inconsistent with the pilot study but were notable for a significant lack of viable exfoliated colonocytes. A critical review of the protocol was made and several deficiencies were identified which may have been responsible for the variable results. 1) Some samples were not collected and processed according to protocol. Any delay in processing allows for both bacterial degradation and death of exfoliated, viable colonocytes. Samples in the pilot study were often processed within 12 hours of collection. A variety of factors contributed to this delay: timing of patient collection relative to submission, proper temperature control of the samples after collection, and availability of staff and laboratory personnel relative of time of submission of the samples. 2) The lectin stock solutions could not be dated because and may have been expired. It is unknown if lectins in solution denature and how their binding affinities change over time; factors which may have negatively affected binding. 3) The lectin solutions were intended to be prepared at a concentration of 10^{-6}. A transcription error was found in the lectin solution preparation instructions, which resulted in the solutions being prepared at a concentration of 10^{-8}. This significantly decreased the flow cytometry signal due to noise ratio and impaired detection of lectin binding. These deficiencies were identified and corrected, however, critical momentum to maintain the study was lost.

Lectin binding to exfoliated colonocytes has been well demonstrated *in vitro* and in limited perspective trials. Peanut agglutinin (PNA) and *Amaranthus caudatus* (ACA) have been shown to selectively bind to antigens produced by dysplastic and carcinomatous tissue. Lectin binding reported in the pilot study was not consistent with what has been demonstrated *in vitro* and reported preferential binding of jacalin (JAC) and wheat germ agglutin (WGA). In his published results of the pilot study, Desilets was not able to explain this difference in binding affinities. Unfortunately, technical errors prevented validation of the pilot study with the additional patients enrolled into the larger prospective trial. This method may yet prove to be a useful non-invasive screening technique for colorectal neoplasia, through its wide spread use, at the present time, is limited by relatively complex specimen handling and processing.

Report Date: 14 September 2000 Work Unit # 1439

DETAIL SUMMARY SHEET

TITLE: A Questionnaire for Gastroesophageal Reflux: Development of a Diagnostic and Research Tool Applicable to the General Population

KEYWORDS: gastroesophageal reflux disease

PRINCIPAL INVESTIGATOR: Osgard, Eric CPT MC
ASSOCIATES: Maydonovitch, Corinne

DEPARTMENT: Medicine
SERVICE: Gastroenterology

STATUS: O
INITIAL APPROVAL DATE: 29 October 1996

STUDY OBJECTIVE

To develop a short-form questionnaire to be used as a screening tool to accurately identify patients in the general population who have gastroesophageal reflux disease (GERD). This questionnaire will be developed from two previously published GERD questionnaires that are available in the literature, each with inherent properties that make their use for screening in the general population less than optimal.

TECHNICAL APPROACH

Phase I: 400 patients, scheduled for endoscopy and manometry with pH testing will be identified. Each will complete the two existing questionnaires. Results will be correlated to the objective findings of the above procedures. The existing questionnaires will then be reduced into a short-form version.
Phase II: The short-form questionnaire will be tested as a screening tool in the population of military health care beneficiaries. Using a mailer, 200 respondents willing to participate will be identified. Each will complete the new questionnaire and undergo endoscopy and manometry with pH testing. The accuracy of the questionnaire will be assessed according to the results of theses objective tests.

PRIOR AND CURRENT PROGRESS

A total of 64 patients have been enrolled in the study with no new patients enrolled this rating period. There have been no adverse events.

CONCLUSIONS

Data collection is incomplete. However, an evaluation showed a poor correlation between the patient questionnaire answers and the pH monitor data. No conclusion can be made at this time.

Report Date: 31 January 2001 Work Unit # 1440

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: A Prospective, Controlled Study to Compare the Diagnostic Yield and Cost Analysis of Methylene Blue Directed Biopsies vs. 4-Quadrant Random Biopsies to Identify Intestinal Metaplasia and Dysplasia in Barrett's Esophagus

KEYWORDS: Esophagus, methylene blue, Barrett's

PRINCIPAL INVESTIGATOR: Horwhat, John David MAJ MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Gastroenterology

STATUS: C
INITIAL APPROVAL DATE: 25 February 1997

STUDY OBJECTIVE

1. Compare the diagnostic yield of identifying intestinal metaplasia and dysplasia using methylene blue directed biopsies (MBDB) vs.4-quadrant random biopsies.
2. Compare the number of biopsies required and pathology cost associated with MBDB vs. 4-quadrant biopsy.

TECHNICAL APPROACH

This study compares standard endoscopic random 4-quadrant surveillance biopsy technique with a directed biopsy technique. The directed technique is being investigated to determine whether it can help the endoscopist to sample the exact areas with Barrett's, which are of clinical concern (due to the pre-cancerous potential of Barrett's esophagus). The methylene blue dye is sprayed onto the esophagus during endoscopy through the endoscope. An addendum on this protocol has allowed us to have select patients (those with dysplasia on earlier exams and who would therefore be coming back for repeat endoscopy within 6 months) to undergo an oral prep with the methylene blue, wherein the patients drink the methylene blue to coat their esophagus prior to procedure. If the oral preparation proves to work as well, we can shorten the time spent under conscious sedation to allow spraying the methylene blue by as much as 10 minutes. A second group of patients undergoing their first endoscopy for the evaluation of heartburn comprises our control group. These patients undergo one endoscopy with methylene blue sprayed- if anything stains, directed biopsies are taken along with 2 biopsies of unstained adjacent mucosa, if nothing stains, 4 quadrant biopsy at the squamocolumnar junction is taken.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

This study is completed and a manuscript is in progress. A total of 102 patients were enrolled in the study, 33 during this reporting period. There were no adverse events. Two patients did not complete the study. Final data analysis will be conducted on 100 patients: 52 patients in the Control group and 48 patients in the Barretts group.

CONCLUSIONS:

The diagnostic yield of Methylene- blue- directed biopsies vs standard 4-quadrant random biopsies is similar in surveillance of Barrett's esophagus. Methylene blue biopsies are more cost effective because fewer biopsies are required.

Report Date: 20 November 2000

Work Unit # 1443

DETAIL SUMMARY SHEET

TITLE: The Effects of Lamivudine on Renal Function in Patients with Chronic Active Hepatitis B and Proteinura

KEYWORDS:

PRINCIPAL INVESTIGATOR: Dunaway, Peter CPT MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Gastroenterology

STATUS: O
INITIAL APPROVAL DATE: 27 January 1998

STUDY OBJECTIVE:
To determine how the immunosuppressant medicine, Lamivudine, affects renal function in patients with proteinura and/or renal insufficiency secondary to chronic active hepatitis B.

TECHNICAL APPROACH:
Screen for patients in the Liver Clinic at Walter Reed who have chronic active hepatitis B, need therapy, and have renal insufficiency and/or preoteinura secondary to hepatitis B. There have been no changes in the initial plan stated in the original protocol.

PRIOR AND CURRENT PROGRESS
There are no patients. They have yet to meet the inclusion criteria to be enrolled in this study.

CONCLUSIONS
None.

Report Date: 29 January 2001 Work Unit #1446-98

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: Hypnosis for the Treatment of Upright Gastro-Esophageal Reflux

KEYWORDS: Upright Reflux

PRINCIPAL INVESTIGATOR: Fincher, Roger K. CPT MC
ASSOCIATES: Roy Wong COL MC, Dr. Harold Wain, Corrinne Maydonovitch

DEPARTMENT: Medicine
SERVICE: Gastroenterology

STATUS: O
INITIAL APPROVAL DATE: 28 April 1998

STUDY OBJECTIVE

A) To study the efficacy of hypnosis versus omeprazole in the treatment of upright reflux
B) To determine the prevalence and types of psychiatric abnormalities in patients with upright reflux
C) To characterize the pathophysiology of successful treatment in patients undergoing hypnosis

TECHNICAL APPROACH

Addendum: The prospective arms of the trial were terminated due to poor enrollment in that phase with an appropriate adjustment of the title. A psychiatric questionnaire (PRIME-MD) was added to streamline psychiatric assessment. Patients are now offered self-hypnosis, with a psychiatric evaluation to determine hypnosis capacity, as a "pilot-study"-like format with repeat pH measurement and gastric emptying at 8 weeks after starting the self-hypnosis

Current Approach- Those patients identified to have upright reflux by symptom pattern would undergo 24-hr pH testing to confirm upright reflux. Those found to have upright reflux on clinically ordered pH tests would also be offered enrollment in the study. A validated psychiatric questionnaire, Prime-MD-II, will be completed and a gastric emptying study will be completed. All subjects will be offered self-hypnosis training in conjunction with the routine medical therapy they were receiving prior to study enrollment. After 8 weeks, the subjects doing self-hypnosis will be asked to return for a repeat 24-hr pH test off medications, but while using self-hypnosis. They would be asked to get another gastric emptying study using self-hypnosis to quantify any potential differences in gastric emptying using self-hypnosis versus the previously attained baseline gastric emptying study. The use of a "partial study", with those patients unwilling to try self-hypnosis still having the validated psychiatric questionnaire and gastric emptying study, would be continued. Patients who completed the study prior to the recent addendum are being contacted, re-consented and are completing the psychiatric questionnaire to complete our database.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Enrollment- 23 patients have been enrolled in the study so far, with 8 being enrolled in the last 12 months.
Adverse Reactions- No adverse reactions have occurred in the past year.

CONCLUSIONS

Preliminary gastric emptying data was presented in poster form at the American College of Gastroenterology, with the abstract published in the American Journal of Gastroenterology Oct 2000. There appears to be no specific gastric emptying pattern characteristic for this type of esophageal reflux, with both an increased prevalence of delayed and "rapid" emptying. Gastric emptying pattern also does not appear to have any role in the severity of upright reflux.

Report Date: 13 June 2001

Work Unit #1447-98

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: The Clinical Utility of Magnetic Resonance Cholangiopancreatography (MRCP) in the Evaluation of Acute Pancreatitis

KEYWORDS:

PRINCIPAL INVESTIGATOR: Frizzell, Eric CPT MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Gastroenterology

STATUS: C
INITIAL APPROVAL DATE: 16 June 1998

STUDY OBJECTIVE

1) Compare the diagnostic yield of magnetic resonance cholangiopancreatography (MRCP) vs. ultrasound in the diagnosis of common bile duct stones in patients with acute pancreatitis.
2) Determine if findings on MRCP add to other commonly used prognostic criteria such as Ranson's criteria in predicting the course of patients with acute pancreatitis.
3) Determine if MRCP results are associated with clinical outcome measures.

TECHNICAL APPROACH

There has been no change in the technical approach than that written in the original protocol. Patients admitted with the diagnosis of acute pancreatitis are recruited and if they agree to participate, undergo an MRCP as previously described.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

MRCP has become the gold standard in centers where it is performed for assessment of the biliary tree prior to invasive assessment with either ERCP or surgery. Two larger randomized trials have been published over the past year, which essentially put the issue of MRCP vs US to rest.
The number of subjects enrolled to the study since last APR at WRAMC is __2__ and the total enrolled to date at WRAMC is __18_____.

CONCLUSIONS

Due to the recent publication of large randomized trials, this protocol is essentially irrelevant due to problems with rapid accrual of patients and will be discontinued.

Report Date: 20 July 2001 Work Unit # 1451-98

DETAIL SUMMARY SHEET

TITLE: The Use of Garlic as an Antimicrobial in Helicobacter Pylori Eradication

KEYWORDS: Helicobacter pylori, garlic

PRINCIPAL INVESTIGATOR: Mulhall, Brian P. CPT MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Gastroenterology

STATUS: O
INITIAL APPROVAL DATE: 22 September 1998

STUDY OBJECTIVE

The objective of this study is to evaluate the possible effectiveness of using a common nutritional supplement (garlic) to eradicate/treat Helicobacter Pylori infections.

TECHNICAL APPROACH

In this study, patients are evaluated for evidence of active infection by Helicobacter pylori (using a serological test) and if positive, undergo a confirmatory breath test. Further, an EGD is performed to obtain material for culture and tissue samples; additionally, the degree of gastric mucosal inflammation is noted. If active infection is confirmed (using these several methods) then all patients are given Omeprazole therapy and are randomized to take either a nutritional supplement (garlic) for four weeks or a placebo. Patients are asked to complete a dietary questionnaire at several points throughout the course of the study and a repeat EGD is completed eight weeks from the beginning of therapy. This second EGD will allow for tissue and culture confirmation of Helicobacter pylori eradication or alteration. All tissue samples are evaluated using in situ hybridization, and the characterisitic virulence factors for this organism are catalogued.
If patients remain Helicobacter pylori positive at the completion of the study, then they are counseled regarding the benefits of organism eradication and an antibiotic regimen is provided, if desired.

PRIOR AND CURRENT PROGRESS

No new studies have been published since the initial protocol submission. Our preliminary data suggests that, although garlic may not eradicate Helicobacter pylori, it may (like Omeprazole) inhibit its in vitro growth. Like patients with Helicobacter pylori on long-term Omeprazole therapy, may cause gastric atrophy or may be protective.

A total of 52 patients, (2 patients during this reporting period) have been enrolled in this study 15 patients have tested "positive" for the H. pylori infection and have participated in the randomized portion of the study. Enrollment at WRAMC was slow, but should accelerate this year. Additionally, enrollment was begun at MAMC and an additional 12 patients tested positive, and will be included in our data set. There have been no adverse reactions thus far and enrollment continues. No patients have withdrawn from the study. No new addenda have been submitted, since the one approved June 22, 2000.

CONCLUSIONS

Data collection is ongoing and should accelerate at WRAMC. Preliminary data has suggested findings not heretofore described in the literature.

Report Date: 20 September 2000 Work Unit # 1453-99

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: Does Vitamin C Decrease Transaminase Levels in Hepatitis C

KEYWORDS: Vitamin C, Ascorbic Acid, Hepatitis C, HCV, Transaminase

PRINCIPAL INVESTIGATOR: Thomas Barry Calvit, LCDR MC USN
ASSOCIATES: Kent Holtzmuller, LTC MC USA; Mark Johnston, CDR MC USN

DEPARTMENT: Medicine
SERVICE: Gastroenterology

STATUS: C
INITIAL APPROVAL DATE: 11 November 1998

STUDY OBJECTIVE

1) To determine if supplementation with ascorbic acid will result in a decrease of $\geq$ 30% of serum aminotransferase enzyme in patients with active hepatitis C infection
2) To explore demographic and clinical characteristics that may be associated with successful treatment with ascorbic acid

TECHNICAL APPROACH

The technical approach is as per the original protocol.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Since my prior APR completed in October of 1999, a single new patient has been enrolled into the protocol and this patient did not complete the study. As I have been reassigned to Naval Hospital Camp Lejeune, NC, and only 5/76 patients have been enrolled, I will be terminating the study at the present time.

CONCLUSIONS

Protocol terminated due to inadequate enrollment. No findings have been generated based on preliminary data.

Report Date: 3 October 2000 Work Unit # 1454-99

DETAIL SUMMARY SHEET

TITLE: Efficacy of Infergen (15meg) for Chronic Hepatitis C in Patients Who Are Non-Responders and Relapsers to Combination Therapy with Intron-A + Ribavirin: A Multicenter Trial.

PRINCIPAL INVESTIGATOR: Sjogren, Maria H., COL, MC
ASSOCIATES: Holtzmuller, Kent LTC, MC

DEPARTMENT: Medicine
SERVICE: Gastroenterology

STATUS: O
INITIAL APPROVAL DATE: 24 November 1998

STUDY OBJECTIVE:
The primary objective of this clinical trial is to determine the efficacy of Infergen 15 mcg 3 times per week or Infergen 9 mcg daily for 40 weeks after an induction dose of 15 mcg daily for 8 weeks in patients who did not respond or relapsed after combination therapy with Intron A + Ribavirin.

TECHNICAL APPROACH:
Patients with biopsy proven chronic hepatitis C, who are non responders or relapsed after receiving Intron A + Ribavirin will be treated with INFERGEN 15ug subcutaneously daily for 8 weeks as induction therapy followed by 15 ug 3 times per week or Infergen 9 mcg daily for 40 weeks. Patients with undetectable HCV-RNA at week 24 will be withdrawn from the study. The total enrollment for this multicenter trial will be approximately 400 patients.

PRIOR AND CURRENT PROGRESS:
The study was closed to enrollment on 12/31/99. To date 510 subjects were enrolled (all sites), 339 new subjects were enrolled during the last year. At WRAMC, 7 subjects participated in the study, 3 were entered in the study during the last year.
The following table shows the viral response to treatment. End of treatment response is measured during the last week of therapy (week 48). Week 72 data are not available yet.

		HCV RNA Negative	
Group	N	Week 24	Week 48
Relapsers - 15 mcg/3 x week*	61	23/39 (59%)	5/22 (22.7%)
Relapsers - 9 mcg/day*	65	27/37 (73%)	9/20 (45%)
Non-responders - 15 mcg/3 x week**	201	30/135 (22.2%)	1/112 (0.89%)
Non-responders - 9 mcg/day**	183	38/114 (33.3%)	6/92 (6.5%)

Discontinuation and adverse event data:

*Relapsers - 62 subjects discontinued early
25 - positive at Week 24 (study design discontinuations)
16 - adverse event
18 - patient withdrew consent
2 - patient non-compliance
1 - investigator discretion

**Non-responders - 286 subjects discontinued early
175 - positive at Week 24 (study design discontinuations)
48 - adverse event
36 - patient withdrew consent
17 - investigator discretion
9 - patient non-compliance
1 - off Infergen > 2 weeks

No deaths occurred. The protocol is now on the monitoring phase.

CONCLUSIONS
9 mcg/day of Infergen appears to be of benefit for prior relapsers to combination therapy, but does not show promising results for prior non-responders.
Data at 72 weeks of follow-up will be used to evaluate sustained response.

Report Date: 5 February 2001

Work Unit # 1456-99

DETAIL SUMMARY SHEET

TITLE: Long-Term Prevention of Recurrent Peptic Ulcer Hemorrhage in Patients Infected with Helicobacter Pylori: A Multi-Center, NIH-Funded, Prospective, Randomized Double-Blind Study

KEYWORDS:

PRINCIPAL INVESTIGATOR: Wong, Roy COL MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Gastroenterology

STATUS: O
INITIAL APPROVAL DATE: 23 March 1999

STUDY OBJECTIVE

The objectives of this study are:

1) To determine the efficacy and safety of H.pylori eradication alone versus H.pylori eradication combined with daily full dose H2RA in preventing recurrences of DU and GU hemorrhage
2) To document whether recurrences of ulcer hemorrhage are associated with NSAIDS-ASA and/or H.pylori recurrence of H.pylori infection

TECHNICAL APPROACH

Patients diagnosed within 6 months with DU or GU hemorrhage with H.pylori infection may enter the study at either phase I or phase II. H.pylori infection will be documented using CLO, ELISA, histopathology and/or C13 breath test. In phase I, study patients will receive 10 days of antimicrobial therapy for H.pylori eradication. Eradication will be documented by C13 urea breath test at least 6 weeks after completion of antimicrobial therapy. Those in whom eradication is successfully achieved will be randomized to the H2RA vs. Placebo in a double-blind fashion. Patients whose H.pylori was not eradicated by two courses of antimicrobial therapy or diagnosed with greater than/equal to 5 gastric and/or duodenal erosions after H.pylori eradication will receive full-dose H2RA and will also be followed up long term as a comparator group. All patients in Phase II will be followed-up long-term for a median of 36 months. The follow-up entails an interview of their symptoms associated with GU and/or other health, changes in health status and direct and indirect costs associated to health reasons.

PRIOR AND CURRENT PROGRESS

At WRAMC, there are currently 10 study patients enrolled in the study. Thus far no adverse reactions associated with this study were found or resulted from the study. Currently 6 patients withdrew from the study. The reasons for withdraw are as follows: discovery of hepatitis C (resulting from a previous transfusion not related to this study), moved, schedule conflicts and patient incompliant to scheduled visits. There are 27 sites participating in this multi-centered study. As of 11 January 2001, the total number of patients in phase I are 317. There is a total of 305 patients enrolled in phase II and 9 patients in the comparator group. There have been no major complications or drug related adverse events for the 305 patients enrolled in phase II of the study. However, there have been 2 incidences of recurrence of ulcer in patients enrolled in phase II of the study. There are total of 197 adverse events reported to the study. Benefits to the patients are close follow-ups and monitor of symptoms and medications as well as education in a better health care associated with the ulcers.

CONCLUSIONS

Patient enrollment is in progress. No conclusion can be drawn at this time.

Report Date: 31 May 2001 Work Unit # 1457-99

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: Colorectal Neoplasia Screening with Colonoscopy in Asymptomatic Women at Regional Navy/Army Medical Centers: The CONCeRN Trial

KEYWORDS: colorectal care, cancer screening, colonoscopy

PRINCIPAL INVESTIGATOR: Brooks D. Cash, MD LCDR MC USN
ASSOCIATES: James Walter Kikendall, MD COL MC USA; Eric Ormseth, MD MAJ MC USA

DEPARTMENT: Medicine
SERVICE: Gastroenterology

STATUS: O
INITIAL APPROVAL DATE: 18 May 1999

STUDY OBJECTIVE

Primary:
To determine the incidence of advanced colonic neoplastic lesions (i.e. adenomas with high grade dysplasia, villous adenomas, colorectal cancers, and/or adenomous polyps $\geq$ 1 cm in diameter) in a cohort of asymptomatic women referred for colorectal cancer screening
To determine if selected factors (i.e. age, race, obesity, tobacco use, aspirin/NSAID use, alcohol use, use of hormonal replacement therapy, family history of colon cancer, and presence of dimunitive adenomatous polyp (adenomatous polyp < 1 cm) in the distal 60 cm of the colon) predict the presence of advanced neoplastic lesions, using both univariate and multiple logistic regression analysis.

Secondary:
To estimate the sensitivity and specificity of flexible sigmoidoscopy for advanced neoplastic lesions in the proximal colon.

Tertiary:
To gather data for cost-effectiveness analysis of colonoscopy among asymptomatic women referred for colorectal cancer screening
To gather a cohort of women with normal screening colonoscopy who can be randomized to have repeat coloscopy in 7 or 10 years in order to ascertain the appropriate interval between screening colonoscopies.

TECHNICAL APPROACH

Request for change in PI submitted 25 Nov 99-Approved

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

117 subjects recruited from WRAMC to date.
1100 patients enrolled in the study to date (all sites included)
No complications or adverse reactions to date
No patients withdrawn from study to date

CONCLUSIONS

At the time of the last data analysis (n-692) 20.7 percent of subjects had tubular adenomas found and removed during colonoscopy. Three percent (21/692) had advanced adenomas. Seventy-five percent of all subjects with tubular adenomas had normal flexible sigmoidoscopy and 76% of subjects with advanced adenomas had normal flexible sigmoidoscopy examinations.
Analysis of risk factors indicated age $\geq$ 65 years as the only risk factor independently associated with the development of adenomatous polyps.

Report Date: 1 September 2000 Work Unit # 00-1501

DETAIL SUMMARY SHEET

TITLE: CALGB 89804 Randomized Phase III Trial of Combinations of Oxaliplatin (OXAL), 5-Fluorouracil (5-FU), and Irinotecan (CPT-11), as Initial Treatment of Patients With Advanced Adenocarcinoma of the Colon and Rectum

KEYWORDS:

PRINCIPAL INVESTIGATOR: Willis, Carl MAJ MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 19 October 1999

STUDY OBJECTIVE

The primary objective of this trial is to compare the time to progression in patients with locally advanced or metastatic colorectal cancer who receive ARM F which is Oxaliplatin plus 5FU plus Leucovorin or ARM G which is Irinotecan plus Oxaliplatin (the two experimental regimens) to those receiving ARM A which is Irinotecan plus 5FU plus leucovorin (the control regimen). The secondary objective is to compare the time to progression of patients receiving the two experimental regimens. The primary secondary outcome measure in this trial is overall survival. Other secondary objectives include evaluation of toxicity, response rate, and time to treatment failure. Also, to compare quality-of-life parameters in-patients on these regimens.

TECHNICAL APPROACH

All eligible patients will be randomized to one of the three treatment regimens. They will be monitored with laboratory values, appropriate scans/studies for tumor measurements, and physical exams to determine response to therapies. ARM A treatment is given weekly for four weeks with a two week rest period; each cycle is 6 weeks. ARM F treatment is given on days 1 and 2 every two weeks; each cycle is 2 weeks. ARM G treatment is given on day 1 every three weeks; each cycle is 3 weeks. Patients continue on therapy until disease progression, in the absence of unacceptable toxicity. If they achieve a complete response on two consecutive cycles' therapy may be discontinued.

PRIOR AND CURRENT PROGRESS

This study was originally designed as a 6-regimen/arm study.
New data presented in March 2000, from two randomized trials, indicated that the addition of Irinotecan to a standard 5FU plus leucovorin regimen resulted in improved patient outcome. The new standard therapy increased response rate, time to progression, and survival. It appeared that the likelihood of a statistical significant difference between regimens of the same drug combination was remote. Because of this, the trial was collapsed from 6 to 3 regimens/arms per update #8, dated 5/15/2000. The changes and a new consent were approved by HUC on 7/18/00.
No patients from WRAMC have been entered on this study to date. No serious adverse events have been reported by the CALGB. Projected accrual remains at 1125 patients.

CONCLUSIONS

No conclusions have been reached.

Report Date: 22 November 2000 Work Unit # 00-1502

DETAIL SUMMARY SHEET

TITLE: CALGB 49906: A Phase III Study of Doxorubicin-Cyclophosphamide Therapy Followed by Paclitaxel or Docetaxel Given Weekly or Every 3 Weeks in Patients With Axillary Node-Positive Breast Cancer

KEYWORDS: Node Positive, Breast Cancer, Paclitaxel vs Docetaxel

PRINCIPAL INVESTIGATOR: Byrd, John MAJ MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Hematology Oncology

STATUS: O
INITIAL APPROVAL DATE: 27 January 2000

STUDY OBJECTIVE

To determine whether docetaxel improves disease-free survival and overall survival when compared to paclitaxel following 4 cycles of doxorubicin-cyclophosphamide therapy, for women with node-positive breast cancer. To determine whether weekly administration of taxanes (paclitaxel or docetaxel) for 12 weeks improves disease-free survival and overall survival when compared with conventional (every 3 weeks) schedule for 4 cycles following 4 cycles of doxorubicin-cyclophosphamide therapy. To compare the toxicity of both drugs docetaxel and paclitaxel, given in the weekly or every 3 week cycles.

TECHNICAL APPROACH

All eligible patients will be randomized to one of 4 possible treatment arms (A, B, C or D). All patients will initially receive 4 cycles of doxorubicin-cyclophosphamide. Subsequent treatment will be according to randomization. Treatment A: Paclitaxel will be given over 3 hours every 3 weeks x 4 cycles. Treatment B: Paclitaxel will be given over 1 hour every 3 weeks x 12 weeks. Treatment C: Docetaxel will be given over 1 hour every 3 weeks x 4 cycles. Treatment D: Docetaxel will be given over 1 hour every week x 12 weeks. Following chemotherapy, all patients with positive estrogen receptors will be given oral Tamoxifen for 5 years.

PRIOR AND CURRENT PROGRESS

One WRAMC patient has been entered on this protocol during this reporting period. No unexpected adverse reactions to study treatment have been reported, and no WRAMC patient has withdrawn from the study. National accrual to the study thus far is 1503 patients with a projected accrual of 2940. No changes have been made to the protocol.

CONCLUSIONS

No conclusions have been reached.

Report Date: 4 April 2001 Work Unit # 00-1503

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: CALGB 159806: ErbB-2 and p53 in response and Outcome After Paclitaxel Chemotherapy for Metastatic Breast Cancer

KEYWORDS: Erb-B-2, p53, paclitaxel, metastatic breast cancer

PRINCIPAL INVESTIGATOR: Joseph P. Drabick COL MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 09 May 2000

STUDY OBJECTIVE:
To correlate the growth factor receptor ErbB-2 and p53 with response rate, time to progression, and overall survival of patients with metastatic breast cancer treated with paclitaxel on CALGB 9342. To determine if amplification and over-expression of ErbB-2 must be present in order to predict response to paclitaxel.

TECHNICAL APPROACH
Primary tissue from patients enrolled on CALGB 9342 will be used for histopathological evaluation, immunohistochemical evaluation, FISH, sequence analysis, p53 analysis and genomic sequencing will be done. The methods for assessing ErbB-2 and p53 will be correlated.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
This is a minimal risk study in that only existing pathological material will be studied. No adverse events have been reported. No changes to the original protocol design, objectives or technical approach have occurred.
The number of subjects enrolled to the study since last APR at WRAMC is 5 and the total enrolled to date at WRAMC is 5. The total number enrolled study-wide is 62, if multi-site study.

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

Report Date: 1 June 2001 Work Unit # 00-1504

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: CALGB 89803: A Phase III Intergroup Trial of Irenotecan (CPT-11) (NSC #6163480 Plus Flourouracil/Leukovorin (5-FU/LV) Versus Flourouracil/Leukovorin Alone After Curative Resection for Patients with Stage III Colon Cancer.

KEYWORDS: Colon Cancer; Stage III; Irinotecan (CPT-11); Fluorouracil/Leukovorin (5FU/LV)

PRINCIPAL INVESTIGATOR: Joseph Drabick, COL MC

DEPARTMENT: Medicine STATUS: O
SERVICE: Hematology/Oncology INITIAL APPROVAL DATE: 25 July 2000

STUDY OBJECTIVES: To determine if the addition of CPT-11 to the standard 5FU/LV treatment improves overall and disease free survival in Stage III colon cancer patients after curative resection.

TECHNICAL APPROACH: Eligible patients will be randomized to one of two treatment regimens. Treatment A is the standard adjuvant treatment with 5FU and Leukovorin (LV) which is given weekly for 6 weeks followed by 2 rest weeks repeated times 4 cycles. Treatment B is the addition of CPT-11 to 5FU/LV which is given weekly for 4 weeks followed by 2 rest weeks repeated times 5 cycles. A CBC and chemistries will be done every treatment week. After therapy is completed the patient will be observed for recurrence. Follow-up will include physical exams, lab-work and chest x-rays. Other follow-up exams, such as CT scans, will be PRN.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE: This study has been closed to any further accrual. However, before this closure, effective 5/15/01, the CALGB identified an unacceptable toxicity profile in the number of thrombotic events. A Broadcast Message was sent to all CALGB members regarding this unexpected number of events, on 3/13/01. The study was temporarily suspended 4/27/01. The CALGB made adjustments to dose modifications for patients experiencing diarrhea and a change made to the protocol was included in the 5/15/01 Monthly Posting from the CALGB. This update of 5/15/01 will be submitted to the IRB under separate cover. The dose modification applies to patients who are presently being treated on the study.
After further independent review of the study's adverse events, by the CALGB and the North Central Cancer Treatment Group's Data and Safety Monitoring Board the analysis revealed an "imbalance in the number of deaths occurring within 60 days after the initiation of treatment". A Letter to the Editor was submitted to the NEJM recommending extreme caution with the regimen used in Treatment B. This letter was sent to the CALGB investigators 5/17/01.

The number of subjects enrolled to the study since last APR at WRAMC is 3 and the total enrolled to date at WRAMC is 3. The national accrual to the study is 481, total number enrolled study-wide was projected to be 1260.

All patients from WRAMC were randomized to Treatment Arm A, which is standard therapy with 5FU/LV. Therefore, none of our patients received CPT-11. None of our patients has experienced a thrombotic event. One patient experienced diarrhea after completing cycle #1 that required a dose modification for cycle 2. She has not had a recurrence of dose limiting diarrhea during cycle 2. One patient had a weekly dose held for nausea and diarrhea. It was not certain if the nausea and diarrhea was related to the treatment as it occurred one week after the last treatment.

CONCLUSIONS: The study objectives have not yet been answered. The study has met accrual and has been closed to further accrual. An unexpected number of thrombotic events and deaths were identified and reported to members of the CALGB, to the NCI and FDA. However, all patients on this study will be monitored closely for signs and symptoms of thrombotic events and treated accordingly. No conclusions have been reached.

Report Date: 30 May 2001

Work Unit # 00-1505

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: CALGB 19901 Phase II Study of Fludarabine Induction Followed by Campath-1 H Consolidation in Untreated Patients with Chronic Lymphocytic Leukemia

KEYWORDS: Phase II; Fludarabine; Campath-1H; Chronic Lymphocytic Leukemia

PRINCIPAL INVESTIGATOR: Drabick, Joseph COL MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 25 July 2000

STUDY OBJECTIVE:
To determine the overall complete response rate, the infectious toxicities, the progression-free and overall survival and the immunologic effects of sequential treatment with fludarabine and Campath-1H in previously untreated patients with active chronic lymphocytic leukemia.

TECHNICAL APPROACH :
INDUCTION with Fludarabine is to be given 5 days per week during weeks 1, 5, 9 and 13 (a total of four 28-day cycles). Two months later, CONSOLIDATION with Campath-1H is to be given three times per week for 6 weeks. Restaging bone marrows will be done after INDUCTION, before CONSOLIDATION, at the end of CONSOLIDATION and two months after CONSOLIDATION.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE:
In February 2001, this study was temporarily suspended after having met its accrual goal while an amendment to the study was being considered. In April 2001, a Broadcast Message was sent notifying all investigators of a higher than expected frequency of primary and secondary cytomegalovirus (CMV) infections in patients treated with Campath-1H on this study. This Broadcast Message was submitted to the WRAMC IRB on 4/20/01 in the form of an Adverse Event report. Effective 5/15/01 the CALGB reactivated this study. Also, on 5/15/01 amendments to the study, per updates #5 and #6, addressed a change in the route of administration of Campath-1H from intravenous dosing to subcutaneous injection, CMV monitoring was defined in detail, and the addition of 18 more patients to the study who will receive Campath-1H via subcutaneous route. No response data has been reported to date. Adverse events are listed in the statistical summary that is attached. There is one patient from WRAMC on the study. She has finished both fludarabine and Campath-1H. She experienced grade 3 insomnia/unusual nightmares, felt to be related to fludarabine. An adverse event report was submitted to the WRAMC IRB 1/16/2001. She has been tested and evaluated for CMV infection and remains negative. The total number of subjects enrolled in the study since it was approved at WRAMC is one. This is the first APR. The total number enrolled study-wide is about 50.

CONCLUSIONS:
No conclusions have been reached at this time-point.

Report Date: 3 August 2001 Work Unit # 00-1506

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: CALGB 99808: Docetaxel and Estramustine Versus Mitoxantrone and Prednisone for Advanced, Hormone Refractory Prostate Cancer, Phase III

KEYWORDS: Advanced Hormone Refractory Prostate Cancer; Docetaxel; Estramustine; Mitoxantrone; Prednisone; Phase III

PRINCIPAL INVESTIGATOR: Flynn, Joseph M. CPT MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 18 September 2000

STUDY OBJECTIVE

To compare overall survival and progression-free survival in patients with hormone refractory metastatic prostate cancer, Stage D1 or D2, who are randomized either to treatment on Arm 1, estramustine + docetaxel, or Arm 2, mitoxantrone and prednisone. To compare the toxicities between the two study arms. To evaluate Quality of Life. To record PSA values for future correlations with response and survival. To compare responses between the two treatment groups.

TECHNICAL APPROACH

Eligible patients will be randomized to ARM 1 or ARM 2. Patients in ARM 1 will receive estramustine orally, three times per day on days 1 and 2, will receive docetaxel IV on day 2, and 3 doses of dexamethasone prior to receiving docetaxel. ARM 1 will be given every 21 days. All patients will take low dose enteric coated aspirin, 325 mg, orally, daily for anticoagulation therapy. A maximum of 12 cycles will be given. If no toxicity occurs during cycle 1 the dose of docetaxel will be escalated. If significant toxicity occurs, the dose of docetaxel will be reduced. Additionally, all patients will require additional prophylaxis against arterial events. One of the following 3 anticoagulants are to be used—coumadin, levenox, or fragmin in addition to the aspirin. Patients on ARM 2 will receive mitoxantrone, IV, on day 1 and prednisone orally twice a day on days 1 to 21. ARM 2 will be given every 21 days. A maximum of 12 cycles will be given. If no toxicity occurs during cycle 1, the mitoxantrone dose will be escalated. If after a dose escalation, significant toxicities occur the dose of mitoxantrone will be reduced.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

One patient from WRAMC has been enrolled on this study. He was randomized to treatment ARM 1. He experienced a grade 3 known toxicity (elevated phosphorous) which required discontinuation of estramustine. Docetaxel continued until he progressed after 7 cycles. He did not experience additional dose limiting toxicities.
Group wide grade 4 toxicities in patients on ARM 1 have included diarrhea, neutropenia, GI bleed, and pulmonary embolism. No grade 4 toxicities have been reported on ARM 2.
This is the first APR required. The total enrolled to date at WRAMC is __1__. The total number enrolled study-wide is __73__. Target accrual is 620.

CONCLUSIONS

This study remains open to accrual. No conclusions have been reached.

Report Date: 3 August 2001 Work Unit # 00-1507

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: CALGB 9764: Genetic Changes in Diffuse Aggressive Non-Hodgkin's Lymphoma

KEYWORDS:

PRINCIPAL INVESTIGATOR: Drabick, Joseph COL MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 19 September 2000

STUDY OBJECTIVE

To estimate the proportions of patients with rearrangements affecting the MYC, BCL2 and BCL6 genes determined by FISH, overtly amplified chromosomal regions, and non-random copy number changes of chromosomal regions determined by CGH.
To investigate the prognostic importance of these genetic markers by studying their relationships with the clinical outcomes: response to therapy, failure-free survival (FFS), and overall survival (OS) (response to therapy).
To investigate the interrelationships among these genetic and biological markers and their relationships with clinical features of the disease, such as disease site (nodal vs. extranodal) and stage.

TECHNICAL APPROACH

There is a retrospective and prospective component. The retrospective component is for patients who were enrolled on CALGB 8852 and CALGB 9351. They are eligible if tissue blocks obtained at diagnosis and at time of refractory/relapsed NHL are available for submission to the CALGB Pathology Coordinating Office (PCO), at the Ohio State University, B054 Graves Hall, 333 West 10th Avenue, Columbus, Ohio 43210-1239 and to Memorial Sloan-Kettering Cancer Center, Department of Human Genetics, 1275 York Avenue, NYC 10021. Only blocks from subjects who are still living will be collected. No consent form is required for the retrospective component.
The prospective component requires that consent be obtained from patients who are being treated for NHL on a CALGB treatment study. Participation in this study is not mandatory for participation in a CALGB treatment study.
Tissue blocks will be obtained from Pathology Departments by a Research Coordinator/Nurse.
When the tissue blocks are received by the above institutions a Unique Patient Number (UPN) will be assigned to each patients blocks to protect the patient's identity.
There has not been any change to the original methodology.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

No patients from WRAMC have been registered to this study. Target accrual is 455. This remains a minimal risk study. The objectives are ongoing. No findings have been reported.
The number of subjects enrolled to the study since last APR at WRAMC is __0__ and the total enrolled to date at WRAMC is __0_____. The total number enrolled study-wide is __41_____, if multi-site study.

CONCLUSIONS

No conclusions have been reached.

Report Date: 30 August 2000

Work Unit # 00-1601

DETAIL SUMMARY SHEET

TITLE: A Feasibility Study of Campath-1H and GM-CSF Combination in Patients with Chronic Lymphocytic Leukemia and Small Cell Lymphocytic Lymphoma

KEYWORDS:

PRINCIPAL INVESTIGATOR: MAJ John C. Byrd MC
ASSOCIATES: CPT Joseph Flynn MC, Margaret Lucas PA-C, Kathy Park RN

DEPARTMENT: Medicine
SERVICE: Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 26 October 1999

STUDY OBJECTIVE

To determine the safety profile of administering Campath 1-H with GM-CSF

TECHNICAL APPROACH

To determine if GM-CSF increases the intensity if CD20 expression on CLL cells and the degree and time sequence of change in CD55 and CD59 expression following treatment with Campath-1H

PRIOR AND CURRENT PROGRESS

A total of 5 patients have been enrolled at WRAMC on this study. A total of 17 patients have been enrolled at other institutions. The following adverse events have been recorded and reported to the FDA.

1) catheter tips pos for coag neg staph
2) 2 anemias
3) hypotension
4) 2 blood positive for gram+ cocci
5) fever of 102.1 F
6) RLE DVT
7) Fever 38.8 C and neutropenic
8) Death/likely related to cardiac event

CONCLUSIONS

No conclusions have been reached as this study is ongoing and accrual continues.

Report Date: 11 January 2001

Work Unit # 00-1602

DETAIL SUMMARY SHEET

TITLE: A Phase II Study of Orzel (UFT+Leukcovorin) Given as a Twice Daily Regimen in the Treatment of Patients with Recurrent Metastatic Breast Cancer

KEYWORDS:

PRINCIPAL INVESTIGATOR: Christie, Robert MAJ MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Hematology-Oncology

STATUS: C
INITIAL APPROVAL DATE: 16 November 1999

STUDY OBJECTIVE:
To determine time to disease progression for patients under the above regimen, evaluate response rate, toxicity profile, and overall survival.

TECHNICAL APPROACH:
This is a multi-center open-label trial of Orzel (UFT+Leucovorin) in patients with recurrent breast cancer. Patients will receive 300mg UFT twice a day on five out of seven days each week (no weekend dosing). 30mg dose of Leucovorin will be given with each UFT dose. Patients will be assessed for time to disease progression, response rate, toxicities and survival. Pharmacogenetic assessments will be performed to analyze the genetic variation in genes involved in the metabolism and efficacy of UFT.

PRIOR AND CURRENT PROGRESS:
A total of 24 patients have been enrolled on this trial. No patients have been enrolled at WRAMC. The Hematology/Oncology staff wishes to close this protocol. Seven (7) deaths have occurred from toxicities of Orzel. These toxicities have included: hepatic cirrhosis, angina pectoralis, gastric ulcer, DIC, anemia, abdominal abscess, hypercholesterolimia, pancreatitis, Raynauld's phenomena, ejection fraction abnormalities, ansosmia, acute MI, cardiac failure, dehydration, stroke and kidney failure.

CONCLUSIONS:
No conclusions have been reached.

Report Date: 01 November 2000

Work Unit # 00-1603

DETAIL SUMMARY SHEET

TITLE: A Multicenter Phase 2 Study of Oral N-Acetyl Dinaline (CI-994) in the Treatment of Patients with Chronic Lymphocytic Leukemia (protocol 994-05)

KEYWORDS: immunology, oncology, leukemia

PRINCIPAL INVESTIGATOR: Byrd, John C. MAJ MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Hematology/Oncology

STATUS: O
INITIAL APPROVAL DATE: 14 December 1999

STUDY OBJECTIVE:
To determine the antitumor activity of N-acetyl Dinaline (CI-994) in patients with chronic lymphocytic leukemia; to determine the safety profile of CI-994 when administered using a chronic daily oral dosing regimen.

TECHNICAL APPROACH:
A multicenter phase 2 study of oral n-acetyl dinaline (ci-994) in the treatment of patients with chronic lymphocytic leukemia.

PRIOR AND CURRENT PROGRESS:
A total of three (3) patients have been enrolled in this study at WRAMC

CONCLUSIONS:
No conclusions have been reached due to this being an ongoing study, which just started enrolling patients.

Report Date: 12 February 2001 Work Unit # 00-1605

DETAIL SUMMARY SHEET

TITLE: Prospective Evaluation of Fatigue in Patients with Chronic B-Cell Chronic Lymphocytic Leukemia

KEYWORDS: Fatigue, Chronic Leukemia

PRINCIPAL INVESTIGATOR: Noel C. Ales DO
ASSOCIATES: CPT Joseph Flynn, DO; MAJ John Byrd, MD; Maragret Lucas, PA-C; Kathy Park, RN

DEPARTMENT: Medicine
SERVICE: Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 18 January 2000

STUDY OBJECTIVE

1) To evaluate fatigue experienced by Chronic Lymphocytic Leukemia (CLL) patients as compared matched members of the general medical population.
2) To evaluate the relationship between fatigue and disease stage of CLL.
3) To evaluate the progression of fatigue over time in patients with untreated CLL.
4) To evaluate the relationship of response to therapy and fatigue in CLL patients.
5) To determine if there is a correlation with cytokines and fatigue experienced by CLL patients.
6) To evaluate the overall quality of life experienced by CLL patients as compared to that experienced by the general medical population.

TECHNICAL APPROACH

None.

PRIOR AND CURRENT PROGRESS

Fifteen patients enrolled last year and to date.
Accrual continuing.
As John Byrd is leaving Walter Reed and Noel Ales is continuing on in an Allergy Fellowship, we will be submitting a change of Primary Investigator.

CONCLUSIONS

Ongoing.

Report Date: 2 January 2001 Work Unit #00-1606

DETAIL SUMMARY SHEET (Human Use Protocol)

TTTLE: A Phase II Evaluation of Rubitecan, A Novel Oral Topisomerase I Inhibitor, in Newly Diagnosed, Recurrent, and Refractory Multiple Myeloma

KEYWORDS: myeloma, rubitecan

PRINCIPAL INVESTIGATOR: Joseph J. Drabick COL MC
ASSOCIATES: John C. Byrd MAJ MC, Carl Willis MAJ MC

DEPARTMENT: Medicine
SERVICE: Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 8 February 2000

STUDY OBJECTIVE

The purpose of this phase II study is to determine if rubitecan, an oral topisomerase I inhibitor, has clinical activity in patients with recurrent, refractory, or newly diagnosed multiple myeloma.

TECHNICAL APPROACH

The structure of the protocols has not been changed to date. Patients found to be eligible are treated with oral rubitecan according to prior treatment status. Patients are evaluated a 2 week intervals for toxicity and at monthly intervals for activity. Dose may be modified according to toxicity or lack thereof.

PRIOR AND CURRENT PROGRESS

To date, one patient has been enrolled. This patient began treatment with rubitecan on 20 December 2000 and is due for first follow-up examination on 3 January 2001. There have been no problems reported by telephone to the study nurse. Rubitecan has not been approved by the FDA for any clinical indication. At WRAMC, we have opened a CALGB study that will determine if this drug has activity in hormone-refractory prostate cancer. Accrual to this myeloma study has been poor to date. Several patients were interested in participation but were found to be ineligible. The usual exclusion criteria were due to baseline cytopenias. These are expected for an advanced hematologic malignancy. Accordingly, an addendum to this protocol was submitted to DCI in late December to loosen the hematologic criteria to allow more patients to participate.

CONCLUSIONS

As of this date, no conclusions can be drawn on the activity or toxicity of rubitecan in multiple myeloma.

Report Date: 22 March 2001

Work Unit # 00-1607

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: A Study of Immunotherapy During Peripheral Stem Cell Collection and Post-Stem Cell Transplant for Patients with Lymphoproliferative Disorders

KEYWORDS:

PRINCIPAL INVESTIGATOR: Byrd, John MAJ MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Hematology-Oncology

STATUS: C
INITIAL APPROVAL DATE: 21 March 2000

STUDY OBJECTIVE

The primary objective of this study is to determine the feasibility of administering rituximab and GM-CSF post transplant to patients with low-grade lymphoproliferative disorders. The secondary objectives of this study are to estimate the effects of GM-CSF on the antibody dependent cellular cytoxicity of rituximab after autologous peripheral blood stem transplant; to characterize immune effector cell function recovery after rituximab an GM-CSF after transplant; to determine if IL-8 levels change after during mobilization and if these correlate with the volume of CD34 cells in the patients with low grade lymphoproliferative disorders.

TECHNICAL APPROACH

This study utilizes weekly dosing of rituximab for four post-transplant doses. A pre-mobilization specimen will be compared to a pre-transplant specimen and a specimen taken in the middle of the post-transplant immunotherapy. NK cells, T cells and B cells will be monitored for reconstitution. This protocol seeks specifically to determine the feasibility of administering immunotherapy post-transplant.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

No patients have been enrolled on this study at WRAMC

CONCLUSIONS

The PI is leaving WRAMC and there is limited interest by the service to keep this protocol open.

Report Date: 20 February 2001 Work Unit #00-1608

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: Phase II Study of Rituxan (Rituxximab, Mabthera) in Lymphoplasmacytic Lymphoma (Waldenstorm's Macroglobulinemia)

KEYWORDS:

PRINCIPAL INVESTIGATOR: Byrd, John C MAJ MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Hematology-Oncology

STATUS: W
INITIAL APPROVAL DATE: 25 April 2000

STUDY OBJECTIVE
This protocol was withdrawn, effective 25 January 2001.

TECHNICAL APPROACH
This protocol was withdrawn, effective 25 January 2001.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
This protocol was withdrawn, effective 25 January 2001, because the Dana Farber Center (sponsor) is going on to another study.

CONCLUSIONS
This protocol was withdrawn, effective 25 January 2001, because the Dana Farber Center (sponsor) is going on to another study.

Report Date: 26 February 2001

Work Unit #00-1609

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: A Multicenter Open Label Trial to Evaluate the Efficacy and Safety and IDEC-Y2B8 Immunotherapy of Relapsed or Refractory Low-Grade of Follicular Transformed B-Cell Non-Hodgkin's

KEYWORDS:

PRINCIPAL INVESTIGATOR: Byrd, John C MAJ MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Hematology-Oncology

STATUS: C
INITIAL APPROVAL DATE: 25 April 2000

STUDY OBJECTIVE

To provide treatment to those patients with low-grade follicular or transformed B-cell Non-Hodgkin's Lymphoma who are not eligible for other IDEC-Y2B8 protocols and to add to the overall efficacy and safety experience in this indication.

TECHNICAL APPROACH

Patients will receive a course IDEC-Y2B8 (90Y-Ibritumomab tiuvetan); a course includes a 250mg/m2 Rituxan infusion followed approximately one week later by a second infusion of Rituxan and IDEC-Y2B8. The patients are then followed for response and/or until disease progression is documented.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

No patients have been entered on this study at WRAMC.

CONCLUSIONS

No scientific conclusions have been reached at this time. A decision has been made to close this study. This decision has been made because the PI is leaving WRAMC and there has been limited interest by the Hematology/Oncology Service to continue this study.

Report Date: 24 April 2001 Work Unit # 00-1610

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: A Phase II Open-Label Study of HuM195 (Recombinant Anti-CD33 Monoclonal Antibody) Administered to Patients with Acute Myelogenous Leukemia (AML) Who Are Documented Regimen Failures of the Control Arm of Study No. 195-301

KEYWORDS:

PRINCIPAL INVESTIGATOR: Byrd, John MAJ MC
ASSOCIATES:

DEPARTMENT: Medicine STATUS: W
SERVICE: Hematology-Oncology INITIAL APPROVAL DATE: 15 August 2000

STUDY OBJECTIVE
A decision has been made to withdraw this study. This decision has been made because the PI is leaving WRAMC and there has been limited interest by the Hematology/Oncology Service to continue this study.

TECHNICAL APPROACH
A decision has been made to withdraw this study. This decision has been made because the PI is leaving WRAMC and there has been limited interest by the Hematology/Oncology Service to continue this study.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
A decision has been made to withdraw this study. This decision has been made because the PI is leaving WRAMC and there has been limited interest by the Hematology/Oncology Service to continue this study.

CONCLUSIONS
A decision has been made to withdraw this study. This decision has been made because the PI is leaving WRAMC and there has been limited interest by the Hematology/Oncology Service to continue this study. There was no enrollment.

Report Date: 24 April 2001

Work Unit # 00-1611

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: A Phase III Randomized, Multicenter Study to Assess the Efficacy and Safety of HuM195 (Recombinant Humanized Anti-CD33 Monoclonal Antibody) in Combination with Standardized Chemotherapy Compared to Standardized Chemotherapy Alone the Treatment of Patients with Refractory or First-Relapsed Acute Myelogenous Leukemia (AML) Protocol No. 195-301

KEYWORDS: refractory, acute myelogenous leukemia, chemotherapy

PRINCIPAL INVESTIGATOR: Byrd, John MAJ MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Hematology-Oncology

STATUS: C
INITIAL APPROVAL DATE: 25 July 2000

STUDY OBJECTIVE

To evaluate the efficacy and safety of HuM195 plus standardized chemotherapy, as compared to standardized chemotherapy alone, in the treatment of patients with refractory or first-relapsed AML.

TECHNICAL APPROACH

All patients will receive a pre-induction bone marrow within 2 weeks prior to induction. During induction, patients will receive a triple chemotherapy regimen over 6 days. Patients will be randomized on Day 5 to either HuM195 + chemotherapy or chemotherapy alone. For these patients randomized to study drug, they will receive HuM195 at 12mg/m^2/day for 4 days on days 6-9 of induction and on days 19-22. Consolidation will consist of standard chemo on days 1-4 and for those previously randomized to HuM195, they will receive HuM195 on days 5-8 and 17-20. Maintenance for those on study drug will consist of HuM195 1 cycle/month for 8 months. Patients may exit the study to receive bone marrow transplant for consolidation.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

One patient was enrolled on this study at WRAMC. This patient was randomized to standard chemotherapy alone arm. She progressed following induction therapy and was withdrawn from the study. She experienced no SAE's while on study. The number of subjects enrolled to the study since the last APR at WRAMC is 1 and the total enrolled to date at WRAMC is 1. The total number enrolled study-wide is 187, if multi-site study.

CONCLUSIONS

This study is ongoing to enrollment and treatment by Theradex and there have been no conclusions to date. A decision has been made to close this study. This decision has been made because the PI is leaving WRAMC and there has been limited interest by the Hematology/Oncology Service to continue this study.

Report Date: 27 March 2001 Work Unit #01-16003

DETAIL SUMMARY SHEET (Human Use Protocol)

TTTLE: A Dose-Escalation/Phase II CRC Study of HMR 1275 (Flavopiridol) Administered as a 30 Minute Loading Dose Followed by a 4 Hour Infusion in Patients with Previously Treated B-Cell Chronic Lymphocytic Leukemia or Prolymphocytic Leukemia

KEYWORDS:

PRINCIPAL INVESTIGATOR: John C. Byrd MAJ MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Hematology-Oncology

STATUS: W
INITIAL APPROVAL DATE: 27 February 2001

STUDY OBJECTIVE
This protocol was withdrawn by the PI before final DCI approval.

TECHNICAL APPROACH
This protocol was withdrawn by the PI before final DCI approval.

PRIOR AND CURRENT PROGRESS
This protocol was withdrawn effective 27 March 2001 because there would not be sufficient funding to do this study as planned and WRAMC was one of the sites dropped.

CONCLUSIONS
This protocol was withdrawn by the PI before final DCI approval.

Report Date: 6 October 2000

Work Unit # 1500-98

DETAIL SUMMARY SHEET

TITLE: CALGB 9633: A Phase III Study of Adjuvant Chemotherapy After Resection for Patients with T2NO Stage I Non-Small Cell Carcinoma of the Lung

KEYWORDS:

PRINCIPAL INVESTIGATOR: Byrd, John C MAJ MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 05 November 1997

STUDY OBJECTIVE

To determine if adjuvant chemotherapy can favorably alter the prognosis for high-risk patients with T2NO NSC carcinoma of the lung. To compare failure-free survival of these patients who have and have not received adjuvant chemotherapy after surgical resection. To determine toxicity associated with adjuvant chemotherapy, and to describe pattern of recurrence.

TECHNICAL APPROACH

Eligible patients with T2NO NSC carcinoma of the lung will be randomized after surgical resection to receive standard therapy/observation or to receive adjuvant chemotherapy with taxol and carboplatin. Chemo will be given in the HemOnc clinic once a week x 3 weeks for a total of four treatments (12 wks). Chemo is IV and the infusion takes one to two hours. Follow-up in clinic is q 4 months x 2 yrs, q 6 months thereafter.

PRIOR AND CURRENT PROGRESS

Three WRAMC patients have been entered on this study since it was opened to accrual, one in this reporting period. No WRAMC patients have withdrawn from this study, and no unexpected adverse events have been reported. All the WRAMC patients survive and continue in study follow-up. National accrual to the study at last report was 156 patients, 61 in this reporting period. Target accrual is for 500 patients. Minor changes to the protocol have been made in this reporting period.

CONCLUSIONS

No conclusions have been reached.

Report Date: 3 November 2000

Work Unit # 1501-98

DETAIL SUMMARY SHEET

TITLE: CALGB 9741: A Randomized Phase III Trial of Sequential Chemotherapy Using Doxorubicin, Placlitaxel and Cyclophosphamide or Current Doxorubicin and Cyclophosphamide Followed by Paclitaxel at 14 or 21 Day Intervals in Women with Node Positive Stage II/IIIA Breast Cancer

KEYWORDS: Chemotherapy, sequential, concurrent

PRINCIPAL INVESTIGATOR:
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 16 December 1997

STUDY OBJECTIVE

To compare sequential chemotherapy with doxorubicin, paclitaxel and cyclophosphamide to combined doxorubicin and cyclophosphamide followed by paclitaxel for disease-free survival and overall survival, and for toxicity. To determine whether increasing the dose density of adjuvant chemotherapy (decreasing the interval between chemotherapy from 21 to 14 days) will improve overall and disease-free survival.

TECHNICAL APPROACH

Eligible patients will be randomly assigned to one of 4 groups. All will receive Adriamycin, Taxol and Cytoxan (ATC). The four treatment plans are: 1) sequential C q3 weeks x 4, 2) sequential A-T-C q 2 weeks x 4, 3) concurrent AC q 3 weeks x 4 followed by T q 3 weeks x 4, 4) concurrent AC q2 weeks x 4 followed by T q 2 weeks x 4. Patients randomized to q 2-week therapy will receive G-CSF during therapy; the other groups receive G-CSF at the physician's discretion. Follow-up after treatment is q 6 months x 5 years, and yearly thereafter.

PRIOR AND CURRENT PROGRESS

A total of 5 WRAMC patients were entered on this protocol before it closed to accrual in March 1999 having met its goal of 2005. During the time the study was open, no WRAMC patients have died or withdrawn from the study, and no unexpected adverse events have been reported. National accrual to the study was 2005 patients. The 5 patients continue in study follow-up.

CONCLUSIONS

Analysis is ongoing

Report Date: 22 November 2000

Work Unit # 1502-98

DETAIL SUMMARY SHEET

TITLE: CALGB 9762: Clinical Pharmacology of Paclitaxel in Relation to Patient Age

KEYWORDS: Pharmacology, paclitaxel, patient age

PRINCIPAL INVESTIGATOR: Byrd, John MAJ MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 27 January 1998

STUDY OBJECTIVE

To determine if there is a relationship between pharmacokinetic measurements of paclitaxel and aging. To determine if there is a relationship between the toxicities of paclitaxel and aging.

TECHNICAL APPROACH

Eligible patients with cancer for whom single agent paclitaxel treatment is appropriate will receive standard paclitaxel treatment as described in protocol with protocol specific pharmacokinetic blood samples drawn prior to therapy and at 1, 6, and 7 hours after completion of first cycle of paclitaxel. All further treatment is at physician discretion. All patients will be followed in the outpatient oncology clinic for 6 weeks following protocol therapy.

PRIOR AND CURRENT PROGRESS

Twelve WRAMC patients have been entered on this protocol, 1 in this reporting period; 8 have died of their progressive disease and four remain in study follow-up. No unexpected adverse reactions have been reported, and no WRAMC patients have withdrawn from the study. National accrual to the study thus far is 142 patients, 96 within this reporting period. Projected accrual is for 120 evaluable samples. Minor changes were made to the protocol and a change was made to the consent form.

CONCLUSIONS

No conclusions have been reached.

Report Date: 28 December 2000 Work Unit # 1504-98

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: CALGB 9763: Prospective Evaluation of Body Surface Area (BSA) as a Determinant of Paclitaxel Pharmacokinetics/Pharmacodynamics in Women with Solid Tumors

KEYWORDS: paclitaxel, pharmacokinetics, pharmacodynamics

PRINCIPAL INVESTIGATOR: Byrd, John C. MAJ MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Hematology-Oncology

STATUS: C
INITIAL APPROVAL DATE: 24 February 1998

STUDY OBJECTIVE

To evaluate the relationships between body-surface area (BSA) and toxicity, BSA and pharmacokinetics, and pharmacokinetics and toxicity in patients receiving a fixed total dose of paclitaxel in the first dose of chemotherapy regardless of BSA. To determine the toxicity of this treatment and to assess the pharmacokinetics of paclitaxel.

TECHNICAL APPROACH

Eligible women for whom paclitaxel is an appropriate chemotherapy will be treated with a fixed total dose of 360 mg (NOT normalized for BSA) as a single dose in the first cycle by IV over 3 hours. Pharmacokinetic blood samples will be drawn prior to treatment, and at 1, 6 and 24 hours. In the second cycle, treatment dosage is at the discretion of the physician. CBCs will be collected 2x per week during the first 2 courses of treatment. After this time (2 months) follow-up will be at the discretion of the treating physician.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

No WRAMC patient has been entered on this study to date. No unexpected adverse reactions have been reported to us by the CALGB. National accrual to the study is 27 patients, 10 in this reporting period. The projected accrual is for 50 patients. No major changes have been made to the protocol in this reporting period. The study is now permanently closed at WRAMC since no patients were enrolled.

CONCLUSIONS

No conclusions have been reached.

Report Date: 28 December 2000

Work Unit # 1505-98

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: CALGB 9781: A Phase III Trial Comparing Trimodality Therapy (Cisplatin, 5-FU, Radiotherapy and Surgery) to Surgery Alone for Esophageal Cancer

KEYWORDS: esophageal, cancer, tromodality

PRINCIPAL INVESTIGATOR: Byrd, John C. MAJ MC
ASSOCIATES

DEPARTMENT: Medicine
SERVICE: Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 24 February 1998

STUDY OBJECTIVE

To compare overall 5-year survival rates between the two treatment arms. To compare treatment failure at 5 years between the two treatment arms; to assess and compare the toxicities of each approach.

TECHNICAL APPROACH

Eligible patients with esophageal cancer will be randomized to receive either:

1. A combination of standard dose radiation therapy and chemotherapy with Cisplatin and 5-FU, given as outpatient therapy and lasting 5 1/2 weeks. This therapy is followed in 3 to 8 weeks with surgical esophageal resection requiring an 8 to 10 day hospital stay.
2. Standard treatment consisting of surgical esophageal resection requiring an 8 to 10 day hospital stay. All patients will be followed 4x per year for 2 years, 2x per year for an additional 2 years, then annually.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

One WRAMC patient has been entered on this study before it was closed to accrual 30 March 2000. One adverse reaction occurred during this reporting period and was reported to the IRB. No WRAMC patients have withdrawn from the study. National accrual to this study was 56 patients, 17 in this reporting period. The projected accrual was for 500 patients.

CONCLUSIONS

No conclusions have been reached.

Report Date: 31 January 2001

Work Unit # 1506-98

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: CALGB 9720: Phase III Study of MDR Modulation with PSC-833 Followed by Immunotherapy with rIL-2 vs. No Further Therapy in Previously Untreated Patients with AML>60 Years

KEYWORDS: AML, PSC-833, rIL-2

PRINCIPAL INVESTIGATOR: Byrd, John C. MAJ MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 24 March 1998

STUDY OBJECTIVE

To determine if the addition of PSC-833 to induction chemotherapy improves complete response rates and if the addition of PSC-833 to induction and consolidation chemotherapy improves survival for patients with AML > 60 years old.
To determine if low-dose, subQ rIL-2 immunotherapy with intermittent high-dose boluses after chemotherapy prolongs disease-free survival.

TECHNICAL APPROACH

Eligible AML patients will be randomly assigned to one of two treatment groups: standard chemotherapy induction and consolidation (cytarabine, etoposide and daunorubicin) with or without PSC-833. After this therapy is complete, patients will be randomly assigned to either standard treatment: observation, or to maintenance therapy with rIL-2. Treatment period is about 6 months with a 28-day hospitalization for induction and a 6-day hospitalization for consolidation.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

One WRAMC patient has been entered on this study in this reporting period. The study group has reported no unexpected toxicities to us, but the protocol and the consent form were updated in April 2000. There were extensive revisions to the protocol and a new protocol package was reissued. A change was made to the consent form explaining that patients would not be randomized to treatment during the induction chemotherapy portion of the study, but instead would be reassigned to receive the standard treatment with ADE. This was added to the end of the consent form. The patient was asked to initial the statement. Also, the target accrual was increased from 400 patients to 485 patients. National accrual as of November 2000 was 354 patients.

The number of subjects enrolled to the study since last APR at WRAMC is 1 and the total enrolled to date at WRAMC is 1. The total number enrolled study-wide is 354, if multi-site study.

CONCLUSIONS

No conclusions have been reached.

Report Date: 31 January 2001

Work Unit # 1507-98

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: CALGB 9730: Single-Agent vs. Combination Chemotherapy in Advanced NSCLC: A CALGB Randomized Trial of Efficacy, Quality of Life and Cost-Effectiveness

KEYWORDS: NSCLC, advanced combination

PRINCIPAL INVESTIGATOR: Byrd, John MAJ MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 24 March 1998

STUDY OBJECTIVE

To compare overall survival and quality of life of patients treated with paclitaxel alone or in combination with carboplatin.
To determine cost-utility and cost-effectiveness of the best strategy.
To compare response rates and toxicities of each arm.

TECHNICAL APPROACH

Eligible patients will be randomized to receive IV chemotherapy treatment with either single-agent taxol or with a combination of taxol and carboplatin. This treatment will be on out-patient basis, requiring 6 six hour visits over 18 weeks. Quality of life questionnaires will be administered at outset and at 2, 6, 9, and 12 months after registration to the study.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Twelve WRAMC patients have been entered on this study, four in this reporting period. Two patients have died of their progressive disease in this reporting period and the remaining six patients continue in study follow-up. The study group has reported no unexpected toxicities to us. The protocol was closed to accrual in December 2000. National accrual to the study as of November 2000 was 530 patients, 202 patients in this reporting period. Projected national accrual is for 600 patients.

The number of subjects enrolled to the study since last APR at WRAMC is 4 and the total enrolled to date at WRAMC is 12. The total number enrolled study-wide is 530.

CONCLUSIONS

No conclusions have been reached.

Report Date: 6 October 2000

Work Unit # 1509

DETAIL SUMMARY SHEET

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

KEYWORDS: fludarabine, chlorambucil, crossover study

PRINCIPAL INVESTIGATOR: Byrd, John C MAJ MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 27 November 1990

STUDY OBJECTIVE

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

TECHNICAL APPROACH

Randomized study for eligible CLL patients comparing the new drug fludarabine with the standard treatment of chlorambucil, or with the two drugs given in combination. Length of treatment depends on patient's response, with the maximum treatment being 2 years. Fludarabine is given intravenously for 5 days every 28 days. Chlorambucil is given by mouth for 1 day every 28 days. On 02 May 94, an addendum closed the third arm of the study. In September 1994, the consent form was revised to include new toxicity data and add new subjects.

PRIOR AND CURRENT PROGRESS

A total of four WRAMC patients were entered on this protocol before it was closed to accrual in December of 1994. No WRAMC patients have withdrawn from the study, and two were removed from the study treatment due to drug toxicity. One serious adverse event was reported to the IRB in February 1995. Two WRAMC patients have died from their continuing disease and the remaining two continue in study follow-up. A total of 544 patients were entered on this study nationally meeting accrual goals.

CONCLUSIONS

This study has identified fludarabine as a highly effective agent in the treatment of CLL. Other analysis continues.

Report Date: 31 January 2001

Work Unit # 1509-98

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: CALGB 9793: A Phase III Trial of CHOP vs. CHOP and Chimeric Anti-CD 20 Monoclonal Antibody (IDEC-C2B8) in Older Patients with Diffuse Mixed, Diffuse Large Cell and Immunoblastic Large Cell History Non-Hodgkin's Lymphoma

KEYWORDS: Lymphoma, elderly, Monoclonal Antibody Maintenance

PRINCIPAL INVESTIGATOR: Byrd, John C MAJ MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 31 March 1998

STUDY OBJECTIVE

To compare CHOP treatment with or without chimeric anti-CD20 monoclonal antibody (IDEC-C2B8) in elderly patients with diffuse mixed, diffuse large cell, and immunoblastic large cell non-Hodgkin's lymphoma of B lineage with respect to response rate, the time to treatment failure, toxicity and survival. To compare the IDEC-C2B8 monoclonal antibody as maintenance therapy to observation alone after CHOP chemotherapy with respect to time to treatment failure, duration of response, toxicity and survival after an initial response to induction therapy of CHOP + IDEC C2B8 and to determine if maintenance therapy with IDEC-C2B8 results in the conversion of any partial responses to a complete response.

TECHNICAL APPROACH

All eligible patients will be randomized to receive CHOP chemotherapy with or without Anti-CD20 therapy. Therapy will be given every 21 days for a minimum of 6 cycles and maximum of 8 cycles depending upon response. Patients who achieve a complete response, after 4 cycles, will subsequently be randomized the second time to receive either anti-CD20 maintenance therapy or observation. Patients who achieve a partial response after 6 cycles will receive 2 additional cycles and then the same subsequent randomization. Patients who have no change in tumor measurements from cycle 4 to 6 and are in partial remission will then be randomized to maintenance therapy or observation. Patients with either stable disease or progressive disease will be taken off study treatment and not further randomized.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

No WRAMC patients have been entered on this protocol since it was approved in March of 1998. No unexpected adverse events have been reported. No changes have been made to the protocol this reporting period. National accrual to the study as of November 2000 was 470. Target accrual was for 630 patients. The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 0. The total number enrolled study-wide is 470, if multi-site study.

CONCLUSIONS

No conclusions have been reached.

Report Date: 28 February 2001

Work Unit #1510-98

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: CALGB 9712: A Randomized Phase II Study of Concurrent Fludarabine+Chimeric Anti-CD 20 Monoclonal Antibody IDEC-C2B8 (Rituximab) [NSC#687451] Induction/Consolidation vs. Fludarabine Induction/Rituximab Consolidation

KEYWORDS: Fludarabine, Rituximab, Phase II

PRINCIPAL INVESTIGATOR: Byrd, John MAJ MC.
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 28 April 1998

STUDY OBJECTIVE

1) To determine in Fludarabine treated CLL patients the complete response (CR) rate and toxicity profile of concurrent and consolidative IDEC-C2138 (arm 1) and of consolidative IDEC-C2B8 therapy (arm II).
2) To assess the CR rate in patients receiving concurrent therapy with IDEC-C2B8 and Fludarabine (the induction phase of arm I).

TECHNICAL APPROACH

Eligible CLL patients will be randomly assigned to Arm 1: Fludarabine plus Rituximab induction followed by Rituximab consolidation therapy or to Arm II: Fludarabine induction (standard therapy) followed by Rituximab consolidation therapy. Induction therapy will last 6 months followed by a monitoring phase of 12 weeks, and if appropriate (patients with CR, partial response or stable disease) 4 weeks of consolidation therapy. Patients will receive prophylactic allopurinal for the first 15 days of treatment. Patients will be entered on CALGB 9665--tissue bank companion study.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Eleven WRAMC patients were entered on this study before it was closed to accrual in January 1999. No WRAMC patients have withdrawn from the study during this reporting period. One WRAMC patient has died of their disease and the others continue in study follow-up. Final national accrual to the study was 104 patients.
The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 11. The total number enrolled study-wide is 104, if multi-site study.

CONCLUSIONS

No conclusions have been reached.

Report Date: 1 June 2001

Work Unit # 1511-98

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: CALGB 9795: A Phase III Prospective Randomized Study of Adjuvant Chemotherapy with Vinorelbine and Cisplatin in Completely Resected Non-Small Cell Lung Cancer with Companion Tumor Marker Evaluation

KEYWORDS:

PRINCIPAL INVESTIGATOR: Drabick, Joseph LTC MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Hematology-Oncology

STATUS: C
INITIAL APPROVAL DATE: 21 July 1998

STUDY OBJECTIVE

To compare the duration of overall survival (OS) and disease free survival between completely resected patients with T2 NO, T1-2N1 non-small cell lung cancer (NSCLC) who have received either adjuvant chemotherapy with vinorelbine and cisplatin or observation alone. To provide a comprehensive tumor bank linked to a clinical database for the further study of molecular markers in resected NSCLC.

TECHNICAL APPROACH

All eligible patients will be randomized to one of two treatment arms: 1) observation alone; 2) chemotherapy every week for 16 weeks with vinorelbine given every week and cisplatin given on days 1 and 8 of a four week cycle, for 4 cycles over 16 weeks.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

No WRAMC patient has been entered on this protocol since it opened to accrual in July 1998. No adverse events have been reported. National accrual to the study was 415 patients. The study is now permanently closed at WRAMC since no patients were enrolled.
The number of subjects enrolled to the study since last APR at WRAMC is __0__ and the total enrolled to date at WRAMC is __0__. The total number enrolled study-wide is __415__, if multi-site study.

CONCLUSIONS

No conclusions have been reached.

Report Date: 1 June 2001

Work Unit # 1512-98

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: CALGB 9732: A Randomized Phase III Study Comparing Etoposide and Cisplatin with Etoposide, Cisplatin and Paclitaxel in Patients with Extensive Small Cell Lung Cancer Includes Update #

KEYWORDS: phase III, small cell lung cancer, extensive

PRINCIPAL INVESTIGATOR: Drabick, Joseph COL MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 28 July 1998

STUDY OBJECTIVE

To determine whether the addition of paclitaxel to standard chemotherapy treatment (etoposide/cisplatin) improves the survival of patients with extensive SCLC.
To compare tumor response rate and failure-free survival of patients in these two treatments groups.
To describe and compare the toxicities of patients in these two treatment groups.

TECHNICAL APPROACH

Eligible patients with extensive SCLC will be randomized to 1) standard chemotherapy: etoposide/cisplatin IV as 3 day treatment q 21 days for a total of 6 treatments, or to 2) standard chemotherapy as above with IV paclitaxel in addition on day one of each treatment. Treatment will be in Hematology-Oncology clinic.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

One WRAMC patient was entered on this protocol and has died during this reporting period. No other unexpected adverse reaction has been reported. There was a minor administrative change to the protocol. National accrual to the study is 389 patients, 153 in this reporting period. Projected accrual is for 670 patients.
The number of subjects enrolled to the study since last APR at WRAMC is __0__ and the total enrolled to date at WRAMC is __1__. The total number enrolled study-wide is __389__, if multi-site study.

CONCLUSIONS

No conclusions have been reached.

Report Date: 30 August 2000 Work Unit # 1514-99

DETAIL SUMMARY SHEET

TITLE: CALGB 39801 Concurrent Carboplatin, Paclitaxel, and Radiation Therapy Verses Induction Carboplatin and Paclitaxel Followed by Concurrent Carboplatin, Paclitaxel, and Radiation Therapy for Patients with Unresectable Non Small Cell Lung Cancer: A Phase III Trial

KEYWORDS: non-small cell lung cancer, unresectable, chemoradiotherapy

PRINCIPAL INVESTIGATOR: Byrd, John, MAJ MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 27 October 1998

STUDY OBJECTIVE

To determine whether the addition of two cycles of induction chemotherapy with carboplatin and paclitaxel to concomitant chemoradiotherapy utilizing carboplatin and paclitaxel leads to an increase in overall response rate, failure-free survival, and survival. To assess the pattern of failure on both treatment arms (loco-regional vs. distant failure). To assess the toxicity on both treatment arms.

TECHNICAL APPROACH

All eligible patients will be randomized to one of two treatments: 1) Chemotherapy with paclitaxel and carboplatin once a week combined with radiation therapy to the chest 5 days per week for a total of 7 weeks, or 2) chemotherapy with paclitaxel and carboplatin, once every 3 weeks for 6 weeks followed by carboplatin and paclitaxel once per week combined with radiation therapy to the chest 5 days per week for 7 weeks. Update # 1, 3/15/99, containing editorial changes was submitted to DCI 4/21/99.

PRIOR AND CURRENT PROGRESS

One WRAMC patient has been entered on this protocol in this reporting period. No adverse events have been reported to WRAMC by the CALGB. National accrual to this study is 142, 116 in this reporting period. Projected accrual is for 360 patients. Minor revisions to the protocol have been made during this reporting period.

CONCLUSIONS

No conclusions have been made.

Report Date: 6 October 2000 Work Unit # 1515-99

DETAIL SUMMARY SHEET

TITLE: CALGB 19805 A Phase II Study of Flavopiridol (NSC # 649890) in Patients With Fludarabine Refractory B-Cell Chronic Lymphocytic Leukemia

KEYWORDS: Chronic Leukemia, refractory, investigational

PRINCIPAL INVESTIGATOR: John Byrd, MAJ MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Hematology Oncology

STATUS: O
INITIAL APPROVAL DATE: 24 November 1998

STUDY OBJECTIVE

To determine the complete response rate, partial response rate, and toxicity profile to flavopiridol therapy in patients with fludarabine refractory Chronic Lymphocytic Leukemia. To determine the effects of flavopiridol on normal t-cell subsets and immunoglobulin levels in these patients.

TECHNICAL APPROACH

All eligible patients will receive flavopiridol by a continuous intravenous infusion for 3 days, repeated every two weeks for a maximum of 12 cycles (approximately 6 months). The first cycle will be given in the hospital and subsequent cycles as an out-patient utilizing an ambulatory infusion pump. Disease reevaluation will be done at the end of 4 and 8 cycles, as well as at completion of therapy. Blood and bone marrow samples will be collected prior to any therapy and submitted to CALGB Leukemia Tissue Bank.

PRIOR AND CURRENT PROGRESS

One WRAMC patient has been entered on this study since it was opened to accrual in November 1998. No WRAMC patient has withdrawn from this study, and no unexpected adverse event has been reported. National accrual to the study at last report was 10 patients, 8 in this reporting period. Target accrual is for 37 patients.

CONCLUSIONS

No conclusions have been reached.

Report Date: 30 August 2000

Work Unit # 1516-84

DETAIL SUMMARY SHEET

TITLE: CALGB 8364: Immunological Diagnostic Studies in Adult ALL

KEYWORDS: immunology, lymphocyte, leukemia

PRINCIPAL INVESTIGATOR: Byrd, John C MAJ MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 25 October 1983

STUDY OBJECTIVE

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

TECHNICAL APPROACH

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

PRIOR AND CURRENT PROGRESS

A total of 34 WRAMC patients have been entered on this study before it were closed 15 April 1999. Twenty-four WRAMC patients have died of their progressive disease and the remaining 10 patients continue in study follow-up. No adverse reactions to the collection of study samples have been reported, and no WRAMC patients have withdrawn from the study. National accrual to the study was 953 patients. Projected accrual was for 1200 patients.

CONCLUSIONS

While final conclusions have not been reached, interim analysis continues on the value of immunophenotype in ALL.

Report Date: 6 October 2000

Work Unit # 1516-99

DETAIL SUMMARY SHEET

TITLE: CALGB 19801 A Phase II Study of 506U78 in Patients With Refractory or Relapsed T-lineage Acute Lymphoblastic Leukemia (ALL) or Lymphoblastic Lymphoma (LBL)

KEYWORDS: refractory disease, investigational therapy, leukemia/lymphoma

PRINCIPAL INVESTIGATOR: John Byrd, MAJ MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Hematology Oncology

STATUS: O
INITIAL APPROVAL DATE: 24 November 1998

STUDY OBJECTIVE

To determine the complete and partial remission rates, as well as the remission duration, in patients with refractory or relapsed T-lineage acute lymphoblastic leukemia or lymphoblastic lymphoma receiving 506U78 (1.5 gram/m2/day) on an alternate day schedule (days 1,3,5). To determine the safety and toxicity associated with 506U78 administered on this schedule.

TECHNICAL APPROACH

All eligible patients will receive the investigational drug, 506U78, intravenously over 2 hours on Days 1,3,5. Their disease will be reevaluated after 21 days. If not in remission, an identical course of treatment will be given. When remission occurs, consolidation therapy will be given. Two additional courses of the same therapy will be given as consolidation. Patients who achieve a complete response would then be candidates to receive a stem cell transplant. Those patients would be removed from this study, at that time, for transplant.

PRIOR AND CURRENT PROGRESS

No WRAMC patient has been entered on this protocol to date. National accrual to this study is 9 patients, 6 in this reporting period. Projected accrual is for 35 patients. No serious adverse events have been reported by the CALGB. A minor editorial and administrative change was made during this reporting period.

CONCLUSIONS

No conclusions have been made.

Report Date: 6 October 2000

Work Unit # 1517-99

DETAIL SUMMARY SHEET

TITLE: CALGB 119801 Telephone Monitoring: Early Identification of Psychological Distress In Cancer Patients 65 or More Years Old During Active Treatment

KEYWORDS: advanced cancer, psychosocial, telephone interview

PRINCIPAL INVESTIGATOR: John Byrd, MAJ MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Hematology Oncology

STATUS: O
INITIAL APPROVAL DATE: 24 November 1998

STUDY OBJECTIVE

To test whether telephone monitoring plus educational materials can reduce elderly cancer patient's psychological distress significantly more than the receipt of educational materials alone, through early identification of psychological problems and referral to treatment. To develop psychosocial profiles of older patients with advanced cancer who show the highest and lowest levels of psychological distress in terms of: medical, psychosocial and sociodemographic characteristics.

TECHNICAI APPROACH

All eligible patients will be randomized to one of two groups. 1) Educational Materials Group. This group will be given educational materials that provide information about emotional problems which cancer patients may have and various agencies or services that are available to them. They will also be contacted by phone, by a trained psycho-oncology interviewer, 3 times during one year to discuss emotional and social issues. 2) Telephone Monitoring Group. This group, in addition to the educational materials, will receive a phone call from the psycho-oncology interviewer once a month for 6 months. The calls will last approximately 15 minutes each. Questions will ask about mood, social life issues and physical problems. If problems are identified, follow up will be done by a WRAMC Oncology nurse, physician, social service or psychologist, depending upon the needs. A written questionnaire will be sent prior to the phone call describing the questions that will be asked.

PRIOR AND CURRENT PROGRESS

Four WRAMC patients have been enrolled on this study since it was approved in November 1998. No patient has withdrawn and no serious adverse events have been reported. National accrual to protocol is 23 patients, 21 in this reporting period. Projected national accrual is for 182 patients.

CONCLUSIONS

No conclusions have been reached.

Report Date: 3 November 2000 Work Unit # 1518-99

DETAIL SUMMARY SHEET

TITLE: CALGB 9865: Tumor Replication Error (RER) Status and Outcome In A Colon Cancer Adjuvant Chemotherapy Trial

KEYWORDS: tissue block, Dukes C Stage, mutations

PRINCIPAL INVESTIGATOR: Byrd, John MAJ MC
ASSOCIATES:

DEPARTMENT: Medicine STATUS: O
SERVICE: Hematology-Oncology INITIAL APPROVAL DATE: 15 December 1998

STUDY OBJECTIVE

To determine the relationship between disease free survival, overall survival, and tumor replication error (RER) status for individuals who have received adjuvant chemotherapy for colon cancer. To develop a database to study the relationship between family history, tumor RER status, and treatment outcome for individuals who have received adjuvant chemotherapy for colon cancer.

TECHNICAL APPROACH

Phase I – All patients who were enrolled on CALGB 8896 for Dukes C Colon Cancer who have tissue blocks available will have two tissue blocks submitted for RER analysis (one with tumor, one with normal tissue). This will include patients who are deceased. The CALGB Pathology Coordinating office will submit a list to the institution of potentially eligible cases for Phase II. This phase involves obtaining consent for completion of a family questionnaire. For deceased patients, a chart review may be obtained and data collected to correlate treatment outcome, disease relapse and survival. The results of the RER analysis will not be received by the institution or the patient.

PRIOR AND CURRENT PROGRESS

Tissue blocks from two WRAMC patients have been entered on this study since it was opened to accrual in August 1998, one in this reporting period. No WRAMC patient has withdrawn from this study, and no unexpected adverse event has been reported. National accrual to this study is 172 patients, 129 in this reporting period. Projected accrual is for 350 patients. A minor revision was made to the protocol in this reporting period.

CONCLUSIONS

No conclusions have been reached.

Report Date: 31 January 2001 Work Unit # 1519-92

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: CALGB 9192: Comparison of Chemotherapy vs. Chemohormonotherapy in Premenopausal Women with Stage II Receptor-Positive Breast Cancer

KEYWORDS: breast cancer, node-positive, receptor-positive

PRINCIPAL INVESTIGATOR: Byrd, John C. MAJ MC
ASSOCIATES:

DEPARTMENT: Medicine STATUS: O
SERVICE: Hematology-Oncology INITIAL APPROVAL DATE: 26 March 1991

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

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

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
A total of 13 WRAMC patients were entered on this protocol before it was closed to accrual in February 1994. Five of these have died of their disease; the remaining eight continue in study follow-up. No WRAMC patients withdrew from this study. One case of a second malignancy occurred and was reported to the IRB in November 1999. No other unexpected adverse events have been reported. Total national accrual to this study was 1330 patients.

The number of subjects enrolled to the study since last APR at WRAMC is __0__ and the total enrolled to date at WRAMC is _13_. The total number enrolled study-wide is __1330_____, if multi-site study.

CONCLUSIONS
Analysis is ongoing; no conclusions have been reached.

Report Date: 3 November 2000 Work Unit # 1519-99

DETAIL SUMMARY SHEET

TITLE: CALGB 9840: A Phase III Study of Paclitaxel Via Weekly 1 Hour Infusion Versus Standard 3 Hour Infusion Every 3 Weeks with Herceptin (Trastuzumab) (NSC #688097) in the Treatment of Patients with/without HER-2/NEU-Overexpressing Metastatic Breast Cancer

KEYWORDS:

PRINCIPAL INVESTIGATOR: Byrd, John MAJ MC
ASSOCIATES:

DEPARTMENT: Medicine STATUS: O
SERVICE: Hematology-Oncology INITIAL APPROVAL DATE: 15 December 1998

STUDY OBJECTIVE

To determine if "dose dense" treatment with paclitaxel via weekly 1-hour infusion significantly improves the response rate as compared to "standard" paclitaxel treatment for metastatic breast cancer. To evaluate the time to progression and survival of patients with metastatic breast cancer treated with either "dose dense" or "standard" paclitaxel.

TECHNICAL APPROACH

Patients will be randomized to receive either paclitaxel, 175mg/m2 over 3 hours every 3 weeks or to paclitaxel 100mg/m2 over 1 hour every week for the first 6 weeks with subsequent infusions of paclitaxel at 80mg/m2 over 1 hour. Both regimens will be given until development of progressive disease, major toxicity, or patient withdraws consent. Follow-up will be done until progression, initiation of non-protocol therapy, or death, whichever occurs first.

PRIOR AND CURRENT PROGRESS

Two WRAMC patients have been entered on this study since its approval 12/15/98. No WRAMC have died or withdrawn from the study, and no unexpected adverse events have been reported. National accrual to the study is 161 patients, 104 in this reporting period. The treatment plan now includes four treatment arms (Update #2, dated 3/15/00). An entirely new protocol with a new title and a change and additions to the consent form was made in June 2000 and received approval on 20 July 2000. The new projected accrual is for 580 patients.

CONCLUSIONS

No conclusions have been reached

Report Date: 28 December 2000

Work Unit # 1520-99

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: CALG 9863: Phase I Study of Irmotecan (CPT- 11) in Patients with Abnormal Liver or Renal Function or with Prior Pelvic Radiation Therapy

KEYWORDS: Phase I, Organ dysfunction, Irmotecan

PRINCIPAL INVESTIGATOR: Byrd, John MAJ MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 23 February 1999

STUDY OBJECTIVE

To determine a tolerable dose of irmotecan to use in patients with ranging degrees of liver or renal dysfunction or prior pelvic radiation. To characterize the pharrnacokinetics of irmotecan in patients with hepatic or renal dysfunction or prior pelvic radiation therapy.

TECHNICAL APPROACH

All eligible patients will receive a specified dose of irinotecan, determined at the time of registration, as a 90-minute infusion every 3 weeks times 4 doses. During the first treatment a total of 14 blood samples will be drawn at specific times to measure the amount of drug in the blood stream. Urine samples will be collected for the first 24 hours also. All samples will be frozen and shipped to the reference lab when all have been collected. All patients will be reevaluated after the 4 doses for response.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

One WRAMC patient has been entered on this study during this reporting period. No unexpected adverse reactions have been reported. National accrual to the study thus far is 35 patients, 20 in this reporting period. The projected accrual is for 75 patients. No changes have been made to the protocol during this reporting period.

CONCLUSIONS

No conclusions have been reached.

Report Date: 28 February 2001 Work Unit #1521-91

DETAIL SUMMARY SHEET (Human Use Protocol)

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

KEYWORDS: postmenopausal, lymph node positive, receptor positive

PRINCIPAL INVESTIGATOR: Byrd, John C, MAJ, MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 30 April 1991

STUDY OBJECTIVE

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

TECHNICAL APPROACH

For 5 years, six courses of CAF followed by tamoxifen for 5 years, or six courses of CAF with concurrent tamoxifen for 5 years. Four addenda to this study were sent to the IRB and approved in the past year.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Three WRAMC patients were entered on this study before it was closed to accrual in August 1995 with a national accrual of 1,539 patients. One WRAMC patient has died of their disease, and the others continue in study follow-up. No unexpected adverse events have been reported to us by the CALGB.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 3. The total number enrolled study-wide is 1,539 (if multi-site study.)

CONCLUSIONS

No conclusions have been reached.

Report Date: 3 August 2001

Work Unit # 1522-84

DETAIL SUMMARY SHEET (Human Use Protocol)

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

KEYWORDS: cytogenics, acute leukemia

PRINCIPAL INVESTIGATOR: Drabick, Joseph COL MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 25 September 1984

STUDY OBJECTIVE

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

TECHNICAL APPROACH

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

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

One hundred three patients have been entered on this study, three in this reporting period. No adverse events have been reported and no WRAMC patients have withdrawn from the study. This study is a lab companion to open leukemia treatment studies. All blood and bone marrow samples continue to be collected and sent to the study lab at intervals required by the protocol. National accrual to the study is 4504 patients, 315 patients were enrolled in this reporting period. Accrual goal is for 4550 patients. The number of subjects enrolled to the study since last APR at WRAMC is __3__ and the total enrolled to date at WRAMC is __103__. The total number enrolled study-wide is __4504__, if multi-site study.

CONCLUSIONS

Analysis is on going.

Report Date: 30 August 2000 Work Unit # 1523-91

DETAIL SUMMARY SHEET

TITLE: CALGB 9111: A Trial of G-CSF vs. Placebo During Remission Induction and Consolidation Chemotherapy for Adult Acute Lymphatic Leukemia

KEYWORDS: adult acute leukemia, G-CSF

PRINCIPAL INVESTIGATOR: Byrd, John C MAJ MC
ASSOCIATES:

DEPARTMENT: Medicine STATUS: O
SERVICE: Hematology-Oncology INITIAL APPROVAL DATE: 25 October 1991

STUDY OBJECTIVE

To: 1) compare time to bone marrow recovery, infection incidence, days of hospitalization, and tolerance of non-hematopoietic organs after intensive chemotherapy for acute lymphatic leukemia (ALL) in patients given either granulocyte colony-stimulating factor (G-CSF) or placebo; 2) determine G-CSF's effect on CR rate and duration and mortality (during neutropenia) during intensive induction and intensification; and 3) compare doses that can be given to G-CSF vs. placebo patients.

TECHNICAL APPROACH

Eligible patients will be randomly assigned to receive subcutaneous injections of either G-CSF or placebo starting 3 days after initial chemotherapy. Injections will continue until the WBC count is normal. The pharmacist will be the only one who knows what the patients will be receiving. The study will remain blinded until after the first month. After being unblinded, patients who received G-CSF will continue to receive it during the next course of therapy. Those who did not receive G-CSF will not receive any further placebo or G-CSF. Patients will receive a series of five different cancer treatments in sequence; each uses combination chemotherapy, and one involves radiation. Total treatment time is 24 months.

PRIOR AND CURRENT PROGRESS

A total of 8 WRAMC patients were entered on this study before it closed to accrual in July 1993. No unexpected adverse reactions were reported and no WRAMC patients withdrew from this study. Five of these patients have died of their disease. The remanding three continue in study follow-up. Total national accrual to the study was 198 patients.

CONCLUSIONS

This study has shown that treatment with G-CSF is effective during induction chemotherapy for ALL. Other results are still undergoing analysis.

Report Date: 4 May 2001

Work Unit # 1523-99

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: CALG13 9862 Molecular Genetic Features of Acute Lymphoblastic Leukemia

KEYWORDS:

PRINCIPAL INVESTIGATOR: Drabick, Joseph LTC MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 22 June 1999

STUDY OBJECTIVE

To use PCR analysis to identify patients with p190 and p210 BCR-ABL positive ALL and to evaluate the clinical significance of these fusion transcripts measured at time of diagnosis. To evaluate the clinical significance of MDR as defined by BCR-ABL fusion transcripts in patients who have achieved a complete response, using both qualitative RT-PCR and quantitative (Real Time) PCR in sequential samples of both blood and bone marrow. To compare blood with bone marrow samples for the detection and quantitation of BCR-ABL transcripts in diagnosis and sequential remission samples. To pilot PCR detection and quantitation of WT-1 expression at diagnosis, remission, and at relapse in BCR-ABL positive and negative ALL, and to determine the impact of this marker on clinical outcome.

TECHNICAL APPROACH

All patients enrolled on the CALGB Leukemia treatment study (currently 19802) will be offered participation in this companion study. A total of 8 plus samples of blood and bone marrow will be collected and sent to the CALG13 Leukemia Tissue Bank in Columbus, Ohio. The number of samples is dependent upon response to therapy and if the disease returns after remission. The tests will only be drawn at a time when diagnostic blood and bone marrow samples would ordinarily be taken.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

One WRAMC patient has been entered on this protocol in this reporting period. There have been no serious adverse events reported and no WRAMC patient has withdrawn from this study. National accrual to the study is 40 patients. Projected national accrual is for 325 patients.

The number of subjects enrolled to the study since last APR at WRAMC is __1__ and the total enrolled to date at WRAMC is __1_____. The total number enrolled study-wide is __75_____, if multi-site study.

CONCLUSIONS

No conclusions have been reached.

Report Date: 27 June 2001 Work Unit #1524-99

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: CALGB 19802 Phase II Study in Adults with Untreated Lymphoblastic Leukemia Testing Increased Doses of Daunorubicin During Induction, and Cytarabine During Consolidation, Followed by High-Dose Methotrexate and Intrathecal Methotrexate in Place of Cranial Irradiation

KEYWORDS: ALL, dose escalation, high-dose methotrexate

PRINCIPAL INVESTIGATOR: Joseph Drabick COL MC
ASSOCIATES:

DEPARTMENT: Medicine STATUS: O
SERVICE: Hematology-Oncology INITIAL APPROVAL DATE: 31 August 1999

STUDY OBJECTIVE

To evaluate the complete response (CR) rate and toxicity in patients < 60 years of age when three days of daunorubicin are given at 60mg/m2/day in Module A and then, if tolerated, when doses of daunorubicin are escalated to 80 mg/m2/day. To evaluate CR rate and toxicity in patients ≥ 60 years of age when three days of daunorubicin are given at 60 mg/m2/day during Module A without cyclophosphamide. To evaluate the toxicity of three days of cytarabine at 2000 mg/m2/day IV over three hours during post-remission therapy (Module B). To measure the CNS relapse rate of ALL when prophylactic intrathecal and high dose intravenous chemotherapy (Module C) replaces cranial irradiation. To target a specific serum methotrexate level at 30 hours following initiation of IV methotrexate infusion.

TECHNICAL APPROACH

All eligible patients who continue to show a response to therapy will receive a seven-course regimen of various chemotherapy agents. Doses of daunorubicin will be different for patients under 60 years than for patients over 60 years. During Course three, high doses of methotrexate will be given in place of standard cranial irradiation for CNS prophylaxis. Serum levels will be monitored to ensure adequate dosing. The seven-course therapy will take 24 months to complete. Post therapy monitoring will be done every 3-6 months for three years after treatment, then annually. Two additional companion studies are required for participation. These studies have separate consent forms but do require submission of blood and bone marrow samples for correlative science with response of the disease to therapy.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

One WRAMC patient has been entered on this study during this reporting period since it was approved in August 1999. No adverse events have been reported from the CALGB. During this reporting period there were editorial and administrative changes and there were updates to the consent form and these were reported to DCI. The study was closed to accrual on 5 January 2001. National accrual to the study is 163. Projected accrual was for 140 patients.
The number of subjects enrolled to the study since last APR at WRAMC is __1__ and the total enrolled to date at WRAMC is __1__. The total number enrolled study-wide is __163__, if multi-site study.

CONCLUSIONS

No conclusions have been reached.

Report Date: 20 November 2000

Work Unit # 1526-92

DETAIL SUMMARY SHEET

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

KEYWORDS: metastatic, breast cancer, leucovorin

PRINCIPAL INVESTIGATOR: Byrd, John C. MAJ MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Hematology Oncology

STATUS: O
INITIAL APPROVAL DATE: 02 January 1992

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

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

PRIOR AND CURRENT PROGRESS
A total of six WRAMC patients were entered on this protocol before it was closed to accrual in August 1995 having met its accrual goal of 240 patients. No WRAMC patients withdrew from this study. Five of these patients have died of their progressive disease. One remains in study follow-up. No unexpected adverse reactions have been reported.

CONCLUSIONS
Analysis is in progress.

Report Date: 22 November 2000

Work Unit # 1527-92

DETAIL SUMMARY SHEET

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

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

PRINCIPAL INVESTIGATOR: Byrd, John C. MAJ MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 02 January 1992

STUDY OBJECTIVE

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

TECHNICAL APPROACH

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

PRIOR AND CURRENT PROGRESS

Two WRAMC patients were entered on this study before it was closed to accrual in June 1995 having met its accrual goal with a national enrollment of 642 patients. Both patients continue in study follow-up. No WRAMC patients have withdrawn from the study, and no unexpected adverse events have been reported.

CONCLUSIONS

No conclusions have been reached.

Report Date: 22 November 2000

Work Unit # 1528-92

DETAIL SUMMARY SHEET

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

KEYWORDS: post-gastrectomy, adjuvant therapy, observation

PRINCIPAL INVESTIGATOR: Byrd, John C MAJ MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 02 January 1992

STUDY OBJECTIVE

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

TECHNICAL APPROACH

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

PRIOR AND CURRENT PROGRESS

Two WRAMC patients have been entered on this study before it was closed to accrual in July 1998 having met its accrual goal of 603 patients. The two patients remain in study follow-up. No unexpected adverse reactions have been reported. The final national accrual was 603 patients. No major changes to the protocol have been made to the protocol.

CONCLUSIONS

No conclusions have been reached.

Report Date: 6 October 2000

Work Unit # 1534-92

DETAIL SUMMARY SHEET

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

KEYWORDS: induction, consolidation, crossover

DEPARTMENT: Medicine
SERVICE: Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 24 November 1992

STUDY OBJECTIVE

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

TECHNICAL APPROACH

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

PRIOR AND CURRENT PROGRESS

Two WRAMC patients were entered on this study before it was closed to accrual in February 1995 having met its accrual goal. Both WRAMC patients survive and continue in study follow-up. No WRAMC patients withdrew from the study, and no unexpected adverse reaction has been reported. Total national accrual to the study was 401 patients.

CONCLUSIONS

No conclusions have been reached.

Report Date: 6 October 2000

Work Unit # 1535-92

DETAIL SUMMARY SHEET

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

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

PRINCIPAL INVESTIGATOR: Byrd, John MAJ MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 24 November 1992

STUDY OBJECTIVE

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

TECHNICAL APPROACH

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

PRIOR AND CURRENT PROGRESS

A total of 5 WRAMC patients were entered on this protocol before it were closed to accrual in December 1995 having met its accrual goal. Three of these patients have died of causes connected to their continuing disease. The remaining 2 patients continue in study follow-up. No WRAMC patients have withdrawn from the study. National accrual to this study was 474 patients.

CONCLUSIONS

No conclusions have been reached.

Report Date: 31 January 2001

Work Unit # 1541-93

DETAIL SUMMARY SHEET (Human Use Protocol)

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

KEYWORDS: low-grade, lymphoma, advanced

PRINCIPAL INVESTIGATOR: Byrd, John C MAJ MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 30 March 1993

STUDY OBJECTIVE

To: 1) determine the percentage of patients with advanced, previously untreated, low-grade lymphomas who respond with complete or partial remissions to treatment with Cladribine; 2) estimate the duration of response for patients with partial and complete responses; and 3) describe the toxicity of Cladribine treatment in this population.

TECHNICAL APPROACH

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

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Two WRAMC patients were entered on this protocol before it was closed to further accrual in December of 1993. No WRAMC patient has withdrawn from this study, and no unexpected adverse reactions were reported. Both WRAMC patients survive and continue to be followed for survival data only since both have had disease progression. Final national accrual to this study was 42 patients.
The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 2. The total number enrolled study-wide is 42, if multi-site study.

CONCLUSIONS

Analysis showed this therapy to have a low level of antineoplastic activity. No conclusion has been reached.

Report Date: 22 November 2000

Work Unit # 1547-94

DETAIL SUMMARY SHEET

TITLE: CALGB 9082 Trial Study of High-Dose CPA/CDDP/BCNU and ABMS as Consolidation to Adjuvant CAF for Patients With Operable Stage II or Stage III Breast Cancer Involving > 10 Axillary Lymph Nodes.

KEYWORDS: breast, autologous, bone marrow transplant

PRINCIPAL INVESTIGATOR: Byrd, John C. MAJ MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 25 January 1994

STUDY OBJECTIVE

To determine if adjuvant chemotherapy [four CAF cycles then high-dose combination CPA/CDDP/BCNU with autologous bone marrow support (ABMS)] produces superior disease-free and overall survival compared to adjuvant chemotherapy (four CAF cycles than standard dose CPA/CDDP/BCNU) in patients with Stage II or III breast cancer in 10 or more lymph nodes. Both arms contain Tamoxifen and radiation therapy to chest walls. To compare toxicities experienced between the two programs.

TECHNICAL APPROACH

Patients entered into this study have pathologically-confirmed Stage II or IIIA breast cancer with >/= 10 lymph nodes involved. The patients are randomized to either of the two treatments. On 6-week schedule they are re-evaluated to determine response to the therapy.

PRIOR AND CURRENT PROGRESS

A total of 12 WRAMC patients were entered on this study before it was closed to accrual in May 1998. Four of these patients have died, and the remaining eight continue in study follow-up. No WRAMC patient withdrew from the protocol and no serious adverse events have occurred in this reporting period. There were seven serious adverse events that had occurred and been reported to the IRB over the course of study enrollment. Total national accrual to this was 777 patients.

CONCLUSIONS

Analysis is in progress.

Report Date: 22 November 2000 Work Unit # 1548-94

DETAIL SUMMARY SHEET

TITLE: CALGB 9395: Phase III Intergroup Study Prospectively Randomized Trial of Perioperative 5-FU after Curative Resection, Followed by 5-FU/Leucovorin for Patients with Colon Cancer

KEYWORDS: colon cancer, chemotherapy, Dukes B3 or C

PRINCIPAL INVESTIGATOR: Byrd, John C. MAJ MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 25 January 1994

STUDY OBJECTIVE

To determine if adjuvant therapy with 1 week of 5-fluorouracil given continuously within 24 hours of a curative colon resection followed by 12 months of 5-FU/Levamisole is effective in prolonging disease-free interval and increasing survival in patients with Dukes' B3 or C colon cancer, when compared to patients who are treated with 5-FU/Levamisole only. Endpoints include treatment failure, as defined by recurrence of local/regional or distant metastasis, and survival.

TECHNICAL APPROACH

All eligible patients will be randomized to receive or not receive 7 days of continuous 5-FU infusion starting within 24 hours of their curative surgery for colon cancer. Those patients found to have evidence of metastatic disease at the time of surgery will be removed from the study. Those patients who have pathologic classification of Dukes' B3 or C colon cancer will receive standard chemotherapy starting 35 days after their surgery; those with Dukes' B1 or 2 will be followed for evidence of recurrence. In December of this year, an addendum to the study was approved by the HUC to include CALGB 9667: Biologic Correlates to Response and Survival in Colon Cancer as a companion to this study; the consent form was modified to include this tissue block study.

PRIOR AND CURRENT PROGRESS

55 WRAMC patients have been entered on this study, 2 in this reporting period before it was closed to accrual in May 2000. Twelve of these patients have died 2 within this reporting period. No WRAMC patients have withdrawn from the study. No modifications to the protocol have been made this year. National accrual was 854, 63 in this reporting period. Projected accrual was for 2000 patients.

CONCLUSIONS

No conclusions have been reached.

Report Date: 28 December 2000

Work Unit # 1550-94

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: CALGB 9342: A Study of Taxol for Advanced Breast Cancer

KEYWORDS: dose response, quality-of-life, metastatic disease

PRINCIPAL INVESTIGATOR: Byrd, John C. MAJ MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Hematology-Oncology

STATUS: C
INITIIAL APPROVAL DATE: 22 February 1994

STUDY OBJECTIVE

To determine if a dose response exists for taxol in the treatment of patients with metastatic breast cancer. To evaluate time to progression and survival in patients treated with one of three doses, to assess the prognostic value of baseline quality-of-life measures, and subsequent changes throughout treatment.

TECHNICAL APPROACH

All eligible patients will be randomized to one of three doses of taxol; standard, moderately high, and high dose. All doses will be given intravenously over 3 hours on an out-patient basis every 3 weeks. Granulocyte Colony-Stimulating Factor will be added if needed. A quality-of-life assessment form will be completed twice by the patient before treatment and after three cycles. Therapy will continue as long as the patient responds. Seven amendments to the protocol have been received and forwarded to the IRB for review. All were editorial or administrative changes.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Seven WRAMC patients were entered on this study before it was closed to accrual 31 July 1997. All patients have died of their progressive disease. No unexpected reactions were reported to us from the CALGB. National accrual to the study was 475 patients. This study is now permanently closed at WRAMC.

CONCLUSIONS

No conclusions have been reached.

Report Date: 28 December 2000 Work Unit # 1551-94

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: CALGB 8869: Laboratory Studies in Breast Cancer Tissue

KEYWORDS: tissue blocks, aneuploidy, breast cancer

PRINCIPAL INVESTIGATOR: Byrd,-John C. MAJ MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Hematology-Oncology

STATUS: O
INITIIAL APPROVAL DATE: 22 February 1994

STUDY OBJECTIVE
To determine if aneuploidy provides independent prognostic information pertaining to recurrence rate of breast cancer and to explore the relationships between ploidy and clinical data regarding tumor grade and steroid receptors.

TECHNICAL APPROACH
Paraffin tissue blocks from all patients registered to CALGB 8541 treatment protocol for Stage II breast cancer will be obtained and mailed to reference pathology lab for subsequent review. This is a retrospective lab study and involves no risk to the patient. No consent form is required. Update #6 was approved by WRAMC HUC, 16 Jan 96, to include tissue block samples from treatment studies CALGB 8642, 8741, and 8944 to those already being collected by this study.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
A total of 57 paraffin blocks from eligible WRAMC patients have been collected and sent to referenced lab per protocol requirements, none in this reporting period. National accrual to the study is 1240 blocks. Projected accrual is for 1572 blocks. This is a retrospective laboratory study and involves no risk to patients. No consent form is required.

CONCLUSIONS
Analysis is ongoing.

Report Date: 28 February 2001

Work Unit #1554-94

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: CALGB 9391: A Randomized Study of Subtotal Nodal Irradiation vs. Irradiation Plus Chemotherapy for Stages I-IIA Hodgkin's Disease

KEYWORDS: radiation therapy, chemotherapy, early-stage disease

PRINCIPAL INVESTIGATOR: Byrd, John C, MAJ MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 26 April 1994

STUDY OBJECTIVE

To compare the progression-free and overall survival of non-laparotomized patients with clinical stage IA or IIEA Hodgkin's disease treated with subtotal nodal irradiation (3,600 - 4,000 cGy) alone to three cycles of doxorubicin and vinblastine plus subtotal nodal irradiation.

TECHNICAL APPROACH

All eligible patients will be randomized to receive one of two treatments. Treatment one will be 8-9 weeks of daily (x 5) radiation therapy. Treatment two will be chemotherapy by vein with two drugs, doxorubicin and vinblastine, over 5-10 minutes, every 14 days X 6 doses. The second group will then receive radiation therapy in the same way that treatment one patients receive it. All patients will be asked to complete a quality-of-life evaluation form before treatment and an additional eight times. The questionnaire takes approximately 20-45 minutes to complete. There is a change from last year's reported accrual goal, which was reported to the HUC in addendum #8 approved in October 1995.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Eight WRAMC patients have been entered on this study before it was closed to accrual in April 2000. No WRAMC patient has withdrawn from the study, and all continue in study follow-up. No adverse events have been reported. National accrual to the study was 348 patients. Projected accrual was for 420 patients. The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 8. The total number enrolled study-wide is 348, if multi-site study.

CONCLUSIONS

No conclusions have been reached.

Report Date: 4 May 2001

Work Unit # 1557-94

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: CALGB 9344: Adjuvant High-Dose vs. Standard-Dose Cyclophosphamide, Adriamycin with/without Taxol for Node-Positive Breast Cancer

KEYWORDS: breast cancer, node positive, adjuvant

PRINCIPAL INVESTIGATOR: Drabick, Joseph LTC MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 28 June 1994

STUDY OBJECTIVE

To determine whether higher doses of doxorubicin used as an adjuvant with cyclophosphamide in patients with early breast cancer will increase disease-free survival and overall survival. To determine whether the use of taxol as single agent after the completion of four cycles of cyclophosphamide and doxorubicin in combination will further improve disease-free and overall survival compared to the two previous drugs alone.

TECHNICAL APPROACH

All eligible patients will be randomized to one of six treatments: 1) standard dose cyclophosphamide with high-dose doxorubicin followed by taxol; 2) same two initial drugs without taxol; 3) standard cyclophosphamide with moderate dose doxorubicin with taxol afterwards; 4) same two initial drugs without taxol; 5) standard doses of cyclophosphamide and doxorubicin with taxol afterwards; or 6) standard doses without taxol. If taxol is given, there will be four courses. Tamoxifen will be given afterwards to receptor positives. The consent was recently revised to include new findings on leukemia risk with high-dose therapy.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Sixteen patients were entered on this study from WRAMC before it was closed to accrual on 4/15/97. Of the patients enrolled at WRAMC, 2 have died of their progressive disease. The remaining 14 patients continue to be followed by the study. Final national accrual was 3170.
The number of subjects enrolled to the study since last APR at WRAMC is __0__ and the total enrolled to date at WRAMC is __16__. The total number enrolled study-wide is __3170____, if multi-site study.

CONCLUSIONS

Analysis continues.

Report Date: 27 June 2001

Work Unit # 1558-94

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: CALGB 9394: A Phase III Comparison of Two Schedules of Cyclophosphamide and Doxorubicin for High-Risk Patients with Breast Cancer Involving 0-3 Axillary Lymph Nodes

KEYWORDS: primary breast cancer, high-risk, 0-3 positive nodes

PRINCIPAL INVESTIGATOR: Drabick, Joseph COL MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 30 August 1994

STUDY OBJECTIVE

To compare disease-free survival, overall survival, and toxicity of high-risk primary breast cancer patients with 0-3 positive axillary lymph nodes treated with adjuvant high-dose chemotherapy with doxorubicin plus cyclophosphamide (AC) or high-dose sequential chemotherapy with doxorubicin followed by cyclophosphamide (AC).

TECHNICAL APPROACH

All eligible patients will be randomized to one of the two treatment arms as described above. Treatment I will consist of both drugs every 3 weeks times 6 cycles. Treatment 2 will consist of 4 cycles of doxorubicin at 21-day intervals followed by 3 cycles of cyclophosphamide at 14-day intervals. All post-menopausal and hormone receptor-positive women will then receive Tamoxifen for 5 years following completion of the chemotherapy.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

A total of 7 WRAMC patients were entered on this protocol before it was closed to further accrual on 1 May 1997 having met its accrual goal of 3,000 patients. One WRAMC patient has died from their progressive disease and the remaining six patients continue in study follow-up. No WRAMC patient has withdrawn from the study. No adverse reactions have been reported from the CALGB.
The number of subjects enrolled to the study since last APR at WRAMC is _0_ and the total enrolled to date at WRAMC is _7_. The total number enrolled study-wide is _3,000_, if multi-site study.

CONCLUSIONS

Analysis is in progress.

Report Date: 3 August 2001 Work Unit # 1559-94

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: CALGB 9351: A Phase II Study of High-Dose Chemotherapy in Previously Untreated Non-Hodgkin's Lymphoma

KEYWORDS: aggressive disease, high-dose CHOP

PRINCIPAL INVESTIGATOR: Drabick, Joseph COL MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Hematology- Oncology

STATUS: O
INITIAL APPROVAL DATE: 27 September 1994

STUDY OBJECTIVE

To: 1) estimate the overall response rate and determine whether dose-intensified CHOP (high-dose CHOP) chemotherapy with G-CSF can be administered with acceptable toxicity to low intermediate-, high intermediate-, and high-risk patients; and 2) determine whether it is possible to identify with early restaging gallium scans a subset of patients who are less likely to achieve a durable complete response.

TECHNICAL APPROACH

All eligible patients will receive chemotherapy with high doses of cyclophosphamide and doxorubicin and standard doses of vincristine and prednisone. Four cycles will be given at 3-week intervals for a total treatment time of 3 months. G-CSF and an oral antibiotic will be given prophylactically for 14 days after each treatment. The first 3 days of treatment will be in the hospital; the remainder will be done as an outpatient.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Four WRAMC patients were entered on this study before it was closed to accrual in July 1996. One patient has died of their progressive disease and two patients have withdrawn from the protocol. One patient continues in study follow-up.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 4. The total number enrolled study-wide is 99, if multi-site study.

CONCLUSIONS

Analysis is in progress.

Report Date: 4 May 2001 Work Unit # 1560-87

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: CALGB 8642: A Master Protocol to Study Single-Agent Chemotherapy vs. Standard Chemotherapy for Advanced Breast Cancer

KEYWORDS: chemotherapy, cancer, breast

PRINCIPAL INVESTIGATOR: Byrd, John C. MAJ MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 30 June 1987

STUDY OBJECTIVE

To evaluate ability of single Phase II agents to achieve responses in previously untreated metastatic breast cancer patients.

TECHNICAL APPROACH

Randomized study in which all eligible patients receive either standard cytoxan, Adriamycin and 5-fluorouracil (CAF) therapy, or a Phase II agent. Those randomized to receive a Phase II agent are treated for two cycles and then reevaluated for response or progression. If progression occurs, they are switched to CAF therapy. The next Phase II drug treatment arm, using alsamitrucin, was approved by the CALGB June 1992 for limited institutions.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 18. The total number enrolled study-wide is 365, if multi-site study.

CONCLUSIONS

This study concluded that in previously untreated metastatic breast cancer patients, the limited use of a single phase II agent prior to treatment within initial standard drugs does not result in any significant increased toxicity, decreased overall response rate or shortened survival.

Report Date: 30 August 2000 Work Unit # 1560-95

DETAIL SUMMARY SHEET

TITLE: CALGB 9491: An Intergroup Study of Rectal Cancer Adjuvant Therapy, Phase III

KEYWORDS: 5-Fluorouracil bolus, prolonged infusion, pelvic radiation

PRINCIPAL INVESTIGATOR: Byrd, John C MAJ MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 25 October 1994

STUDY OBJECTIVE

To compare the effectiveness of 5-FU by bolus injection vs. 5-FU by prolonged infusion given prior to and following combined pelvic radiation therapy plus protracted venous infusion vs. 5-FU by bolus injection plus leucovorin plus levamisole given prior to and following combined pelvic radiation plus bolus 5-FU plus leucovorin in the treatment of stage B2, B3, and C rectal cancer.

TECHNICAL APPROACH

All eligible patients will be randomized to receive one of three treatments: 1) 5-FU bolus for 5 consecutive days, repeated in 4 weeks; 2) continuous 5-FU for 6 weeks intravenously through a portable pump; or 3) 5-FU bolus, similar to treatment 1, but given with levamisole and leucovorin. Radiation therapy to the pelvis is given in all three treatments. Total treatment time is about 6 months.

PRIOR AND CURRENT PROGRESS

Two WRAMC patients have been entered on this study, none in this reporting period. Both of these patients continue in study follow-up. No unexpected adverse reactions have been reported, and no WRAMC patients have withdrawn from the study. Projected accrual was for 2400 patients. This study was closed to further accrual 1 August 2000 with a final accrual of 1757 patients, 582 in this reporting period.

CONCLUSIONS

No conclusions have been reached at this time.

Report Date: 30 August 2000

Work Unit # 1561-95

DETAIL SUMMARY SHEET

TITLE: CALGB 9497: Health Status and Quality-of-Life in Patients with Early Stage Hodgkin's Disease: A Companion Study to CALGB 9391

KEYWORDS: quality-of-life, early stage, Hodgkin's

PRINCIPAL INVESTIGATOR: Byrd, John C. MAJ MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 25 October 1994

STUDY OBJECTIVE

To evaluate prospectively the health status and quality-of-life (QOL) of early-stage Hodgkin's disease patients receiving either subtotal nodal irradiation or short-course chemotherapy plus subtotal nodal irradiation. To describe the short-term, acute effects of two treatments for early-stage disease on patient reports of symptoms of QOL.

TECHNICAL APPROACH

All patients eligible for treatment on the treatment study #9391 will be registered to this companion study and complete questionnaires related to current health status and QOL. These questionnaires will be completed prior to treatment and at eight specified time points during their treatment. The results will be reviewed and analyzed by the Psycho-Oncology Committee at CALGB.

PRIOR AND CURRENT PROGRESS

Eight WRAMC patients have been entered on this study, one in this reporting period. No adverse effects of taking this questionnaire have been reported and no WRAMC patients have withdrawn from the study. All questionnaires have been completed per protocol requirements. This study was closed to further accrual on April 20, 2000 with a final national accrual of 260 patients, 30 patients in this reporting period. Projected accrual was for 288 patients.

CONCLUSIONS

No conclusions have been reached.

Report Date: 6 October 2000

Work Unit # 1562-95

DETAIL SUMMARY SHEET

TITLE: CALGB 9343: Evaluation of Lumpectomy, Tamoxifen, and Irradiation of the Breast Compared with Lumpectomy plus Tamoxifen in Women 70 Years of Age or Older Who Have Carcinoma of the Breast That Is Less Than or Equal to 4 Cm and Clinically- Negative Axillary Nodes

KEYWORDS: Tamoxifen, breast, lumpectomy

PRINCIPAL INVESTIGATOR: Byrd, John MAJ MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 29 November 1994

STUDY OBJECTIVE

To determine the net value of radiation therapy in eligible patients with breast cancer, all of who receive Tamoxifen. To assess whether radiation therapy decreases rate of recurrence and incidence of eventual mastectomy. To estimate overall survival, disease-free survival, and breast cancer-specific morbidity for the two groups.

TECHNICAL APPROACH

Eligible breast cancer patients will be randomized to receive either a lumpectomy followed by Tamoxifen, or lumpectomy followed by radiation therapy (for approximately 6 weeks) plus Tamoxifen. Patients will be followed closely for recurrence. In the event of mastectomy subsequent to initial lumpectomy, patients will go off study and be followed for second primary and mortality.

PRIOR AND CURRENT PROGRESS

A total of 13 WRAMC patients were entered on this protocol, one in this reporting period before it was closed to accrual in February 1999 having met its goal of 647 patients. One of these has died of a non-related cause, the remaining 12 continue in study follow-up. During the time the study was open, no WRAMC patients have withdrawn from the study, and no unexpected adverse events were reported. A rare side effect of treatment was reported to us by the CALGB (cataract formation). This was reported to the IRB in April 1997, and all WRAMC patients on this treatment were notified as required by the NCI and CALGB. An editorial, administrative change was made during this reporting period. National accrual to the study was 647 patients.

CONCLUSIONS

No conclusions have been reached.

Report Date: 3 November 2000

Work Unit # 1563-95

DETAIL SUMMARY SHEET

TITLE: CALGB 9312: Phase III Comparison of Standard vs Myeloablative Therapy for Previously Untreated Symptomatic Multiple Myeloma

KEYWORDS: myeloma, transplant, interferon

PRINCIPAL INVESTIGATOR: Byrd, John C. MAJ MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 20 December 1994

STUDY OBJECTIVE

1) To perform a randomized trial in newly diagnosed systemic myeloma (MM) patients, of standard therapy vs myeloablative therapy in order to examine whether intensive therapy translates into extended survival and progression-free survival. 2) To randomize responding patients to interferon vs no maintenance to evaluate the role of interferon in MM.

TECHNICAL APPROACH

All eligible patients will receive standard chemotherapy (vincristine, doxorubicin, and dexamethasone) for 4 cycles. Responding patients will be randomized to receive autologous stem cell transplant with high dose chemotherapy or standard chemotherapy for 12 months. All patients will initially receive high-dose Cytoxan before transplant. After completion of transplant or chemotherapy, all patients will be randomized to observation or maintenance with interferon.
This study has been amended several times this year to afford all patients the opportunity of bone marrow transplantation at some point in their treatment.

PRIOR AND CURRENT PROGRESS

22 WRAMC patients have been entered on this study, none in this reporting period before it was closed to accrual 1 October 2000. Eleven patients have died; four have withdrawn from study treatment, but continue to be followed for survival. Five serious adverse events (one death this reporting period, 11 September 2000) were reported to HUC. Total national accrual to this study is 825 patients (480 eligible for randomization to step 2), 118 in this reporting period. Projected accrual was for 500 patients eligible for randomization to step 2, see protocol section 11.2. Minor revisions to the protocol concerning eligibility and therapy changes were reported to the HUC. No change was made to the consent form.

CONCLUSIONS

No conclusions have been reached.

Report Date: 22 November 2000 Work Unit # 1564-95

DETAIL SUMMARY SHEET

TITLE: CALGB 9498: A Phase III Randomized Trial of 5-FU/Levamisole/Flucovorin vs.5-FU/Levamisole as Adjuvant Therapy for Colon Cancer

KEYWORDS: colon cancer, levamisole, leucovorin

PRINCIPAL INVESTIGATOR: Byrd, John C. MAJ MC
ASSOCIATES:

DEPARTMENT: Medicine STATUS: O
SERVICE: Hematology-Oncology INITIAL APPROVAL DATE: 31 January 1995

STUDY OBJECTIVE

To compare the effectiveness of bolus 5-FU/leucovorin/levamisole vs. continuous infusion 5-FU/levamisole as adjuvant therapy for patients with Stage B2, C1, or C2 colon cancer. This will be measured in terms of overall survival. Disease-free survival will be secondary endpoint.

TECHNICAL APPROACH

Eligible patients will be randomized to either bolus 5-FU/leucovorin/levamisole or to infusion 5-FU/levamisole. In arm 1, cycles will be repeated at the end of 4 weeks, 8 weeks, and then every 5 weeks for a total of 6 cycles; levamisole will continue for 6 months. In arm 2, following each of the initial 2-week cycles, there will be a 1-week rest followed by a resumption of chemotherapy. Patients with progressive disease or unacceptable toxicities will be removed from the study. All patients will be followed until death.

PRIOR AND CURRENT PROGRESS

One WRAMC patient was entered on this protocol before it was closed to accrual in December 1999. No WRAMC patient has withdrawn from the study and no unexpected adverse reactions have been reported. The one WRAMC patient continues in study follow-up. National accrual to this study is 1044 patients. Projected accrual was for 1800 patients. No revisions have been made to the protocol.

CONCLUSIONS

No conclusions have been reached.

Report Date: 27 June 2001

Work Unit # 1567-95

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: CALGB 9511: A Pilot Trial with Limited Pharmacokinetic Monitoring during Remission Induction and Consolidation Chemotherapy for Adult Acute Lymphoblastic Leukemia

KEYWORDS: PEG-Asparaginase, pharmacokinetic, ALL

PRINCIPAL INVESTIGATOR: Drabick, Joseph COL, MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 29 August 1995

STUDY OBJECTIVE

To: 1) determine toxicity profile for PEG-Asparaginase given as part of intensive multi-agent chemotherapy in patients with previously untreated ALL;

2) determine incidence and significance of neutralizing antibodies, and levels of asparaginase after early treatment with PEG-Asparaginase; and

3) obtain estimate of relationship of these to outcome in ALL.

TECHNICAL APPROACH

Eligible consenting patients with previously untreated ALL will receive aggressive chemotherapy that includes PEG-Asparaginase in place of L-Asparaginase during induction and early intensification phases of treatment (lasting 60 days), and standard chemotherapy for remaining phases of treatment (lasting 2 years). Patients will be monitored weekly during maintenance therapy, every 3 months for the following year if the patient is in remission, and every 6 months for 4 additional years.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

A total of six WRAMC patients were entered on this protocol before it was closed to further accrual on 31 March 2000. Four of these patients have died from their progressive disease and the remaining two patients continue in study follow-up. National accrual to the study was 104 patients. The study was closed to further accrual having met its accrual goal in December 1997.

The number of subjects enrolled to the study since last APR at WRAMC is __0__ and the total enrolled to date at WRAMC is __6_____. The total number enrolled study-wide is __104___, if multi-site study.

CONCLUSIONS

No conclusions have been reached.

Report Date: 6 October 2000

Work Unit # 1569-96

DETAIL SUMMARY SHEET

TITLE: CALGB 9251: A High Intensity, Brief Duration Phase II Chemotherapy Trial in Small, Non-Cleaved Lymphoma and L-3 Acute Lymphoblastic Leukemia (ALL)

KEYWORDS: high intensity, Phase II, chemotherapy

PRINCIPAL INVESTIGATOR: Byrd, John MAJ MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 28 November 1995

STUDY OBJECTIVE

To determine: 1) response rate and disease-free survival of patients with category "J" NHL and L3 ALL, not associated with HIV infection, when treated with high intensity, brief duration chemotherapy; and 2) toxicity of this regimen in an HIV-negative patient population.

TECHNICAL APPROACH

All eligible patients will receive the same therapy. All drugs have been used previously to treat these diseases, but will be given at higher doses for a shorter time period. Course I (day 1-7) includes CPA (IV) and prednisone (po). Course II (day 8-12) includes IFF, Mesna, MTX, Leuco, VCR, Ara-C, Etop (IV), Dex (po), and intrathecal combination chemotherapy (day 8 and 12). This therapy is repeated for Course IV (day 50-54) and Course IV (day 92-96). Course III (day 29-33) includes CPA, MTX, Leuco, VCR, Adr (IV), Dex (po), and intrathecal combination chemotherapy (day 29 and 31). This is followed by cranial radiation therapy on days 34 to 49 in Course III only. Course III chemotherapy is repeated for Course V (day 71-75) and Course VII (day 113-117). All patients will receive first three courses at full dose and on time. In event of slow marrow recovery, later doses may be delayed.

PRIOR AND CURRENT PROGRESS

Two WRAMC patients were entered on this protocol before it was closed to accrual in February 2000. One patient was removed due to a change in the pathologist's diagnosis. This patient suffered no adverse event as a result of study treatment and continues to be followed for survival. The second patient is undergoing therapy having completed three courses without unexpected toxicity. National accrual to the study was 123 patients.

CONCLUSIONS

No conclusions have been reached.

Report Date: 22 November 2000 Work Unit # 1570-96

DETAIL SUMMARY SHEET

TITLE: Cancer and Leukemia Group B

KEYWORDS: grant, NIH, cancer

PRINCIPAL INVESTIGATOR: Byrd, John C. MAJ MC
ASSOCIATES:

DEPARTMENT: Medicine STATUS: O
SERVICE: Hematology-Oncology INITIAL APPROVAL DATE: 25 January 1996

STUDY OBJECTIVE
This is the NIH "umbrella" grant for all CALGB studies at WRAMC. CALGB brings together more than two dozen academic institutions and their affiliates in order to conduct cancer treatment trials and related research.

TECHNICAL APPROACH
At WRAMC, through the CALGB program, over 30 active protocols are available to eligible DOD patients. All WRAMC protocol patients are followed by CALGB staff for life regardless of status of protocol enrollment. Patients are treated per individual protocol.

PRIOR AND CURRENT PROGRESS
During this reporting period, WRAMC has maintained steady enrollment to active protocols, new protocol submissions in many areas of oncology research, timely and complete patient follow-up, and up to date continuing review on all open protocols. WRAMC's affiliate hospitals have continued to organize for full participation; NNMC has several protocols approved and is expected to begin accruing patients soon. CALGB researchers at WRAMC continue to participate in CALGB national meetings, serve on CALGB committees, publish in their fields, and provide appropriate study information to the staff and patients at WRAMC.

CONCLUSIONS
CALGB continues to be a healthy and growing research organization at WRAMC aspiring to provide the best study opportunities for our patients that desire them.

Report Date: 22 November 2000

Work Unit # 1571-96

DETAIL SUMMARY SHEET

TITLE: CALGB 9480: A Phase III Study of Three Different Doses of Suramin (NSC #34936) Administered with a Fixed Dosing Schedule in Patients with Advanced Prostate Cancer.

KEYWORDS: Suramin, Phase III, Prostate

PRINCIPAL INVESTIGATOR: Byrd, John C. MAJ MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Hematology-Oncology

STATUS: C
INITIAL APPROVAL DATE: 30 January 1996

STUDY OBJECTIVE

To measure response rates of hormone refractory advanced prostate cancer when treated with low-, intermediate- and high-dose regimens of Suramin. To measure differences in toxicity of the 3 doses. To describe overall survival and failure-free survival for the 3 treatment groups. To determine pharmacokinetics of the 3 groups. To determine relationship of PSA and FGF levels to treatment response. To determine if different dose levels will have differing effects on the patients' quality of life.

TECHNICAL APPROACH

All eligible patients will be randomized to one of 3 treatments: low-dose Suramin + hydrocortisone, intermediate-dose Suramin + hydrocortisone, or high-dose Suramin + hydrocortisone and fluorocortisone. Suramin is given IV over 1 hour, twice weekly for a 10-week period per protocol schedule. Steroids are given to compensate for possible adrenal insufficiency. Suramin levels are monitored on days 1,2,8,9, 29, and 65. Each patient will complete questionnaires on pain and quality of life before treatment and by phone 3 times during treatment, and once 3 months after completion of treatment.

PRIOR AND CURRENT PROGRESS

Three WRAMC patients were entered on this protocol. All patients have died of their progressive disease as of April 2000. This is the final WRAMC report since the study was closed to further accrual in July 1998. National CALGB accrual to the study was 390 patients. This study will now be closed at WRAMC.

CONCLUSIONS

Analysis is in progress.

Report Date: 30 August 2000

Work Unit # 1573-87

DETAIL SUMMARY SHEET

TITLE: CALGB 8762: Molecular Subtypes in Acute Lymphatic Leukemia with Philadelphia Chromosome

KEYWORDS: Philadelphia chromosome, ALL

PRINCIPAL INVESTIGATOR: Byrd, John C MAJ MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 27 October 1987

STUDY OBJECTIVE

To determine the incidence of pH positivity in patients with previously untreated acute lymphatic leukemia (ALL).

TECHNICAL APPROACH

Non-randomized comparison study in which all eligible patients who consent allow a sample of blood and bone marrow to be sent to a reference laboratory at the time of diagnosis, first intensification, and at relapse.

PRIOR AND CURRENT PROGRESS

15 WRAMC patients were entered on this study before it was closed to accrual 15 April 1999. No WRAMC patients have withdrawn from this study, and no adverse events have been reported due to the collection of study samples. Twelve WRAMC patients have died of their disease and the remaining 3 patients continue in study follow-up. Samples were collected and sent to reference lab as required by the protocol. Final national accrual to the study was 393 patients.

CONCLUSIONS

While final conclusions have not been reached, analysis is ongoing and has shown correlation between chromosomal features and disease outcome and response to treatment.

Report Date: 28 February 2001 Work Unit #1573-96

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: CALGB 9334: Sclerosis of Pleural Effusions by Talc Thoracoscopy vs. Talc Slurry: A Phase III Study

KEYWORDS: Pleural Effusion, Talc Slurry, Thoracoscopy

PRINCIPAL INVESTIGATOR: John C. Byrd, MAJ MC
ASSOCIATES:

DEPARTMENT: Medicine STATUS: O
SERVICE: Hematology-Oncology INITIAL APPROVAL DATE: 23 April 1996

STUDY OBJECTIVE
To compare a proportion of patients with successful pleurodesis at 30 days post-treatment for malignant pleural effusion (MPE) by talc slurry via chest tube or thoracospic talc insufflation. To compare the cost of treating MPE patients with these methods. To compare treatments with respect to time to recurrence of effusion, duration of drainage, extent of post treatment complications and toxicities, and patient quality-of-life and pain.

TECHNICAL APPROACH
Eligible patients with MPE will be randomly assigned to receive either thoracoscopy with talc insufflation or talc slurry via chest tube at the bedside. Patients will be closely monitored for medical and surgical complications for 30 days, and actively followed for 6 months. Patients will complete quality-of-life instruments before treatment and 30 days after treatment. Pain will be assessed 2x per day while patient has a chest tube in place after procedure. Monthly follow-up visits with chest x-rays will be done for 6 months.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
Twelve WRAMC patients have been entered on this protocol before it was closed to accrual in September 1999. Eleven of these patients have died, and the remaining one continues in study follow-up. One death was reported to the IRB in April 2000. No WRAMC patient has withdrawn from the study. National accrual to the study was 348 patients.
The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 12. The total number enrolled study-wide is 348, if multi-site study.

CONCLUSIONS
No conclusions have been reached.

Report Date: 30 August 2000

Work Unit # 1574-87

DETAIL SUMMARY SHEET

TITLE: CALGB 8763: Immunoglobulin and T Cell Receptor Gene Rearrangement in Adult Acute Lymphatic Leukemia

KEYWORDS: immunoglobulin, T-cell receptor, ALL

PRINCIPAL INVESTIGATOR: Byrd, John C MAJ MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 27 October 1987

STUDY OBJECTIVE

To determine the incidence of Ig and T-cell receptor gene rearrangements from samples of patients with previously untreated adult acute lymphatic leukemia (ALL).

TECHNICAL APPROACH

Non-randomized companion study in which all eligible patients who consent allow a sample of bone marrow and blood to be sent to CALGB reference laboratory at the time of diagnosis, prior to first intensification, and at relapse.

PRIOR AND CURRENT PROGRESS

A total of 10 WRAMC patients were entered on this study before it was closed to accrual in May 1996. Eight WRAMC patients have died of their progressive disease and the remaining two continue in study follow-up. No WRAMC patients have withdrawn from the study, and no adverse events have been reported as a result of the sample collection. National accrual to the protocol was 370 patients.

CONCLUSIONS

No conclusions have been reached.

Report Date: 3 November 2000 Work Unit # 1577-80

DETAIL SUMMARY SHEET

TITLE: CALGB 8361: Immunologic Diagnostic Studies in AML (Blood Drawing Phase; previously CALGB 7921); A Comparative Study of Three Remission Induction Regimens and Two Maintenance Regimens for AML (Treatment Phase; Previously CALGB 8321).

KEYWORDS: immunology, oncology, leukemia

PRINCIPAL INVESTIGATOR: Byrd, John C. MAJ MC
ASSOCIATES:

DEPARTMENT: Medicine STATUS: O
SERVICE: Hematology-Oncology INITIAL APPROVAL DATE: 31 December 1981

STUDY OBJECTIVE
1) To determine the incidence of various markers in acute myelogenous leukemia (AML); 2) To correlate the presence of these markers and the surface antigen phenotype they determine with the FAB histological classification; and 3) To correlate the presence of the various markers with the initial and subsequent clinical characteristics of the disease.

TECHNICAL APPROACH
All eligible patients are registered prior to the initial therapy. From the diagnostic bone marrow procedure, 2 cc of bone marrow and 7 cc of peripheral blood are collected and sent by express mail to the CALGB reference laboratory for analysis and confirmation of classification. Samples are again obtained at relapse.

PRIOR AND CURRENT PROGRESS
A total of 65 WRAMC patients were entered on this protocol before it was closed to further accrual in May 1997. Total National accrual was 2405 patients. Blood and bone marrow samples continue to be collected and sent to reference lab at times specified by the protocol. No WRAMC patients have withdrawn from the protocol, and no adverse events have been reported.

CONCLUSIONS
Immunophenotyping has provide useful in the stratification of some leukemia at high risk for relapse. Analysis is ongoing.

Report Date: 4 April 2001 Work Unit # 1579-96

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: CALGB 9254: Anti-B4-Blocked-Ricin (NSC #639185) Adjuvant Post-Autologous Bone Marrow Transplant: A Phase III Study

KEYWORDS: ABB, ricin, NHL

PRINCIPAL INVESTIGATOR: Drabick, Joseph LTC MC
ASSOCIATES:

DEPARTMENT: Medicine STATUS: O
SERVICE: Hematology-Oncology INITIAL APPROVAL DATE: 28 May 1996

STUDY OBJECTIVE
To determine the effect on disease-free survival of Anti-B4-bR administered by 7-day continuous infusion to patients in complete remission after ABMT for B-cell NHL.

TECHNICAL APPROACH
All eligible NHL patients who consent to this study will receive standard ABMT therapy. If they achieve complete remission, they will be randomized to receive Anti-B4-Blocked-Ricin or observation. Patients who receive ABB will receive a 7-day continuous infusion between 60 and 120 days post ABMT, and another course 14 days later. Treatment is done on an outpatient basis with frequent (6 visits) clinic monitoring. Lab studies are routine for ABMT patients with 1 extra tube for pharmacokinetic samples in patients receiving drug treatment. Patients will be followed by clinic visits every 6 months for 3 years.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
A total of two WRAMC patients were entered on this study before it was closed to accrual in March 1997. No unexpected adverse reactions have been reported and no WRAMC patients have withdrawn from the study. Final national accrual to the study was 511 registered and 157 randomized. The study, when it closed to accrual in March 1997, was short of its projected accrual of 750 when interim analysis by the CALGB Data and Safety Monitoring Board found that it was highly unlikely that ABB would show a statistically significant benefit, even if the study were to continue to its original accrual goal.
The number of subjects enrolled to the study since last APR at WRAMC is 2 and the total enrolled to date at WRAMC is 2. The total number enrolled study-wide is 668, if multi-site study.

CONCLUSIONS
Study closed since no significant benefit to patients is projected.

Report Date: 4 May 2001 Work Unit # 1584-96

DETAIL SUMMARY SHEET

TITLE: CALGB 9665: The CALGB Leukemia Tissue Bank

KEYWORDS: leukemia, tissue bank

PRINCIPAL INVESTIGATOR: Drabick, Joseph J. LTC MC
ASSOCIATES:

DEPARTMENT: Medicine STATUS: O
SERVICE: Hematology-Oncology INITIAL APPROVAL DATE: 25 June 1996

STUDY OBJECTIVE
To collect and store specimens from every newly diagnosed patient with acute leukemia or myelogysplastic syndrome (MDS) who is entered on a CALGB protocol for previously untreated patients.

TECHNICAL APPROACH
All consenting eligible patients with newly diagnosed leukemia or MDS entered on a CALGB treatment protocol will have blood, bone marrow, and cell samples (by twirling special brush inside cheek for 30 seconds): 2) during remission – similar blood and bone marrow samples at intervals specified in treatment protocol; and 3) at relapse – similar blood and bone marrow specimens x 1. All samples will be sent per protocol to CALGB Tissue Bank at Roswell Park Cancer Institute for use in further studies (no heritable genes).

PRIOR AND CURRENT PROGRESS
Twenty-nine WRAMC patients have been enter3d on this protocol, four in this reporting period. Six of these patients have died, the remaining 23 patients continue in study follow-up. No WRAMC patients have withdrawn from the study, and no adverse events have occurred because of sample collection. All samples have been collected and sent to the appropriate reference laboratory. Minor changes have been made to the protocol. National accrual to the study is 1293 patient samples, 508 in this reporting period.

The number of subjects enrolled to the study since last APR at WRAMC is 4 and the total enrolled to date at WRAMC is 29. The total number enrolled study-wide is 1293, if multi-site study, 508 in this reporting period.

CONCLUSIONS
No conclusions have been reached.

Report Date: 1 June 2001 Work Unit # 1587-96

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: CALGB 9551: Phase II Study of 9-Aminocamptochecin (9-AC/CD, NSC #603071) in Previously-Treated Hodgkin's Disease and Non-Hodgkin's Lymphoma: IWF Grades A-H

KEYWORDS: phase II, 9-AC/CD, Hodgkin's

PRINCIPAL INVESTIGATOR: Drabick Joseph LTC MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Hematology-Oncology

STATUS: C
INITIAL APPROVAL DATE: 30 July 1996

STUDY OBJECTIVE
To evaluate response rate, describe response duration, and assess toxicity of treatment with 9-AC/CD for previously treated Hodgkin's disease and NHL IWF A-F. To validate a preliminary pharmacodynamic model relating drug concentration, albumin and bilirubin to toxicity. To determine if 9-AC concentrations correlate with response.

TECHNICAL APPROACH
All eligible, consenting lymphoma patients will receive cycles of 9 AC/CD-1.1 mg/m2/d (total dose 3.3 mg/m2) by continuous IV infusion on days 1-3. Infusions require a central venous catheter and ambulatory pump. Pharmaco-kinetics will be done during first cycle. Barring toxicity or progression, all patients will receive at least three cycles. Responders may be treated for two cycles past best response. Cycles are repeated every 14 days. Patients will be pretreated with anti-emetics IV. After treatment, patients will be followed 6q 6 months x 2 years and yearly for life.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
The two WRAMC patients that were entered on this protocol have died of their progressive disease. The deaths were not related to the protocol therapy. This protocol was closed to accrual 15 October 2000. No unexpected adverse reactions have been reported. National accrual to the study was 133 patients.
The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 2. The total number enrolled study-wide is 133, if multi-site study.

CONCLUSIONS
No conclusions have been reached.

Report Date: 7 September 2001 Work Unit # 1589-96

DETAIL SUMMARY SHEET

TITLE: CALGB 9620 Autologous Stem Cell Transplantation for Acute Myeloid Leukemia in Second Remission: A Phase II Study

KEYWORDS: AML; autologous; stem cell transplant

PRINCIPAL INVESTIGATOR: Drabick, Joseph COL MC
ASSOCIATES:

DEPARTMENT: Medicine STATUS: C
SERVICE: Hematology-Oncology INITIAL APPROVAL DATE: 27 October 1996

STUDY OBJECTIVE

To: 1) evaluate ability of this 2-step treatment program to generate 2 yr. survival of >30%; 2) determine ability to deliver this therapy with treatment-related mortality 20%; 3)evaluate ability to collect adequate numbers of peripheral blood stem cells from patients in second remission AML; 4)evaluate engraftment kinetics of primed peripheral blood stem cells in second remission AML

TECHNICAL APPROACH

Consenting eligible adult patients with documented AML in second remission will be entered on this study. The study utilized a 2-step treatment program for consolidation therapy:
Step 1. IV chemotherapy with Etoposide, Ara-C and G-CSF, will require in-patient stay of 28 days. PBSC collection is done during this time.
Step 2. Following a rest period of at least 28 days, eligible patients will be admitted for 28-42 days. They will receive chemotherapy with Busulfin, Etoposide and G-CSF, followed by autologous stem cell infusion with antibiotic and palliative support.

PRIOR AND CURRENT PROGRESS

One WRAMC patient had been entered on this study in the last reporting period and has died of her progressive disease. No unexpected adverse reactions have been reported from the CALGB. National accrual to the study was 51 patients. This study is now permanently closed at WRAMC since the one patient has died.

CONCLUSIONS

No conclusions have been reached.

Report Date: 22 November 2000 Work Unit # 1590-89

DETAIL SUMMARY SHEET

TITLE: CALGB 8852: A Study of CHOPE in Diffuse Lymphomas

KEYWORDS: lymphoma, CHOPE, high-dose

PRINCIPAL INVESTIGATOR: Byrd, John C. MAJ MC
ASSOCIATES:

DEPARTMENT: Medicine STATUS: O
SERVICE: Hematology-Oncology INITIAL APPROVAL DATE: 31 January 1989

STUDY OBJECTIVE

To identify the maximum tolerated dose of cyclophosphamide, doxorubicin, vincristine, prednisone, and etopsoside (CHOPE) in the treatment of lymphoma, and to assess the safety of giving multiple cycles of high-dose CHOPE therapy.

TECHNICAL APPROACH

Standard doses of CHOPE will be given to the first 20-25 patients enrolled. If tolerated, the doses will be escalated for the next groups sequentially, until the maximum tolerated dose is reached.

PRIOR AND CURRENT PROGRESS

Five WRAMC patients were entered on this study before it was closed to accrual in May 1993 having met its accrual goal with a national accrual of 227 patients. Four of these patients have died of progressive, the remaining one continues in study follow-up. No WRAMC patients withdrew from this study and no unexpected adverse reactions have been reported.

CONCLUSIONS

Analysis is in progress.

Report Date: 22 November 2000 Work Unit # 1591-97

DETAIL SUMMARY SHEET

TITLE: CALGB 9583 A Phase III Two-Arm Randomized Study Comparing Antiandrogen Withdrawal vs. Antiandrogen Withdrawal Combined with Ketoconazole and Hydrocortisone in Patients with Advanced Prostate Cancer

KEYWORDS: advanced, prostate cancer, ketoconazole

PRINCIPAL INVESTIGATOR: Byrd, John C. MAJ MC
ASSOCIATES:

DEPARTMENT: Medicine STATUS: O
SERVICE: Hematology-Oncology INITIAL APPROVAL DATE: 28 January 1997

STUDY OBJECTIVE
To compare the response proportion and duration of response to antiandrogen withdrawal alone vs. antiandrogen withdrawal combined with ketoconazole and hydrocortisone in patients with advanced hormone refractory prostatic carcinoma.

TECHNICAL APPROACH
All eligible, consenting men will be randomly assigned to #1 stop flutamide or Casodex or #2 stop Flutamide or Casodex and start treatment with ketoconazole po tid and hydrocortisone po bid. Patients entering this will also have a bone marrow biopsy done as part of companion study CALGB 9663 (consented separately). Treatment is out patient with clinic visits every 4 weeks. Study treatment will continue until there is clinical evidence that it is no longer effective.

PRIOR AND CURRENT PROGRESS
Four WRAMC patients have been entered on this study before it was closed to accrual in May 2000. Two patients have died of their progressive disease and the other two continue in study follow-up. No WRAMC patient has withdrawn from the study, and no unexpected adverse event has been reported. National accrual to the study is 260 patients. Projected accrual was for 250. Minor changes to the protocol and the consent form were reported to the IRB in August 1999.

CONCLUSIONS
No conclusions have been reached.

Repo.t Date: 28 December 2000 Work Unit # 1592-97

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: CALGB 9484 Linkage of Molecular and Epidemiological Breast Cancer Investigations with Treatment Data: A Specialized Registry

KEYWORDS: breast cancer, registry, epidemiological

PRINCIPAL INVESTIGATOR: Byrd, John C. MAJ MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 25 February 1997

STUDY OBJECTIVE
To form a specialized registry of clinical, scientific, epidemiologic (including personal, family and environmental exposures), and psycho-social information about breast cancer patients to be used by qualified investigators in a variety of studies in order to seek new knowledge about breast cancer.

TECHNICAL APPROACH
Consenting WRAMC patients entered on CALGB breast cancer treatment protocols will donate one paraffin tissue block, and urine and blood samples as specified by protocol. The will be sent to central lab and stored for breast cancer research. Additional blood will be collected for DNA study if patient consents. This information is not available to patient or any parties outside this research project. Patients will fill out a personal and family cancer information questionnaire.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
Nine WRAMC patients had been entered on this study before it was closed to accrual in September 1999. No WRAMC patient has withdrawn. No adverse reactions have been reported to us by the CALGB. National accrual to the study was 347 patients. Projected accrual was for 5000 patients.

CONCLUSIONS
No conclusions have been reached.

Report Date: 4 May 2001

Work Unit # 1594-97

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: CALGB 9760: Multidrug Resistance Studies in Acute Leukemia

KEYWORDS: resistance, multidrug, AML

PRINCIPAL INVESTIGATOR: Byrd, John MAJ MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 24 June 1997

STUDY OBJECTIVE

To study Pgp antigen expression in MDR in patients with acute leukemia at diagnosis, relapse and refractory disease. To correlate Pgp mediated MDR with pretreatment patient characteristics. To study PSC-833 Pgp modulation. To study MDR mediated by other mediators including MRP and LRP. To determine frequency of Pgp, MRP and LRP mediated MDR in adult leukemic cells, and correlate with pretreatment characteristics and with treatment outcome.

TECHNICAL APPROACH

Bone marrow and/or peripheral blood samples as specified in protocol are collected from consenting patients with acute leukemia at the time of diagnosis (before treatment), and at time of relapse or diagnosis of refractory disease. These samples at taken at times when the procedure is already being carried out for standard diagnostic care. The laboratory results are then correlated with clinical outcome.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Thirteen WRAMC patients have been entered on this protocol, three in this reporting period. There have been no adverse events related to specimen collection reported to the CALGB group in this reporting period. No WRAMC patients have withdrawn from the study. All samples have been collected and sent to the appropriate laboratory. National accrual to the study is 573 patients, 183 in this reporting period. Projected accrual is for 600 patients.
The number of subjects enrolled to the study since last APR at WRAMC is _3__ and the total enrolled to date at WRAMC is _13___. The total number enrolled study-wide is _573__, if multi-site study.

CONCLUSIONS

No conclusions have been reached.

Report Date: 28 February 2001 Work Unit #1595-89

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: CALGB 8961: RAS Mutations in Myelodysplasia

KEYWORDS: Ras gene, oncogenes, myelodysplasia

PRINCIPAL INVESTIGATOR: Byrd, John C MAJ MC
ASSOCIATES:

DEPARTMENT: Medicine STATUS: O
SERVICE: Hematology-Oncology INITIAL APPROVAL DATE: 25 April 1989

STUDY OBJECTIVE
To determine: 1) the prevalence of mutant RAS genes in myelodysplasia; and 2) if the presence of such a mutation predicts subsequent leukemic development.

TECHNICAL APPROACH
Non-randomized, non-treatment protocol in which all eligible patients are registered. Blood and bone marrow samples and slides are obtained at entry and, again, when acute leukemia develops.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
A total of 13 WRAMC patients were entered on this study before it was closed to accrual in September 1996 having met its accrual goal. Eleven of these patients have died and the remaining two continue in study follow-up. National accrual was 304 patients. No WRAMC patients withdrew from this study and no unexpected adverse reactions to the collection of these laboratory samples were reported. All blood and bone marrow samples have been collected and sent to reference lab per protocol requirements. Samples continue to be sent for study patients in the event that they develop acute leukemia in the future.
The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 13. The total number enrolled study-wide is 304, if multi-site study.

CONCLUSIONS
Analysis is ongoing.

Report Date: 1 June 2001 Work Unit # 1596-97

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: CALGB 9640: A Comparison of Intensive Sequential Chemotherapy Using Doxorubicin Plus Paclitaxel Plus Cyclophosphamide with High-Dose Chemotherapy and Autologous Hematopoietic Progenitor Cell Support for Primary Breast Cancer in Women with 4-9 Involved Axillary Lymph Nodes

KEYWORDS: chemotherapy, breast, progenitor cell support

PRINCIPAL INVESTIGATOR: Drabick, Joseph LTC MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 29 July 1997

STUDY OBJECTIVE

To compare induction chemotherapy followed by high dose chemo and autologous stem cell support vs. intensive sequential chemo with G-CSF support with respect to disease free survival, toxicity and overall survival in operable patients with 4-9 positive nodes.

TECHNICAL APPROACH

Eligible women will be randomly assigned to receive either 1) high-dose chemo with doxorubicin, paclitaxel and cyclophosphamide over 17 weeks with G-CSF support; or 2) standard dose chemo over 10 weeks, followed by higher dose chemo with cyclophosphamide, thiotepa, and carboplatin with autologous stem cell collection after week 10, and reinfusion 4 days after completion of high dose chemo. Both groups will be given radiation treatment 4-6 weeks post therapy, and tamoxifen therapy for 5 years.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

One WRAMC patient has been entered on this protocol in the last reporting period. No adverse reactions have been reported from the CALGB. There have been minor editorial and administrative changes to the protocol in the last reporting period. At last report, 562 patients had been entered nationally, 58 in this reporting period. Projected accrual is for 1,000 patients.
The number of subjects enrolled to the study since last APR at WRAMC is 1 and the total enrolled to date at WRAMC is 1. The total number enrolled study-wide is 562, if multi-site study.

CONCLUSIONS

No conclusions have been reached.

Report Date: 27 June 2001 Work Unit # 1597-97

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: CALGB 9621: Phase I Study of MDR Modulation with PSC-833 with a Pilot Study of Cytogenetic Risk-Adapted Consolidation Followed by a Phase II Pilot Study of Immunotherapy with rIL-2 in Previously Untreated Patients with AML < 60 Years

KEYWORDS: PSC-833, MDR Modulation, rIL-2

PRINCIPAL INVESTIGATOR: Drabick, Joseph COL MC
ASSOCIATES:

DEPARTMENT: Medicine STATUS: O
SERVICE: Hematology-Oncology INITIAL APPROVAL DATE: 26 August 1997

STUDY OBJECTIVE
To determine the MTD for the intensive chemotherapy used in the study. To establish the feasibility and toxicity of administering post remission therapy in a risk adapted fashion. To establish feasibility of maintenance therapy with rIL-2.

TECHNICAL APPROACH
Eligible patients with AML will receive standard induction chemotherapy plus minus PSC-883 followed by risk stratified therapy with either stem cell transplant or intensive chemotherapy, followed by immunotherapy with rIL-2. Therapy duration is 24 weeks. Patients will be followed for life.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
A total of 10 WRAMC patients were entered on this protocol before it were closed to accrual in March 2000. Four of these patients have died of their progressive disease. The remaining six patients continue in study follow-up. No WRAMC patients have withdrawn from the study. Three adverse events were reported to the IRB during this reporting period. Total national accrual to the study was 410 patients. The number of subjects enrolled to the study since last APR at WRAMC is __0__ and the total enrolled to date at WRAMC is __10__. The total number enrolled study-wide is __410__, if multi-site study.

CONCLUSIONS
No conclusions have been reached.

Report Date: 27 June 2001 Work Unit # 1598-89

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: CALGB 8952: Combination Chemotherapy for Advanced Hodgkin's Disease, Phase III

KEYWORDS: chemotherapy, Hodgkin's disease

PRINCIPAL INVESTIGATOR: Drabick, Joseph COL, MC
ASSOCIATES:

DEPARTMENT: Medicine STATUS: O
SERVICE: Hematology-Oncology INITIAL APPROVAL DATE: 29 August 1989

STUDY OBJECTIVE
To compare ABVD to the MOPP/ABV hybrid as therapy for patients with Hodgkin's disease in terms of complete response rates, disease-free survival, failure-free survival, and both intermediate and long-term toxicities.

TECHNICAL APPROACH
Randomized study in which eligible patients receive either ABVD or the MOPP/ABV hybrid combination for a minimum of six cycles unless progression is documented.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
A total of nine WRAMC patients were entered on this protocol before it was closed to further accrual in November 1995. Three of these patients have died of their progressive disease. The remaining six continue in study follow-up. Total national accrual to this study was 856 patients at the time of its closure due to an increased incidence of treatment-related deaths and second malignancy reported in one arm of the study. No treatment related deaths or second malignancies have been reported in WRAMC patients. No WRAMC patients have withdrawn from the study or have reported other unexpected adverse events. The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 9. The total number enrolled study-wide is 856, if multi-site study.

CONCLUSIONS
Analysis is in progress.

Report Date: 16 May 2001 Work Unit # 1598-97

DETAIL SUMMARY SHEET

TITLE: CALGB 9663: Androgen Receptor Mutations in Hormone Refractory Prostate Cancer.

KEYWORDS: prostate, androgen receptor, mutations

PRINCIPAL INVESTIGATOR: Drabick, Joseph LTC MC
ASSOCIATES:

DEPARTMENT: Medicine STATUS: C
SERVICE: Hematology-Oncology INITIAL APPROVAL DATE: 30 September 1997

STUDY OBJECTIVE

To test feasibility of obtaining bone marrow samples in a cooperative group setting. To determine the frequency of bone marrow invasion by prostate cancer cells in patients with HRPC. To evaluate the frequency of AR mutations in bone marrow samples in this patient population.

TECHNICAL APPROACH

Eligible consenting men with hormone refractory prostate cancer, being treated on one of the specified CALGB treatment studies for this population will have a bone marrow biopsy performed before the start of treatment, and also will contribute one 20cc sample of peripheral blood. This sample collection is performed only once. Samples are frozen immediately per protocol and shipped to study lab. No further samples are collected and no study follow-up is required.

PRIOR AND CURRENT PROGRESS

No patients have been entered on this study at WRAMC. National accrual thus far is 195 patients, 1 in this reporting period. The projected accrual is for 243 patients. No adverse events have been reported due to this sample collection. A change was made to the consent form in August 1999 and approved by the IRB.

The number of subject enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 0. The total number enrolled study-wide is 195, if multi-site study.

CONCLUSIONS

No conclusions have been reached.

Report Date: 30 August 2000

Work Unit # 1599-98

DETAIL SUMMARY SHEET

TITLE: CALGB 9581: Phase III Randomized Study of Adjuvant Immunotherapy with Monoclonal Antibody 17-LA vs. No Adjuvant Therapy Following Resection for Stage II (Modified Astler-Coller B2) Adenocarcinoma of the Colon

KEYWORDS:

PRINCIPAL INVESTIGATOR: Byrd, John MAJ MC.
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 28 October 1997

STUDY OBJECTIVE

1) To determine whether adjuvant treatment with MoAb 17-1A will improve the probability of overall and disease-free survival, and increase disease-free intervals in patients who have undergone resection of a stage II colon cancer. 2) To evaluate a panel of prognostic markers, in order to correlate these measures with survival and disease recurrence in these patients.

TECHNICAL APPROACH

Eligible patients with colon cancer will be randomly assigned after surgery to receive either adjuvant treatment with MoAb 17-1A, or standard treatment-observation. Patients receiving adjuvant therapy will receive doses of study IV over 2 hrs in the outpatient clinic, every 4 wks for a total of 5 doses. Treated group will have weekly clinic evaluations during treatment. Both groups will be followed q 6 months for 5 yrs.

PRIOR AND CURRENT PROGRESS

Two WRAMC patients have been entered on this protocol, one in this reporting period. No unexpected adverse reactions have been reported, and no WRAMC patient has withdrawn from the study. National accrual to this study is 696, 625 patients in this reporting period. Projected national accrual is for 2100 patients. Minor editorial revisions have been made to the protocol in this reporting period.

CONCLUSIONS

No conclusions have been reached.

Report Date: 02 April 2001 Work Unit # 1605

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: Hemapheresis for Collection of Platelets for In Vitro Study of Platelet Cryopreservation

KEYWORDS: platelets, aphersis, storage, freezing, platelet induced clot retraction, thromboelastography, protein phosphorylation, dynein, kinesin, nitric oxide, permeability coefficient, membrane phase transition, DMSO, blood storage bags – physical and thermal properties, dynamic mechanical analysis, glass transition temperature

PRINCIPAL INVESTIGATOR: Reid, Thomas COL MC
ASSOCIATES:

DEPARTMENT: Medicine STATUS: O
SERVICE: Hematology-Oncology INITIAL APPROVAL DATE: 24 June 1997

STUDY OBJECTIVE

To study the effects of storage (freezing, 4°C, 20-24°C) on *in vitro* platelet function. To study the intracellular mechanisms (e.g. contractile proteins, membrane integrity, activation) of damage during storage. To study the biochemical mechanism of platelet induced clot retraction (PICR) and platelet activation.

TECHNICAL APPROACH

Fresh platelets are stored at 22°C for 5 days and tested for *in vitro* platelet function, emphasizing PICR. Fresh, stored or processed platelets and "platelet substitutes" are compared using *in vitro* function testing. Phosphorylated proteins identified with PAGE with ^{32}P or MoAb against serine-P. Post-translational modifications are identified using MoAb directed against modification. Using NO donors and various platelet agonists, platelets are tested for their ability to induce clot retraction and effect $[Ca]_i$ and $[cGMP]_i$. Platelets are incubated with fluorescein diacetate-platelets damaged during storage with a loss of membrane integrity can be identified by the release of fluorescein. The phase transition (T_m; liquid crystalline → gel) is evaluated using Fourier transform infrared spectroscopy (FTIR), nuclear magnetic resonance (NMR), differential scanning calorimetry (DSC) and electron paramagnetic resonance (EPR).

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Sixty-eight potential donors have been screened. Five were considered ineligible for donation, none in the past year. Forty-five participants have withdrawn from the study since its inception due to leaving the area. Seventeen individuals are available and eligible for apheresis (25%). One hundred seventy three apheresis procedures have been performed, all but two successful (98.8 %), one in the past year - there was a pump malfunction and a unit of red blood cells was taken along with the apheresed platelets. There was no harm to the donor and the donor was deferred for six weeks to replenish his RBC supply. Platelet membrane integrity is damaged on cooling or freezing without cryoprotectants. The platelet T_m is approximately 15-18°C; DMSO appears to increase the T_m. Model membrane studies are in the preliminary stages. To date, there has been no direct benefit to patients. The glass transition temperature and tensile module of several blood storage bags were studied. Polyolefin bags appear ideal.

The number of subjects enrolled to the study since the last APR at WRAMC is 10 and the total enrolled to date is 69.

CONCLUSIONS

Substantial progress has been made identifying those parameters that will affect platelet storage. From this research, a method will be developed to provide platelets with a long shelf life.

Report Date: 18 September 2001 Work Unit # 1606

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: Prostate Cancer in the Patient with Chronic Lymphocytic Leukemia

KEYWORDS: chronic lymphocytic leukemia, prostate cancer, second primary malignancy

PRINCIPAL INVESTIGATOR: Flynn, Joseph CPT MC
ASSOCIATES:

DEPARTMENT: Medicine STATUS: C
SERVICE: Hematology-Oncology INITIAL APPROVAL DATE: 7 July 1997

STUDY OBJECTIVE

1. To estimate the risk of patients with Chronic Lymphocytic Leukemia(CLL) developing prostate cancer.
2. To determine if the stage specific outcome of prostate cancer is worse in patients with chronic lymphocytic leukemia when compared with those patients without chronic lymphocytic leukemia.

TECHNICAL APPROACH

This is a retrospective case-controlled study examining the incidence of prostate cancer in men with CLL and comparing the stage specific outcome of prostate cancer in these patients.
Charts of all patients with CLL in the Hematology-Oncology clinic and the flow cytometry database from July 1, 1987 to July 10, 1999 were reviewed. All cases of prostate cancer and second primary malignancy were reviewed for demographic and clinical information.
A control group of patients without CLL having prostate cancer or other associated malignancy were selected as a consecutive sample from the tumor registry and a population of patients seen in the Internal Medicine clinic over the same time period. Charts for patients with prostate cancer or associated second malignancy who were matched by age, presenting stage and therapy utilized to treat the underlying malignancy were used to compare the course of malignancy of the control population with the CLL patients.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

There have been no further accruals to this protocol and no changes since last APR. There is no significant changes in the body of literature on this subject.
The number of subjects enrolled to the study since last APR at WRAMC is __0__ and the total enrolled to date at WRAMC is __396 study subjects and controls.

CONCLUSIONS

A significant occurrence of Hodgkin's disease was seen only in those treated with Fludarabine($p=0.016$) and was uniformly Epstein Barr virus related. In our population we noted an increased trend toward development of a SPM that became significant when controlled for surveillance time. Males in the CLL subgroup were much more likely than females to have an associated second malignancy which was in contrast to the control group where there was no such difference. Patients treated with a fludarabine had no proclivity to develop a SPM, though a greater chance of subsequent development of Hodgkin's disease. Our study demonstrates that treatment with newer agents such as fludarabine does not result in greater risk for development of SPM in CLL. As a result of this research, further investigation into cause of an increased risk is warranted.

Report Date: 6 August 2001 Work Unit # 1607

DETAIL SUMMARY SHEET

TITLE: Evaluation of Multiple Cycles of High Dos Chemotherapy Supported with Filgrastim and Peripheral Blood Prognitor Cells with Metastatic Breast Cancer

KEYWORDS:

PRINCIPAL INVESTIGATOR: Byrd, John MAJ MC
ASSOCIATES:

DEPARTMENT: Medicine STATUS: C
SERVICE: Hematology-Oncology INITIAL APPROVAL DATE: 30 September 1997

STUDY OBJECTIVE

To investigate the efficacy of administrating a regimen of cyclosphophamide, paclitaxel and Filgrastim to mobilize peripheral blood progenitor cells followed by two cycles of carboplatin and paclitaxel, followed by a cycle of melphlan, each supported by previously mobilized peripheral blood progenitor cells and Filgrastim in patient with advanced breast cancer. Efficacy to be evaluated in terms of two-year disease free survival.

TECHNICAL APPROACH

This is a non-comparative, single-arm multi-study.

PRIOR AND CURRENT PROGRESS

A total of eight (8) patients have been enrolled on this study at WRAMC. Five patients have been enrolled this fiscal year. One patient has had a disease free survival of two years; two patients have progressive disease and are receiving salvage chemotherapy/radiation. Four patients have died after progression of disease. One patient died from peripheral blood stem cell transplant or disease unrelated event.

CONCLUSIONS

This study is closed to accrual. Follow-up continues study-wide to ascertain disease free intervals for those patients who are less than two years from high-dose chemotherapy and peripheral blood progenitor cell transplant.

ADDENDUM

This APR from 8/1/00 is being resubmitted noting that the study was closed to WRAMC patients at the time that this APR was submitted. All 8 of the patients treated on this study here had reached the completion point at that time.

Report Date: 1 September 2000 Work Unit # 1608

DETAIL SUMMARY SHEET

TITLE: Acute Hypoxemic Respiratory Failure in Bone Marrow Transplant Patients: An Imbalance of the Immunomodulating Cascade?

KEYWORDS: Bone marrow transplantation; Acute Lung Injury; ARDS; Cytokines

PRINCIPAL INVESTIGATOR: Moores, Lisa MAJ MC
ASSOCIATES: Christie, Robert MAJ MC; Fitzpatrick, Tom LTC MC; Ling, Geoffrey LTC MC

DEPARTMENT: Medicine
SERVICE: Pulmonary and Critical Care Medicine

STATUS: O
INITIAL APPROVAL DATE: 28 October 1997

STUDY OBJECTIVE

To determine the relationship between the inflammatory cytokine response and neutrophil activity and the development of acute respiratory failure at the time of engraftment in adult patients undergoing high-dose chemotherapy with autologous bone marrow transplantation.

TECHNICAL APPROACH

All patients undergoing high-dose chemotherapy with autologous bone marrow transplantation at WRAMC are asked to participate in the study. If enrolled, patients have serum measurements of 6cytokines (TNF-a, IL1-B, IL-6; IL2, IL-10, IL-8) every other day throughout the hospitalization. In addition, these same cytokines are measure from the lung via fiberoptic bronchoscopy with bronchoalveolar lavage at three different times—Day 0 of chemotherapy, day of engraftment, and hospital day 21. Cell counts are also done on this fluid. Demographic features as well as information from the hospital course are collected in the data collection sheet for descriptive purposes.

PRIOR AND CURRENT PROGRESS

A total of 13 patients have been enrolled. Due to difficulties obtaining significant enrollment, data from these first thirteen patients has been preliminarily analyzed. Most patients decline participation secondary to the fiberoptic bronchoscopies, which are required. No further enrollment is taking place at this time, as we would like to determine if the initial data would support the use of a serum only study (i.e. if serum cytokines mirror the bronchoalveolar cytokines, then perhaps we could follow serum only levels, leading to increased enrollment.)

CONCLUSIONS

No conclusions at this time. Data is being analyzed by a statistician.

Report Date: 4 October 2000 Work Unit # 1609

DETAIL SUMMARY SHEET

TITLE: A Dose Escalation and Biological Modulatory Study of Pentostatin (Nipent), Chlorambucil, and Theophylline in Relapsed Lymphoproliferative Disorders

KEYWORDS: pentostatin, cyclic amp, chronic lymphocytic leukemia, bcl-2

PRINCIPAL INVESTIGATOR: Byrd, John MAJ MC
ASSOCIATES:

DEPARTMENT: Medicine STATUS: C
SERVICE: Hematology-Oncology INITIAL APPROVAL DATE: 12 November 1997

STUDY OBJECTIVE
To determine the ideal dose of the combination of pentostatin, chlorarnbucil, and theophylline in patients with relapsed, low-grade lymphoproliferative disorders.

TECHNICAL APPROACH
Patients will be treated with the above-mentioned combination every 3 weeks. Correlative laboratory studies are done with the first cycle only.

PRIOR AND CURRENT PROGRESS
A total of 12 patients have been enrolled at WRAMC on this study, and a total of 8 patients have been enrolled at other institutions.

CONCLUSIONS
This study is closed.

Report Date: 26 April 2001 Work Unit # 1611-98

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: A Phase II Study of CAMPATH-IH in Patients with B-Cell Chronic Lymphocytic Leukemia Who Have Received an Alkylating Agent and Failed Fludarabine Therapy

KEYWORDS: chronic lymphocytic leukemia, monoclonal antibody, refractory, alkylator

PRINCIPAL INVESTIGATOR: Byrd, John MAJ MC
ASSOCIATES:

DEPARTMENT: Medicine STATUS: C
SERVICE: Hematology-Oncology INITIAL APPROVAL DATE: 24 February 1998

STUDY OBJECTIVE
To determine the efficacy and toxicity of Campath-IH in fludarabine refractory CLL.

TECHNICAL APPROACH
Campath-IH is administered thrice weekly for up to 12 weeks. Response evaluations occur monthly during treatment and then at the 2-month juncture post-treatment.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
The study has closed to enrollment. Originally, ILEX Oncology had planned on treating 75 patients on this study, but was finally approved for 93 patients. 3 patients were enrolled and treated at WRAMC. None of these patients were enrolled in the last year. All 3 of the patients enrolled here at WRAMC had an initial response to therapy, but have since progressed and received other treatments. This was the endpoint for study follow-up on this study. A representative from ILEX oncology will be on site on 24 May 2001 to complete closeout inspection.

CONCLUSIONS
Campath has been shown to be effective in the treatment of CLL and has been submitted to the FDA for approval for this use.

Report Date: 13 December 2000

Work Unit #1612-98

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: A Randomized, Double-Blind, Placebo Controlled, Phase III Study of the Matrix Metalloproteinase Inhibitor AG3340 in Combination with Mitoxantrone and Prednisone with Provision for Subsequent Change in Therapy on Patients Having Metastatic Hormone-Refractory Prostate Cancer

KEYWORDS: Prostate Cancer, chemotherapy, mitoxantrone, matrix metalloproteinase inhibitor

PRINCIPAL INVESTIGATOR: Joseph M. Flynn CPT MC
ASSOCIATES: Cheryl A. Aylesworth MAJ MC; John C. Byrd MAJ MC

DEPARTMENT: Medicine
SERVICE: Hematology-Oncology

STATUS: C
INITIAL APPROVAL DATE: 26 May 1998

STUDY OBJECTIVE

To compare symptomatic progression-free survival among patients having metastatic, hormone-refractory prostate cancer receiving one of two doses of AG3349 or placebo initially in combination with mitoxantrone and prednisone with provision for subsequent change in therapy. Other objectives are to compare symptomatic benefit, symptomatic response, quality of life, serologic response, PSA progression-free response, radiographic progression-free survival, one-year survival and overall survival, and to evaluate the safety of AG3340 (generic name prinomastat), with mitoxatrone/prednisone and the safety of AG3340 in combination with subsequent therapies.

TECHNICAL APPROACH

This study is for patients who have hormone-refractory prostate cancer and have undergone orchiectomy or treatment with LH-RH analog. Patients are treated with mitoxantrone at 3-week intervals. Disease progression/response is evaluated every 12 weeks. Walter Reed Army Medical Center is authorized to enroll 20 patients. The original protocol was approved with Addendum 1. Addendum 2 was submitted and approved 9/98. Addendum 3 and consent revision was approved 5/17/99. Request for change of principal investigator from Dr. Aylesworth to Dr. Flynn was approved 28 August 2000. Addenda I and II to the Revision 4 of the Investigator's Brochure were submitted in November 2000 and approval is pending.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Nine patients were randomized here at Walter Reed. Six of them had disease progression and were not on the study drug at the time of study closure. Four of the six have since died to prostate cancer progression and the other two have gone on subsequent therapy. The three patients who were active in the study at closure went on subsequent therapy. One of them died in late October.
Two adverse events occurred at Walter Reed. One was a case of hypophosphatemia, reported on 15 Nov 99. Cause for the event was attributed to long time Maxzide use was not related to Ag3340. A second adverse event of hospitalization due to dehydration with pulmonary complications was reported to DCI in September 2000. The pulmonary complications were judged by the PI as possibly related to the study drug and or Mitoxantrone/prednisone/ All patients have been unblended and informed of their respective drug assignments.

CONCLUSIONS

The study closed to enrollment earlier than planned after an interim analysis review that included 406 patients and one-half of the number of primary endpoints required for the final analysis. Results available indicated a low probability of positive outcome for the study. Neither detrimental nor convincing beneficial effect if the combination of AG3340 with mitoxantrone/prednisone was observed, therefore it was considered inappropriate to continue the study. The safety profile for AG3340 was not a factor in the decision to discontinue the study.

Report Date: 16 January 2001 Work Unit # 1613-98

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: Fludarabine, Cyclophosphamide, and Il-2 with Filgrastim Support for the Treatment of Previously Untreated Indolent Lymphoproliferative Disorders

KEYWORDS: Fludarabine, Cyclophosphamide, IL-2, Chronic Lymphocytic Leukemia

PRINCIPAL INVESTIGATOR: Byrd, John MAJ MC
ASSOCIATES:

DEPARTMENT: Medicine STATUS: C
SERVICE: Hematology-Oncology INITIAL APPROVAL DATE: 26 May 1998

STUDY OBJECTIVE
To determine if concurrent IL-2 can abrogate the immunosuppresion observed following treatment with Fludarabine and Cyclophosamide.

TECHNICAL APPROACH
Clinical trial combining fludarabine, cyclophosphamide, G-CSF and IL-2 or placebo in patients with untreated lymphoproliferative disorders.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
A total of 25 patients have been enrolled on this study. 12 patients have been enrolled at WRAMC. There have been no adverse events reported as part of this study. The PI wishes to close this study as accrual goals have been met and all patients have completed protocol follow-up.

CONCLUSIONS
No conclusions have been reached at this time. Study information is being reviewed at this time.

Report Date: 05 April 2001

Work Unit # 1614-98

DETAIL SUMMARY SHEET

TITLE: A Uniformed Services Comprehensive Database and Tissue Repository for the Study of Epidemological, Detection, Natural History and New Management Strategies for Prostate Cancer

KEYWORDS: prostate, cancer, tissue

PRINCIPAL INVESTIGATOR: McLeod, David COL MC
ASSOCIATES:

DEPARTMENT: Surgery
SERVICE: Urology

STATUS: O
INITIAL APPROVAL DATE: 26 May 1998

STUDY OBJECTIVE

1) Create a Uniformed Services Comprehensive Database and Tissue Repository for the study epidemiological, detection, natural history, and new management strategies for prostate cancer prevention and treatment. 2) Initiate a clinical project at three medical centers to demonstrate the feasibility of establishing a Tri-Service Tissue and Serum Repository at AFIP.

TECHNICAL APPROACH

This will be achieved by: 1) prospectively collecting standardized data on all prostate cancer patients treated at specified military centers beginning in 1998; and 2) samples will be obtained from radical prostatectomy specimens which will include cancerous and normal tissue. Informed consent will allow intraoperative collection of blood and tissue biopsies of the excised organ. It will allow the use of these specimens as well as the retrieval and use of their original archival biopsy tissue. Blood samples will be used to measure specific molecular markers and will be compared to clinical features.

PRIOR AND CURRENT PROGRESS

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 0. The total number enrolled study-wide is 0, if multi-site study. No progress has been made with this project as the funding has not yet been approved by USAMRMC and the protocol is still receiving revisions at USAMRMC. Since this is a multi-center study, once approval has been received at USAMRMC, HMJF will then resubmit the revised proposal body and consent form to all local sites and DCI for approval. At the present time, there are 5sites participating in the study.

CONCLUSIONS

None at this time.

Report Date: 30 March 2001 Work Unit # 1615-98

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: D-dimer as a Marker for Endothelial Injury and Outcome in Critically Ill Patients

KEYWORDS: d-dimer, cytokine, endothelial

PRINCIPAL INVESTIGATOR: Thomas, Stephen CPT MC
ASSOCIATES: Shorr, Andrew CPT MC; Alkins, Stephen CPT MC; Ling, Geoffrey MAJ MC

DEPARTMENT: Medicine
SERVICE: Hematology-Oncology

STATUS: C
INITIAL APPROVAL DATE: 16 June 1998

STUDY OBJECTIVE

To determine if an association exists between d-dimer status, endothelial injury, cytokine activation, and outcomes in critically ill patients.

TECHNICAL APPROACH

This study is a prospective observational study of patients admitted to the MICU at WRAMC. Combined endpoints include; development of sepsis, ARDS, or MSOF. Secondary endpoints are MICU survival and survival to hospital discharge. Within twelve hours of admission to the MICU the patient will have blood samples drawn and d-dimer status determined. We measured d-dimer and serum cytokine levels (TNF alpha, IL-6, IL-8, IL-10). Upon admission, illness severity will be assessed using APACHE II and MPM calculations. If 72 hours after admission the patient remains in the MICU, the process (blood draw, APACHE II, MPM) will be repeated.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

We have completed the patient enrollment phase of this study and have embarked upon data analysis, synthesis, and reporting. Selected data has been submitted in poster and abstract form to scientific and medical societies with the intent of presenting the data at the corresponding scientific meetings. Below is a summary of a selected portion of that data.

The study cohort included 64 patients (mean age 66.0±14.2 years, 51.6% male, mean APACHE II 15.8±8.0). DD was positive in 33 patients (51.6%). Data are shown in the table below.

Cytokine (pg/ml)	DD – (n=31)	DD 1+ (n=10)	DD 2+ (n=23)	p (ANOVA)
TNF alpha	45.74	82.20	104.96	0.001
IL-6	0.97	27.00	99.91	0.019
IL-8	11.71	10.20	75.43	0.016
IL-10	1918.70	1947.89	1904.74	0.998

Area under the curve analysis revealed that as a screening test for either multisystem organ failure or mortality, TNF alpha, IL-6 and DD performed comparably.

CONCLUSIONS

In critically ill patients, DD, and therefore coagulation system dysregulation, correlates with elevations in pro-inflammatory cytokines. DD does not appear to reflect anti-inflammatory cytokine levels. DD testing may represent a clinically available surrogate means for assessing cytokine activation in critically ill patients.

Report Date: 20 February 2001

Work Unit # 1617-98

DETAIL SUMMARY SHEET

TITLE: PGAA2003-A Multicenter Study to Assess the Efficacy of 506U-78 in Patients with Chronic Lymphocytic Leukemia Who Have Previously Failed Fludarabine Therapy

KEYWORDS: chronic lymphocytic leukemia, ara-g, refractory, alkylator

PRINCIPAL INVESTIGATOR: Byrd, John MAJ MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Hematology-Oncology

STATUS: C
INITIAL APPROVAL DATE: 01 September 1998

STUDY OBJECTIVE

To estimate antitumor efficacy of 506U78 in patients with chronic lymphocytic leukemia who are refractory to fludarabine therapy and at least one alkylator (or alkylator containing regimen). To further define the efficacy and safety of 506U78 in patients with chronic lymphocytic leukemia.

TECHNICAL APPROACH

Patients will be treated with 506U78 on days 1, 3 and 5 of a treatment cycle. The drug will be administered as a 2-hour infusion on these days. Cycles will be repeated every 28 days until the patient experiences: 1) disease progression, 2) unmanageable toxicity, 3) continued treatment with 506U78 is deemed not beneficial, or 4) a maximum of 8 cycles of 506U78 have been administered.

PRIOR AND CURRENT PROGRESS

A total of 76 patients have been enrolled at all participating sites, 56 of those patients were enrolled after the dose modification. 0 patients have been enrolled at Walter Reed. The dose first outlined in the protocol has been modified from 2.2 grams/m^2 to 1.5 grams/m^2. No unexpected adverse events at WRAMC have been noted. 65 serious adverse events have been reported study wide. All serious adverse events have been reported to the IRB. This study is now being closed here at WRAMC as no patients have been enrolled to date and no patients have been interested in going in study due to the nature of the side effect profile.

CONCLUSIONS

No conclusions have been drawn at this time. Study is still accruing patients, but will not be open to accrual here.

Report Date: 2 November 2001 Work Unit # 1618-98

DETAIL SUMMARY SHEET

TITLE: Drug Sensitive and Apoptosis Studies in Hematological Malignancies and Related Disorders.

KEYWORDS: Antibodies, Drugs, Leukemia, Lymphoma, Apoptosis

PRINCIPAL INVESTIGATOR: Murphy, Timothy MAJ MC
ASSOCIATES: Byrd, John C. MAJ MC

DEPARTMENT: Medicine
SERVICE: Hematology-Oncology

STATUS: C
INITIAL APPROVAL DATE: 22 September 1998

STUDY OBJECTIVE

To identify active new experimental agents for the treatment of hematologic malignancies.

TECHNICAL APPROACH

Peripheral blood and bone marrow is obtained from patients with hematologic malignancies and is processed and assessed for factors associated with drug resistance. Additionally cells are screened for activity against a variety of new experimental therapeutic agents.

PRIOR AND CURRENT PROGRESS

The WRAMC Human Use Committee approved this protocol on 16 September 1998. There have been previous addenda to this study. There have been no ADRs reported to date. Sixty-seven patients have given blood as part of this study, including thirty-six during the past calendar year. There have been no adverse events during the past year and no patients have withdrawn consent.

CONCLUSIONS

No conclusions can be made.

Report Date: 11 January 2001 Work Unit # 1620-99

DETAIL SUMMARY SHEET

TITLE: Dose Escalation Feasibility Study of Rituximab Adminstered Thrice Weekly to Patients with Chronic Lymphocytic Leukemia and Small Cell Lymphocytic Lymphoma

KEYWORDS: rituxan, chronic lymphocytic leukemia, lymphoma, pharmacokinetics, pharmacodynamics

PRINCIPAL INVESTIGATOR: Byrd, John MAJ MC
ASSOCIATES:

DEPARTMENT: Medicine STATUS: C
SERVICE: Hematology-Oncology INITIAL APPROVAL DATE: 20 October 1998

STUDY OBJECTIVE

To determine the ability, safety, and toxicity of rituximab administration in a thrice weekly schedule for a total of 4 weeks in patients with CLL and SLL. To investigate the pharmacokinetics and cellular pharmacodynamics of rituximab administered on this schedule. To preliminary assess if rituximab has anti-tumor activity with this novel schedule of administration.

TECHNICAL APPROACH

Patients will be treated with rituximab thrice weekly for weeks. The first 3 patients were treated at 250mg/m^2, and the remaining patients treated at 375mg/m^2. Correlative laboratory studies are done during the first week only. A follow-up visit will take place 2 months after the last treatment. Patients will then be followed every 3 months for up to one year.

PRIOR AND CURRENT PROGRESS

A total of 20 patients were enrolled at WRAMC and 13 patients were enrolled at Johns Hopkins University, with 31 of these patients completing the 4 weeks of therapy. There have been no adverse since the last APR was filed. Of the 31 patients treated on this study, 1 attained a CR, 14 a PR, 14 had SD and 2 patients experienced PD. Accrual, treatment, and one year follow-up has been completed on all patients, so the study is being closed.

CONCLUSIONS

This is an active regimen of CLL and NHL.

Report Date: 29 September 2000 Work Unit # 1623-99

DETAIL SUMMARY SHEET

TITLE: Pilot Study to Compare and Evaluate the Safety and Impact of IDEC-C2B8 (IDEC-120) on Immunization Potential

KEYWORDS:

PRINCIPAL INVESTIGATOR: Byrd, John MAJ MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Hematology-Oncology

STATUS: C
INITIAL APPROVAL DATE: 24 November 1998

STUDY OBJECTIVE

To determine whether therapy with IDEC-C2B8 (anti-CD20) alters the antibody titer to a specific antigen.
To determine the effects of IDEC-C2B8 therapy on the formation of new antibodies to representative immunogens.
To evaluate and compare the safety of specific immnunizations in B-cell lymphoma patients treated with IDEC-C2B8, to other nonmurine based anticancer therapies and to healthy volunteers.

TECHNICAL APPROACH

This is a multi-center, open-label, three-arm pilot study in which patients and healthy volunteers will receive one or two series of three immunizations directed against tetanus, Haemophilus influenza and streptococcus pneumoniae. Serum blood samples will be collected and serum antibody titers will be determined at specific intervals.

PRIOR AND CURRENT PROGRESS

A total of forty-three (43) patients have been enrolled on this study. Six (6) patients have been enrolled at WRAMC. One patient received the wrong vaccination and although no harm was done to the patient, she was removed from the study by the PI. All patients enrolled on this study at WRAMC have completed study requirements. The PI is leaving WRAMC and the decision has been made to complete the study.

CONCLUSIONS

No conclusions have been reached on this study.

Report Date: 01 November 2000

Work Unit #1625-99

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: A Phase II Study of Daunaxome, Cyclophosphamide, Vincristine, and Prednisone Followed by Rituximab and GM-CSF for Patients with Low-Grade Lymphoma

KEYWORDS:

PRINCIPAL INVESTIGATOR: Byrd, John C MAJ MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Hematology-Oncology

STATUS: C
INITIAL APPROVAL DATE: 27 April 1999

STUDY OBJECTIVE

To evaluate the complete response rate of Daunoxone and CVP (treatment Phase A) in patients with recurrent indolent lymphomas. To evaluate the response rate of rituximab and GM-CSF (treatment Phase B) in patients who fail to achieve a complete remission with chemotherapy.

TECHNICAL APPROACH

This is a multi-center, phase II study to assess the anti-cancer effects of Daunoxone, Cyclophosphamide, Vincristine, Prednisone, Rituximab and GM-CSF. This study has two phases, Phase A and Phase B.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

A total of two (2) patients have been enrolled in this study at WRAMC. Six patients have been enrolled on this study at John Hopkins Medical Center. JUH closed this study in June 2000 due to poor patient enrollment. No adverse events have occurred related to chemotherapy administration. At this time the PI would like to close this study at WRAMC due to poor patient enrollment.

CONCLUSIONS

No conclusions have been reached for this study as information and follow-up continues on those patients who have been entered on study.

Report Date: 24 April 2001 Work Unit # 1628-99

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: Phase I Trial of Humanized ID10 Monoclonal Antibody (Hu1D10) in Patients with Relapsed Non-Hodgkins' Lymphoma

KEYWORDS:

PRINCIPAL INVESTIGATOR: Byrd, John MAJ MC
ASSOCIATES:

DEPARTMENT: Medicine STATUS: C
SERVICE: Hematology-Oncology INITIAL APPROVAL DATE: 22 June 1999

STUDY OBJECTIVE
To evaluate the safety and tolerability and determine the maximally tolerated dose it reached, of increasing doses of humanized monoclonal antibody HU1D10 administered to patients with previously treated NHL expressing the antigen recognized by 1D10. To measure pharmakonetics, to compare pharmacology at different dose levels and determine the optimal biological dose of HU1D10. To observe for anti-lymphoma effects of Hu1D10.

TECHNICAL APPROACH
This is a multi-center Phase I study to assess the safety and tolerability of increasing doses of HU1D10. To determine the optimal biological dose of HU1D10.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
14 patients have been enrolled to this study at WRAMC. However, only 3 of these patients have been treated on study. It is a study requirement to enroll patients on study before determining their eligibility to receive study drug (i.e. Hu1D10 positivity). Adverse events experienced by these 3 treated patients at WRAMC included hypophospotemia, edema, hypoxia, dyspnea, transient, hypotension, fever, nausea and vomiting, tachycardia, pleural effusion and edema.

CONCLUSIONS
HU1D10 is active in non-Hodgkin's lymphoma.

Report Date: 26 April 2001

Work Unit # 1629-99

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: CLL Research Consortium Human Subjects Protocol for Sample Collection

KEYWORDS: chronic lymphocytic leukemia

PRINCIPAL INVESTIGATOR: Byrd, John MAJ MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Hematology-Oncology

STATUS: C
INITIAL APPROVAL DATE: 31 August 1999

STUDY OBJECTIVE

To achieve an understanding of the biologic basis for chronic lymphocytic leukemia (CLL) and to define curative treatment strategies for this disease.

TECHNICAL APPROACH

Blood is separated and lymphocytes are cryopreserved for future scientific study.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

A total of 52 have been enrolled at WRAMC on this study, 14 since the last APR. Study-wide there have been 492 patients enrolled. This study is being closed at WRAMC as the PI, Dr. Byrd, is leaving and there is limited interest by the hematology-oncology staff in continuing this study.

CONCLUSIONS

No conclusions have yet been reached from this study.

Report Date: 03 January 2001 Work Unit # 1630-99

DETAIL SUMMARY SHEET

TITLE: A Randomized Multicenter, Open-Label Study of Single Dose Filgratim-SD/01 Versus Daily Filgrastim Following ESHAP Chemotherapy for Non-Hodgkin's Lymphoma

KEYWORDS:

PRINCIPAL INVESTIGATOR: Byrd, John MAJ MC
ASSOCIATES:

DEPARTMENT: Medicine STATUS: C
SERVICE: Hematology-Oncology INITIAL APPROVAL DATE: 21 September 1999

STUDY OBJECTIVE
To assess the duration of sever neutropenia in Cycle 1 following ESHAP chemotherapy for patients with non-Hodgkin's lymphoma. Sever neutropenia is defined as an absolute Neutrophil Count <0.5 x 10 9/1.

TECHNICAL APPROACH
Eligible patient with a diagnosis of non-Hodgkin's lymphoma and who will receive ESHAP chemotherapy are randomized to receive either daily Filgrastim of Filgrastim-SD/01 and then followed for duration of neutropenia.

PRIOR AND CURRENT PROGRESS
A total of one (1) patient has been enrolled on this study at WRAMC. Sixty-six (66) total patients have been enrolled study-wide. The patient enrolled at WRAMC had progressive disease and subsequently expired.

CONCLUSIONS
This study was closed by Amgen as study accrual was met and protocol objectives were completed. Conclusions regarding this study are pending at this time.

Report Date: 31 July 2001 Work Unit # 1631-99

DETAIL SUMMARY SHEET

TITLE: A Phase II Study of Rituximab in Patients with CD20 Positive Intermediate-Grade and Select High-Grade Non-Hodgkins's Lymphoma Who Have Relapsed After High Dose Chemotherapy and Autologous Stem Cell Transplantation

KEYWORDS: Non-Hodgkins lymphoma, autologous, transplant

PRINCIPAL INVESTIGATOR: Byrd, John MAJ MC
ASSOCIATES

DEPARTMENT: Medicine STATUS: C
SERVICE: Hematology-Oncology INITIAL APPROVAL DATE: 21 Sept 2000

STUDY OBJECTIVE
To determine the 1) response rate 2) duration of response and 3) overall survival in patients with CD20 positive intermediate grade and select high grade Non Hodgkins Lymphoma who have relapsed after high dose chemotherapy and autologous stem cell transplantation.

TECHNICAL APPROACH
Twelve consecutive patients with CD 20 positive intermediate-grade and select high-grade NHL who have relapsed after high dose chemo and autologous stem cell transplantation will receive one of the following schedules:
Patients with circulating peripheral blood tumor cells <5 x 10/L will receive rituximab 375 mg/m2 IV weekly x 8 doses.
Patients with circulating peripheral blood tumor cells $\geq$ 5 x 10/L will receive rituximab 100 mg IV on day 1 and the remainder of the rituximab will be given on day 2 for a total of 375 mg/m2 for week 1 only followed by 375mg/m2 IV weekly x7 doses.

PRIOR AND CURRENT PROGRESS
A total of 5 patients have been enrolled to this study, none her at WRAMC. There have been no SAE's reported.

CONCLUSIONS
This study is being closed here at WRAMC as the principal investigator has left this facility and there is limited interest in keeping this study open by the remaining staff. The study does remain open to accrual at other sites. No conclusions have yet been drawn.

Report Date: 16 October 2000 Work Unit # 1689

DETAIL SUMMARY SHEET

TITLE: Chemoprevention of Prostate Cancer with Finasteride (Proscar) vs. Placebo

KEYWORDS: prostate cancer, finasteride, prevention

PRINCIPAL INVESTIGATOR: Joseph m. Flynn CPT MC
ASSOCIATES: Cheryl A. Aylesworth MAJ MC, John C. Byrd MAJ MC

DEPARTMENT: Medicine
SERVICE: Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 30 November 1993

STUDY OBJECTIVE

To determine if the medication, finasteride, can prevent prostate cancer. The effect of this treatment on the quality-of-life of the participants will also be determined.

TECHNICAL APPROACH

A total of 40-60 men aged 55 or greater who are in good health will be enrolled in the study over one to two years. The digital rectal exam (DRE) must be normal, and the prostate specific antigen (PSA) must be three or less for all participants. There will be an annual visit, a 6-month visit and two phone contacts each year for seven years. At the annual blood visit a blood sample will be taken for PSA determination and a physical exam including DRE will be done. A six-month supply of placebo or finasteride will be dispensed. Quality-of-life information will be obtained at each contact.

PRIOR AND CURRENT PROGRESS

The study stopped accrual on 6 December 1996. Sixty-three patients were randomized to the clinical trial at WRAMC. Three have transferred in and five transferred out. Four have withdrawn consent, two in the last year (one moved to Florida and one went into a nursing home, which precluded visits to the hospital). Two patients have died, one of pancreatic cancer and one during vascular surgery. Fifty-five patients remain active in the study, forty-five on drug. One patient developed prostate cancer, an end point. He elected prostatectomy and is doing well. Three patients had prostate biopsies in the past year, all for elevated PSA. Two were negative and one is pending. There are 18,882 subjects enrolled nationwide. Addendum 10 requesting change in protocol to allow an extra blood sample be drawn for analysis of white blood cells was submitted to DCI and is being held for consideration until the consent letter is received. A request for change of Principal Investigator from Cheryl Aylesworth to Joseph Flynn was included with Addendum 10.

CONCLUSIONS

There have been none to date.

Report Date: 6 February 2001 Work Unit # 00-1701

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: Does Use of a Temporary Silencer Adjustable Airway Dilator Predict Outcome Using Permanent Silencer Adjustable Airway Dilator in Treatment of Obstructive Sleep Apnea?

KEYWORDS:

PRINCIPAL INVESTIGATOR: Kristo, David MAJ MC
ASSOCIATES: Cteotima Andrada MS RPSGT; Christine Griffin BA; LTC Kevin McGlynn DDS; Robin Howard MA; David Bitonti DMd CDR DC USN; Scott A. Synnott DDS CPT DC USN

DEPARTMENT: Medicine
SERVICE: Pulmonary & Critical Care Medicine

STATUS: O
INITIAL APPROVAL DATE: 28 March 2000

STUDY OBJECTIVE

To determine whether a Silencer adjustable temporary airway dilator (AD) is predicative of outcome of a permanent Silencer adjustable airway dilator in treating obstructive sleep apnea (OSA).

TECHNICAL APPROACH

Subjects receive acoustic three-dimensional assessment of the airway, are given a temporary airway dilator to wear for two weeks, and then undergo a sleep study with the temporary AD. Next, subjects are given a permanent AD, wear it for six weeks and undergo a sleep study with the permanent AD. This study will examine whether a strong correlation exists between successful treatment of OSAHS with the temporary AD and successful treatment with the permanent AD. Additionally, the acoustic airway measurements will be examined to see if they have predictive value.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

The number of subjects enrolled to the study since the last APR is 19 and the total enrolled to date at WRAMC is 19. There have been no serious adverse events to date. One patient withdrew from the study due to other time commitments.

CONCLUSIONS

No conclusions have yet been drawn.

Report Date: 6 February 2001 Work Unit # 00-1702

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Safety and Efficacy of 12 Weeks of 2 Oral Doses (200 mg and 400 mg Once Daily) of PROVIGIL (Modafinil) as Treatment for Adults with Excessive Daytime Sleepiness

KEYWORDS:

PRINCIPAL INVESTIGATOR: Kristo, David MAJ MC
ASSOCIATES: COL Arn Eliasson, MC, USA; Yvonne Taylor, RN, MSN, CFNP; Tim Andrada, MS

DEPARTMENT: Medicine STATUS: O
SERVICE: Pulmonary & Critical Care Medicine INITIAL APPROVAL DATE: 28 March 2000

STUDY OBJECTIVE

The objectives of this study are to determine the safety and efficacy of PROVIGIL 200 mg/day (once in the morning) and 400 mg/day (once in the morning) as a treatment for excessive daytime sleepiness (EDS) in patients with obstructive sleep apnea/hypopnea syndrome (OSAHS) who need nasal continuous positive airway pressure (CPAP), and who have been characterized with regard to their actual CPAP use patterns. The primary efficacy objective will be tested by comparing the change from baseline to week 12 (or endpoint) in the Epworth Sleepiness Scale (ESS) score between the group treated with PROVIGIL 400 mg/day and the placebo-treated group.

TECHNICAL APPROACH

CPAP-using patients who are still experiencing excessive daytime sleepiness will be extensively screened to exclude variables such as concomitant sleep disorders, acute illness, prior Modafinil use, use of medications that might interact with Modafinil, etc. After initial screening, patients will undergo at-home CPAP testing for 2 nights to insure that their CPAP titration level is adequate to treat their OSAHS. They will also undergo 14 nights of at-home CPAP testing to insure that they do have at least partial CPAP compliance. Patients who pass all of the above screening procedures are then randomized (1:1:1) to receive PROVIGIL 200 mg/day or 400 mg/day or placebo for a 12-week period. During this period, they are seen once a month for a variety of procedures, including EKG, blood labs, Maintenance of Wakefulness tests, questionnaires, etc. after completing at least 8 weeks of double-blind treatment, patients are eligible of an optional 12 months of open label treatment with Modafinil.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

The number of subjects enrolled to the study since last APR at WRAMC is 5 and the total enrolled to date at WRAMC is 5. At the WRAMC site, one patient has withdrawn from the open-label portion of the study because she wishes to take a medication prohibited by the study guidelines. The total number of subjects enrolled study-wide for all sites is 271. (The goal is 300 subjects.) Also, there have been no serious adverse events to date for any of the sites, including the WRAMC site, and no serious adverse events are expected.

No applicable recent research has been published since the study began, and there are no study findings to date.

CONCLUSIONS

No conclusions have yet been drawn.

Report Date: 30 July 2001 Work Unit # 1701-98

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: The Diagnostic Utility of Capnography in Bronchoprovociation Testing

KEYWORDS: asthma, bronchoprovocation

PRINCIPAL INVESTIGATOR: Moores, Lisa MAJ MC
ASSOCIATES:

DEPARTMENT: Medicine STATUS: C
SERVICE: Pulmonary & Critical Care Medicine INITIAL APPROVAL DATE: 18 August 1998

STUDY OBJECTIVE

To evaluate the utility of capnography compared to forced spirometry in bronchoprovocation testing. We enrolled 50 patients that presented to the pulmonary function lab for bronchoprovocation testing.

TECHNICAL APPROACH

Study subjects will be recruited from patients referred to the WRAMC pulmonary function lab for clinical bronchoprovocation testing, or for other approved research bronchoprovocation protocols. All subjects will be military healthcare beneficiaries. All subjects must be 18 years or older and eligible for care at WRAMC. Exclusionary criteria include significant cardiopulmonary disease (such as pulmonary malignancy, congestive heart failure, and angina) other than that being studied a baseline FEV <60% of predicted at the time of enrollment, or the inability to give informed consent. Asthmatics who cannot withhold medication 12-24 hours prior to testing will also be excluded.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

There has been no activity on this protocol since the prior APR October 2000. Data analysis has been completed. It appears that capnography overestimates acute changes in airway function. We are not sure if this is a technical problem related to capnography or if capnography is a more sensitive measure of changes in small airway function or V/Q mismatch. As further study is needed to sort this out, no publication is currently planned.
The number of subjects enrolled to the study since last APR at WRAMC is _0__ and the total enrolled to date at WRAMC is _49____. The total number enrolled study-wide is __NA___, if multi-site study.

CONCLUSIONS

Capnography may be a more sensitive measure of changes in airway function and V/Q matching. Further study is needed in order to develop standards and potential diagnostic criteria of this form of pulmonary function measurement.

Report Date: 10 October 2000 Work Unit # 1704-99

DETAIL SUMMARY SHEET

TITLE: A Randomized, Double-Blind, Parallel-Group, Comparative Trial of Inhaled Fluticasone Propionate 250 mcg BID, 500 mcg BID, and Placebo BID via the DISKUS in Patients with Chronic Obstructive Pulmonary Disease (COPD)

KEYWORDS: COPD, Fluticasone, Propionate

PRINCIPAL INVESTIGATOR: Lepler, Lawrence MAJ MC
ASSOCIATES:

DEPARTMENT: Medicine STATUS: C
SERVICE: Pulmonary & Critical Care Medicine INITIAL APPROVAL DATE: 15 December 1998

STUDY OBJECTIVE
To assess the efficacy and safety of fluticasone propionate (FP), administered to patients with COPD as a micronized powder via a multidose powder inhaler (DISKUS) over six months

TECHNICAL APPROACH
Amendments 1, 2 and 4 contain editorial and administrative changes only. No change to the approved consent was required.

PRIOR AND CURRENT PROGRESS
Ten patients enrolled and completed. Data forwarded to Glaxo-Wellcome. Study completed.

CONCLUSIONS
Data forwarded to Glaxo-Wellcome for analysis. Study completed.

Report Date: 16 May 01 Work Unit # 1705-99

DETAIL SUMMARY SHEET (Human Use Protocol)

TTTLE: The Effect of Nocturnal BIPAP on Exercise Performance in Patients with Severe Obstructive Pulmonary Disease

KEYWORDS: BiPAP, COPD. Work of Breathing

PRINCIPAL INVESTIGATOR: Lepler, Lawrence MAJ MC
ASSOCIATES:

DEPARTMENT: Medicine STATUS: C
SERVICE: Pulmonary & Critical Care Medicine INITIAL APPROVAL DATE: 16 February 1999

STUDY OBJECTIVE

Bilevel positive airway pressure (BiPAP) is a non-invasive form of mechanical ventilation that employs a mask, which fits over the nose and supplies positive pressure throughout the respiratory cycle. The level of positive pressure during inspiration and expiration can be separately adjusted.

1. Reaffirm the results of our study in which an improvement in minute ventilation, dead space ventilation and mean inspiratory flow was noted following 30 days of nocturnal non-invasive ventilation with BiPAP.
2. Define the mechanisms responsible for the improvement in ventilatory and gas exchange response to exercise.
3. Confirm the initial findings and observe for a return to baseline conditions following a washout period.
4. Define gas exchange kinetics improvement using a constant work exercise protocol.
5. Individualize the BiPAP level of inspiratory and expiratory pressures.
6. Observe the difference in response of hypercapnic and non-hypercapnic COPD patients.
7. Assess the impact of nocturnal BiPAP on patient's quality of life.

TECHNICAL APPROACH

The experimental design will be randomized, crossover, repeated measures study. Patients will have nocturnal polysomnography (sleep study) to exclude significant sleep related breathing disorder associated with nocturnal desaturations. During the sleep study, patients will have a video camera and microphones in their bedroom to monitor and record their behavior during sleep.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Ten patients had been consented. Three patients withdrew, 3 patients were excluded due to severe sleep apnea, 2 patients were discontinued due to COPD exacerbations, one patient was excluded due to improvement in FEV1 and 1 patient completed the study. Four patients were consented and randomized, three to the usual care arm and one to the BIPAP arm. Two patients developed an exacerbation of their COPD prior to the crossover and were discontinued from study. One dropped out of the study prior to completion and one patient completed the study.

CONCLUSIONS

I respectfully request that this study be closed. Difficulty with patient enrollment and limited space available in the WRAMC sleep clinic prohibit us from continuing this project

Report Date: 07 February 2001 Work Unit # 1706-99

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: A Multicenter Prospective Randomized Trial Comparing Circulaire vs. Conventional Nebulization Treatment Guided by a Respiratory Therapist-Driven Protocol

KEYWORDS:

PRINCIPAL INVESTIGATOR: Kristo, David MAJ MC
ASSOCIATES: Mary Jones CRT; Michael Kallish CRT; SSGT Adam Jones CRT

DEPARTMENT: Medicine STATUS: C
SERVICE: Pulmonary & Critical Care Medicine INITIAL APPROVAL DATE: 16 March 1999

STUDY OBJECTIVE

To establish whether the Circulaire system under a respiratory therapist driven protocol (TDP) allows for decreased length of stay, faster drug delivery time and decreased therapist time when compared to conventional nebulization under casting standard operating procedures.

TECHNICAL APPROACH

The study was designed in four arms, consisting of a conventional nebulizer either physician driven care or therapist driven care, and a Circulaire nebulizer using either physician driven care or therapist driven care. Patients are driven to metered dose inhaler under the directive of type physician or therapist driven care.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

One patient was enrolled in this study. Subsequently, the study was abandoned. This patient experienced no adverse events.

CONCLUSIONS

No conclusions were drawn from this study.

Report Date: 07 February 2001 Work Unit # 1707-99

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: Does Formal Patient Asthma Education in NHI.BI Guidelines Equate with Improved Morbidity and Mortality?

KEYWORDS:

PRINCIPAL INVESTIGATOR: Kristo, David MAJ MC
ASSOCIATES: Yvonne Taylor CFMP; Diane Hatcher CPNP; Robin Howard

DEPARTMENT: Medicine
SERVICE: Pulmonary & Critical Care Medicine

STATUS: C
INITIAL APPROVAL DATE: 23 March 1999

STUDY OBJECTIVE

To ascertain whether found education improves morbidity and mortality in asthma care. To determine whether the found education teaching is effective more than our current unstructured asthma education program.

TECHNICAL APPROACH

Subjects were assessed for severity of asthma, and given a WRAMC Asthma Education Packet and peak flow meter. Then for six months patients keep a logbook documenting their ongoing asthma severity. Next, subjects are randomized to two groups: test group (formal education, including one-on-one tutoring and testing patients' knowledge) or control group (conventional education—standard WRAMC teaching materials). All subjects are followed for twelve months and then asthma severity is compared for the two groups.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

As of 18 February 2000, the progress was: 8 subjects; 5 enrolled; and no adverse reactions. No further progress was made, as the study was abandoned.

CONCLUSIONS

No conclusions were drawn from this study.

Report Date: 7 February 2001 Work Unit # 1708-99

DETAIL SUMMARY SHEET

TITLE: Four Weeks of Provigal (Modaflnil) Treatment on Excessive Daytime Sleepiness in Obstructive Sleep Apnea Patients Treated with Nasal Continuous Positive Airway Pressure

PRINCIPAL INVESTIGATOR: Kristo, David MAJ MC

DEPARTMENT: Medicine STATUS: C
SERVICE: Pulmonary & Critical Care Medicine INITIAL APPROVAL DATE: 23 March 1999

STUDY OBJECTIVE

Primary: To determine the efficacy and safety of modafinil 400 mg/d, as a treatment for residual excessive daytime sleepiness (EDS) in obstructive sleep apnea (OSA) patients who are documented regular users of nasal continuous positive airway pressure (CPAP) treatment. Secondary. To determine whether modafinil treatment affects patient vigilance, functional capacity or use of CPAP.

TECHNICAL APPROACH

This study was designed to determine whether modafinil can safely and effectively serve as an adjunct treatment for EDS in apnea, patients who have residual sleepiness while regularly using CPAP treatment. Patients must have been using CPAP for at least 2 months prior to study entry. Patients were screened and had their CPAP effectiveness monitored for 2 days. If effectiveness was confirmed, a 21-day assessment period was then begun to determine the regularity of patient use of CPAP treatment (defined regular use: > 4 hours per night for 70% of the 21 day period). Patients who demonstrated regular use and met inclusion /exclusion criteria were then randomized to receive either modafinil or placebo for a 4 week period. Patients assigned to modafinil received 200 mg/day in the morning for 1 week and then received 400 mg/day in the morning for the remainder of the study (Weeks 2, 3, and 4). The total number of clinic visits was a maximum of 7 visits. Patients were considered to have completed participation in the double-blind arm of the study when all clinical and laboratory evaluations were obtained at the end of Week 4. Following the 4-week double-blind arm, patients who continued to meet study were offered the option of continuing on study in the 12 weeks open label arm. These patients received 400mg/day in the morning for 1 week, then, returned for a clinic visit. Based on clinical findings and evaluation of symptoms, they received the same dose or a reduced dose as determined by the PI. Clinic visits were scheduled at weeks 2, 6 and 12. At week 12 study patients were evaluated for post study treatment planning.

PRIOR AND CURRENT PROGRESS

Study-wide, 157 patients were enrolled One serious adverse event occurred: a patient became pregnant while taking Modafinil and gave birth to twins: the boy was born with Beckwith-Wiedemann Syndrome and the girl was diagnosed with Metatarsus Adductus.
Study-wide, the most common non-serious adverse events were headache (Modafinil, 22%, placebo, 14%) and nervousness (Modafinil, 12%, placebo, 3%). Eight patients (10%) receiving Modafinil discontinues the study because of adverse events (headache, insomnia, dizziness) compared with one patient (1%) receiving placebo.
At the WRAMC site, the number of subjects enrolled to the study since last APR is zero and the total enrolled to date is 15. No serious adverse events have occurred at the WRAMC site since the last APR. For the WRAMC site, as reported in 1/28/00 APR, some minor side effects did occur: "Randomized study subjects experience only minor side effects, such as nervousness, dry mouth or headache. Most symptoms resolved after a few days or were not considered by the subjects to be a deterrent to continuing study drug."

CONCLUSIONS

Cephalon has not yet completed the final report. However, some preliminary study-wide information is available. Patients taking Modafinil had significantly improved Epworth Sleepiness Scores and improved Multiple Sleep Latency Test time compared to controls. Of the patients taking Modafinil, 68% were clinically improved compared with 34% of patients receiving placebo. All patients taking part in the open label arm have reported dramatic changes in their ability to stay awake as reflected in changes in ESS scores. This group consistently reports increase in activity to accomplish tasks. All study subjects believe that there has been an improvement in their quality of life due to study drug.

Report Date: 16 May 2001

Work Unit # 1709-99

DETAIL SUMMARY SHEET

TITLE: Use of Impulse Oscillometry in Adult Bronchoprovocation Testing

KEYWORDS:

PRINCIPAL INVESTIGATOR: Niven, Alexander CPT MC
ASSOCIATES: Hnatiuk, Oleh LTC MC; Hurwitz, Kenneth, MAJ MC; Sierra, Angel CPFT CRRT

DEPARTMENT: Medicine
SERVICE: Pulmonary & Critical Care Medicine

STATUS: C
INITIAL APPROVAL DATE: 25 May 1999

STUDY OBJECTIVE

To evaluate the correlation between impulse oscillometry and forced spirometry in bronchoprovocation testing.

TECHNICAL APPROACH

All patients over 18 years old with an FEV1 > 60% predicted referred to the WRAMC pulmonary function lab for clinical bronchoprovocation testing with a clinical suspicion for asthma were enrolled after informed consent from Jun 99 – Jan 00. Subjects completed a routine PFT lab questionnaire and underwent bronchoprovocation testing with methacholine as per WRAMC PFT lab protocol. In addition to the usual spirometric measurements, oscillometry was also measured during the challenge at regular intervals. Change in all oscillometry values from baseline were calculated after each methacholine dose and compared to change in FEV_1 from baseline. Bronchoprovocation testing was terminated when either a positive response was obtained based on drop in FEV_1 or following the fifth methacholine dose. Absolute change in oscillometry values for impedance (Z), resistance at 5 Hz (R5), reactance at 5 Hz (X5), resonant frequency (frs), and peripheral resistance (RP) from baseline were compared to the absolute change in FEV_1 using a nonparametric Pearson correlation equation.

PRIOR AND CURRENT PROGRESS

50 patients have been enrolled, 2 were excluded from analysis (one due to inadequate oscillometer calibration and one due to an incomplete data set). The remaining 48 patients include 22 females and 26 males, with a mean FVC of 99 +/- 16 % predicted and FVC/FEV1 ratio of 0.80 +/- 0.6 %. Sixteen patients had a positive methacholine challenge (defined as an FEV_1 decrease of 20% from baseline) with PD20s ranging from 4.6 to 129.9 breath units (BU). Absolute changes in all oscillometry values were found to have statistically significant correlation coefficients to absolute changes in FEV_1 at methacholine doses above 1.375 BU. Z demonstrated the strongest correlation with coefficients ranging from -.419 to -.554 ($p < 0.03$). There were no adverse outcomes during this study.

CONCLUSIONS

Absolute change in all measured oscillometry parameters show a statistically significant correlation to absolute changes in FEV_1 at methacholine levels above 1.375 BU in bronchoprovocation testing. This study confirms the hypothesis that oscillometry represents a promising tool in bronchoprovocation testing using methacholine, and is worthy of further study.

Report Date: 1 March 2001 Work Unit # 1759

DETAIL SUMMARY SHEET

TITLE: Post-operative Pulmonary Changes Following Video-Assisted Thoracic Surgery vs. Lateral Thoracotomy

KEYWORDS: Video-Assisted Thoracic Surgery, Thoracotomy

PRINCIPAL INVESTIGATOR: Corcoran, Philip LTC MC
ASSOCIATES:

DEPARTMENT: Medicine STATUS: C
SERVICE: Pulmonary & Critical Care Medicine INITIAL APPROVAL DATE: 26 January 1993

STUDY OBJECTIVE

1) To assess the severity and duration of postoperative pulmonary changes (measured by spirometry, ABG's and chest x-ray) following video-assisted thoracic surgery (VATS); and 2) to compare changes following VATS to changes following lateral thoracotomy (LT).

TECHNICAL APPROACH

All adult patients undergoing thoracic surgical procedures (pleural or lung biopsy, diagnosis of solitary pulmonary nodules, wedge resection of metastatic nodules, resection of blebs and/or pleurodesis for spontaneous pneumothorax, and mediastinal lymph node biopsy) performed either by VATS or LT, will be invited to participate in this study of preoperative, 24-hour postoperative, and 48-hour postoperative testing with spirometry, ABG's, and chest x-rays. The study will not affect patient care.

PRIOR AND CURRENT PROGRESS

No further accrual in this protocol since last APR.

CONCLUSIONS

Plan to terminate the protocol and examination of the current 20 patients enrolled in the protocol. No further patients will be enrolled on the protocol.

Report Date: 27 March 2001 Work Unit # 1780

DETAIL SUMMARY SHEET

TITLE: The Presence of Airway Hyperreactivity to Methacholine Eucapnic Voluntary Hyperventilation and Inhaled Hypertonic Saline In Non-Asthmatic Pulmonary Disease

KEYWORDS: asthma bronchoprovocation, airway hyperreactivity

PRINCIPAL INVESTIGATOR: Hurwitz, Kenneth MAJ MC
ASSOCIATES: Niven, Alexander CPT MC; Argyros, Gregory LTC MC; Eliasson Arn COL MC; Philips, Yancy COL MC

DEPARTMENT: Medicine
SERVICE: Pulmonary & Critical Care Medicine

STATUS: T
INITIAL APPROVAL DATE: 19 December 1995

STUDY OBJECTIVE

To compare the incidence of airway hyperreactivity to methacholine inhalation, eucapnic voluntary hyperventilation, and nebulized hypertonic saline in non-asthmatic subjects

TECHNICAL APPROACH

Subjects in five groups undergoing bronchprovocation: normal non-smokers, normal smokers, allergic rhinitis, COPD, and sarcoidosis. After completing a questionnaire and spirometry pre/post an inhaled broncholidator, subjects take in random order a methacholine challenge, a eucapnic voluntary hyperventilation (dry air) challenge, and a hypertonic saline inhalation. Results are compared to determine the relative specificity of the three tests. The protocol was addended in 1998 to allow retesting of 5 normal subjects in order to confirm abnormal findings.

PRIOR AND CURRENT PROGRESS

This study was administratively terminated by the HUC for failure of the PI to submit an APR.

CONCLUSIONS

This study was administratively terminated by the HUC for failure of the PI to submit an APR.

Report Date: 16 July 2001 Work Unit # 1785

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: Association of Sleep-Disordered Breathing with Pulmonary Embolism

KEYWORDS: sleep apnea, pulmonary embolism

PRINCIPAL INVESTIGATOR: Straight, Timothy CPT MC
ASSOCIATES: Glass K, Loube D, Kristo D

DEPARTMENT: Medicine
SERVICE: Pulmonary & Critical Care Medicine

STATUS: C
INITIAL APPROVAL DATE: 09 July 1996

STUDY OBJECTIVE

To determine if patients with a diagnosis of pulmonary embolism (PE) have an increased prevalence of obstructive sleep apnea (OSA) when compared with the general population.

TECHNICAL APPROACH

Patients diagnosed with a PE at Walter Reed AMC are contacted and asked to undergo a one-night polysomnogram to evaluate for underlying OSA.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

No other recent literature regarding this area of research
One new patient enrolled since last review in 2000
No adverse events (AE).
No patients withdrawn from study
The number of subjects enrolled to the study since last APR at WRAMC is __1__ and the total enrolled to date at WRAMC is ___17____.

CONCLUSIONS:

This study was designed to establish or refute an association between two potentially fatal diseases. To date no control subjects have been advertised for, contacted, enrolled, or studied. Of the test group, 17 patients have been enrolled, out of which 16 have been studied.
Results - 10 of 16 study patients were diagnosed with obstructive sleep apnea (OSA), which is a prevalence of prevalence of 63%. This is in marked contrast to that of the general population, for whom the prevalence of OSA is estimated at approximately 15%. Of interest, age, sleep history, and BMI did not differ significantly between patients with OSA and those without OSA. Also, the likely etiology of the pulmonary embolus in the majority of patients was unknown. Based on this limited data, it would appear that there is some association between OSA and PE. OSA has not been identified previously as a risk factor for pulmonary embolus. This data also reveals that the typical symptoms of OSA may be absent in those suffering from PE who indeed have OSA. It would seem from our data that PE patients have a higher prevalence of PSA than that of the general population. The medical literature would support that identifying patients and treating OSA reduces morbidity and mortality - perhaps then, patients diagnosed with pulmonary embolus should be evaluated with polysomnography to screen for OSA as this potentially treatable problem may go otherwise undetected. In addition, OSA may be a previously unidentified treatable risk factor for pulmonary embolus.
Interpretation of this data should be done carefully, realizing there are several major limitations to this study including lack of a specific control population, and very small sample size.
Due to logistical difficulties of completing this study, it will not be continued by the primary investigator

Report Date: 30 November 2000 Work Unit # 1788

DETAIL SUMMARY SHEET

TITLE: The Diagnostic Utility of Hypertonic Saline Bronchoprovocation in Asthmatics

KEYWORDS: asthma, bronchoprovocation

PRINCIPAL INVESTIGATOR: Lee, Daniel CPT MC
ASSOCIATES:

DEPARTMENT: Medicine STATUS: T
SERVICE: Pulmonary Disease INITIAL APPROVAL DATE: 24 September 1996

STUDY OBJECTIVE

To compare the sensitivity and specificity of hypertonic saline (HS) bronchoprovocation testing (BPT) to methacholine (McH) and eucapnic voluntary hyperventilation (EVH) bronchoprovocation testing in asthmatics and normals.

TECHNICAL APPROACH

Normal and asthmatic patients who are eligible for care will be enrolled from the Pulmonary Clinic. On the day of enrollment, subjects will be interviewed and their informed consent will be obtained. Baseline screening function tests (PFT) and a bronchodilator response test will be performed as per standard PFT protocol. Each subject, whether asthmatic or normal, will receive McH, HS, and EVH challenges on different days, between 2 and 14 days apart. Sensitivity and specificity of the three BPTs will be calculated in patients with and without known asthma.

PRIOR AND CURRENT PROGRESS

This protocol was administratively terminated by the HUC for failure of the PI to submit an APR

CONCLUSIONS

This protocol was administratively terminated

Report Date: 26 January 2001 Work Unit #1790

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: Acute Hypoxemic Respiratory Failure in Bone Marrow Transplant Patients; A Retrospective Review

KEYWORDS: acute lung injury, ARDS, bone marrow transplantation

PRINCIPAL INVESTIGATOR: Moores, Lisa MAJ MC
ASSOCIATES:

DEPARTMENT: Medicine STATUS: O
SERVICE: Pulmonary & Critical Care Medicine INITIAL APPROVAL DATE: 25 April 1997

STUDY OBJECTIVE
To determine the incidence of ALI occurring at the time of bone marrow engraftment (Engraftment Syndrome – ES) in autologous bone marrow transplant patients, and to determine associated risk factors for the development of the syndrome

TECHNICAL APPROACH
A retrospective chart review of all autologous bone marrow transplants done at WRAMC from 1991 to July 1971. Demographic, treatment and clinical course variables were collected in Excel spreadsheet. Patients who developed ES were compared to those who did not. Chi square and Mann-Whitney-U tests were used as appropriate for statistical analysis.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
A total of 159 ABMT records were reviewed and entered into the database. No further work was done with the database since the prior APR. However, the PI recently reviewed a manuscript regarding long-term pulmonary function in children undergoing BMT. The plan would thus be to submit an addendum to this protocol in order to review the pulmonary function databanks and add follow-up PFT's for our original cohort and report on this in the literature.

CONCLUSIONS
Nothing new since the prior APR.

Report Date: 16 May 2001 Work Unit # 1798-98

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: Quantitative Analysis of Acid-Base Balance in the Critically Ill

KEYWORDS: Strong Ion Difference, Acid-Base Analysis, Strong Ion Gap, Physical-Chemical Analysis

PRINCIPAL INVESTIGATOR: Fitzpatrick, Thomas COL MC
ASSOCIATES: O'Neil, KM CDR MC

DEPARTMENT: Medicine
SERVICE: Pulmonary and Critical Care Medicine

STATUS: C
INITIAL APPROVAL DATE: 26 May 1998

STUDY OBJECTIVE

We will perform quantitative analysis of the individual metabolic components of the acid-base changes in the critically ill; strong ion difference, strong ion gap, and weak acids. We will evaluate the relationship of the strong ion difference and strong ion gap to diagnosis, degree of organ dysfunction and utility as predictors of duration of ICU stay. The relationship of serial strong ion difference and strong ion gap levels to anion gap, serum lactate, pH and base excess derivatives will also be assessed.

TECHNICAL APPROACH

This is a retrospective review of data from patients admitted to the surgical and medical intensive care units at WRAMC. The relationship between serial strong ion gap, strong ion difference, degree of organ dysfunction, and duration of ICU stay is being investigated. This study is providing insight into the natural history of acid base derangements in the critically ill.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Retrospective studies thus far have revealed that metabolic acid-base status as determined by physical chemical analysis is profoundly discordant with conventional assessment in the critically ill. Metabolic acid-base status is more accurately assessed by physical chemical analysis then by the base excess derivatives. Further, the base excess derivatives misrepresent the true metabolic acid-base status in the critically ill by a magnitude approximating the plasma weak acid deficit. The strong ion gap concept is superior to the anion gap concept in identifying unmeasured acid load.

CONCLUSIONS

Physical-chemical analysis provides unique insight into the acid-base derangements of the critically ill patient.

Report Date: 15 January 2001 Work Unit # 1828

DETAIL SUMMARY SHEET

TITLE: Light Microscopic Immunohistochemistry to Identify Leishmania on Formalin Fixed Human Tissue

KEYWORDS: leishmania, immunohistochemistry

PRINCIPAL INVESTIGATOR: G. Todd Bessinger CPT MC
ASSOCIATES: Aronson, Naomi COL MC; Krivida, Steve LTC MC

DEPARTMENT: Medicine
SERVICE: Dermatology

STATUS: O
INITIAL APPROVAL DATE: 07 January 1997

STUDY OBJECTIVE

Identify Leishmania organisms in formalin-fixed tissues using light microscopic immunohistochemistry (IHC). Should this technique prove useful, it would provide a simple rapid test for diagnosing leishmaniasis, determining the infecting species, and thereby directing appropriate treatment.

TECHNICAL APPROACH

Eight species-specific anti-Leishmania monoclonal antibodies will be studied as potential candidates for use in the IHC diagnosis of leishmaniasis. Each of these antibodies will be evaluated on fixed tissues known to contain Leishmania organisms (positive controls) and known not to contain Leishmania organisms (negative controls), at different antibody concentrations, and using standard technical controls. Once the assay parameters have been optimized, these antibodies will be used in the IHC technique to evaluate approximately 40 biopsied tissue specimens from individuals evaluated over the last few years for suspected leishmaniasis at WRAMC. The results of the IHC assay will be compared to the other diagnostic methods used for these specimens: H&E, culture and animal inoculation

PRIOR AND CURRENT PROGRESS

Previously, it was shown that one of the antibodies, G2D10 showed good sensitivity and specificity for diagnosing Leishmania infection as compared to hematoxylin and eosin staining. These results were published in the Journal of Cutaneous Pathology. The present study seeks to expand the role of IHC in determining the species identity of the infecting parasite. So far, lab space, the monoclonal antibodies, and some of the archived tissue specimens have been procured. However because PI was sent to work at NNMC for the last 8 months, the project has not further advanced. Now that he has retuned to WRAMC, we expect to continue the study immediately.

CONCLUSIONS

The study is still ongoing.

Report Date: 6 October 2000

Work Unit # 1829

DETAIL SUMMARY SHEET

TITLE: Gene Regulation in Lymphocytes from Patients with Cutaneous T-Cell Lymphoma (CTCL)

KEYWORDS:

PRINCIPAL INVESTIGATOR: Wong, Henry MAJ MC
ASSOCIATES: Tsokos, George LTC MC

DEPARTMENT: Medicine
SERVICE: Dermatology

STATUS: C
INITIAL APPROVAL DATE: 25 November 1997

STUDY OBJECTIVE

Identify biochemical abnormalities in CTCL lymphocytes.

TECHNICAL APPROACH

Isolation of peripheral lymphocytes from control individuals and CTCL patients was conducted. Lymphocytes were purified on ficoll gradient and nuclear proteins were prepared by extraction with NaCl followed by centrifugation. Extracted proteins were analyzed for DNA binding activity corresponding to NFkB, AP-1, and NF-AT. Additional studies include Western immunoblotting.

PRIOR AND CURRENT PROGRESS

No new patients have been enrolled into the study over past year. The Principle Investigator is leaving the Army and the protocol will be closed to further patient accrual.

CONCLUSIONS

No conclusions can be determined at this time.

Report Date: 16 August 2000 Work Unit # 00-1901

DETAIL SUMMARY SHEET

TITLE: Development of HIV Specific CD+ T Cells

KEYWORDS: HIV, T Cell Lines

PRINCIPAL INVESTIGATOR: COL Naomi Aronson
ASSOCIATES: Dr. Jerome Kim

DEPARTMENT: Medicine
SERVICE: Infectious Disease

STATUS: O
INITIAL APPROVAL DATE: 26 October 1999

STUDY OBJECTIVE

Compare epitope recognition between HIV negative individuals vaccinated with gp160 MN/LAI and HIV infected individuals 2. Generate *Pneumocystis carini* specific CD4+T cell lines to assess the clonal deletion in disease progression 3. Generate *Candida albicans* specific T cell lines from archived samples.

TECHNICAL APPROACH

Six HIV infected patients WR stage 1, 2 with CD4>400 and no history of gp160 immunization, six HIV infected patients with CD4 50-200, and twelve HIV infected patients with archived PMBC in the HIV repository from past times that they were not Candida anergic who are now Candida anergic will be enrolled. GP 160, Pneumocystis, Candida specific T-cells will be developed. Proliferation assays, T-cell repertoire by BV gene analysis and spectratyping will be performed.

PRIOR AND CURRENT PROGRESS

Four patients have been enrolled. There have been no withdrawals. Two patients have completed the protocol and two are ongoing. No adverse events are noted. No direct benefit to patients has been assessed.

CONCLUSIONS

Thus far the development of antigen specific T cell lines seem to be possible. We are proceeding with further enrollment that may allow us to extend some observations.

Report Date: 1 June 2001 Work Unit # 00-1902

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: Clinical and Immunological Evaluations of Dengue Viruses as Challenge Strains in Susceptible Volunteers

KEYWORDS: Dengue, Challenge, Vaccine, Virus

PRINCIPAL INVESTIGATOR: Arthur G. Lyons, MAJ MC
ASSOCIATES: Stephen Thomas, Denise McKinney, Niranjan Kanesa-thasan, Wellington Sun, David Vaughn, Raymond C.Y.Chung, and Scott Norton.

DEPARTMENT: Medicine
SERVICE: Infectious Disease

STATUS: C
INITIAL APPROVAL DATE: 15 August 2000

STUDY OBJECTIVE

Primary:
To characterize clinical responses to each of 5 candidate dengue challenge viruses in susceptible volunteers to judge their suitability as challenge strains for human vaccine efficacy studies.
Secondary:
To generate hypotheses regarding the immune correlates of protection from dengue fever.

TECHNICAL APPROACH

Sixty volunteers were screened for the study after they passed a comprehension test. Most of the 51 volunteers who were excluded from participation were excluded due to medical conditions, positive flavivirus serologies and/or abnormal laboratory results. Two volunteers excluded themselves from participation.
Nine volunteers were enrolled in the study and were challenged on 15 MAR 2001 with either dengue virus or placebo by the subcutaneous route. They were observed in the Mologne House for a 14-day period and all were admitted to WRAMC on day 7 after challenge. This observation period ended 29 MAR 2001. All four dengue virus serotypes were tested.

PRIOR AND CURRENT PROGRESS

Six of the nine volunteers developed presumed dengue illness (five with fever). The other three volunteers (including 2 placebo recipients) exhibited no illness. All volunteers received serial ultrasounds of the abdomen as per the approved protocol. Three volunteers were noted to have asymptomatic and clinically silent effusions, specifically small perihepatic, perisplenic and pericardial effusions in one, small perihepatic effusion in another, and another perihepatic effusion in the third. All effusions resolved within 5 days. Three volunteers were noted to have decreases in their absolute neutophil counts, all of which returned to normal values by the conclusion of the study. A number of serological evaluations, including IgM/IgG, and neutralizing antibodies as well as EM studies of the peripheral blood and skin samples are currently in progress and results are pending.

CONCLUSIONS

The implementation of the second iteration of the Dengue Challenge Model was executed sucessfully. Procedures were documented in numerous standard operating procedures to facilitate future iterations. This second iteration further validated the candidate DEN-1 and DEN-3 viruses as challenge strains but invalidated the current candidate DEN-2 and DEN-4 (341750 strain). The DEN-4 (H-241 strain) will need further evaluation, possibly in a future challenge study. The cumulative data on the current DEN challenge strains are summarized in the table below:

TABLE 1: CUMULATIVE CLINICAL EXPERIENCE WITH CURRENT CANDIDATE DENGUE CHALLENGE VIRUSES, FROM PREVIOUS CHALLENGE EXPERIENCES TO ITERATION TWO, INCLUSIVE.

Virus	Passage	Clinical experience in volunteers			
		# Volunteers	Fever	Rash	WBC nadir
DEN-1 45Az5	FRhL-8	4	4-5 days	5 days	2000-2700
DEN-2 S16803	Tox-1, PGMK-4, PDK-10, FRhL-3	2	none	5 days	2000-4200
DEN-2 PR-159	PGMK-2, FRhL-1	1	none	none	6100
DEN-3 CH53489 cl24/28	PGMK-4, C6/36-7, FRhL-1	5	3-5 days	3-5 days	1400-4900
DEN-4 341750	Tox-1, PDK-6, FRhL-3	2	none	none	5300-5400
DEN-4 341750	M1, PGMK-4, FRhL-4	1	none	none	2600
DEN-4 H-241	2AP6, C6/36-2, FRhL-1	1	1 day	5 days	2400

FRhL = fetal rhesus lung cells; PGMK = primary green monkey kidney cells; AP = Aedes albopictus mosquitoes; C6/36 = mosquito culture cell line
Tox = *Toxorhynchites amboinensis* mosquitoes cells; PDK = primary dog kidney cells

In future challenge studies, we propose to challenge dengue vaccine recipients with the current DEN-1 and DEN-3 challenge viruses in order to gauge vaccine protective efficacy.

Report Date: 05 April 2001

Work Unit # 1903-98

DETAIL SUMMARY SHEET

TITLE: Development of New Leishmania Diagnostic and Prognostic Indicators

KEYWORDS: leishmaniasis, nitric oxide, PCR

PRINCIPAL INVESTIGATOR: Aronson, Naomi COL MC
ASSOCIATES: Wortmann, Glenn LTC MC

DEPARTMENT: Medicine
SERVICE: Infectious Disease

STATUS: O
INITIAL APPROVAL DATE: 26 May 1998

STUDY OBJECTIVE

Obtain patient samples to identify new diagnostic and prognostic indicators for Leishmania diagnosis.

TECHNICAL APPROACH

Patient with suspected leishmaniasis and normal controls will be followed prospectively and have blood drawn before therapy (or day 0 for controls) and at days 7, 14 and 20 at 6-8 weeks. Urine will be collected for days 0-7 for measurement of nitrates. Skin biopsies from suspected patients will be used PCR, leishmania culture and histopathology. Serum is obtained for measurement of soluble exoantigen and nitrates.

PRIOR AND CURRENT PROGRESS

17 individuals have been enrolled to date; 10 cases and 7 controls (4 in the past year). Two controls dropped out for noncompliance with sample collection. A third case previously thought to drop out returned for follow up this year and completed protocol. No adverse events have been noted (protocol is blood and urine collection only). No amendments or modifications to the protocol have occurred. The number of subjects enrolled to the study since the last APR at WRAMC is 4 and the total enrolled to date at WRAMC is 17. The total number enrolled study-wide is N/A, not multi-site study

CONCLUSIONS

No results are available, as study has limited enrollment to date. Samples are being collected to be run in aggregate.

Report Date: 15 May 2001 Work Unit # 1905-98

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: Evaluation of the Clinical Efficacy of Antiretroviral Resistance Testing (CERT)

KEYWORDS: HIV, antiretroviral resistance

PRINCIPAL INVESTIGATOR: Aronson, Naomi COL MC
ASSOCIATES: Wortmann, Glenn LTC MC; Hawkes, Clifton LTC

DEPARTMENT: Medicine
SERVICE: Infectious Disease

STATUS: O
INITIAL APPROVAL DATE: 07 July 1998

STUDY OBJECTIVE

To determine the impact of genotypic and phenotypic antiretroviral resistance on the effectiveness of clinical care of HIV-1 infected subjects. To determine the feasibility of GeneChip HIV PRT assay and Antivirogram assays within clinical practice.

TECHNICAL APPROACH

Local HIV patients are randomized to receive monitoring with genotypic, phenotypic (Antivirogram assay) or control (Roche Amplicor ultra sensitive PCR) viral load testing. All patients receive their viral loads at 4-month intervals. Those randomized to phenotypic or genotypic resistance testing arms, which have detectable viral loads > 1000 viral copies/ml will also have resistance testing done. Clinical changes in medications and the clinician use or non-use of the results of resistance testing to guide changes is information collected. An addendum (March 99) allows Virco therapeutic drug level monitoring for HIV drug levels in previously enrolled patients. An addendum (May 01) permits P450 polymorphism testing of cohort who enrolled and ere taking the antiretroviral efavirenz.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Review of PubMed for the past year shows that field of HIV resistance testing continues to evolve with initial enthusiasm tempered by the need for more precise interpretations, and understanding of the clinical utility of the various tests. At this point, no FDA approval for HIV resistance tests of any type exists. Study was closed to enrollment in October 2000 after reaching target accrual. There were 80 enrollments at WRAMC, 13 since last APR. Since starting this study, there have been 32 terminations, 15 met study endpoints, 2 transferred to other study sites out of area, 3 PCSed out of study area, 4 terminated due to protocol violation (generally untimely notification of medication changes/interruption), 6 terminated for failure to keep visits, 1 patient withdrew consent. 15 terminations occurred in the past year.
The number of subjects enrolled to the study since last APR at WRAMC is 13 and the total enrolled to date at WRAMC is 80. The total number enrolled study-wide is 455, if multi-site study.

CONCLUSIONS

The study is ongoing and outcomes analyzed by study arm are not known at this time.

Report Date: 01 May 2001 Work Unit # 1906-98

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: Preveon (adefovir dipivoxil) Expanded Access Program: Protocol GS-97-423

KEYWORDS: HIV, adefovir

PRINCIPAL INVESTIGATOR: Wortmann, Glenn LTC MC
ASSOCIATES:

DEPARTMENT: Medicine STATUS: O
SERVICE: Infectious Disease INITIAL APPROVAL DATE: 07 July 1998

STUDY OBJECTIVE
To provide adefovir on a compassionate use basis to patients infected with the HIV virus who are failing or intolerant of other medications.

TECHNICAL APPROACH
To provide adefovir on a compassionate use basis to patients infected with the HIV virus who are failing or intolerant of other medications.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
4 patients have been enrolled in this study, and none since the last APR. Two patients were discontinued due to non-compliance, and a third patient stopped the drug due to lack of efficacy. One patient still remains on study and continued to take medication.
The FDA has not approved this drug, and by report the company is no longer continuing attempts to seek FDA approval. The drug is being provided on a compassionate use basis. Once an alternative medication becomes available for this patient, he will be taken off this study. Multiple adverse event reports have been filed with DCI (none of which occurred at this site).
The number of subjects enrolled to the study since the last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 4. The total number enrolled study-wide is 170 (currently), if multi-site study.

CONCLUSIONS
The study is now closed to new enrollment. One patients remains on the study on a compassionate use basis.

Report Date: 6 March 2001 Work Unit #1908-99

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: Clinical and Immunological Evaluations of Four Dengue Viruses as Challenge Strains in Immune and Susceptible Volunteers

KEYWORDS: dengue, challenge, vaccine, virus

PRINCIPAL INVESTIGATOR: Mammen P. Mammen, Jr., MAJ MC
ASSOCIATES: Stephen Thomas, Henry Wong, Niranjan Kanesa-thasan, Wellington Sun, David W. Vaughn, and Raymond C.Y. Chung

DEPARTMENT: Medicine and Dept of Virus Diseases, WRAIR STATUS: C
SERVICE: Infectious Disease INITIAL APPROVAL DATE: 27 April 1999

STUDY OBJECTIVE

Primary:
To characterize clinical responses to each of 4 candidate dengue challenge viruses in susceptible and immune volunteers to judge their suitability as challenge strains for human vaccine efficacy studies.
Secondary:
To generate hypotheses regarding the immune correlates of protection from dengue fever.

TECHNICAL APPROACH

Twenty-three volunteers were screened for Set #1 and Set #2 after they passed a comprehension test. Most of the fourteen volunteers who were excluded from participation were excluded due to medical conditions, positive flavivirus serologies and/or abnormal laboratory results. Three volunteers excluded themselves from participation. Six volunteers were enrolled in Set #1 (none in Set #2) and were challenged on February 24, 2000 with either dengue virus or placebo by the subcutaneous route. They were observed for a 14-day period in the Mologne House (and WRAMC if ill) as per the approved protocol. This observation period ended on March 9, 2000. Given the approved randomization scheme and the fewer than ten volunteers presenting for challenge, three of the available four serotypes of dengue were used.

PRIOR AND CURRENT PROGRESS

Three of six volunteers developed presumed dengue illness (only one with fever) and were hospitalized as per the approved protocol at WRAMC. The other three volunteers exhibited no illness and remained in the Mologne House for the duration of the observation period as per the approved protocol. All volunteers received serial ultrasounds of the abdomen as per the approved protocol. Two volunteers were incidentally noted to have asymptomatic and clinically silent effusions, specifically a small pleural effusion and ascites in one and a mild to moderate pericardial effusion in another. The pleural effusion and ascites resolved sonographically within 2 days; the pericardial effusion, though asymptomatic, took 8 days to resolve.

CONCLUSIONS

The implementation of the first iteration of the Dengue Challenge Model was executed uneventfully. Procedures were documented in numerous standard operating procedures to facilitate future iterations. This first iteration further validated the candidate DEN-3 virus as a challenge strain but invalidated the current candidate DEN-2 and DEN-4 viruses as challenge strains given that they produced inadequate disease in 2 volunteers each. Replacement candidate DEN-2 and DEN-4 challenge strains have been identified. The cumulative data on the current DEN challenge strains are summarized in the table below. Three candidate dengue challenge strains were tested. The desired 10 volunteers to enable testing of all 4 candidate challenge strains could not be obtained due to our stringent enrollment criteria.

TABLE 1: CUMULATIVE CLINICAL EXPERIENCE WITH CURRENT CANDIDATE DENGUE CHALLENGE VIRUSES, FROM PREVIOUS CHALLENGE EXPERIENCES TO ITERATION ONE, INCLUSIVE.

Virus	Passage	Clinical experience in volunteers			
		# Volunteers	Fever	Rash	WBC nadir
DEN-1 45Az5	FRhL-8	2	4-5 days	8-9 days	2700 2300
DEN-2 S16803	Tox-1, PGMK-4, PDK-10, FRhL-3	2	none	5 days	2000 4200
DEN-3 CH53489 cl24/28	PGMK-4, C6/36-7, FRhL-1	3	3-5 days	3-5 days	1400 3100 4900
DEN-4 341750	Tox-1, PDK-6, FRhL-3	2	none	none	5300 5400

FRhL = fetal rhesus lung cells; PGMK = primary green monkey kidney cells;
Tox = *Toxorhynchites amboinensis* mosquitoes cells; PDK = primary dog kidney cells

In Iteration #2, we propose the further testing of the current DEN-1 and DEN-3 challenge strains and the testing of replacement candidate DEN-2 and DEN-4 challenge strains (DEN-2 PR159, DEN-4 H-241 and DEN-4 341750 Carib) in 2 volunteers each.

Report Date: 04 April 2001

Work Unit # 1909-99

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: Analytical Analysis of Recombinant Malaria Proteins

KEYWORDS:

PRINCIPAL INVESTIGATOR: Moran, Kim CPT MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Infectious Diseases

STATUS: O
INITIAL APPROVAL DATE: 18 May 1999

STUDY OBJECTIVE

Characterize malarial proteins produced in bacterial hosts with respect to purity, amino acid sequence and identify disulfide linkages

TECHNICAL APPROACH

Purify proteins from bacterial lysates by affinity chromatography. Characterize the proteins with MALDI-TOF and HLPC instruments.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Instrumentation upgraded at Research Operations, Department of Clinical Investigations WRAMC. The MALDI-TOF instrument was upgraded in the winter of 2000 to make sure possible protein identification by direct analysis of tryptic digests of proteins. The accurate molecular weight determinations of tryptic peptides can be submitted to public database sites and possible matched to known proteins are provided. Mr. Fileta has successfully utilized this capability to analyze malarial proteins. Presently, the capability to measure small misincorporated amino acids in peptides is being tested. The purity of the in vitro synthesized proteins is an important property to determine for peptides considered for FDA approval for clinical trials.

The number of subjects enrolled to the study since last APR at WRAMC is NA and the total enrolled to date at WRAMC is NA. The total number enrolled study-wide is NA, if multi-site study.

This protocol does not use any human subjects or animals.

CONCLUSIONS

The MALDI-TOF instrument can be utilized to make very accurate determinations of peptide molecular weights, and data can be submitted through the Internet to databases for identification of possible peptide sequences. Minor peaks with single amino acid changes can be predicted and then tested by means of Post Source Decay (PSD). PSD relates decay molecules to the parent molecules to the parent peptide and allows amino acid sequence determinations of the peptide.

Report Date: 18 September 2000 Work Unit # 1976

DETAIL SUMMARY SHEET

TITLE: Cytokine Expression in Leishmanias Patients Treated with Sodium Stibugluconate (Pentostam) Therapy

KEYWORDS: leishmanias, Pentostam, cytokines

PRINCIPAL INVESTIGATOR: Aronson, Naomi COL MC
ASSOCIATES: Wortmann, Glenn MAJ MC

DEPARTMENT: Medicine
SERVICE: Infectious Disease

STATUS: O
INITIAL APPROVAL DATE: 30 November 1993

STUDY OBJECTIVE

To describe and characterize cytokine expression of patients infected with leishmanias when receiving sodium stibogluconate or amphotericin. Based on cytokine expression, host immune responses will be classified as T-helper 1 or T-helper type CD4 subsets. Change in TH1 and TH2 responses will be described during therapy for insight into disease pathogenesis and therapy. Specific cytokine measurements will be performed and correlated to onset of pancreatitis.

TECHNICAL APPROACH

Patients will be followed prospectively and have blood drawn before therapy and at days 7, 14, and 20 during therapy and at 6 weeks post-treatment. Serum is obtained for measurement of soluble CD4, IL-1B and TNF-a. Peripheral blood mononuclear cells will be obtained for RNA isolation and cell culture with phorbol ester simulation. Enzyme immunoassay for specific cytokine measurement will be performed on serum and supernatant of cell cultures. Specific cytokine expression will be detected by reverse transcriptase polymerase chain reaction using specific cytokine primers. Addenda 8/99 to change assays to ELISPOT and ELISA for gamma interferon, IL4, IL 10, IL 12 and use Leishmania specific stimulation with various antigens and a control of Pentostam. Addenda 6/2000 to allow leishmania TAQman PCR of 40 samples of banked PBMC pretreatment and if positive, at subsequent collection timepoints.

PRIOR AND CURRENT PROGRESS

45 patients and 10 controls have been entered into this protocol. Enrollment has been terminated. No patients withdrew or suffered any unexpected adverse reactions. Much of the year was used to find, catalog samples after WRAIR move and then send to AFRIMS where the cytokine assays are being performed. Specific leishmania antigens were obtained from collaborators.

CONCLUSIONS

Initial studies suggest that Pentostam produced elevations in pancreatic enzymes during therapy and this does not seem due to cytokine expression of TNF-alpha, IL-1B or IL 6. Transient elevation of serum nitric oxide with treatment correlated with successful outcome.

Report Date: 14 April 2001

Work Unit # 1978

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: Treatment of Leishmaniasis with Sodium Stibogluconate (Pentostam)

KEYWORDS: Pentostam, leishmaniasis

PRINCIPAL INVESTIGATOR: Aronson, Naomi COL MC
ASSOCIATES: Oster, Charles COL MC; Wortmann, Glenn LTC MC; Miller, Robert MAJ MC; Gasser, Robert COL MC

DEPARTMENT: Medicine
SERVICE: Infectious Disease

STATUS: O
INITIAL APPROVAL DATE: 28 June 1994

STUDY OBJECTIVE:
To provide therapy with the drug Sodium stiboglucante (Pentostam) to patients with the confirmed diagnosis of leishmaniasis.

TECHNICAL APPROACH:
Cutaneous leishmaniasis is treated with Pentostam 20 mg/kg/d for 20 days, and visceral infection for 28 days. Minor modifications to the protocol include changes in laboratory monitoring replacing P4 with P1, P2, P3 and LDH permitting flexibility +/- 24 hours in collection of laboratory and EKG monitors. Post treatment photos will suffice rather than measurement if cutaneous lesions appear healed. Addendum in December 1996 allowed 15 patients to have serial T-cell subset analysis. Addendum in June 1996 allowed liberalization of enrollment criteria.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE:
To date, 39 cutaneous leishmaniasis (with 2 re-enrolled due to relapse and needing second course) and 2 visceral leishmaniasis patients have been treated under this protocol, none in the past year were treated under. There has been one withdrawal for toxicity (increased creatinine and pancreatitis) and uncertainty as to leishmania diagnosis. Three adverse (SAE or UAE) events have been reported including one death due to the complication of AIDS, increased creatinine in patient described above, and fever, eosinophilia, interstitial nephritis in a patient at end of Sodium stibugluconate treatment attributed to ibuprofren. Significant patient benefit is noted in that all patients were healed from their infection (those requiring 2 course healed after second). The number of subjects enrolled to the study since the last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 41 (and 2 re-enrollments). The total number enrolled study-wide is N/A, if multi-site study.

CONCLUSIONS:
The treatment of leishmaniasis with Sodium stibugluconate is generally effective with only 2 relapses to date. Toxicity was noted, primarily noted muscoskeletal and pancreatic, but appeared reversible with drug discontinuation.

Report Date: 24 January 2001 Work Unit #1980

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: Pilot Investigation of Selected Desert Storm Veterans

KEYWORDS: Desert Strom, endogenous, retroviruses, immunologic evaluation

PRINCIPAL INVESTIGATOR: Oster, Charles COL MC
ASSOCIATES: Chung, Raymond COL MC; Gartner, Suzanne Ph.D.; Polonis, Victoria Ph.D.

DEPARTMENT: Medicine
SERVICE: Infectious Disease

STATUS: O
INITIAL APPROVAL DATE: 14 March 1995

STUDY OBJECTIVE

To perform a pilot descriptive evaluation of selected Gulf War veterans to include patients with neurologic findings and/or persistent fatigue, autoimmune disorder, lymphopenia, or T-cell cytopenia. To determine if there is scientific evidence for laboratory-based abnormalities which warrant further systemic investigation.

TECHNICAL APPROACH

One blood draw (120 cc) is collected from each patient, samples are blinded, and the following are performed; immunophenotyping, whole blood smears, peripheral blood mononuclear cells (PBMC) isolation, low density cell quantitation, and PBMC and macrophage culture. The cultures are monitored for retroviral protein production [reverse transcriptase (RT) assay by classical and PCR-based methods] and for unusual morphologic changes such as the formation of multinucleated giant cells or cell fusion. Culture fluids are frozen at several time points, and patient serum, plasma, and PBMC are cryopreserved. The presence of viral RNAs in culture fluids are studied using molecular cloning and automated nucleic acid sequencing. Patient sera are analyzed for antibodies to viral proteins by immunoblotting.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

The number of subjects enrolled to the study since the last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 85. The total number enrolled study-wide is N/A, if multi-site study. There have been no adverse reactions to the blood collection. This study provides no direct benefit to the patients.
During the past year, we have continued to study the specimens already collected. Two manuscripts are in preparation. The first details nucleotide sequences of a retrovirus-like reverse transcriptase gene cloned from cDNA prepared from particle-associated RNA recovered from cell-free culture fluids of cultured patient leukocytes. The second pertains to immunological abnormalities observed in patient specimens, which are suggestive of immune activation. Also, effort has been forth this past year to attempt to (1) transmit our putative retrovirus in vitro and (2) develop a biological assay for detection of its expression. Thus far, we have been unable to find a permissive host cell. Some syncytia formation has been observed, suggesting that an assay based on the induction of "fusion-from-without" following short-term cocultivation of patient cells and target indicator cells, may be possible.
In the coming year, we will not enroll any new patients. However, we do plan to continue data analysis and perform further laboratory experiment using the previously collected specimens.

CONCLUSIONS

We have observed an increased incidence of retroviral expression within our selected Gulf War Veteran group. This expression may be either the initiator or the consequence of immune activation and relate to the immunological changes we have detected in some patients. Retroviral expression and immune activation may serve as potential indicators and/or effectors of stress-related illness.

Report Date: 02 October 2000

Work Unit # 1984

DETAIL SUMMARY SHEET

TITLE: The Long-Term Efficacy of BCG Vaccine: A 56-Year Follow-Up

KEYWORDS: BCG, vaccine, tuberculosis

PRINCIPAL INVESTIGATOR: Aronson, Naomi COL MC
ASSOCIATES: Santosham, Mathuram MD; Harrison, Lee MD

DEPARTMENT: Medicine
SERVICE: Infectious Disease

STATUS: O
INITIAL APPROVAL DATE: 05 December 1995

STUDY OBJECTIVE

The primary objective of this study is to determine the duration of BCG vaccine efficacy in a Native American placebo-controlled trial with vaccination in the time period 1935-1942. Other related objectives are to describe the chronic disease morbidity and mortality, and to assess risk of malignancy in this group.

TECHNICAL APPROACH

A total of 3,287 study participants are located, and Indian Health Service medical records reviewed. Death certificates are requested for all deceased. State tuberculosis and cancer registries are reviewed. Interviews are done for medical history for those without reviewed medical records.

PRIOR AND CURRENT PROGRESS

There has been no change in enrollment. There have been no withdrawals although several duplications in the original database have been identified (so 3287 is actual number of unique enrollees). No serious or unexpected adverse reactions were noted. Data collection has been completed. Databases have been completed and merged. Initial statistical analysis is completed with final modeling underway. Manuscript preparation is the current protocol effort.

CONCLUSIONS

After exclusions and lost to follow-up prior to 1/1/48, 2793 individuals are analyzed (1483 in BCG arm and 1310 in placebo). Kaplan Meier time to TB since 12/31/47 shows a significant divergence of two arms with p value (log rank) .0003. Life table suggests 36 cases in BCG arm and 66 in placebo. There was no significant difference in tuberculosis mortality since 1948 between the vaccine and the placebo (BCG 0.022 TB deaths per 100 person years follow-up versus placebo 0.039 TB deaths per 100 person years of follow-up). The percent reduction in TB attributable to BCG: 15-30 years after BCG showed 55% reduction, at 30-45 years follow-up 34% reduction.

Report Date: 14 April 2001

Work Unit # 1990

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: Sodium Stibugluconate (Pentostam) Pharmacokinetics Protocol

KEYWORDS: pharmacokinetics, Pentostam, leishmaniasis

PRINCIPAL INVESTIGATOR: Aronson, Naomi COL MC
ASSOCIATES: Wortmann, Glenn LTC MC

DEPARTMENT: Medicine
SERVICE: Infectious Disease

STATUS: O
INITIAL APPROVAL DATE: 11 June 1997

STUDY OBJECTIVE:
To obtain pharmacokinetic data for patients varying in weight to provide information about the safety and appropriateness of daily dosing of sodium stibugluconate (Pentostam) at 20 mg/kg/d. A sub-objective will be to assess if daily dosing should be on the total or lean body weight.

TECHNICAL APPROACH:
Blood and urine samples are obtained before, during and after pentostam (sodium stibugluconate) therapy as specified in the protocol. Serum and urine antimony levels are determined by two assays at Ft. Detrick and Yale University. No modifications or addenda to protocol have occurred.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE:
Nine patients have been enrolled in the WRAMC protocol, none in the past year. Serum and urine antimony levels have been assayed. Currently modeling of the pharmacokinetics is being performed. The only adverse event was a vasovagal episode in one volunteer post-draw. No patients withdrew from the protocol. Data from other sites is not available to me. No benefit to participants.
The number of subjects enrolled to the study since the last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 9. The total number enrolled study-wide is not known, if multi-site study.

CONCLUSIONS:
Analysis to provide final interpretation of the results is pending. WRAMC participation in this protocol provided up to 16 hours post infusion data, which is a unique observation. Data from this study may lead to changes in recommendations as to best dosing and treatment regimen.
We request that protocol be changed to closed for enrollment, open for data analysis status.

Report Date: 2 July 2001 Work Unit # 1993

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: A Comparison of Treatment with Short-Course (10-Day) Sodium Stibogluconate (Pentostam) vs. a 20-Day Course of Pentostam for the Treatment of Cutaneous Leishmaniasis

KEYWORDS: leishmaniasis, Pentostam, treatment

PRINCIPAL INVESTIGATOR: Wortmann, Glenn LTC MC
ASSOCIATES: Aronson, Naomi COL MC; Miller, Robert MAJ MC; Jackson, Joan MD; Oster, Charles COL MC

DEPARTMENT: Medicine
SERVICE: Infectious Disease

STATUS: C
INITIAL APPROVAL DATE: 24 September 1996

STUDY OBJECTIVE

To determine if a 10-day course of Pentostam at a dose of 20 mg/kg/day is as efficacious as the standard 20-day course of Pentostam in the treatment of cutaneous leishmaniasis.

TECHNICAL APPROACH

Patients with biopsy-proven cutaneous leishmaniasis are randomized to receive either 10 or 20 days of Pentostam at a dose of 20 mg/kg/day. Patients randomized to the 10-day treatment arm receive 10 days of placebo infusion to complete a 20-day course of parenteral therapy. The study is double-blinded, with randomization performed by a pharmacist. Follow-up is performed at 1, 6, and 12 months after completion of therapy. Photographs and a physical examination are performed at each follow-up visit.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

33 patients have been enrolled in this study (21 in 1997, 7 in 1998, 3 in 1999 and 2 in 2000). Since the last APR, no patients have been enrolled. With the closure of the Jungle Operations Training School in Panama, we are no longer seeing very many patients with leishmaniasis, and it is highly unlikely that the target enrollment of 60 patients would be reached. Therefore, this study was closed several months ago, and data analysis is currently underway. Of the 33 patients enrolled, 1 suffered a relapse of his leishmaniasis (and was cured with a repeat course of Pentostam). 31/33 patients had elevated pancreatic enzymes develop on therapy, of which 7 required temporary discontinuation of therapy (all 7 tolerated resumption of therapy). 11 patients experienced asymptomatic mild elevations in liver associated enzymes and 14 patients complained of arthralgias or myalgias during therapy.
The number of subjects enrolled to the study since last APR at WRAMC is _0__ and the total enrolled to date at WRAMC is __33_____. The total number enrolled study-wide is _NA_____, if multi-site study.

CONCLUSIONS

This study is now closed. With only one patient suffering a relapse of leishmaniasis, 10 days of Pentostam appears to be as efficacious as 20 days of Pentostam.

Report Date: 11 August 2000 Work Unit # 1994

DETAIL SUMMARY SHEET

TITLE: Electrocortical Underpinnings of Dissociation

KEYWORDS: PTSD, dissociation, EEG

PRINCIPAL INVESTIGATOR: Engel, Charles C. LTC MC
ASSOCIATES: Cardeña, E. Ph.D.

DEPARTMENT: Medicine
SERVICE: Infectious Disease

STATUS: O
INITIAL APPROVAL DATE: 29 October 1996

STUDY OBJECTIVE

To evaluate the relationship between presentation of trauma-related words, dissociative and anxiety reactions, and cortical and sympathetic response, in a group of PTSD and non-PTSD Gulf-War veterans.

TECHNICAL APPROACH

Participants are given a battery of questionnaires that evaluate demographic information, dissociative, hypnotizability and general psychiatric symptomatology. They are then presented with a modified Stroop test, with 4 lists of words (Gulf-War related, generally positive ones, generally negative ones, neutral) while event related potentials and heart rate are monitored. They are also shown a list of trauma-related and neutral words mixed together. Demographic features as well as information from the hospital course are collected in the data collection sheet for descriptive purposes.

PRIOR AND CURRENT PROGRESS

Since the previous report, four participants were enrolled. There were no adverse reactions. Total number of participants: 25

CONCLUSIONS

Final analyses have not been carried out, but preliminary analyses reveal that PTSD patients have greater hypnotizability, trait and state dissociation, and the dissociation seems to increase when presented with threat related stimuli. Event-related potential amplitude seems to be negatively correlated with dissociative tendencies. These results have implications for our understanding of how individuals with PTSD process trauma-related stimuli. They also suggest that hypnosis may be useful in the treatment of PTSD, considering the high hypnotizability of these individuals.

Report Date: 01 September 2000 Work Unit # 1997

DETAIL SUMMARY SHEET

TITLE: Testing for Mycoplasmal Infection: Criterion Validity and Replicability of Nucleoprotein Gene Tracking and Forensic Polymerase Chain Reaction Tests

KEYWORDS: Mycoplasma, Gulf War

PRINCIPAL INVESTIGATOR: Engel, Charles C. LTC MC
ASSOCIATES: Shyh-Ching, Lo, MD PhD, Joel Baseman PhD, Garth Nicholson PhD, Joseph Tully PhD, William Reeves MD MSPH

DEPARTMENT: Medicine
SERVICE: Infectious Disease

STATUS: O
INITIAL APPROVAL DATE: 28 October 1997

STUDY OBJECTIVE

The purpose of the current proposal is to study the replicability of NGT and FPCR compared to that for the more commonly used CPCR. This will be assessed mainly through two comparisons: 1) comparison of agreement for NGT and FPCR results between 3 labs newly trained in NGT and FPCR and a lab experienced at running these tests to agreement achieved with CPCR; and 2) comparison of agreement repeat NGT and FPCR results at the experienced lab to agreement achieved when experienced lab repeats CPCR.

TECHNICAL APPROACH

As per original protocol and addenda dated 6 Jan 98, 9 Apr 98, and 17 Dec 98.

PRIOR AND CURRENT PROGRESS

Data collection was completed 22 Feb 2000 and enrollment has ended. There have been 27 patients enrolled during the last annual reporting period and 55 patients this period for a total of 82 patients. There have been no adverse reactions or patients withdrawn from the study. Blood samples have been run and results reported from all labs. Data is currently being analyzed.

CONCLUSIONS

None to date.

Report Date: 12 February 2001 Work Unit # 00-2001A

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: Pressor Effects of Hemoglobin Based Oxygen Carrying Solution in Human Blood Vessels

KEYWORDS:

PRINCIPAL INVESTIGATOR: Mongan, Paul LTC MC
ASSOCIATES:

DEPARTMENT: Surgery STATUS: O
SERVICE: Anesthesia-Operative INITIAL APPROVAL DATE: 7 March 2000

STUDY OBJECTIVE

The aim of this study is to determine the effects of hemoglobin-based oxygen-carrying solutions (HBOCs) on human blood vessels.

TECHNICAL APPROACH

After surgical resection of the specimen, a small portion (1.5") of vessels that will be discarded will be taken from the specimen before its transfer to anatomic pathology. No tissue will be taken if its absence would alter the pathological reading of the specimen or potentially obscure the diagnosis. The use of the tissue at USUHS is not a standard part of patient care at USUHS and is thus research. The specimen will be placed in Krebs solution and transported to the Department of Anesthesiology research laboratory at the Uniformed Services University of the Health Sciences by the PI or his designee.

Vessels will be prepared and tested using routine vessel ring methodology in our laboratory. In brief, at USUHS, the vessels will be cleaned of excessive adherent tissue, with care being taken not to damage wither the vascular endothelium or surrounding neurons in the adventitia. Blood vessels will then be cut into rings (4-5 mm in length). Multiple rings from each vessel will be tested simultaneously. Theses rings will be placed on stainless steel hooks and lowered into water-jacketed organ baths maintained at 37°C and filled with Krebs-Ringer solution of the following composition (in mM); NaCl, 119; KCl, 4.7; CaCl2, 2.5; KH2PO4, 1.2; MgSO4, 1.2; NaHCO3, 25; and glucose, 5.6. Each vessel will be stretched to its optimal length as determined by the tension response to serotonin (5-HT) measured by a Grass FT10 force transducer. After a 90 min equilibration period, phenylephrine (PE) or 5HT concentration response relationships will be determined. After washing and return to basal tension, vessels will be contracted with increasing concentrations of HBOCs (10^{-8M} to $6x10^{-6}$ M). Data will be expressed as a percent of the maximum tension developed in response to a maximum effective dose of PE or 5-HT. To determine the endothelial independent activity of the HBOCs, we will remove the endothelium by gently scraping the luminal wall of the blood vessel. The effectiveness of the removal of functional endothelium will be verified by the absence of a relaxant response to acetylcholine (Ach, 10^{-6}M). These scraped rings will then be used to examine the direct actions of HBOCs on vascular smooth muscle activity. Clarification of the mechanism of changes in tension related to the HBOC will be done by incubating the vessel rings with specific blockers of nitric oxides synthase, soluble guanyl cyclase, endothelial phoshpodiesterase, endothelin, cAMP, IP3, pathways and K_{ATP} channels.

After study, excess tissue will be appropriately disposed of as medical waste according to USUHS guidelines. Genetic testing will not be done.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

No progress has been made in the past year due to an inability to procure additional equipment to support these studies. The number of subjects enrolled to the study since the last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 0. The total number enrolled study-wide is 0, if multi-site study.

CONCLUSIONS

When money for additional equipment is obtained, we will begin enrolling subjects.

Report Date: 12 February 2001 Work Unit # 00-2002A

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: Developing a Control Population for Alternative Phenotyping for Malignant Hypothermia Using Peripheral B Lymphocytes

KEYWORDS:

PRINCIPAL INVESTIGATOR: Mongan, Paul LTC MC
ASSOCIATES:

DEPARTMENT: Surgery
SERVICE: Anesthesia-Operative

STATUS: O
INITIAL APPROVAL DATE: 14 March 2000

STUDY OBJECTIVE

The objective of this proposal is to develop normal values for a control population to compare with MH susceptible populations for MH phenotyping using peripheral B lymphocytes. The central hypothesis of this proposed research is that functional abnormalities in skeletal muscle type isoform RYR1-mediated Ca^{2+} regulation is a ubiquitous phenomenon in MH susceptible individuals. This abnormality can be demonstrated not only in skeletal muscles, but in other cells which the RYR1. The rationale for the proposed research is based on our recent findings in peripheral B cells. Firstly, B cells express the RYR1 which appear to function as a Ca^{2+} responses release channel during B cell activation. Secondly, our preliminary studies also indicate that the Ca^{2+} responses of B cells to the RYR1 activating agents caffeine ($p<0.0001$) or 4-chloro-m-cresol ($P<0.05$) are significantly greater in MH susceptible than in MH negative individuals. In the present study, we propose to study Ca^{2+} signaling in B cells with the RYR activating agent caffeine or 4-chloro-m-cresol in B cells to develop a normal control population to which we can compare MH susceptible (MHS) individuals. We will enroll normal patients and compare Ca^{2+} responses in B cells with results obtained from MHS patients.

Specific Aim:
1. To develop normal values for the Ca^{2+} response in B cells to caffeine and 4CmC in a normal control population.
2. To validate the Ca^{2+} response with precise fluorimetric measurements.

TECHNICAL APPROACH

We will test the Ca^{2+} response of B cells to caffeine and 4CmC in normal individuals. Stock solutions for caffeine and (100 mM) and 4CmC (100 mM) will be freshly made in HBSS and DSMO, respectively. Changes in $[Ca^{2+}]i$ will be directly measured in B cells by measuring the fluorescence intensity if fluo-3-loaded cells (Sei and Arora 1991; sei et al. 1991). This technique requires no cell separation. Cells (2×10^6)/ml) will be loaded with 1 mM fluo-3 (Molecular Probes, Inc.) by incubation in subdued light (60 min, 25°C0 with acetoxy-methyl ester. The cells are permeant to this form of the dye and intracellular esterases hydrolyze the fluo-3 ester to the active and impermeant fluo-3 form in the cytoplasm. Fluo-3-loaded cells will then be stained with either phycoerythrin (PE)-conjugated CD4, CD8, leu12, or LeuM3 mAB. Cells will then be washed three times with HBSS and resuspended in 1 ml of HBSS and analyzed by FACScan (Becton-Dickinson). Forward and right angle scatter signals will be displayed on a linear scale, with the forward scatter adjusted to gate cells from debris. For dual color analysis of intracellular fluo-3-fluorescence (excitation at 488 nm with emission at 525 nm) and PE (excitation at 488 nm, with emission at 585 nm) signals will be detected after separation with 530 (FL-1) and 585 (FL-2) band pass filters respectively. FL-1 fluorescence is recorded as a log amplified signal but displayed as a linear signal, whereas FL-2 (PE) fluorescence is recorded and displayed as a log amplified signal. Cross-over of FL-1 fluorescence into the FL-2 detection window will be compensated by analog subtraction at the preamplifier stage. The FL-1 signal for fluo-3 will be calibrated by transporting in saturating Ca^{2+} with ionomycin (Molecular Probes) to obtain the minimum signal (F_{min}). The $[Ca^{2+}]i$ can be calculated from the fluo-3-fluorescence intensity using the formula: $[Ca^{2+}]i = Kd\ (F - F_{min})/\ (F_{max} - F)$, where $[Ca^{2+}]i$ = intracellular ionized calcium concentration; Kd = 400 nM for the intracellular dye. Previous experiments

indicate that Ca^{2+} response in $CD4^+T$, $CD8^+T$, B cells and $LeuM3^+$ monocytes was clearly detectable within mixed mononuclear cell preparations.
Precise quantitative confirmation of the flow cytometric analysis $[Ca^{2+}]i$ measurements will be performed by fluorescence scanning techniques after CD magnetic bead reverse isolation of the B-cell population. This technique is more sensitive and precise for $[Ca^{2+}]i$ measurements than flow cytometry. However, due to the complexity of isolation and setup, this measurement technique would not be suitable for a screening test. It can, however, support the results and applicability of the flow cytometry tests.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
Technical difficulties in the past year have precluded the study of any patients. Our flow cytometer was out of service for five months. In addition, the technician trained to perform the fluorescence scanning techniques has found another employer.
The number of subjects enrolled to the study since the last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 0. The total number enrolled study wide is 0, if multi-site study.

CONCLUSIONS
Once a new technician is hired that is capable of performing the fluorescence measurements we will enroll patients.

Report Date: 20 July 2001 Work Unit # 2078A

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: In Vitro Diagnosis of Malignant Hyperthermia With 4-Chloro-M-Cresol and Ryanodine

KEYWORDS:

PRINCIPAL INVESTIGATOR: Mongan, Paul LTC MC
ASSOCIATES: Dr. Sheila Nuldoon, MAJ John Armstrong, CPT Lynn Giarrizzo, CPT Grant Lynde, Saiid Bina, Ph.D

DEPARTMENT: Surgery
SERVICE: Anesthesia and Operative

STATUS: O
INITIAL APPROVAL DATE: 25 May 1999

STUDY OBJECTIVE

Our objective is to determine if 4-Chloro-M-Cresol (4-CmC) and ryanodine would be useful adjunctive agents to be used as our supplemental tests for the diagnosis of malignant hyperthermia (MH). The contracture response of normal skeletal muscle obtained from volunteers without MH or any other neuromuscular disease to 4-CmC and ryanodine will be characterized.

TECHNICAL APPROACH

The muscle specimens for the ryanodine and 4-chloro-M-Cresol (4-CmC) contracture tests will be obtained from a total of 15 consenting subjects between the ages of 18 and 60 years scheduled for elective surgery at Walter Reed (WRAMC) or the National Naval Medical Center (NNMC). The location of the surgery dictates the muscle group to be sampled. Patients undergoing lower extremity surgery such as total hip or total knee arthroplasty will have the muscle taken from the vastus muscle group. Patients undergoing abdominal surgery will have the muscle specimen taken from the rectus abdominis. Patients with a history of malignant hyperthermia (MH), neuromuscular disorders or any neuromuscular disease are excluded from participation. As an added precaution to the prevention of enrollment of individuals with neuromuscular disease, a screening creatine phosphokinase (CPK) is obtained. An elevated CPK excludes the volunteer from participation. The type of anesthesia used during the surgery will not influence the results of the tests and will be determined by the anesthetizing team. Shortly after initial approval of the protocol at Walter Reed, approval for this study was obtained at NNMC, and an addendum to the protocol was submitted to and approved by DCI to that effect.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

No new findings to report.
The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 5. The total number enrolled study-wide is N/A, if multi-site study.

CONCLUSIONS

None

Report Date: 02 March 2001 Work Unit #00-2001

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: Cytoxic T Lymphocyte Recognition of Epithelial Cancers.

KEYWORDS:

PRINCIPAL INVESTIGATOR: LTC George E. Peoples MC
ASSOCIATES: CPT Gayle Ryan MC; CPT Bryan Fisk MC; Dr. Vasantha Srikantan

DEPARTMENT: Surgery
SERVICE: General Surgery

STATUS: O
INITIAL APPROVAL DATE: 4 April 2000

STUDY OBJECTIVE

To collect discarded tissue, blood, body fluids in order to investigate the cellular immune response to epithelial cancers in order to identify common tumor antigens that may serve as the target of immunotherapeutics such as vaccines.

TECHNICAL APPROACH

Patients with a known epithelial malignancies such as ovarian, breast and prostate who are having blood drawn, malignant pleural effusions or ascites removed, or surgical removal of large tumors are identified by their providers. These providers contact us to inform us of tissue or body fluids that are to be discarded. Prostate patients who have been enrolled in the serum bank CPDR trial have been identified since the cellular components of their blood draw are discarded. The patients are consented unless the samples are collected without patient identification. The lymphocytes and/or tumor cells are isolated and stored for future studies.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

So far we have collected 3 specimens of ovarian ascites, 1 breast cancer pleural effusion, and 44 prostate cancer patients' blood samples. The lymphocytes have been isolated from all these patients, and their HLA-A2 status determined. Two of the ascites were positive, and the third negative as was the breast pleural effusion. Eleven of the prostate cancer patients are HLA-A2 positive. These HLA-A2 positive lymphocytes will serve as a source if effectors to screen for tumor antigens in future studies.
The number of subjects enrolled to the study since last APR at WRAMC is 48 and total enrolled to date at WRAMC is 48. The total enrolled study-wide is 48, if multi-site study.

CONCLUSIONS

We have been able to establish an inventory of 13 HLA-A2 positive and multiple HLA-A2 negative control lymphocyte populations from which to choose effectors for future studies. These effector populations allow us to do comparative analysis on multiple potential target antigens. If any preliminary results are obtained, then a directed protocol investigating the specific antigen will be submitted. The low HLA-A2 positivity rate (expected is 50%) for prostate cancer patients is being reviewed. There is data to support that certain HLA types are correlated with good and poor prognosis in melanoma.

Report Date: 02 March 2001 Work Unit #00-2002

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: Sentinel Lympho Node (SLN) Evaluation in Colorectal Cancer (CRC)

KEYWORDS:

PRINCIPAL INVESTIGATOR: LTC George E. Peoples MC
ASSOCIATES: COL Daniel Otchy MC; LTC(P) Craig Shriver MC; LTC Carol Adiar MC; CPT Darin Cox MC; CPT Dwight Kellicut MC

DEPARTMENT: Surgery
SERVICE: General Surgery

STATUS: O
INITIAL APPROVAL DATE: 18 April 2000

STUDY OBJECTIVE

To determine the feasibility and usefulness of sentinel lymph node (SLN) biopsy in colorectal cancer (CRC)

TECHNICAL APPROACH

The surgery performed for these patients is standard. The blue dye is injected intramurally around the tumor either in vivo or cx vivo. The blue nodes are labeled as sentinel and submitted separately to pathology.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

We have completed our 10 patient pilot trial. We were able to find sentinel nodes in all 10 patients. The average number of SLN was 6. Of the 10 patients, 6 had negative nodes and 4 had positive nodes on final path. The SLN accurately predicted the nodal basin in all 10 patients. There were no false negatives. Of the positives, two patients would have been called positive without the AID of the SLN; however in the other 2 patients, the positive nodes were picked up as a result of the serial step sectioning and the immunohistochemical staining of the SLN. Therefore, in the pilot trial, we demonstrated a 20% upstaging of the group, or a doubling of the positive nodes found utilizing this new staging technique. We have continued to accrue patients. We have not seen any reactions to the isosulfan blue dye. The technique appears to work just as well ex vivo (n=4) as in vivo (n=6). There are 2 reports from the same group on the utility of SLN in CRC, but this technique is not widely used yet. CALGB is starting a limited access feasibility trial of SLN in CRC in which we have been invited to participate.
The number of subjects enrolled to the study since last APR at WRAMC is 13 and total enrolled to date at WRAMC is 13.

CONCLUSIONS

The SLN technique is feasible and would appear to improve staging in CRC from our limited preliminary results.

Report Date: 01 March 2001 Work Unit #00-2003

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: Evaluation of Neutrophil Activation in Diabetes After Carotid Endarectomy

KEYWORDS:

PRINCIPAL INVESTIGATOR: CPT Scott Rehrig MC
ASSOCIATES: Sherry Fleming, PhD., Terez Shea-Donohue, PhD

DEPARTMENT: Surgery
SERVICE: General Surgery

STATUS: O
INITIAL APPROVAL DATE: 18 April 2000

STUDY OBJECTIVE

Diabetes is a known risk factor for increased morbidity and mortality following most surgical procedures and traumatic injuries. The primary hypotheses if this study is that in diabetes, surgical intervention alone alters the neutrophil (PMN)-endothelial cell interaction, which may play a role in the increased organ injury observed in these patients. The aim of this study is to evaluate the effect of non-insulin dependent (NIDDM) diabetes on neutrophil cell adhesion molecule expression and hydrogen peroxide production in the context of a surgical procedure.

TECHNICAL APPROACH

Patients were informed if the protocol and consented prior to their operation. Patients served as their own controls. Preoperative blood was collected prior to procedure through an indwelling line placed for the purpose of intraoperative monitoring. A second blood draw was obtained intraoperatively via the same indwelling catheter one hour after skin incision. The third and final collection was obtained within 20 minutes upon arrival to postanesthesia care unit via indwelling catheter. The samples were then transported to USUHS at room temperature. Red blood cells were lysed using 1x lysis buffer for 20 minutes. The samples were then centrifuged, red cells decanted and the neutrophil pellets were washed in buffered saline. To determine expression of CD18 and CD11b, the isolated neutrophils were exposed to anti-human CD18 and CD11b antibody for 15 minutes on ice. The amount of hydrogen peroxide produced by neutrophils was then determined by incubation with dichlorohydroxfluorescein (DCF) and phorbol myristate acetate (PMA), for maximally stimulated oxidative burst. After incubation, the cells were rewashed and suspended in PBS for flow cytometric analysis. The neutrophils were identified on forward and right angle scatter of a 488nm argon laser on an EPICS XL. The cellular fluorescence of each of three measures (DCF, CD 11b and CD 18) were measured with logarithmic amplification and expressed as percent positive cells compared to cells stained with isotype control antibody.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

A total of 5 patients have been accrued to the study to date. There have been 4 control patients and one diabetic thus far. The expression of CD18, CD11b and DCF were determined as detailed above. The one diabetic has higher CD11b and CD18 surface marker expression than controls at all time points. This increased expression may be responsible for increase neutrophil-endothelial cell interaction in diabetic patients. We have observed no difference in DCF (H2O20 production between the control patients and the one diabetic patient. When PMN H2O2 production is maximally stimulated with PMA there may be a decreased H2O2 production. This was seen in our one diabetic to date and would need to be repeated to if the difference persists.

CONCLUSIONS

We have presented evidence that our flow cytometry protocol represents a sensitive method of evaluating neutrophils. We have observed differences between adhesion molecule expression and oxidative burst capacity between the diabetic and non-diabetic patient. At present, our numbers are small and the observed difference will need to observed in more diabetics.

Report Date: 2 April 2001 Work Unit # 00-2004

DETAIL SUMMARY SHEET

TITLE: Phase 1b Trial of HER-2/neu Peptide (E75) Vaccine in Patients at High Risk for Recurrence after Surgical Extirpation of Prostate Cancer

KEYWORDS: Vaccine, Her2 neu, prostate cancer

PRINCIPAL INVESTIGATOR: LTC George E. Peoples MC
ASSOCIATES: CPT Gayle Ryan, CPT Jennifer Gurney, CPT Raj Bannerji

DEPARTMENT: Surgery
SERVICE: General Surgery

STATUS: O
INITIAL APPROVAL DATE: 23 May 2000

STUDY OBJECTIVE

1) To assess safety and document local and systemic toxicity to the peptide vaccine (E75+ GM-CSF).
2) To determine maximum tolerated dose (MTD) and optimal biologic dose (OBD) for the peptide vaccine.
3) To evaluate the in vivo cellular immune response to the peptide vaccine.
4) To evaluate time to recurrence in the vaccinated patients vs. matched controls.

TECHNICAL APPROACH

Eligible patients are identified and offered study participation after referral from their urologist. Consenting patients are tested for HLA A2 type: A2+ patients receive vaccine, A2- patients are observed clinically Q3 months for 18 months. Patients assigned to vaccine are skin tested to assess immunologic intactness and then vaccinated q 3 to 4 weeks x 6 with blood draw before each vaccine to assess peptide-specific immune response. Patients are observed with serial vital signs for 1 hour after each vaccine and at 48 hours for delayed hypersensitivity reaction. Vaccinated patients return for a final blood test and skin test 4 weeks after series is complete, then followed clinically Q3 months for 18 months.
Vaccine is given by intradermal injection 0.5 cc X 2 with a dose escalation scheme for 3 patients at 100 mcg of peptide, 3 patients at 500 mcg of peptide, and 3 at 1000 mcg of peptide—with this dose for remaining patients if well tolerated. This study was amended to add FDA administrative changes and to add a group of intermediate risk patients thus expanding enrolment.

PRIOR AND CURRENT PROGRESS

Sixteen men have enrolled in this study at WRAMC. Seven were typed as A2 neg and are being observed; nine were A2 positive and assigned to receive vaccine. No patients have withdrawn from the study. One serious hypotensive event occurred and was reported to IRB 2/7/01. This patient recovered well, had no sequelae, and continues to be observed by the study while receiving no further vaccinations.

CONCLUSIONS

No conclusions have been reached; however data analyzed did indicate a possible link between Her2 neu and prognosis in prostate cancer patients. This data continues to be studied.

Report Date: 2 April 2001 Work Unit # 00-2005

DETAIL SUMMARY SHEET

TITLE: Phase 1b Trial of HER-2/neu Peptide (E75) Vaccine in Breast Cancer Patients at High Risk for Recurrence after Surgical and Medical Therapies

KEYWORDS: Vaccine, Her2 neu, Breast cancer

PRINCIPAL INVESTIGATOR: LTC George E. Peoples MC
ASSOCIATES: CPT Gayle Ryan, CPT Jennifer Gurney, CPT Raj Bannerji

DEPARTMENT: Surgery
SERVICE: General Surgery

STATUS: O
INITIAL APPROVAL DATE: 23 May 2000

STUDY OBJECTIVE

1) To assess safety and document local and systemic toxicity to the peptide vaccine (E75).
2) To determine maximum tolerated dose (MTD) and optimal biologic dose (OBD) for the peptide vaccine.
3) To evaluate the in vivo cellular immune response to the peptide vaccine.
4) To evaluate time to recurrence in the vaccinated patients vs. matched controls.

TECHNICAL APPROACH

Eligible patients are identified and offered study participation after referral from their oncologist or radiation oncologist. Consenting patients are tested for HLA A2 type: A2+ patients receive vaccine, A2- patients are observed clinically Q3 months for 18 months. Patients assigned to vaccine are skin tested to assess immunologic intactness and then vaccinated q 3 to 4 weeks x 6 with blood draw before each vaccine to assess peptide-specific immune response. Patients are observed with serial vital signs for 1 hour after each vaccine and at 48 hours for delayed hypersensitivity reaction. Vaccinated patients return for a final blood test and skin test 4 weeks after series is complete, and then are followed clinically Q3 months for 18 months.
Vaccine is given by intradermal injection 0.5 cc X 2 with a dose escalation scheme for 3 patients at 100 mcg of peptide, 3 patients at 500 mcg of peptide, and 3 at 1000 mcg of peptide—with this dose for remaining patients if well tolerated. This study was amended to: 1) add FDA changes; 2) to add a group of intermediate risk patients; 3) to clarify recruiting procedures and approve a telephone script and patient letter for use in patient recruiting.

PRIOR AND CURRENT PROGRESS

Ten women have enrolled in this study at WRAMC. Eight were typed as A2 neg and are being observed; one is pending A2 determination; and one is A2 pos., will receive anergy testing this week and plans to receive first vaccination soon thereafter. No patients have withdrawn from the study. No adverse events have occurred in this study; however, one serious hypotensive event occurred in a prostate cancer patient receiving this vaccine at WRAMC and was reported to IRB 2/7/01. This patient recovered well and had no sequelae.

CONCLUSIONS

No conclusions have been reached

Report Date: 6 August 2001 Work Unit # 00-2006

DETAIL SUMMARY SHEET

TITLE: Creation of a Retrospective and Prospective Database of Patients Evaluated and Treated for Breast Cancer

KEYWORDS:

PRINCIPAL INVESTIGATOR: Peoples, George E. LTC MC
ASSOCIATES: Shriver, Craig LTC(P) MC; Maniscalco-Theberge, Mary COL MC; Arciero, Cletus CPT MC

DEPARTMENT: Surgery
SERVICE: General Surgery

STATUS: O
INITIAL APPROVAL DATE: 25 July 2000

STUDY OBJECTIVE

1) To collect data beginning on DCI approval of this protocol on all patients 18 and older who present to the General Surgery clinic at WRAMC with breast cancer.
2) To utilize this database to analyze the diagnosis treatment and treatment outcomes for patients undergoing treatment for breast cancer. Analysis will include but not be limited to: risk factors for developing breast cancer, effectiveness of various modalities of treatment, risk of recurrence.

TECHNICAL APPROACH

The patients are identified by the CBCP nurse case managers in the Comprehensive Breast Center. These patients are counseled and consented to be a part of this prospective clinical database. The information is collected on dataforms by the nurses and physicians seeing the patient, then, the data is entered into the database by CBCP data managers. The patients are assigned unique CBCP numbers to protect their confidentiality. The identifier code is kept secured in the CBCP Director, Dr. Shriver's office. He is the only person having access to the code.

PRIOR AND CURRENT PROGRESS

Thus far, 45 new breast cancer patients have been consented and have had data collected and entered into the database. No data analysis has been performed on these patients. No publications have resulted from this protocol. New data sheets are being designed and will be submitted as an addendum. Additionally, we are hoping to expand this database to include all breast care patients being seen in the CBCP Breast Center that are undergoing breast biopsies for concern of breast cancer. This expansion will also be covered in the addendum.
The number of subjects enrolled to the study since last APR at WRAMC is 45 and the total enrolled to date at WRAMC is 45. The total number enrolled study-wide is 45. No adverse events have been reported.

CONCLUSIONS

This protocol is progressing as planned. The planned changes that have been alluded to above will be submitted in an addendum.

Report Date: 1 May 2001 Work Unit #2070

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: Cyclical Mastalgia as a Predictor of Atypical Ductal Hyperplasia and Breast Cancer

KEYWORDS:

PRINCIPAL INVESTIGATOR: Shriver, Craig LTC MC
ASSOCIATES: Ader, Deborah PhD

DEPARTMENT: Surgery
SERVICE: General Surgery

STATUS: C
INITIAL APPROVAL DATE: 02 April 1996

STUDY OBJECTIVE

To determine whether cyclical mastalgia (CM) may be associated with increased risk for atypical hyperplasia or breast cancer.

TECHNICAL APPROACH

Patients presenting for biopsy complete a questionnaire on premenstrual breast discomfort before the biopsy is performed. Pathologists, blind to questionnaire results code the biopsies as per normal procedure (with validity checks to be performed by independent pathologists).

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

The number of subjects enrolled to the study since last APR at WRAMC is 0 (zero) and the total enrolled to date at WRAMC is 461. It is not a multi-site study. There have been no adverse events.

CONCLUSIONS

Accrual was slower than expected throughout the course of the protocol. Over the past year, we have lost our Research Associate and the Co-Investigator has moved on to another position elsewhere. No accruals over the past year and changes in personnel have resulted in the decision to end the study.

Report Date: 20 September 2001 Work Unit # 2071

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: A Double-Blind, Placebo-Controlled Crossover Trial of Evening Primrose Oil in the Treatment of Cyclical Mastalgia

KEYWORDS: evening primrose oil, cyclical mastalgia

PRINCIPAL INVESTIGATOR: Shriver, Craig LTC(P) MC
ASSOCIATES:

DEPARTMENT: Surgery
SERVICE: General Surgery

STATUS: C
INITIAL APPROVAL DATE: 30 July 1996

STUDY OBJECTIVE

To test the efficacy of evening primrose oil (EPO) in reducing the severity of cyclical mastalgia (CM).

TECHNICAL APPROACH

Participants rate daily breast pain and premenstrual symptoms for 8 weeks. If their symptom pattern indicates a clinical level of CM, breast exam is negative, and they are not pregnant, they are randomly assigned to receive either EPO or placebo daily for 6 months, while continuing to make daily symptom ratings. This treatment phase is followed by a 3-month washout period, which is followed by a 6-month crossover treatment phase. Daily symptom ratings are made throughout the study period.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

A total of 88 patients were enrolled on this study, none in this reporting period. All participants have completed the two arms of the trial. No patients withdrew from the study and no adverse events occurred as a result of study treatment. Study has been voluntarily closed due to lack of administrative and financial support.

CONCLUSIONS

It has been concluded that due to low patient accrual numbers, the data obtained is not sufficient to reach meaningful conclusions from this data.

Report Date: 01 November 2000 Work Unit # 2076

DETAIL SUMMARY SHEET

TITLE: Gamma Probe Assisted Detection of Micrometastasis in Well-Differentiated Thyroid Cancer

KEYWORDS:

PRINCIPAL INVESTIGATOR: Shriver, Craig LTC MC
ASSOCIATES:

DEPARTMENT: Surgery STATUS: O
SERVICE: General Surgery INITIAL APPROVAL DATE: 25 November 1997

STUDY OBJECTIVE
To determine if the gamma probe can be used to identify micrometastasis to cervical lymph nodes in well-differentiated thyroid cancers.

TECHNICAL APPROACH
Patient ingests a small amount of radioactive iodine pre-operatively and during thyroidectomy a gamma-detecting probe is used to assess lymph nodes for evidence of iodine-containing cells (thyroid cancer mets).

PRIOR AND CURRENT PROGRESS
A total of five patients have been accrued to the protocol. One patient has accrued in the last 12 months. There have been no unexpected complications. There is not enough data to state whether the technique is viable.

CONCLUSIONS
Accrual is slower than initially expected. However, there are no unexpected adverse events. The technique itself while hypothetically feasible, needs further study.

Report Date: 25 September 2000 Work Unit # 2078-99

DETAIL SUMMARY SHEET

TITLE: Characterization of the Perioperative Serum Cytokine Elaboration in Patients Undergoing Hepatic Resection.Cryoablation

KEYWORDS:

PRINCIPAL INVESTIGATOR: Shriver, Craig LTC MC
ASSOCIATES:

DEPARTMENT: Surgery STATUS: O
SERVICE: General Surgery INITIAL APPROVAL DATE: 20 October 1998

STUDY OBJECTIVE
To characterize the temporal elaboration of serum inflammatory mediators in patients undergoing hepatic resection or cryoablation.

TECHNICAL APPROACH
Serial blood samples are drawn perioperatively and then the serum is withdrawn and preserved for eventual cytokine analysis.

PRIOR AND CURRENT PROGRESS
Had collected six patients at last year's APR, now with 13 total patients.

CONCLUSIONS
Still working to accrue patients for a goal of thirty.

Report Date: 14 November 2000 Work Unit # 2079-99

DETAIL SUMMARY SHEET

TITLE: Intraductal Carcinoma of the Breast Treated by Conservative Surgery: Insights Based on Histopathologic Evaluation Using Computer Graphic Three-Dimensional Reconstruction

KEYWORDS: breast, DCIS, cancer, CT

PRINCIPAL INVESTIGATOR: Shriver, Craig LTC MC
ASSOCIATES: Gayle, Ryan CPT MC

DEPARTMENT: Surgery
SERVICE: General Surgery

STATUS: O
INITIAL APPROVAL DATE: 15 December 1998

STUDY OBJECTIVE

Determine the extent of involvement of the ducts of the breast in DCIS using a novel imaging modality

TECHNICAL APPROACH

Tissue breast biopsy is performed in the usual fashion and after standard pathology analysis; a computerized 3-dimensional reconstruction is generated to assess the involvement of the ductal system of the breast in a more analytical fashion.

PRIOR AND CURRENT PROGRESS

Beginning patient accrual; change of PI form to be submitted to Gayle Ryan. Enrollment to date is 0 patients.

CONCLUSIONS

No conclusions as yet.

Report Date: 01 March 2001 Work Unit #2080-99

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: Alteration in Colonic Motility Secondary to Inflammatory Bowel Disease

KEYWORDS:

PRINCIPAL INVESTIGATOR: CPT Jimmie Anderson
ASSOCIATES: Terez Shea-Donohue, PhD; CPT Steve Lawson

DEPARTMENT: Surgery
SERVICE: General Surgery

STATUS: O
INITIAL APPROVAL DATE: 20 April 1999

STUDY OBJECTIVE

This study was designed to evaluate changes seen in the innervation of the colon affected by inflammatory bowel disease. Specifically to determine the 1) *in vitro* changes in the neutral control of colonic smooth muscles responses undocked by inflammation in both affected and unaffected sites and 2) contribution of nitric oxide to changes in the control of smooth muscles in colitis.

TECHNICAL APPROACH

At the time of operation for either resection due to colon cancer of inflammatory bowel disease a portion of colon is harvested with the enlistment of the pathologist to ensure all material needed for pathologic diagnosis is obtained. This portion of the colon is then transported to Dr. Shea-Donohue's laboratory, Department of Medicine, USUHS in oxygenated Kreb's solution. The mucosa is then stripped using microdissection techniques. Mucosa-free strips of muscle are then oriented circularly or longitudinally and mounted in 10ml organ baths at 37 degrees C, gassed with 95% O2/5% CO2 and rinsed every 10 minutes throughout the experiment. One end of the tissue is connected to stationary mounting point at the bottom of the bath and connected to a Grass FT03 force displacement transducer. Prior to addition of drugs or to nerve stimulation the muscle strips are pre-stretched to their optimal length (Lo) for generation of active tension. Lo is defined as that degree of stretch that gives a maximal contraction to cetylcholine. Recordings of isometric tension development at Lo will be made on a bench top polygraph. Muscle strips will be exposed to noncumulative concentrations of drugs with at least 30 minutes before addition of the next concentration. Concentration responses to agonist and antagonist are expressed as tension generated per surface area (mN/cm^2).

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Inflammatory bowel disease (IBD) is a chronic condition resulting in major human morbidity and mortality. It is also a chronic condition characterized by periods of quiescence interrupted by disease relapse. The major clinical manifestation of IBD is debilitating diarrhea, which may be due to abnormalities in mucosal secretion, absorption and/or smooth muscle contractility. Abnormal motility is a defining characteristic of IBD. The involvement if the enteric nervous system is supported by observations of neural hyperplasia, axonal necrosis, and ganglion cell degeneration. Two major inhibitory neurotransmitters are norepinephrine released from sympathetic nerves and nitric oxide released from enteric nerves. Ablation of sympathetic nerves attenuates inflammation in animal models of IBD. Stimulation of these nerves (stress) has been implicated in acute relapse. Moreover, neural nitric oxide levels are reduced during inflammation. Thus, loss of inhibitory neural input may contribute to the diarrhea of IBD and therefore, we investigated the contribution of inhibitory nerves to the abnormal motility in IBD patients.

Mucosa-free strips of smooth muscle were suspended in organ baths to assess contraction in response to acetylcholine (1nM – 1mM) or to stimulation of enteric nerves (electrical field stimulation, EFS; 1-20 Hz, 0.1 ms duration, 80V). Responses were determined in the presence and absence of inhibitors of nitrergic (nitric oxide containing nerves; L-NNA) and α (phentolamine) and β (propanolol) adrenergic nerves (P+P).

All strips were challenged with KCl (60mM) to assess the basic contractile properties of smooth muscle. In both controls and IBD, responses to acetylcholine were elevated significantly after inhibition of nitergic or adrenergic nerves. Smooth muscle contractions in response to nerve stimulation were increased after blockade of inhibitory nerves in IBD patients, but not in controls. IBD significantly decreased responses to nerve stimulation and to acetylcholine. Responses remained depressed after blocking nitric oxide nerves. Blocking adrenergic nerves; however, normalized responses to EFS and to acetylcholine in IBD patients. Responses to KCl were comparable in controls and IBD (4 ± 1 vs 3 ± 0.05 n/cm^2).

	ACETYLCHOLINE			NERVE STIMULATION (EFS)		
	VEH	L-NNA	PP	VEH	L-NNA	PP
Control	5.4 ± 2.1	8.8 ± 2.1*	9.6 ±	3.4 ± 0.8	4.5 ± 0.9	4.1 ± 0.5
IBD	2.0 ± 0.1**	4.7 ± 0.8* φ	7.7 ± 1.2 φ	1.3 ± 0.3*	2.0 ± 0.3* φ	3.9 ± 0.5 φ

All values are means ± SEM; AMP and EFS are expressed as tension in N/cm^2; EFS = maximum tension to 5 Hz; Acetylcholine = 1mM; * $p > 0.05$ vs respective Control; φ $p < 0.05$ IBD VEH.

CONCLUSIONS

Smooth muscle contractile responses to nerve stimulation reflect the net input from cholinergic (acetylcholine) sympathetic adrenergic (norepinephrine) and non-cholinergic excitatory (e.g. substance P and neurokinin A) and inhibitory (e.g. nitric oxide and VIP) nerves. In controls and in IBD, there is a basal regulation of responses to acetylcholine by nitergic or adrenergic nerves. Responses to EFS are also modulated by inhibitory nerves in IBD, but not in controls, suggesting that inflammation upregulates inhibitory nerves. In the absence of nitergic nerves (+L-NNA) contractions in IBD remain lower than that in controls. In contrast, in the absence of adrenergic nerves (P+P) responses are similar in both controls and IBD. These data indicate that there is an increased contribution of sympathetic nerves that may be central to the maintenance of inflammation and abnormal motility in IBD.

Report Date: 6 November 2000 Work Unit #00-2101

DETAIL SUMMARY SHEET

TITLE: Intraoperative Carotid Duplex: A Prospective Study of the Clinical Significance of Residual Defects Following Carotid Endarterectomy

KEYWORDS: intraoperative, carotid, duplex

PRINCIPAL INVESTIGATOR: Patricio Rosa, MAJ MC
ASSOCIATES: MAJ James M. Goff MC, LTC Sean D. O'Donnell MC, LTC David L. Gillespie MC, MAJ Neal Hadro MC, Margaret Kidwell, RVT

DEPARTMENT: Surgery
SERVICE: Peripheral Vascular Surgery

STATUS: O
INITIAL APPROVAL DATE: 18 January 2000

STUDY OBJECTIVES:
To compare the rate of neurologic events, restenosis, reoperation and death in patients who undergo carotid endarterectomy and in whom: 1) the intraoperative carotid duplex is normal and no repair is performed, 2) the intraoperative carotid duplex shows a minimal abnormality that is not repaired, 3) the intraoperative duplex shows an abnormality that is repaired, 4) the carotid artery was opened only once versus two or more times.

TECHNICAL APPROACH :
This is a prospective observational study. Once patients are identified in the clinic meeting the indications for carotid endarterectomy, they undergo the standard medical and preoperative evaluation to ensure that there are no contraindications to surgery. This will include a thorough history and physical examination, laboratories, radiographs, electrocardiograms and consultations as dictated by their medical condition. Once scheduled for surgery, they are approached regarding their willingness to participate in the study. Informed consent is obtained. A datasheet is initiated on the patient to record demographic data, risk factors for atherosclerotic vascular disease, history of chronic medical problems, and previous vascular surgery. In the operating room, the findings of the initial duplex, any further surgical management decision should the duplex be abnormal, findings if re-explored, number of times reopened and final duplex findings prior to leaving the operating room are recorded.

The intraoperative carotid duplex is standardized as follows. An ATL HDI 3000 machine, with a 10 MHz CL-10-5 sterile probe and sterile gel or saline to obtain acoustic coupling is used, with the probe in direct contact with the artery, using an incident angle of 60 degrees. Care is taken to avoid the presence of bubbles between the probe and artery or pressure against the artery. B-mode is first used to longitudinally scan the CCA, beginning proximal to the proximal endpoint of the endarterectomy and continuing into the ICA as far as accessible. The proximal endpoint of the endarterectomy and the clamp site in the CCA are then examined longitudinally and in transverse views in B-mode, followed by color flow and spectral analysis and measurement of the peak systolic velocity. The distal endpoint and the clamp site in the ICA are examined next, in color and with spectral analysis, with measurement of the peak systolic and end diastolic velocities and particular attention paid to the presence of mosaicism, spectral broadening or lack of acoustic window. In the cases in which the presence of a prosthetic patch precludes direct visualization of the distal endpoint, the most proximal portion of the ICA distal to the patch will be examined. The ECA will then be examined in B-mode followed by spectral analysis and measurement of the peak systolic velocity. The velocities recorded will be those that are the highest within the area of interest. Color pictures are obtained of the CCA at the proximal endpoint, the ICA at the distal endpoint and of the proximal ECA. If a defect is identified, minor or major, its characteristics, namely dimensions, location and associated velocities, are recorded, and a photograph obtained. This is repeated each time that a defect is identified. If a defect is identified which requires re-operation, once it has been repaired, a new study will be initiated, covering all the areas usually covered in the completion study, as if this was the first time the carotid artery is closed. This new study is recorded into the Vascular Database as a separate study. The

amount of time required to perform each study is recorded separately by annotating in the space provided in the datasheet the time of the day when the study was initiated and when it was completed. The attending surgeon will proceed with termination of the operation when the intraoperative duplex is normal or shows a minor abnormality as defined by our protocol in the section on background and significance, or re-exploration versus termination if a major defect is present. The patients are divided into three groups: 1) patients with normal duplex, 2) patients with a minor defect on the duplex, and 3) patients with an abnormal finding on the duplex. Any changes in the neurologic exam as noted by the care team is recorded. The patients are followed with the standard post-operative duplex schedule at 6 months, and yearly after that. This is modified following the standard management algorithm as dictated by abnormal findings if any. The endpoints of the study are: 1) a carotid duplex of the operated side that remains stable for one year and does not meet criteria for re-operation, 2) the occurrence of a transient ischemic attack, amaurosis fugax or stroke in the cerebral distribution of the operated side, 3) the occurrence of criteria for reoperation of the operated side, namely, neurologic symptoms in the distribution of the ipsilateral carotid artery associated to a lesion considered to be hemodynamically significant or a possible source of embolic material, and restenosis compatible with 60% or greater diameter reduction, 4) death, 5) two years from the time of the operation elapse. The current standard of care at Walter Reed AMC is for patients to undergo an intraoperative duplex following their CEA. The attending surgeon then chooses to revise the procedure or not based on the duplex findings and his choice of intraoperative neurologic assessment. The vascular surgeons in Walter Reed do not currently have a uniform, agreed upon definition of what would constitute a minor defect. The change in the current standard of care is that a uniform definition is agreed upon, and the attending surgeon is expected to abide by this definition when considering whether to reexplore the carotid or not. This definition is supported by the medical literature. The research is the observation of any immediate and long-term difference in outcome among the three groups of patients.

PRIOR AND CURRENT PROGRESS:

A total of 26 patients have been enrolled in this study since it was given permission to start enrolling patients on 3 March 2000. That is a period of 8 months. No adverse reactions have occurred. No patients have withdrawn from the study.

CONCLUSIONS:

If we can demonstrate that minor defects have no clinical significance in the incidence of neurologic events following carotid endarterectomy, unnecessary reopening following carotid endarterectomy, together with the associated increase in operative time, morbidity, time of anesthesia and cost can be avoided.

Report Date: 15 June 2001

Work Unit # 00-2102

DETAIL SUMMARY SHEET

TITLE: Clinical And Pathophysiologic Efficacy Of SEPS The Endoscopic Treatment Of Incompetent Perforating Veins Of The Lower Extremity In Patients With Chronic Venous Insufficiency (CEAP classes 4-6).

KEYWORDS gene expression, skin, venous ulcer

PRINCIPAL INVESTIGATOR: David L. Gillespie, LTC MC
ASSOCIATES: Bader B. Fileta BS, MT(ASCP), AACC; Aneeta Patel MSc; Audrey S. Chang PhD; Jeffrey Anderson

DEPARTMENT: Surgery
SERVICE: Peripheral Vascular Surgery

STATUS : O
INITIAL APROVAL DATE: 25 July 2000

STUDY OBJECTIVES: Determine if the addition of SEPS (subfascial endoscopic perforator surgery) to a treatment regimen including conventional surgery and compression therapy alters patient outcomes. Parameters to be observed during the study include;

a) rate of ulcer healing
b) ulcer recurrence
c) post-operative pain and disability
d) post-operative wound complications
e) venous hemodynamics as measured by duplex derived valve closure times and air plethysmography
f) improved overall quality of life as measured by SF 36. This will be the first study to address these critical questions.

Compare the physical characteristics under confocal microscopy of fibroblasts grown in tissue culture from areas of diseased lower extremity skin to normal skin of the thigh before SEPS and 6 months after SEPS. Examine the effect of correcting lower extremity venous hypertension on the expression of the matrix metalloproteases MMP-1, MMP-2, MMP-9, MMP-13 and the inhibitor of metalloprotease activity TIMP-1 in fibroblasts grown from areas of diseased lower extremity skin to normal skin of the thigh before SEPS and 6 months after SEPS.

TECHNICAL APPROACH: In this study skin biopsies obtained from patients undergoing venous surgery. Total RNA and protein isolated are isolated. The RNA is then reverse transcribed using the First Strand cDNA Synthesis Kit (Boerhinger Mannheim, Indianapolis, IN) using primers specific for MMP-1, MMP-2, MMP-9, MMP-13 and TIMP-1. RT-PCR product is then separated over 2% agarose gel containing ethidium bromide (0.5 &g/&ml) and visualized by UV irradiation and will be photographed using a Polaroid documentation system.

Western blots are performed using monoclonal mouse anti-human antibodies MMP-1, MMP-2, MMP-9, MMP-13 and TIMP-1 will be used as the primary antibodies (Oncogene Science, Cambridge, MA). Goat anti-mouse horseradish peroxidase coupled antibodies will be used as secondary antibodies. Scanning densitometry is then performed (NIH imager v.1.57) to quantify the amount of these proteins in each sample. Activity of these enzymes is then performed using gel substrate zymography. There are no addenda to the original protocol.

PRIOR AND CURRENT PROGRESS: To date there have been 19 patients enrolled in this study. There have been no complications or adverse events associated with this study. We are preparing to perform the PCR analysis at present.

CONCLUSIONS: We have enrolled 19 patients in this and are preparing to perform the PCR analysis

Report Date: 17 January 2001 Work Unit # 2125

DETAIL SUMMARY SHEET (Human Use Protocol)

TTTLE: Post-Sclerotherapy Pigmentation. Can Early Microthrombectomy Prevent It? A Controlled Trial in Varicose Vein Patients

KEYWORDS: varicose veins, sclerotherapy, pigmentation, thrombectomy

PRINCIPAL INVESTIGATOR: J. Leonel Villavicencio MD
ASSOCIATES:

DEPARTMENT: Surgery STATUS: O
SERVICE: Peripheral Vascular Surgery INITIAL APPROVAL DATE: 25 February 1997

STUDY OBJECTIVE

To investigate the effects of microthrombectomy (thrombus extrusion) on the development of post-sclerotherapy pigmentation.

TECHNICAL APPROACH

Patients with venous spiders (1 mm or less) and varicose veins 1-3 mm will be randomly treated with a sclerosing agent. A selected area of the lower extremity will be divided into two equal halves. One week after sclerotherapy, one half will be thrombectomized and the other one will be left as control. Photographs will be taken before the injection, one-week and 16 weeks after. Two independent investigators will score the photographs. The study includes a total of 100 patients, 50 at WRAMC and 50 at NNMC.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

The total number of patients enrolled up to date is 43. The number of completed patients is 29; there are 9 currently being treated. There have been three patients lost to follow-up and one patient withdrew voluntarily. The reason for withdrawal was that the patient was unhappy for having a longer than expected waiting time to be treated. In addition, there was a protocol violation consisting of practicing thrombectomy in the entire area instead of only one half the area as stated in the protocol. This information is clearly stated in the CRF (Patient # 403). From the total of 43 patients, there were 36 Caucasians, 3 Hispanics and 4 Blacks. This is a multicenter study and the National Naval Medical Center has a total of 34 patients enrolled. We are actively pursuing enrollment.

CONCLUSIONS

No definite conclusions can yet be derived from the observations of the patients who have been completed. The two independent judges who will review the photographs have been properly trained to interpret the findings. However, there is no statistical analysis yet performed.

Report Date: 31 July 2001

Work Unit # 2126

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: Hemodynamic Effect of Cardiac Valve Disease on Carotid Duplex Ultrasonography

KEYWORDS: Valvular heart disease, carotid stenosis, duplex ultrasonagraphy

PRINCIPAL INVESTIGATOR: David L. Gillespie LTC MC
ASSOCIATES: Sean D. O'Donnell COL MC

DEPARTMENT: Surgery
SERVICE: Peripheral Vascular Surgery

STATUS: T
INITIAL APPROVAL DATE: 06 May 1997

STUDY OBJECTIVE

1. To identify abnormalities of carotid duplex waveforms in patients with normal carotid arteries who have aortic valve stenosis or aortic insufficiency.
2. To determine which parameters are most altered with disease valvular disorders.
3. To evaluate whether these duplex waveform findings are still present after surgical valve replacement
4. To quantify carotid duplex velocities in patients with both extracranial carotid artery disease and cardiac valvular disease before and after aortic valve replacement

TECHNICAL APPROACH

Prospective study looking at carotid duplex imaging of patients with aortic stenosis vs controls with normal aortic valves. Study patients followed either for 1 year if valve disease is being treated medically, by having a carotid duplex and cardiac echo before and immediately after surgery and then 3 months post-op. Data will be compared between groups and against controls with normal aortic valves.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

This study was terminated by the 31 July 2001 Human Use Committee because a completed Annual Progress Report was not submitted.

CONCLUSIONS

This study was terminated by the 31 July 2001 Human Use Committee because a completed Annual Progress Report was not submitted.

Report Date: 18 October 2000 Work Unit # 2127

DETAIL SUMMARY SHEET

TITLE: A Phase III Controlled Multi-Center Randomized Parallel-Group Single Blind Study to Compare the Safety and Hemostatic Efficacy of the Fibrin Sealant, Beriplasst P, with Standard Care of Thrombin-Soaked Gelfoam in the Treatment of Bleeding Anastomosis

PRINCIPAL INVESTIGATOR: Gillespie, David LTC MC
ASSOCIATES: Goff, James MAJ MC; Johnson, Linzeka RN BSN

DEPARTMENT: Surgery STATUS: C
SERVICE: Peripheral Vascular Surgery INITIAL APPROVAL DATE: 27 November 1997

STUDY OBJECTIVE
To compare the percentage of patients achieving hemostasis within 4 minutes from the time of randomization to either the fibrin sealant, Beriplast P, or the standard treatment of Thrombin-soaked Gelfoam.
To compare the time to randomization to commencement of primary wound closure, time of hemostasis of suture line bleeding following randomization, rebleeding rates, volume of blood loss, length of stay in the ICU/hospital, and post operative mortality following treatment with fibrin sealant, Beriplast P, or standard treatment Thrombin-soaked Gelfoam.

TECHNICAL APPROACH
There have been 6 amendments since the original protocol dated 7 August 1997. Amendment #1 basically reflects changes that were made for the investigators and/or the FDA. These changes includes updates to surgical procedures, improved clarity of responsibilities, changing the study from being non-randomized to being randomized, improved safety features, and changes to the inclusion/exclusion criteria. In addition, revisions were made to the SAE reporting procedure. A list of adverse events was devised and revisions were made to the pilot study. Also, the statistical methods section was revised to give more detail for the methods used for the primary endpoint of achieving hemostasis within 4 minutes of randomization. Amendment #2 was created to allow for all accelerated clotting time measurement after surgery to become optimal procedures, to update the Beriplast P contact list and Investigator list, and to ensure that any unused Beriplast P be removed from the operating room immediately after randomization has been revealed. Amendments #1 and 2 were submitted together as Addendum #1 dated 24 February 1998. Amendment #3 was submitted as addendum #2 dated 24 July 1998. It eliminated the number of cases per participating surgeon in the pilot phase of the study. Amendment #4 was submitted as addendum #3 dated 8 September 1998. It encourages a single dose application of 2-3 ml of Beriplast P with a repeat dose only if hemostasis is not achieved at 4 minutes following randomization, allows for assessment to be performed within 4 minutes at randomization or 4 minutes following randomization, states that this study may be included in an upcoming study called MetaStudy, states that 5 additional study sites may be recruited, and clarifies the timeframe to report adverse events. Amendment #5 was submitted as addendum #4 dated 3 February 1999. It states that Beriplast P will be made available in 1ml and 3 ml kits and that newly recruited surgeons will a) treat their first pilot patient with Beriplast P only, b) sign a statement that s/he is familiar with the administration of thrombin soaked gelfoam, and c) treat the first exposure to thrombin soaked gelfoam as part of the main studyAmendment #6 was submitted as addendum #5 dated 4 August 1999. It states that there will be secondary data analysis in addition to the primary efficacy analysis as proposed by the FDA. It also clarifies the 4-minute assessment time following randomization, and states some minor administrative changes as well. There are no changes to the consent form.

PRIOR AND CURRENT PROGRESS
Enrollment to the study was closed on 20 August 1999. Currently, data collection is being reviewed and fine-tuned for data analysis. The total number of patients enrolled to completion is 7. There were 3 pilot and 4 main study patients. There were also 3 screen failures. Of the 7 that have completed enrollment, 1 patient (#3281) participated without serious adverse events. The other 5 patients (#3801, #3822, #3823,

#3901, #3902 and #3921) experienced serious adverse/adverse events. Patient #3901, whose surgery date was 14 September 1998, experienced a prolonged intensive care unit stay with failure to wean while on mechanical ventilation leading to subsequent tracheotomy placement. He also developed atrial fibrillation, atrial flutter, acute congestive heart failure, acute renal failure, pneumonia, pressure sore development, and a low blood count. Although, this patient did experience a prolonged hospitalization, he was discharged on 21 October 1998. According to patient per telephone conversation on 20 September 1999 and corresponding medical records, all these issues have been resolved. Patient #3902, whose surgery was 18 September 1998, also experienced a prolonged intensive care unit stay due to the need for a pacemaker placement for 2nd and 3rd degree heart block. This issue was resolved on 22 September 1998. Also, this patient was discharged and subsequently readmitted twice for evisceration/dehissence of three wound sites. Two sites were found to be infected. These issues were resolved on 30 September 1999. Patient #3801, whose date of surgery was 25 September 1998 was noted to have hypovolemia on 25 September 1998 and a low hemoglobin on 28 September 1998. Both events were resolved on the day of discovery with the administration of one unit PRBC's. Patient #3822, whose surgery was on 16 November 1998, experienced infection to the right groin and lower abdomen postoperative sites. He has been treated subsequently with abx. According to a recent telephone conversation on 20 September 1999, the patient verbalizes continued pain to right groin, failure of right groin to heal and difficulty ambulating. This patient has a history of NIDDM. Patient #3921, whose surgery was 3 February 1999, experienced several adverse events to include nausea, an increase in renal insufficiency with a temporary foley placement, a decrease in total blood count, neurological dysfunction, metabolic acidosis, mental status changes. This patient had a history of chronic renal insufficiency and microcytic anemia. As of 17 July 1999, this patient's condition had returned to baseline and each event resolved. This patient also experienced a loss of appetite. There is no documentation suggesting resolution this event.
None of these serious adverse events are believed to be related to the study drug, Beriplast P. They are believed to be more closely related to the patient population and their preexisting histories and diagnoses. As of the end of enrollment on 20 August 1999, the grand total of enrollees is 199 main study patients with 24 participating surgeons. Information concerning adverse reactions at other sites is not available at this time.

CONCLUSIONS

There are seven patients that have gone on to completion. Four randomized to Thrombin-soaked Gelfoam (#3901, #3822, #3921 and #3823). Three patients were randomized to Beriplast P (#3902,#3801 and #3821) Three of the four patients randomized to Thrombin-soaked Gelfoam (#3901, #3822 and #3823) received application without incident. One patient (#3921) did not achieve hemostasis within 10 minutes following randomization. Once hemostasis was achieved, an episode of rebleeding greater than 1.5 hours following hemostasis occurred. Gelfoam was used at the time to stop the bleeding. The patients randomized to Beriplast P received the drug, but were also given Thrombin-soaked Gelfoam 4 minutes after randomization because bleeding had not ceased. After application of the Thrombin-soaked Gelfoam, the bleeding subsided. It took greater than 10 minutes following randomization to achieve hemostasis for patients #3801 and #3902. It took less than 10 minutes for hemostasis for patients to patient #3821.

The studying of all patients was closed in December 1999. Since that time, all sites completed required paperwork and were carefully reviewed by experienced clinical research associates on several occasions to insure meeting FDA standards. Also, one major correction was made to all sites concerning the consent forms. During the study, it was a requirement that each patient submit a Day 1 (preprocedure) and Day 30 (postprocedure) viral sample since Beriplast P is made from human blood plasma. Although, the product is chemically treated for HIV and hepatitis B or C and the chance of contracting these viruses was minimal, these samples were obtained for later testing. Permission to perform these tests was not mentioned on the consent forms. Revised consent forms were drafted and sent by mail. Patients desiring to grant permission for testing sent the revised consent back via mail. Following the completion of this task by all participating sites, the study was closed on 4 October 2000.
According to the final closure letter submitted by Aventis Behring, the Final Summary Report is complete and the results were stated to be favorable. No further details have been noted at this time.

Report Date: 21 February 2001 Work Unit # 2130-99

DETAIL SUMMARY SHEET

TITLE: Does Protease Gene Expression Vary by Location in the Lower Extremity in Patients with Primary Varicose Veins or Chronic Venous Insufficiency as Compared to Controls?

KEYWORDS: MMP, varicose veins

PRINCIPAL INVESTIGATOR: Gillespie, David LTC MC
ASSOCIATES:

DEPARTMENT: Surgery STATUS: O
SERVICE: Peripheral Vascular Surgery INITIAL APPROVAL DATE: 2 February 1999

STUDY OBJECTIVE

1. Compare the expression of MMP-1 MMP-3, MMP-7 MMP-13 and tryptase in varicose veins as compared to nonvaricose veins
2. To quantify and localize these protein levels comparing the upper thigh vein to lower leg vein.
3. To compare their enzymatic activity.

TECHNICAL APPROACH

In this study segments of greater saphenous vein are obtained from patients undergoing CABG or varicose vein surgery. These veins are processed and both total RNA and total protein isolated. The RNA is then reverse transcribed using the First Strand cDNA Synthesis Kit (Boerhinger Mannheim, Indianapolis, IN) using primers specific for MMP-1,3,7,13 and tryptase. RT-PCR product is then separated over 2% agarose gel containing ethidium bromide (0.5 &g/&ml) and visualized by UV irradiation and will be photographed using a Polaroid documentation system.

Western blots are performed using monoclonal mouse anti-human antibodies MMP-1 MMP-3, MMP-7 MMP-13 and tryptase will be used as the primary antibodies (Oncogene Science, Cambridge, MA). Goat anti-mouse horseradish peroxidase coupled antibodies will be used as secondary antibodies. Scanning densitometry is then performed (NIH imager v.1.57) to quantify the amount of these proteins in each sample. Activity of these enzymes is then performed using gel substrate zymography are prepared.

There are no addenda to the original protocol.

PRIOR AND CURRENT PROGRESS

To date 21 patients have been enrolled in the study. All specimens have been processed for RNA and protein extraction. Western Blots have been completed. We are in a final data analysis and interpretation phase.

MMP-l, MMP-13 and tryptase mRNA was expressed in both proximal and distal segments of GSV. MMP-3 mRNA however was not found in either segment. The quantity of MMP-l protein (active form) was higher in proximal vein segments as compared to distal segments (69.27 vs. 54.18)(p=0.006). Similarly we found a significant difference in the quantity of MMP-13 protein (latent form) in proximal segments of the GSV as compared to the distal segments (177.84 vs. 131.64) (p=0.012). We found no difference however, in the quantity of tryptase between proximal and distal segments of GSV.

MMP-l, MMP-13 and tryptase mRNA was expressed in all segments of GSV. MMP-3 mRNA however was not found in any segment. We found a direct correlation between elevated MMP-1 (latent form) gene expression and worsening venous reflux ($r_s = 0.547$)(p=0.043). Similarly we found a significant difference in the quantity of MMP-13 protein (active form) ($r_s = 0.618$) (p=0.019) and MMP-13 protein (latent form) ($r_s = 0.618$) (p=0.027) and elevated VFI. We found no such correlation however, in the quantity of tryptase in segments of GSV.

To date there have been no adverse events in this study.

CONCLUSIONS

This study lends supportive evidence that expression of the matrix remodeling proteins MMP-l and MMP-13 varies by location in the lower extremity in patients with incompetence of the greater saphenous vein.

This study shows a direct correlation exists between worsening venous reflux and the up regulation of the matrix remodeling proteins MMP-l and MMP-13. We believe this is the first example connecting physiologic observations with induced molecular changes, ultimately leading to venous pathology.

Report Date: 14 February 2001 Work Unit # 2131-99

DETAIL SUMMARY SHEET

TITLE: Is the Bacterium Chlamydia Pneumoniae a Possible Inciting Agent for the Development of Atherosclerosis of the Carotid or Coronary Arteries?

KEYWORDS infection , atherosclerosis

PRINCIPAL INVESTIGATOR: Gillespie, David LTC MC

DEPARTMENT: Surgery
SERVICE: Peripheral Vascular Surgery

STATUS: O
INITIAL APPROVAL DATE: 6 April 1999

STUDY OBJECTIVE: 1. To investigate whether there is Chlamydia pneumoniae DNA within the atheromas of coronary or carotid atherosclerotic plaques of patients.
2. To characterize this with serologic evidence of Chlamydia pneumoniae

TECHNICAL APPROACH: In this study we are analyzing atherosclerotic plaques from fresh carotid endarterectomy specminen and paraffin embedded post mortem specimen coronary specimen stored in our tissue bank. DNA is isolated and then PCR performed looking for Chlamydia pneumoniae. Specific primers are used to perform the real time quantitative PCR assay using a sequence detection system (ABI Prism 7700). The PCR data is then automatically analysed by the computer program.

Patient records will be reviewed. From the chart we will record patient gender, age, presenting symptoms and the presence of any risk factors for atherosclerotic cerebrovascular disease (hypertension, smoking, hyperlipidemia, and diabetes mellitus. There are no addenda to the original protocol

PRIOR AND CURRENT PROGRESS: Atherosclerotic plaques were collected from 81 patients. There were 64 men and 17 women. The age range 27-83 years (mean 51 ± 21 yrs). Atheromas were obtained from carotid arteries (n = 9) and coronary arteries (n =72). Coronary atherosclerotic plaques were collected from tissue banked post mortem specimens which were paraffin embedded. Carotid atherosclerotic plaques were collected after patients underwent carotid endarterecomy for ≥ 60% internal carotid artery stenosis. These specimens were placed in M1-99 tissue buffer and then stored at -70° C. DNA was extracted from these specimens in order to search for evidence of C. pneumoniae DNA fragments using polymerase chain reaction (PCR) analysis. All 81 specimens were examined using a set of primers which were chosen to amplify the major outer membrane protein gene of C. pneumoniae- (OMP-1). A subset (16) of these 81 specimens were further examined using a second primer set designed to amplify a fragment of C. pneumoniae DNA obtained by a restriction digestion using the Pst-1 endonuclease. Amplification products were visualized by agarose gel electrophoresis. Confirmation of the PCR products was accomplished using Southern hybridization to a digoxigen-labelled probe. The presence of DNA was confirmed by human cellular oncogene (Her-2) analysis. A purified C. pneumoniae (from TWAR strain) was used in each PCR run as positive control.

Human DNA was identified in all cases using Her-2 analysis. Controls for C. pneumoniae (TWAR) were also positive in all cases. All 81 specimen studied by PCR for the OMP-1 gene however, were negative. Similarly none of the subset of 16 DNAs were amplified by the primers for the 474 bp Pst I fragment of the C. pneumoniae genome.

We submitted this for publication to the Journal but were told that due to the overwhelming evidence in the literature that C. pneumoniae is present we need to do more work. We have been re-analyzing our data using a more sensitive assay and are in the process of completing this work.

CONCLUSIONS: In an analysis of both surgical and preserved atheromas we were unable to confirm the presence of C. pneumoniae by PCR using either the OMP-1 gene or the 474 bp Pst I fragment. From this data it is hard to implicate C. pneumoniae as a causative agent for the development of complex atherosclerotic disease carotid or coronary disease.

Report Date: 31 July 2001 Work Unit # 2132-99

DETAIL SUMMARY SHEET

TITLE: Pre-operative Duplex Sonography Prior to Arterial Bypass Surgery for Limb Salvage; A Streamlined Approach to Identify Candidates for Reconstruction.

KEYWORDS: duplex vascular surgery

PRINCIPAL INVESTIGATOR: Hadro, Neal C. MAJ MC
ASSOCIATES: O'Donnell. Sean D. LTC MC

DEPARTMENT: Surgery
SERVICE: Peripheral Vascular Surgery

STATUS: T
INITIAL APPROVAL DATE: 25 May 1999

STUDY OBJECTIVE

To evaluate the utility of a pre-operative duplex ultrasound exam to identify which patients with limb threatening ischemia could forego pre-operative angiography

TECHNICAL APPROACH

In addition to standard pre-operative history, physical examination and inter-arterial contrast arteriography patients receive an additional non-invasive ultrasound mapping of the arteries in their legs. The anatomy as defined by the ultrasound is compared to the arteriogram and an operative plan proposed on the ultrasound data only is compared to the actual operation performed according to arteriogram. We have not changed any details from the original protocol.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

This study was terminated by the 31 July 2001 Human Use Committee because a completed Annual Progress Report was not submitted.

CONCLUSIONS

This study was terminated by the 31 July 2001 Human Use Committee because a completed Annual Progress Report was not submitted.

Report Date: 20 November 2000 Work Unit # 00-2301

DETAIL SUMMARY SHEET

TITLE: Evaluation of Digital Fundus Images as a Diagnostic Method For Surveillance of Diabetic Retinopathy

KEYWORDS: Diabetes mellitus, Retinopathy, Telemedicine

PRINCIPAL INVESTIGATOR: Robert M. Bauer II, MAJ MC
ASSOCIATES: John S.B. Dick II, LTC MC, Rodney D. Hollifield, LTC MC, David Jones, LTC MC and Thomas P. Ward, LTC MC

DEPARTMENT: Surgery
SERVICE: Ophthalmology

STATUS: O
INITIAL APPROVAL DATE: 14 December 1999

STUDY OBJECTIVE:
The objective of this study is to assess accuracy in diagnosis of diabetic retinopathy by review of digital non-mydriatic fundus images and compare results with those obtained by opthalmoscopic examination of the same patients.

TECHNICAL APPROACH:
Non-mydriatic digital fundus images are obtained from diabetic patients in the WRAMC Endocrinology Clinic. Images are forwarded to OIS imaging system in WRAMC Ophthalmology Clinic by T1 Connection. Review of digital images and clinical examination by indirect ophthalmoscopy are used by retina sub-specialists to independently assess qualitatively the presence and extent of diabetic retinopathy in each patient. Non-parametric assessment of the data will involve kappa analysis to ascertain the level of agreement between these methods for diagnosing diabetic retinopathy.

PRIOR AND CURRENT PROGRESS:
No work has been done on this protocol to date. A purchase request was submitted to the Telemedicine Directorate on three different occasions over the past six months for which to purchase imaging equipment and a non-mydriatic camera from Ophthalmic Imaging Systems. For further details on the delay in purchasing this equipment please refer to Ms. Daisy DeWitt of the WRAMC Telemedicine Directorate.

CONCLUSIONS:
None to date.

Report Date: 21 March 2001

Work Unit #00-2302

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: Expression of Markers of Vascular Proliferation in Human Choroidal Neovascular Membranes

KEYWORDS: neovascularization, retinal degeneration

PRINCIPAL INVESTIGATOR: Prem S. Subramanian MAJ MC
ASSOCIATES: Thomas P. Ward LTC(P) MC

DEPARTMENT: Surgery
SERVICE: Ophthalmology

STATUS: O
INITIAL APPROVAL DATE: 4 April 2000

STUDY OBJECTIVE

To identify cellular markers of neovascuolarization by determining the expressive of putative vasogenic and tumourigenic genes in surgically-excised choroidal neovascular membranes.

TECHNICAL APPROACH

Please see the original protocol for technical details. The strategy remains harvesting mRNA from surgical and eyebank specimens; this mRNA then will be used in RT-PCR to determine expression levels of the genes of interest (VEGF, TGF-beta, 67-kd laminin receptor, alpha-beta integrin). The PCR technique has been modified to allow the use of fluorescent-tagged primer sequences which may be used in an automated thermocycler to obtain direct quantitation of amplified products. All analyses are to be performed in the DCI labs.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

One patient has been enrolled in the study to date. The surgical specimen has been stored in appropriate medium and is being kept in storage per the original protocol. Enrollment of patients has been hampered by the lack of suitable candidates presenting to the Ophthalmology Service. Therefore, we have submitted an addendum to the protocol requesting addition of two additional investigators (former Army retinal surgeons) in academic practice to the protocol. We have also requested reinstatement of funding lost in FY2000. These funds were not spent because of the inability to recruit enough patients to the study. The purchase of expensive reagents with a limited shelf life was not warranted, given the likelihood that they would expire prior to our being able to use them for data collection.

Review of the literature: No new articles have been published addressing the question of markers of proliferation in choroidal neovascular membranes.

The number of subjects enrolled to the study since last APR at WRAMC is 1 and the total enrolled to the date at WRAMC is 1. The total number enrolled study wide is __, if multi-site study.

CONCLUSIONS

None.

Report Date: 21 May 2001 Work Unit #2328

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: The Effect of Differing Enucleation Techniques on Cure Rate and Survival Time of Patients with Uveal Malignant Melanoma: A Comparison of Standard Enucleation, "No-Touch" Enucleation and Enucleation with Stabilization of Intraocular Pressure

KEYWORDS: melanoma, enucleation, eye

PRINCIPAL INVESTIGATOR: Ward, Thomas MAJ MC
ASSOCIATES: Lovas, Thomas MAJ MC; McLean, Ian MD

DEPARTMENT: Surgery
SERVICE: Opthalmology

STATUS: O
INITIAL APPROVAL DATE: 05 March 1996

STUDY OBJECTIVE

This study seeks to determine whether the surgical technique employed for enucleation of an eye containing a uveal malignant melanoma has nay effect on cure or survival. The three methods to be compared are standard enucleation, "no-touch" enucleation, and enucleation with stabilization of intraocular pressure (STOP).

TECHNICAL APPROACH

The Registry of Opthalmic Pathology at the AFIP has accessioned all cases utilizing "no-touch" enucleation and STOP enucleation. These cases will be compared to a registry database of standard enucleation. The National Death Index (NDI) will be queried, at AFIP expense, to determine mortality. The results will be analyzed utilizing multivariate analysis (Cox's proportional hazards model). In addition, both cure and survival time will be estimated by regression analysis.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

A total of 1789 cases were sent to the NDI, representing all malignant tumors accessioned by the Department of Opthalmic Pathology at the AFIP from about 1977 through 1989. Included among these tumors are the 89 "no touch" and 29 SIOP enucleations that this research protocol is concerned with. The SIOP enucleations were performed at WRAMC during the years 1978 through 1989. Also included in the search are a large number of cases of malignant melanomas treated by standard enucleation during the same time period. These latter cases will be used as the control group.

During data analysis it was discovered that 4 SIOP cases were inadvertently omitted from the initial NDI search. Since there are only a total of 29 total SIOP cases, the omission of these 4 cases is significant. Data analysis has been halted until another NDI search is completed on the 4 missing cases. Dr. McLean at the AFIP is responsible for the search.

The number of subjects enrolled to the study since the last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 29. The total number enrolled study-wide is 1789.

CONCLUSIONS

There are no conclusions at the present time. When the final NDI search is completed, Dr. McLean will perform multivariate analysis of survival.

Report Date: 12 April 2001

Work Unit # 2332-98

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: Congential Esotropia Observational Study (CEOS)

KEYWORDS:

PRINCIPAL INVESTIGATOR: COL William Madigan, MC
ASSOCIATES:

DEPARTMENT: Surgery
SERVICE: Ophthalmology

STATUS: C
INITIAL APPROVAL DATE: 23 June 1998

STUDY OBJECTIVE
To observe the early course of congenital isotropy in order to determine the probability of spontaneous resolution and to try to correlate this finding with various aspects of the esotropia as the (1) size of the esotropia, (2) variability, and (3) presence of hyperopia.

TECHNICAL APPROACH
Identify patients between the ages of 8 and 17 weeks, who were born after 37 weeks gestation and weighed at least 2000 grams who have esotropia. There should be no other ocular abnormalities or history of prior medical intervention. Examine and record appropriate data on enrollment form initially, at 2-4 weeks post entry and finally between 28-32 weeks of age.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
The report is being written at the multi-center headquarters and will be available soon.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 1. The total number enrolled study-wide is 70, if multi-site study.

CONCLUSIONS
Pending

Report Date: 21 September 2000

Work Unit # 2334-99

DETAIL SUMMARY SHEET

TITLE: 5 Fluorouracil-Induced Dacryostenosis and Lid Malposition

KEYWORDS:

PRINCIPAL INVESTIGATOR: Eisman, Andrew MAJ MC
ASSOCIATES:

DEPARTMENT: Surgery
SERVICE: Opthalmology

STATUS: O
INITIAL APPROVAL DATE: 24 November 1998

STUDY OBJECTIVE

To determine the prevalence of 5-Fluorouracil induced dacryostenosis and lid malposition in a cohort of patients receiving systemic 5-FU for at least 3 months.

TECHNICAL APPROACH

No changes or addenda have been required or submitted. The approach remains the same as in the original protocol.

PRIOR AND CURRENT PROGRESS

10 new patients have been enrolled during the past year. This brings the total to 50. 25 of the patients were recruited from Wills Eye Hospital before arrival at Walter Reed. The total number of patients recruited at Walter Reed is 25. Enrollment is complete and data analysis is also complete. Write up of results is currently in progress.

CONCLUSIONS

14 patients have tearing, 2 have dermatitis of the eyelids, 1 has an ectropin, and 3 have dacryostenosis.

Report Date: 29 January 2001 Work Unit #2335-99

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: Initial Evaluation of Photorefractive Keratectomy in U.S. Army Personnel

KEYWORDS: Refractive surgery, laser, excimer laser, lamellar, photorefractive keratectomy, contrast sensitivity

PRINCIPAL INVESTIGATOR: Bower, Kraig LTC MC.
ASSOCIATES: LTC Edward Trudo, MAJ Richard D. Stutzman

DEPARTMENT: Surgery
SERVICE: Ophthalmology

STATUS: O
INITIAL APPROVAL DATE: 20 April 1999

STUDY OBJECTIVE

The objective of this study is to conduct a prospective clinical trial to evaluate the safety and efficacy of the VISX Excimer Laser System for the treatment of naturally occurring low to moderate myopia, with or without low levels of astigmatism, in U.S. Army personnel.

TECHNICAL APPROACH

In October 2000 a modification request was submitted. A summary of the new protocol modifications requested are as follows.

1. Change protocol WU #2335-99, "Initial Evaluation of Excimer Laser Keratorefractive Surgery in US Army Personnel" to a Master Protocol.
2. Change in investigators to delete MAJ. Bruce A. Brown (Ophthalmology Service-PCS) and add MAJ Prem Subramanian and MAJ Robert Bauer (Ophthalmology Service) and add LTC Jeff Rabin (currently arranging PCS to WRAMC this Fall to serve as Director of Research at the new Walter Reed Laser Center).
3. Background section has been updated with more current references and with illustrations detailing the surgical procedures.
4. Added forward light scatter, glare testing and wavefront analysis to measurements
5. NVG test methods detailed previously in the parent protocol have been removed and put into a separate sub-protocol.
6. Testing methods section has been expanded to include references on testing methods.
7. Data analysis section has been expanded with references and a table to summarize the study design.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

There have been no new subjects enrolled since the modification request of October 2000. There have been 5 new subjects enrolled to the study at WRAMC since the 6 March 2000 APR. The total enrolled to date at WRAMC is 19. A recent literature review was performed and submitted with the modification requests in October 2000. In October 2000 the study underwent CIRO audit. There were no significant discrepancies noted on that review.

CONCLUSIONS

Myopic PRK has proven safe and effective in the treatment of Army soldiers. Questions remain unanswered regarding the effects on visual function and duty performance and the role of LASIK. The study modifications allow us to begin to address some of these questions. Patient enrollment is on hold until we receive final approval of the protocol modification requests.

Report Date: 29 August 2000

Work Unit # 00-2401

DETAIL SUMMARY SHEET

TITLE: The Effect of Pedicle Screw Fit Using Image-Guided Surgery Techniques

KEYWORDS:

PRINCIPAL INVESTIGATOR: Polly, David LTC MC
ASSOCIATES:

DEPARTMENT: Orthopaedics and Rehabilitation
SERVICE: Orthopaedic Surgery

STATUS: O
INITIAL APPROVAL DATE: 05 October 1999

STUDY OBJECTIVE

To assess the effect of pedicle screw fit using image guided surgery techniques.

TECHNICAL APPROACH

A cadaveric study that will assess the accuracy of pedicle screw placement with and without the use of Stealth 3-D imaging.

PRIOR AND CURRENT PROGRESS

Waiting for the availability of cadaveric specimens from USUHS.

CONCLUSIONS

Study in progress.

Report Date: 29 August 2000 Work Unit # 00-2402

DETAIL SUMMARY SHEET

TITLE: A Comparison of Standard Intraoperative Fluoroscopy vs. Fluoroscopy Using FluoroNav Stereotactic System

KEYWORDS:

PRINCIPAL INVESTIGATOR: Polly, David LTC MC
ASSOCIATES:

DEPARTMENT: Orthopaedics and Rehabilitation STATUS: O
SERVICE: Orthopaedic Surgery INITIAL APPROVAL DATE: 26 October 1999

STUDY OBJECTIVE

The primary objective of this study is to determine the amount of x-ray radiation used during the placement of spinal instrumentation with standard intraoperative fluoroscopy vs. fluoroscopy using the FluoroNav Stereotactic system.

TECHNICAL APPROACH

The investigator will perform the spinal fusion surgery using standard methods as determined by the investigator. The first ten procedures will be performed without the use of the FluoroNac system. The next twenty procedures will be performed with the use of the FluoroNav system. To allow surgeons to become familiar and comfortable with the system, the first ten of the twenty procedures with the FluoroNav will be treated as the learning curve. In the event the FluoroNav system experiences operational difficulty, standard fluoroscopy will be used.

During all procedures, the amount of time required to place all instrumentation will be recorded on the case report form. The beginning of instrumentation placement will be deemed as the placement of the first awl, curette, probe or drill that begins the exposure of the bone for subsequent instrumentation placement. The beginning should be announced to the OR personnel responsible for recording time. The end of the instrumentation placement will be deemed as the placement of the last surgical instrument or confirming fluoroscopic image of implant(s), if taken. This point in the procedure should also be announced for recording purposes.

At the end of the procedure, the amount of radiation exposure as measured by the c-arm manufacturer's timing mechanism shall be recorded on the case report form. Also, other operative facts such as total OR time and number of implants placed will be recorded.

PRIOR AND CURRENT PROGRESS

To date, data has been collected on the ten procedures where FluoraNav was not used and three of the twenty using FluoroNav have been completed and the data recorded.

CONCLUSIONS

The study is in progress and any conclusions would be premature at this time.

Report Date: 28 August 2000 Work Unit # 00-2403

DETAIL SUMMARY SHEET

TITLE: The Relationship of Femoral Notching, Osteoporosis, and Supracondylar Fractures

KEYWORDS: femoral notching, total knee arthroplasty, osteoporosis

PRINCIPAL INVESTIGATOR: Scott B. Shawen, CPT MC
ASSOCIATES: William Klemme, LTC MC; John Xenos, LTC MC; Philip J. Belmont, Jr., CPT MC; Joseph Orchowski, CPT MC, Timmie Topoleski, Ph.D.

DEPARTMENT: Orthopaedics and Rehabilitation
SERVICE: Orthopaedic Surgery

STATUS: O
INITIAL APPROVAL DATE: 30 November 1999

STUDY OBJECTIVE:
To examine the effect of femoral notching and osteoporosis on femoral torsional strength.

TECHNICAL APPROACH:
- Obtain cadaveric femurs for study (13 paired femurs)
- Perform DEXA scan to the proximal/distal femur to determine bone mineral density
- Take radiographs of femurs to rule out evidence of bony tumor
- Randomize femurs into "notched" and "un-notched" groups
- Perform CT scans of femurs to determine cortical thickness and amount of notching
- Perform mock total knee replacement surgery to femurs, notching selected specimens
- Embed specimens in fixtures and perform torsional testing for strength (N-m)
- Dispose of specimens
- Analyze data utilizing Student's t-test and correlation values
- Review data and statistics with biostatistician

PRIOR AND CURRENT PROGRESS:
- 26 femurs (13 pairs) were obtained from University of MD through USUHS (February-April 2000)
- DEXA Scan femurs (April-May 2000)
- Take radiographs of femurs (April-May 2000)
- Mock surgeries performed at USUHS (April-May 2000)
- CT scans of femurs performed at WRAMC (April-May 2000)
- Mechanical testing performed at University of Maryland (April-May 2000)
- Specimens disposed of at USUHS
- Data analyzed utilizing Student's t-test and correlation values obtained
- Data and statistics reviewed with Ms. Robin Howard (June 2000)
- Manuscript in preparation (present)

CONCLUSIONS:
Femoral notching significantly decreases the torsional strength of the distal femur. Proximal and distal bone mineral densities correlated consistently. Torsional strength measurements were closely correlated to bone mineral density.

Report Date: 09 April 2001

Work Unit #00-2404

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: The Radioscaphoid Interval. A Sensitive Indicator of Early Perilunar Instability

KEYWORDS: Wrist, Instability, Radiographic correlation

PRINCIPAL INVESTIGATOR: Kenneth Taylor, MAJ MC
ASSOCIATES: Philip Belmont CPT MC, Scott Shawnen CPT MC, Christopher Litts MAJ MC

DEPARTMENT: Orthopaedics and Rehabilitation
SERVICE: Orthopaedic Surgery

STATUS: O
INITIAL APPROVAL DATE: 18 April 2000

STUDY OBJECTIVE

To establish the diagnostic sensitivity and specificity of the radioscaphoid interval in determining early peripheral carpal instability.

TECHNICAL APPROACH

Patients presenting to the WRAMC Orthopaedic Hand Surgery clinic with physical examination consistent with carpal instability, and matched controls meeting inclusion/exclusion requirements are being enrolled in this study. Measurement from plain film radiographs, clinical examination data and subsequent inoperative findings are recorded as previously outlined in the DCI-approved protocol. There have been no modifications to the methodology of this study.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

There have been no significant additions to the current orthopaedic literature concerning the topic of this study. In order to assure blinded assessment by the investigator, no radiographic measurements have been performed to date as only subject in the treatment have been enrolled. Matching with control subjects will begin once we approach that which was determined by power analysis. Of note, this has not resulted in delay of appropriate surgical intervention as the operative surgeon is by design also blinded to these additional measurements. No subjects have withdrawn from the study and there have been no adverse events.

The number of subjects enrolled to the study since last APR at WRAMC is 8 and the total enrolled to date at WRAMC is 8. The total number enrolled study-wide is N/A, if multi-site study.

CONCLUSIONS

Patients will continue to be enrolled in this study in accordance with DCI-approved protocol.

Report Date: 19 June 2001

Work Unit # 00-2405

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: MOSS-Miami and VertiGraft 2 Open-Label Study # 199901

KEYWORDS:

PRINCIPAL INVESTIGATOR: Polly, David LTC MC
ASSOCIATES:

DEPARTMENT: Orthopaedics and Rehabilitation
SERVICE: Orthopaedic Surgery

STATUS: O
INITIAL APPROVAL DATE: 22 August 2000

STUDY OBJECTIVE

The VertiGraft2 with the MOSS®-MIAMI® Spinal Fixation System has been approved by the FDA for treatment of spondylolisthesis and it is commercially available. The purpose of this study is to assess the performance of the implant using a transforaminal lumbar interbody infusion (TLIF) procedure and report the outcomes. The basis of comparison for this study is the historical controls from prior surgeries and previous WRAMC experience.

TECHNICAL APPROACH

Preoperative Evaluation: Within three months prior to the surgical intervention procedure, the study subject must be evaluated using the standard health status survey (SF-36) and the Oswetry Disability Index, which they will complete. All procedures in this protocol are normal standard of care. The research part of this study comes from the data collection information from the SF-36, the Oswestry Disability Index and the Clinical Evaluation sheets.
Surgical Procedure: On the date of the surgery, the Operative Case Report Form will be completed to include all relevant and required surgical data.
Postoperative Evaluations: The study subject is allowed to ambulate when able to do without undue discomfort and at the discretion of the Investigator. The study subject will be discharged when afebrile and ambulating comfortably, as soon as deemed appropriate by the Investigator.
Radiographic Evaluation: In addition to the radiographic evaluation performed prior to surgery, all subjects will be evaluated postoperatively by radiograph. The films will be evaluated on the basis of the standard for fusion ratings. The criteria for the standards are: a score of 0 = no fusion procedure performed, 1 = obvious Pseudoarthrosis, 2 = Possible Pseudoarthrosis, 3 = Fusion status uncertain, 4 = Probable fusion and 5 = Fusion (included sentinel sign and/or bridging trabecular bone). The radiographic views required include: A-P and lateral views, at all time frame points. The flexion and extension views will be done at the twelve (12) month and the twenty-four month follow-ups. In addition to these radiographic views, a CT scan will be performed at the three (3) month follow-up. These views are normal standard of care to all patients. There have been no modifications to this study.

PRIOR AND CURRENT PROGRESS

There have been no amendments or modifications to the study. Total number of patients enrolled in this study is 23. With one patient withdrawn due to patient's voluntary withdrawal. There have been two adverse events. One patient was in a motor vehicle accident at 12 weeks post-op with no significant adverse sequelae present. The second patient had an intra-operative pedicle fracture of her right L5 pedicle. A routine CT was done to verify that the screw placement was still okay. Three weeks post-op when her 100-pound dog jumped on her, her pain worsened. She returned to the clinic for evaluation. Her screw displaced further and she went back to the OR to have the screw removed. The number of subjects enrolled to the study since last APR at WRAMC is 23 and the total enrolled to date at WRAMC is 23. The total number enrolled study-wide is 0, if multi-site study.

CONCLUSIONS

None to date.

Report Date: 24 August 01

Work Unit #00-2406

DETAIL SUMMARY SHEET

TITLE: The Porous-Coated Anatomic Total Hip Prosthesis, Inserted Without Cement; Results After 15 years in prospective study

KEYWORDS: Uncemented, total hip arthroplasty, porous coating

PRINCIPAL INVESTIGATOR: Xenos, John S. LTC, MC
ASSOCIATES: Bojescul, John A. CPT, MC

DEPARTMENT: Orthopaedics and Rehabilitation
SERVICE: Orthopaedic Surgery Service

STATUS: O
INITIAL APPROVAL DATE: 12 September 2000

STUDY OBJECTIVE

To determine the long-term durability of the Porous-Coated Anatomic Total Hip Arthroplasty at least 15 years of follow-up.

TECHNICAL APPROACH

No new modifications. In 1983 we began a prospective study of 100 total hip arthroplasties using the PCA system. We have published the 2, 5-7 and 10 year results. We have recently completed the 15-yearfollow-up and have presented the results at the American Academy of Orthopaedic Surgeons. We analyzed the PCA system for a number of revisions, loosening, osteolysis and migration. We performed internal X-rays of the patients at their normal 15 year follow-up. All of our measurements were taken from the internal X-rays of the hip.

PRIOR AND CURRENT PROGRESS

There is no new literature. We are the first to begin to publish the results of an uncemented total hip system at 15 years. Currently, there are 55 patients (64 hips) enrolled in this study. All living patients were included in this study. There have been no adverse effects in this study. This is a minimal risk protocol without any deviations from standard of care, therefore, we do not expect any adverse effects. We analyze the radiographs taken at normal intervals during normal follow-up.

CONCLUSIONS

The ace tabular component has an 84% survival rate at 15 years. The femoral component has a 92% survival rate and the PCA system as a whole has an 88% survival rate at 15 years.

Report Date: 18 March 2001 Work Unit #2402

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: The Effect of Rigid Orthoses on Weight-Bearing Radiographs of the Adult Foot - A Cadaver Study

KEYWORDS: Rigid, Orthoses, Adult Cadaver Foot Study

PRINCIPAL INVESTIGATOR: McHale, Kathleen COL MC
ASSOCIATES: Bojescul, John CPT MC; Taylor, Kenneth CPT MC

DEPARTMENT: Orthopaedics & Rehabilitation
SERVICE: Orthopaedic Surgery

STATUS: C
INITIAL APPROVAL DATE: 08 April 1997

STUDY OBJECTIVE

To assess the radiologic change effected by use of a rigid arch support on the foot.

TECHNICAL APPROACH

X-rays are taken before and after application of a rigid arch support to the plantar surface of a cadaver foot in weight-bearing position. The cadaveric lower extremity was weighted with 50-75 pounds for the simulated weight-bearing films to effect the weight applied by the average young child/young adult who may need orthotics.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Total number of 23 cadaver feet were used in this study. The study is complete with the abstract completed and the paper being written.

CONCLUSIONS:

Rigid orthotics do not significantly change a patient's foot parameters (i.e. measurement angles) except in the most severe hallux valgus state.

Report Date: 8 March 2001 Work Unit # 2407-98

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: An Open-Label, Randomized, Parallel-Group Study to Confirm the Safety and Efficacy of PROCRIT (Epoetin Alfa) Administered Perioperatively vs. the Standard Care in Blood Conservation in Subjects Undergoing Major Elective Spinal Surgery

KEYWORDS:

PRINCIPAL INVESTIGATOR: LTC David Polly MC
ASSOCIATES:

DEPARTMENT: Orthopaedic Surgery and Rehabilitation STATUS: C
SERVICE: Orthopedic Surgery INITIAL APPROVAL DATE: 07 July 1998

STUDY OBJECTIVE
To compare the efficacy of erythropoetin alone to autologous blood donation in minimizing heterologous blood transfusion and associated in adult spinal surgery.

TECHNICAL APPROACH
WRAMC is a site in a multi-center FDA Randomized controlled clinical trial comparing erythropoetin to autologous donation for spinal surgery in adults.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
To date, three subjects have been recruited for the study. Two subjects were unable to participate as they lived too far away to make the required trips to WRAMC and one subject's hemoglobin outside of acceptable range for participation in study.

CONCLUSIONS
The study design is incompatible with the lifestyle of most active military spine patients and their dependents. For that reason, a decision has been made to withdraw from the study.

Report Date: 30 November 2000 Work Unit # 2410-99

DETAIL SUMMARY SHEET (Human Use Protocol)

TTTLE: Braided Hamstring Grafts vs. Unbraided Grafts and Pastellar Tendon Graft: A Biomechanical Study

KEYWORDS: ACL reconstruction, Hamstring tendons, Biomechanics

PRINCIPAL INVESTIGATOR: Tis, John CPT MC
ASSOCIATES: William R. Klemme MD LTC

DEPARTMENT: Orthopaedics
SERVICE: Orthopaedic Surgery

STATUS: C
INITIAL APPROVAL DATE: 09 February 1999

STUDY OBJECTIVE

To determine whether braided or unbraided hamstring tendons offer significant biomechanical advantages/disadvantages when used for ACL (knee) reconstruction

TECHNICAL APPROACH

Mechanical clamps with teeth were used instead of hydraulic clamps to hold the tendons in place during mechanical testing. These were chosen because of comparable fixation and availability.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

The biomechanical comparison and statistical analysis has been completed. The manuscript is in process and should be completed shortly.

CONCLUSIONS

The study demonstrates a statistically significant biomechanical disadvantage for woven hamstring tendons. The manuscript will be completed by January 2001. The protocol can be closed.

Report Date: 21 February 2001 Work Unit # 2411-99

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: The Effect of Tibial Malrotation on the Tibiotalar Joint Contact Area

KEYWORDS: Malrotation, Tibiotalar Joint

PRINCIPAL INVESTIGATOR: McHäle, Kathleen COL MC
ASSOCIATES: Svoboda, Steven CPT MC

DEPARTMENT: Orthopaedics and Rehabilitation
SERVICE: Orthopaedic Surgery

STATUS: C
INITIAL APPROVAL DATE: 09 March 1999

STUDY OBJECTIVE

To determine the effects of tibial malrotation on the biomechanics of the tibiotalar joint.

TECHNICAL APPROACH

We performed a cadaveric study using lower extremities mounted in a load frame in a materials testing device. A pressure monitoring system was used to record contact areas, total loads, and peak pressures

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

We complemented the study by also determining the peak pressures and total loads in the joint in addition to the contact area. This was a cadaveric study that used 23 fresh frozen specimens.

CONCLUSIONS

We found that all rotational conditions decreased joint contact area and that peak pressures with highest at the extremes of internal and external rotation. Total load was found to decrease as tibial rotation increased in either direction. Rotational deformities were found to have significant effects on the biomechanics of the tibiotalar joint and should be minimized.

Report Date: 15 March 2001

Work Unit # 2412-99

DETAIL SUMMARY SHEET

TITLE: A Prospective and Randomized Controlled Study to Evaluate the Performance of Inflatable Bone Tamps in the Percutaneous Treatment of Painful Osteopenic Vertebral Body Compression Fractures

KEYWORDS:

PRINCIPAL INVESTIGATOR: Polly, David LTC MC
ASSOCIATES: Klemme, William LTC MC; Depper, Mark MAJ MC

DEPARTMENT: Orthopaedics and Rehabilitation
SERVICE: Orthopaedic Surgery

STATUS: C
INITIAL APPROVAL DATE: 25 May 1999

STUDY OBJECTIVE
To compare kyphoplasty to medical therapy for treatment of acute osteoporotic compression fractures.

TECHNICAL APPROACH
This is a prospective, randomized, multicenter study. Kyphoplasty is a four step procedure performed under general or local anesthesia:
Step 1 – a narrow half-inch incision is made in the back creating a small pathway into the fractured bone.
Step 2 – a small orthopaedic balloon is placed through the pathway into the fractured vertebra.
Step 3 – the balloon is inflated, raising the collapsed vertebra. The balloon is then removed leaving a space.
Step 4 – the space is filled with a material to support the bone and prevent further collapse

PRIOR AND CURRENT PROGRESS
This protocol was approved by the WRAMC HUC on 25 May 1999 and by CIRO on 12 October 1999. This study has two previous addenda. Addendum #2, dated 5 May 1999, has been submitted to WRAMC DCI. Addendum #3, dated 8 May 2000, calls for a single revision to the original protocol that was approved at WRAMC. After discussion with the study's principal investigator, Kyphon has decided to modify the protocol observation that patients treated outside this protocol during the past three months have had an average fracture age of 14 weeks, with a minimum of up to 61 weeks. Increasing the maximum allowable fracture age limit to six months is both safe and appropriate. To date no patients have enrolled in this study at WRAMC. The sponsor for this study remains Kyphon, Inc., 3110 Coronado Drive, Santa Clara, CA 95054.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 0. The total number enrolled studywide is 0, if multi-site study.

CONCLUSIONS
The study was approved 10/23/98 and to date no subjects have been enrolled. A decision has been made to close the trial at WRAMC.

Report Date: 01 September 2000 Work Unit # 2496

DETAIL SUMMARY SHEET

TITLE: PRO OSTEON Implant 500 Coralline Hydroxyapatite Bone Void Filter for Use in Filling the Iliac Crest Bone Donor Site

KEYWORDS: bone graft, spinal fusion, hydroxy appetite

PRINCIPAL INVESTIGATOR: Polly, David LTC MC
ASSOCIATES:

DEPARTMENT: Orthopaedics and Rehabilitation STATUS: O
SERVICE: Orthopaedic Surgery INITIAL APPROVAL DATE: 29 October 1996

STUDY OBJECTIVE

Bone substitutes are being developed for various applications. Coralline hydroxy appetite is commercially available for use in the human body. Its capacity to induce bone formation in the human body has not been well documented. This study is designed to document the effect of HA on bone formation.

TECHNICAL APPROACH

For spinal fusions, bone is harvested from the iliac crest. Previous work done at WRAMC has shown that the donor site does not regenerate bone. In this study, half of the patients have the donor site backfilled with HA, half have no backfill. They are followed with imaging studies.

PRIOR AND CURRENT PROGRESS

A total of 12 patients were enrolled before enrollment closed. Four patients have not completed the 2-year follow up and arrangements are being made to facilitate their completion.

CONCLUSIONS

The data set remains incomplete. Initial evaluation appears to show that the corraline hydroxy appetite shows activity on bone scan at 1-year post surgery.

Report Date: 28 August 2000

Work Unit # 00-2501

DETAIL SUMMARY SHEET

TITLE: Spectro-Temporal Properties of Auditory-Visual Integration for Understanding Spoken Language

KEYWORDS: Speech Recognition, Auditory-Visual, Sensory Integration

PRINCIPAL INVESTIGATOR: Kenneth W. Grant
ASSOCIATES: Steven Greenberg, Ph.D., International Computer Science Institute, Berkeley, CA

DEPARTMENT: Surgery
SERVICE: Army Audiology and Speech Center

STATUS: O
INITIAL APPROVAL DATE: 30 November 1999

STUDY OBJECTIVE:
To determine the effects of across-modality temporal asynchrony on the recognition of nonsense syllables and sentences.

TECHNICAL APPROACH:
Speech sentence materials and nonsense syllables were filtered into two or four narrow spectral slits with at least one octave separation between adjacent slits. In the main condition, the audio signal consisted of two filtered speech bands making up the low and high end of the speech spectrum (i.e., 298-375 Hz and 4762-6000 Hz). The visual channel consisted of a video image of female speaker of American English (head, neck, and shoulders) speaking each of the different speech tokens. The stimuli were presented audiovisually with a range of temporal asynchrony conditions between audio and visual stimulus components (-400 ms – audio leading to 400 ms – video leading) being tested. The subject task was to either press a designated area on a touch screen terminal, write down on paper, and or speak back verbatim what s/he heard. Touch screen responses are stored on computer for later analyses.

PRIOR AND CURRENT PROGRESS:
Six normal hearing subjects have completed the protocol using sentence materials with no adverse effects reported. A seventh subject has been recruited and has begun testing. A total of ten subjects will be enrolled in the project. Results from the subjects who have completed testing has been tallied and plotted and presented to study the sponsor (The International Computer Science Institute, Berkeley, CA). An initial report of a portion of these data was presented at the International Hearing Aid Research Conference, Lake Tahoe, CA (23 August-27 August, 2000).

CONCLUSIONS: Although there are substantial differences across subjects regarding their overall speech recognition scores, the pattern of performance as a function of cross-modality temporal asynchrony is remarkably similar. Al subjects thus far obtain their best speech recognition performance when audio signal is slightly delayed with respect to the visual signal (approximately 80-120 ms). Sentence recognition scores for zero audio delay (i.e., synchronous condition) through approximately 200 ms were fairly similar and relatively high (compared to the visual alone or audio alone conditions). In contrast, when the audio signal led the visual signal, sentence recognition scores fell off as precipitously demonstrating a highly asymmetric temporal speech integration window when audio and visual speech signals are combined.

Report Date: 15 November 2000 Work Unit # 00-2502

DETAIL SUMMARY SHEET

TITLE: Efficacy of Endobrondial Adhesives in Experimental Lung Volume Reduction

KEYWORDS: Endoscopic, cyanaocrylate, volumetric lung reduction

PRINCIPAL INVESTIGATOR: LTC Mair
ASSOCIATES: CPT Cote, MAJ Lane

DEPARTMENT: Surgery
SERVICE: Otolaryngology

STATUS: O
INITIAL APPROVAL DATE: 7 December 1999

STUDY OBJECTIVE:
Study the safety and effectiveness of endoscopic cyancrolate volumetric lung reduction (ECVLR0 of the right upper lobe in a goat model. This protocol studies a new non-surgical minimally invasive alternative for treatment of severe chronic obstructive pulmonary disease.

TECHNICAL APPROACH:
Under general anesthesia, the right upper lobe bronchus is bronchoscopically occluded with a biocompatible cyanoacrylate in hopes of reducing lung volume. No change from protocol.

PRIOR AND CURRENT PROGRESS:
All 10 animals underwent ECVLR without complication. Serial radiography and endoscopy was accomplished as set forward in the protocol. An animal was found dead in his cage 3 months after the procedure. This was presumably due to partial obstruction of the glue with a subsequent development of pneumonia. Histopathology is pending. All 10 animals were enrolled in the protocol. There have been no animals withdrawn from the study.

CONCLUSIONS:
Results and conclusions pending analysis of data.

Report Date: 3 January 2001 Work Unit # 00-2503

DETAIL SUMMARY SHEET (Human Use Protocol)

TTTLE: Auditory-Visual Integration for Improved Human/Machine Interaction

KEYWORDS:

PRINCIPAL INVESTIGATOR: Grant, Kenneth Ph.D.
ASSOCIATES:

DEPARTMENT: Surgery
SERVICE: Army Audiology & Speech Center

STATUS: O
INITIAL APPROVAL DATE: 22 February 2000

STUDY OBJECTIVE

This is a multi-year umbrella grant submitted to the National Science Foundation (NSF). The primary goals of the grant are to characterize in detail the pattern of co-modulated activity shared in common between the visible speech articulators and the acoustic output associated with the speech utterance under a variety of background conditions and to apply the insights and quantitative data obtained to improve the performance of both automatic speech recognition and speech synthesis.

TECHNICAL APPROACH

To achieve the various goals outlined in the proposal several study areas have been identified. These are:

1. Identify the parts of a talking face that are primarily responsible for shielding the acoustic speech signal from background noise,
2. Determine the robustness of bimodal masking protection by substituting animated and synthetic objects for natural faces and speech sounds,
3. Computationally model the human behavioral results on speech detection in noise by developing new procedures for integrating visible speech information with acoustic speech signals based on recent research pertaining to the importance of the low-frequency modulation spectrum for intelligibility, and
4. Develop software "agents" (talking avatars) that can be used to assist human/computer interactions via integration of appropriate visual movement and synthesized speech.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Efforts to fund this proposal are ongoing. The proposal was not funded by the NSF in its current form. Efforts to revise and/or resubmit this proposal to other funding agencies are underway.

CONCLUSIONS

No subjects have been contacted and no studies have been initiated due to lack of funding.

Report Date: 01 March 2001 Work Unit #00-2504

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: Radiofrequency Ablation of Oral Lymphangiomas, A Pilot Study

KEYWORDS: Radiofrequency Ablation, Lymphangiomas

PRINCIPAL INVESTIGATOR: Benjamin Cable
ASSOCIATES: Eric Mair

DEPARTMENT: Surgery
SERVICE: Otolaryngology

STATUS: O
INTIAL APPROVAL DATE: 18 April 2000

STUDY OBJECTIVE
To determine the efficacy of radiofrequency ablation techniques in the treatment of patients with oral lymphangiomas.

TECHNICAL APPROACH
Pilot Study, single therapy

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
No new data is available in the literature regarding this subject. An update literature review was completed in February 2001.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 0. The total number enrolled study-wide is 0, if multi-site study.

CONCLUSIONS
Two prospective candidates were available this year but were unable to travel to WRAMC for logistical reasons. (One was a foreign national that was denied secretary of defense status.) As the overall population with this disease is relatively small, we would request that this protocol be continued.

Report Date: 14 July 2001

Work Unit # 00-2505

DETAIL SUMMARY SHEET

TITLE: Investigation of Alternative Sclorotherapy Agents for Injection Snoreplasty Palatal Stiffening Using the Beagle Canine Model: Pilot Study.

KEYWORDS:

PRINCIPAL INVESTIGATOR: Eric A. Mair, LTC MC USAF
ASSOCIATES: Scott E. Brietzke, CPT MC USA

DEPARTMENT: Surgery
SERVICE: Otolaryngology

STATUS: O
INITIAL APPROVAL DATE: 6 June 2000

STUDY OBJECTIVE

The objective of this study is to investigate the use of hyper tonic saline, ethyl alcohol, tetracycline, and palatal implants as potential palatal sclerotherapy/stiffening agents for the treatment of snoring as compared to the current agent in use, Sotradecol. Each agent's efficacy as a palatal stiffening agent will be investigated and compared to Sotradecol using a previously employed canine model. Agents that cause significant palatal mucosal breakdown will be ruled out as potential agents for use in humans.

TECHNICAL APPROACH

Twenty-four adult beagles of the approximate same size and weight were utilized for this protocol. The twenty-four dogs will be divided randomly into six palatal injection groups: Group 1 (4 dogs) will be a saline (0.9% Normal Saline) palatal injection control group, Group 2 (4 Dogs) will be a sotradecol (1% Sotradecol®, Elkins Sinn Inc., Cherry Hill, NJ, USA) injection group, Group 3 (4 dogs) will be a hypertonic (23.6% normal saline) saline injection group, Group 4 (4 dogs will be an ethyl alcohol (99% inject able) injection group, Group 5 (4 dogs) will be a tetracycline (10mg/cc solution, inject able) injectin group, and Group 6 (4 dogs) will be a palatal implant group

Each animal is to undergo three separate procedures during which the snoring level will be measured using the above technique. The first will be a baseline snoring measurement that will be immediately followed by a palatal injection of the selected sclerothrapy agent (Isotonic saline, Sotradecol®, Hypertonic saline, Ethyl alcohol, tetracycline, or palatal implant. The animals will be recovered and a period of 3-4 weeks will elapse between procedures. During this time, the animal's weight and oral intake will be carefully monitored on a daily basis as will the injection site and neck incisions. The second procedure will consist of a repeat measure of snoring as well as a repeat application of the selected sclerotherapy agent if snoring is still present. After another period of three to for weeks to allow sufficient scar formation, the third and final procedure will be performed and will consist of a final measurement of snoring, as well the sacrifice of the animal and the harvesting of the palate for histologic analysis.

PRIOR AND CURRENT PROGRESS

All animal work has been completed. Data analysis is ongoing as is manuscript preparation for planned publication.

CONCLUSIONS

Ethyl alcohol appears to have palatal stiffening efficacy comparable to 3% Sotradecol. A human-use protocol has been approved and is ongoing currently.

Report Date: 13 July 2001 Work Unit # 00-2506

DETAIL SUMMARY SHEET

TITLE: Investigation of Different Methods for Performing Myringotomy Patency Using the Guinea Pig Model

KEYWORDS: Myringotomy, Mitomycin C, laser, needle myringotomy, guinea pig

PRINCIPAL INVESTIGATOR: LCDR George Pazos MC
ASSOCIATES: LtCol Eric Mair MC

DEPARTMENT: Surgery
SERVICE: Otolargynology

STATUS: C
INITIAL APPROVAL DATE: 5 July 2000

STUDY OBJECTIVE: Infection of the middle ear, especially in the pediatric population, is pervasive and demands a significant allocation of medical resources and personnel in its treatment and management. Introducing a treatment modality that would be less invasive and require less medical resources would have a major impact on our health care system. Using the guinea pig model, this study explores the average number of treatments, the therapeutic duration among various innovative treatment modalities used to treat ear infections and any sequela due to repeated applications of these treatment modalities. The modalities studied are as follows: Standard Myringotomy and Tympanostomy Tube Placement, Laser Assisted Myringotomy (LAM), Laser Assisted Myringotomy following the pre-treatment of the tympanic membrane with topical mitomycin C (LAMC), Needle Myringotomy, Needle Myringotomy following the pre-treatment of the tympanic membrane with topical mitomycin C (NMC)

TECHNICAL APPROACH: A total number of 51 animals were used for this study. Each guinea pig ear was randomly assigned to different treatment modalities or to the control group. Paparella Type I tubes were placed through a standard myringotomy. The OtoLAM CO2 laser (ESC/Sharplan, Yokneam, Israel) was employed for the creation ofLAM. Needle Myringotomy was performed with the use of the Channel Directed Tympanocentesis (CDT) device(Casper, Wyoming). For a period of four months, each tympanic membrane was visualized endoscopically on a weekly basis and was noted to be either patent (open) or closed. On odd numbered weekends, tympanic membranes noted to be closed were treated to re-establish patency with the treatment modality to which it was originally assigned. To allow for adequate healing, a period of 6 weeks was allowed to elapse between the end of this 4-month period of investigation prior to final endoscopic inspection and harvesting the tympanic membranes for histological analysis.

PRIOR AND CURRENT PROGRESS: During this 16-week period, tympanic membranes treated with the standard myringotomy and tympanostomy tubes required an average of 1.2 treatments to maintain patency for the entire study period with a median of 16 weeks and a range of 12 to 16 weeks. The group of tympanic membranes treated with LAM required an average of 6.3 treatments with a median of 7 weeks and a range of 2 to 15 weeks. For the group treated with Needle Myringotomy (NM) an average of 7.6 treatments were required to maintain patency with a median time of patency of 4 weeks and a range of 1 to 13 weeks. Laser Assisted Myringotomy following the pre-treatment of the tympanic membrane with topical Mitomycin C (LAMC) required on average 1.53 treatments with a median of 15 weeks and a range from 12 to 16 weeks. Needle Myringotomy following the pre-treatment of the tympanic membrane with topical Mitomycin C (NMC) required on average 2.37 treatments with a median of 14 weeks and a range of 11 to 16 weeks. Repeated applications of a treatment within a specific treatment group whether accompanied by Mitomycin C or not did not correlate to increasing duration of myringotomy patency.

CONCLUSIONS: We introduce the CDT, a device for performing speculum-assisted myringotomoy. LAMC and NMC offer a novel approach to establishing ventilation of the middle ear by extending the duration of patency created at the myringotomy. Although the duration of tympanic membrane patency with these two modalities approaches that of classic myringotomy with tympanostomy tube placement, failure rates for these two groups are higher

Report Date: 2 July 2001 Work Unit # 00-2507

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: Auditory Supplements of Speechreading

KEYWORDS: Audiovisual Speech Perception, Speechreading, Hearing-Impaired

PRINCIPAL INVESTIGATOR: Grant, Kenneth Ph.D. DAC
ASSOCIATES:

DEPARTMENT: Surgery STATUS: O
SERVICE: Army Audiology & Speech Center INITIAL APPROVAL DATE: 1 August 2000

STUDY OBJECTIVE
This is a 5-year NIH application describing a research program to further understand the benefits and limitations of auditory-visual speech recognition in normal and hearing-impaired individuals. The proposed studies include examinations of the effects of aging, hearing status, and visual acuity on speech recognition in noise and reverberation.

TECHNICAL APPROACH
Methods will include identification and discrimination of speech sounds (nonsense syllables, words, and sentences) with and without visual cues (i.e., speechreading). Speech signals will be presented in a variety of background noises and under conditions of room reverberation to simulate typical real-world conditions encountered by normal ad hearing-impaired individuals. Special purpose equipment to measure various aspects of static and dynamic visual acuity will be employed to determine if elderly subjects are placed under additional processing demands due to deteriorating peripheral vision, especially for motion detection.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
The proposed NIH grant application has not yet been approved. A revision to the original application will be submitted following receipt of reviewer's comments. To date, no studies have been initiated and no subjects enrolled.
The number of subjects enrolled to the study since last APR at WRAMC is __0__ and the total enrolled to date at WRAMC is __0__. The total number enrolled study-wide is ___, if multi-site study.

CONCLUSIONS
None

Report Date: 13 July 2001 Work Unit # 00-2508

DETAIL SUMMARY SHEET

TITLE: Storadecol Injection Sclerotherapy in the Base of Tongue for the Treatment of Sleep Apnea Using the Ferret Model

KEYWORDS: Ferret, Sleep Apnea, Tongue, Radiofrequency Ablation, Storadecol

PRINCIPAL INVESTIGATOR: CPT Scott E. Brietzke MC
ASSOCIATES: LtCol Eric Mair MC

DEPARTMENT: Surgery
SERVICE: Otolaryngology

STATUS: C
INITIAL APPROVAL DATE: 08 August 2000

STUDY OBJECTIVE

The purpose of this study is to evaluate injection sclerotherapy of the base of the tongue as an alternative to Radiofrequency Ablation (RFA) using the ferret animal model. Sclerotherapy is a technique in which an agent (a sclerotherapy agent, e.g. Storadecol) is injected into a tissue to produce a chemical "bum" by obliterating nearby blood vessels. It is postulated that the resulting injury from the chemical burn will produce a similar scar and a similar tissue reduction as with RFA. Sclerotherapy has already been demonstrated by the investigators to be a viable alternative to RFA of the palate for the treatment of primary snoring. Injection sclerotherapy of the tongue base has the potential to be an even simpler, much more inexpensive procedure than RFA. It could help fill a void in the outpatient treatment of moderate to severe sleep apnea secondary to BOT obstruction, and eliminate the need for many patients to undergo invasive surgery.

TECHNICAL APPROACH

Ten ferrets will be utilized in a small pilot study to optimize model design. Two ferrets will receive a saline control injection and four each will randomly receive a Storadecol injection or RFA to the base of tongue. Serial endoscopy will be performed on a weekly basis after treatment to assess for the visual evidence of treatment effectiveness, e.g. tongue induration, visible scar at treatment site, palpable stiffening, visible tongue volumetric reduction or airway space enlargement. After four weeks, the tongues will be harvested and the precise details of the standardized harvesting procedure will be finalized at this time. The volume and mass of the specimens will be measured and compared as detailed in the protocol described above. If there is no visual evidence of treatment effectiveness in the RFA or Storadecol groups and/or less than 15% measured reduction in tongue volume or mass as compared to the saline controls, the study will be halted and the model reassessed

PRIOR AND CURRENT PROGRESS

The animal work with the ten animal pilot study has been completed. One animal in the storadecol group developed a severe tongue infection and had to be euthenized. The tongues were harvested at the 4-week period as planned. There was significant difference in the appearance, weight, volume, or density of either the RFA group or the storadecol group versus the control group. Final histologic analysis is still pending. We are currently reassessing model design given the lack of findings as stipulated by the protocol.

CONCLUSIONS

There are significant concerns with the validity of this animal model and the safety of the procedure of base tongue sclerotherapy. We are re-examining the animal model and clinical feasibility of this procedure. No active plans have been made to enroll any further animals into this protocol as currently designed.

Report Date: 5 September 2001 Work Unit # 00-2509

DETAIL SUMMARY SHEET (Animal Protocol)

TITLE: The Determination of a Suitable Animal Model for Teaching Endoscopic Surgery of the Paranasal Sinuses Based on CT Imagining, Endoscopic Examination and Anatomical Skull Analysis

KEYWORDS:

PRINCIPAL INVESTIGATOR: Casler, John LTC MC
ASSOCIATES:

DEPARTMENT: Surgery STATUS: O
SERVICE: Otolaryngology INITIAL APPROVAL DATE: 5 September 2000

STUDY OBJECTIVE:
This study is in the final appoval process and has not started.

TECHNICAL APPROACH:
This study has not received final approval.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE:
This study has not received final approval.

CONCLUSIONS:
None.

Report Date: 9 July 2001 Work Unit # 00-2510

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: Characteristics of Everyday Listening Situations Which Favor Either Omnidirectional or Directional Hearing Aid Microphones

KEYWORDS: hearing aids, two microphone modes, characteristics of everyday listening situations, daily journal, preference scale

PRINCIPAL INVESTIGATOR: Surr, Rauna CIV
ASSOCIATES: Cord, MT, Walden, BE, Summers, WV, and Olson, L.

DEPARTMENT: Surgery
SERVICE: Army Audiology & Speech Center

STATUS: C
INITIAL APPROVAL DATE: 12 September 2000

STUDY OBJECTIVE:
The purpose of the investigation was to characterize everyday listening situations in which hearing aid omni-directional and dual adaptive directional microphones provided a performance advantage to persons with impaired hearing.

TECHNICAL APPROACH:
Twelve hearing-impaired patients were fit binaurally with GN ReSound CANTA 770-D hearing aids. These are fully software based digital hearing aids that the user can switch into an omni-directional or a directional microphone mode (program or memory) of operation. The participants wore these hearing aids for six weeks. They were not informed of the specific differences between the two programs. Each day during this period the hearing-aid user was required to identify and to describe in detail one listening situation encountered in daily living in which one of the two programs (microphone configurations) provided superior performance in comparison to the other. A structured questionnaire ("daily journal"), with a preference rating scale and a scale for estimating speech intelligibility for each program, was used to obtain these data. These reports were reviewed at weekly clinic visits. In addition, standard laboratory tests (Connected Speech Test: CST) and field measures of hearing aid benefit (Profile of Hearing Aid Benefit: PHAB) were administered for each microphone mode at the end of the six-week period.

The preference ratings from the daily journal data were analyzed to determine the characteristics of listening situations favoring one microphone type or the other. The listening situations in which the omni-directional mode was preferred were considered as one group and the listening situations in which the directional mode was preferred were considered as a separate group. Each group of listening situations was then characterized according to the situational variables described in the daily journals such as the characteristics of the primary talker (e.g., gender, distance, location, loudness), the environment (e.g., type of space, size of space, furnishings), and the background noise (e.g., type of noise, loudness, location). A Chi-square test was employed to examine the possible differences between the two groups.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE:

The number of subjects enrolled in the study since last APR at WRAMC is 12 and the total enrolled to date at WRAMC is 12. One subject was removed from the study after two weeks of participation because he was unable to identify situations in which one or the other microphone mode was superior. Stated differently, the one subject who was withdrawn was unable to provide the data required for the study.

No new studies have been presented, to our knowledge, that specifically address the performance of omni-directional vs. directional hearing aid microphone modes in real-life listening situations. In the present study, as in many previous studies, the laboratory tests (CST) demonstrated a highly significant directional advantage for specific listening situations. In contrast, the PHAB results showed no significant advantage for either microphone mode across the four subscales of the inventory. A total of 382 daily journal entries were obtained from the 11 participants. Of these 155 (40.6%) were in favor of the

omni-directional and 227 (59.4%) in favor of the directional microphone mode, although an equal number of reports for each program had been requested.

The first notable finding of this study was that all participants reported difficulty in finding listening situations in which they could perceive a difference between the two microphone modes. Secondly, when a preference was perceived, it was most often relatively small, both in terms of preference ratings and intelligibility estimates. Thirdly, the listening situations that favored the directional mode were more frequent and stronger than those favoring the omni-directional mode.

In general, preference for either microphone was most often perceived indoors, when background noise was present, the talker in front and located relatively close to the listener, and in average or larger than average spaces. The omni-directional mode was favored relatively more frequently in listening situations in which the talker was in the back of the listener and at a greater distance, in relatively smaller size spaces, and in quiet. In addition, the omni-directional mode tended to be preferred out-of-doors. In contrast, the directional microphone mode tended to be preferred when the talker was in front, at closer distances, when the source of the background noise was TV, radio or music, and in average size rooms.

The preliminary results of this study were presented at the Annual Convention of American Academy of Audiology, April 2001, in San Diego, CA, and at Indiana University Hearing-Aid Outcome Measures Research Conference, May, 2001, Bloomington, IN. A manuscript for publication is in preparation.

CONCLUSIONS:

Experienced hearing aid users, newly fitted with switchable omni-directional/directional instruments, were able to perceive advantages in both modes of operation in specific types of everyday listening situations. The differences in the performance of the two microphones modes tended to be small but stronger for the directional mode. Further the directional was favored more frequently. The characteristics of the listening situations that favored one microphone type or the other were generally consistent with the engineering data for the two microphone types. The greater overall preference for the directional mode for most, but not all, of the subjects differed significantly from clinical experience with the earlier generation (fixed polar patterns) of directional microphones.

Report Date: 27 November 2000 Work Unit # 2550

DETAIL SUMMARY SHEET

TITLE: Neuromotor Control of Speech Rate During Syllable Repetition

KEYWORDS: speech rate, orofacial, EMG

PRINCIPAL INVESTIGATOR: McClean, Michael PhD
ASSOCIATES:

DEPARTMENT: Surgery
SERVICE: Army Audiology & Speech Center

STATUS: O
INITIAL APPROVAL DATE: 03 January 1996

STUDY OBJECTIVE:
To determine how orofacial muscle activity and movement vary with rate of syllable repetition, and to apply resulting physiologic data to development of a realistic computer model of the neuromotor mechanisms underlying speech rate control.

TECHNICAL APPROACH:
Acquisition of experimental data on orofacial motor control during speech involves the use of an electromagnetic movement recording system to study the kinematics of the lip, tongue and jaw during speech. Surface electrodes are used to obtain electromyographic (EMG) recordings of associated activity in lip and jaw muscle. Realistic computer stimulation eventually will be applied to better interpret resulting data in terms of neural and mechanical systems underlying rate control.

PRIOR AND CURRENT PROGRESS
No new EMG data have been acquired during the past year. Analysis of previously acquired kinematic data has been carried out, and work has continued on development of signal acquisition software for EMG data. A total of 3 subjects have been enrolled together, none during the past year. There has been no evidence of adverse events at any time during this protocol.

CONCLUSIONS
No conclusions have been warranted at this time.

Report Date: 27 September 2000

Work Unit # 2558

DETAIL SUMMARY SHEET

TITLE: Orofacial Movement Velocities in Adult Stutterers Undergoing a Motor Based Approach to Speech Therapy

KEYWORDS: stuttering, movement, therapy

PRINCIPAL INVESTIGATOR: McClean, Michael D., Ph.D.
ASSOCIATES:

DEPARTMENT: Surgery
SERVICE: Army Audiology & Speech Center

STATUS: C
INITIAL APPROVAL DATE: 19 November 1996

STUDY OBJECTIVE

The objective of this study is to determine the nature of changes in the movement velocities of the lips, tongue, and jaw during speech in adult stutterers prior to and following their participation in the CAFET speech therapy program. Specific questions concern the correlation levels relating the velocities of different structures, changes in velocity level with therapy and the association of velocity with clinical measures of speech performance.

TECHNICAL APPROACH

Movements of the upper lip, tongue blade, and jaw are recorded in the midsagittal plane during speech using a Carstens AG100 electromagnetic movement analyzer. Semi-automated measurement and analysis routines are used to extract peak tangential velocities associated with repetitions of the utterance " a bad daba". Resulting measures are read to a statistical spreadsheet for subsequent analysis.

PRIOR AND CURRENT PROGRESS

No additional subjects were run in this experiment during the past year. There were no adverse reactions, and no subjects have withdrawn from the study. Data measurement and analysis have been completed. Continued analyses have confirmed that there were marked individual differences in the pattern of speed change across the lips, tongue, and jaw associated with stuttering treatment. However a significant positive association was obtained across subjects between jaw opening speed and degree of reduction in stuttering severity following treatment. That is subjects showing the greatest improvements in speech performance showed reduced jaw speeds. Qualitative differences in the patterns of jaw speed across movements also were noted between individuals showing the greatest and the least reduction in stuttering severity following treatment.

CONCLUSIONS

Results suggest that reductions in jaw speed during speech have a fluency enhancing effect. This points to the potential value of biofeedback on jaw motor output in motor-based stuttering treatment programs. In agreement with previous studies of the PI, results indicate that jaw motor control may be especially important in understanding the mechanisms of speech disfluency.

Report Date: 01 March 2001 Work Unit # 2561

DETAIL SUMMARY SHEET

TITLE: The Incidence of Pharyngeal and Laryngeal Dysfunction Following the Anterior Cervical Approach: A Prospective Study

KEYWORDS: ACD, vocal cord paralysis

PRINCIPAL INVESTIGATOR: Benjamin Cable, MD
ASSOCIATES:

DEPARTMENT: Surgery
SERVICE: Otolaryngology

STATUS: C
INITIAL APPROVAL DATE: 28 January 1997

STUDY OBJECTIVE

To determine the true incidence of vocal cord dysfunction and pharyngeal dysfunction after the anterior cervical approach to the cervical spine via a prospective study

TECHNICAL APPROACH

The patient, after completing a questionnaire, undergoes videostroboscopy prior to and at set intervals after surgery is completed. If the patient has dysphagia or vocal cord paresis, he/she then undergoes a laryngeal EMG and/or modified barium swallow study.

PRIOR AND CURRENT PROGRESS

I administratively accept the PI role for this study with the PCS moves of the prior Principal Investigators. Since this time, I have reviewed the data with the speech therapy team and reviewed new progress within the literature. It was the determination of the team that the underlying question of this study has been answered by other works. A number of the data points being collected with acoustical analysis have recently been shown to poorly correlate with clinical outcomes. To date, no DCI funding has been used in the pursuit of data. No new patients have been enrolled in this study during the previous year. No patient enrolled in previous years experienced any complication from video-stroboscopic examination or acoustic analysis.

CONCLUSIONS

This protocol no longer offers the potential to contribute to the literature. I request that it be closed from active status.

Report Date: 29 January 2001

Work Unit #2565

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: Auditory Processing and Sensorineural Hearing Loss

KEYWORDS: hearing loss, active mechanism

PRINCIPAL INVESTIGATOR: Summers, Van Ph.D.
ASSOCIATES: Leek, Marjorie Ph.D.

DEPARTMENT: Surgery
SERVICE: Army Audiology & Speech Center

STATUS: O
INITIAL APPROVAL DATE: 14 March 1997

STUDY OBJECTIVE

This work unit is a grant proposal; submitted to the National Institutes of Health to obtain funding. The grant involves a physiological process in the inner ear referred to as the active mechanism. The research examines 1) a possible psychoacoustic means of evaluating active mechanism status in individual listeners and 2) the role of the active mechanism in improving signal detection and speech recognition in selected competing sounds.

TECHNICAL APPROACH

Each of the proposed experiments involves auditory testing of normally hearing and hearing-impaired listeners. The basic task of the subjects is similar to procedures used clinically to evaluate hearing. Subjects listen to sounds (both speech and non-sppech) over earphones while seated in a sound-treated booth and make responses indicating their detection or identification of these sounds by touching specific areas on a touch screen terminal.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Three experimental studies described in the NIH grant have been or are currently being carried out under individual work unit numbers. Experimental programming, pilot testing, and data collection, and manuscript preparation have been completed for two of these studies and the third is underway. No patients have been or will be enrolled under this work unit number for these three experiments.

An addendum to this work unit number was approved by the Human Use Committee on 20 June 2000 which will allow the remaining experiments described in the NIH grant to be carried out under this work unit number (experiment 5-8 on the grant). A revised consent form, appropriate to these experiments was approved at that time. Program development is currently underway for these experiments. No patients have been enrolled under this work unit number for experiments 5-8 on the grant.

CONCLUSIONS

The experimental data gathered to this point has been collected under separate work unit numbers and the conclusions are described in the Detail Summary Sheets for those work unit numbers.

Report Date: 05 July 2001 Work Unit # 2570

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: Hearing Loss and the Perception of Complex Sounds

KEYWORDS: hearing impairment, frequency resolution, time perception

PRINCIPAL INVESTIGATOR: Leek, Marjorie PhD
ASSOCIATES: Lentz, Jennifer PhD

DEPARTMENT: Surgery
SERVICE: Army Audiology & Speech Center

STATUS: O
INITIAL APPROVAL DATE: 26 August 1997

STUDY OBJECTIVE

Patients with hearing loss have difficulty understanding speech in noise because of many functional impairments within the ear, including reductions in the ability to carry out precise spectral and temporal analyses of sound. Studies in this program of research explore these analytic abilities in hearing-impaired and in normal hearing people, with the ultimate goal of increasing the benefits derived by hearing-impaired patients through the use of hearing aids.

TECHNICAL APPROACH

All of the experimental techniques used in these studies involve earphone presentation of sounds to a subject, who indicates his perception through the use of a touch-screen terminal. Experiments often require listeners to detect a low-intensity sound buried in noise or ask listeners to judge whether two sounds are the same or different. Acoustic stimuli are generated to test specific hypotheses concerning functional effects of hearing loss.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

This is a NIH grant that contains a number of experiments. During the past year, we have completed data collection on an experiment testing the changes in phase response of normal and impaired ears with increases in stimulus level. We have also nearly completed data collection on a study measuring perception of dynamic intensity contours by hearing-impaired listeners. The number of subjects enrolled to the study since the last APR at WRAMC is 10 and the total enrolled to date at WRAMC is 43. There have been no adverse reactions and no patients have withdrawn from these studies. There is no direct benefit to patients who participate in this study.

CONCLUSIONS

The phase response across frequency of normal-hearing listeners tends to flatten at higher stimulus levels, in a manner similar to the response in hearing-impaired persons. Both these findings are consistent with the broadening of auditory filters with level and hearing impairment and the resultant change in the filter's phase response. In determining the shape of dynamic contours in temporal waveforms (i.e., discriminating damped sounds from ramped sounds), performance increases with stimulus level for both normal hearing and hearing impaired listeners, but more rapidly for the latter group. The loss of comprehension in damaged cochleas does not adversely affect the discrimination of these complex sounds.

Report Date: 25 September 2000 Work Unit # 2572

DETAIL SUMMARY SHEET

TITLE: Determining the Prevalence of Occult Carotid Disease in Patients with Head and Neck Squamous Cell Carcinoma Using Color Flow Duplex Imaging

KEYWORDS: carotid disease, squamous cell carcinoma

PRINCIPAL INVESTIGATOR: Cote, Christopher CPT MC
ASSOCIATES: Casler, John LTC MC; Mair, Eric LtCol MC; Chang, Audrey PhD.; Blair, Elizabeth MAJ MC; Sinha, Christopher MAJ MC; O'Donnell, Sean LTC MC; Goff, James MAJ MC; Gillespie, David MAJ MC

DEPARTMENT: Surgery
SERVICE: Otolaryngology

STATUS: O
INITIAL APPROVAL DATE: 28 October 1997

STUDY OBJECTIVE

This is a cross-sectional study to find the prevalence of atherosclerotic carotid artery disease (ACAD) in the specific population of patients with a diagnosis of squamous cell carcinoma of the head and neck region. The specific objectives include the following:

1. To estimate the proportion of head and neck patients with clinically significant carotid stenosis with the use of noninvasive color flow duplex imaging.
2. To describe the characteristics of head and neck cancer patients in our population in terms of the demographic variables and risk factors for head and neck cancer and for carotid disease as identified in the literature.
3. To compare the difference, if any, between patients with and without carotid stenosis regarding the demographic variables and risk factors.

TECHNICAL APPROACH

Patients enrolled complete a standardized questionnaire and undergo carotid duplex scanning.

PRIOR AND CURRENT PROGRESS

To date, fifty patients have been enrolled. One patient found to have carotid disease and none found to have critical stenosis. Please refer to manuscript for more details.

CONCLUSIONS

While we cannot conclude from this study that widespread screening of HNSCCA patients with carotid duplex ultrasound should be done, head and neck surgeons should be carefully aware of the risk factors for cerebrovascular disease so that patients who do require further intervention may be identified. This includes careful history and physical exam, including auscultation of carotid arteries for bruits. We do know that the perioperative risk for stroke in these patients is significant and pre-operative intervention may improve the outcome for head and neck cancer patients.

Report Date: 27 March 2001

Work Unit # 2575

DETAIL SUMMARY SHEET

TITLE: The Association of Epstein-Barr Virus and Human Papilloma Virus in Sino-Nasal Undifferentiated Carcinoma and Esthesioneuroblastoma (1/98)

KEYWORDS: Epstein-Barr Virus; Human Papilloma Virus; Sino-Nasal Undifferentiated Carcinoma; Esthesioneuroblastoma; SNUC; EBV; HPV; polymerase chain reaction

PRINCIPAL INVESTIGATOR: Faulkner, Jeffrey CPT MC
ASSOCIATES: Sinha, Christopher M.D.; Adair, Carol M.D.

DEPARTMENT: Surgery
SERVICE: Otolaryngology

STATUS: T
INITIAL APPROVAL DATE: 13 January 1998

STUDY OBJECTIVE

a) Tests the hypothesis that Sinonasal Undifferentiated Carcinoma, like Undifferentiated Nasopharyngeal carcinoma contains genomic material of EBV and HPV.
b) Compares the presence of the EBV and HPV DNA in SNUC to their presence in poorly differentiated Esthesioneuroblastoma, a tumor that is frequently confused with SNUC histologically.
c) Explores the association of EBV and HPV with disease extent and clinical outcome.
d) Examines the role of EBV and HPV as markers in differentiating SNUC from poorly differentiated Esthesioneuroblastoma

TECHNICAL APPROACH

Eight samples of SNUC and sixteen samples of Esthesioneuroblastoma will be evaluated for the presence of HPV and EBV using polymerase chain reaction. If either is detected, then the presence will be confirmed with Southern Blot. Demographic information, tumor characteristics and health information will be collected on each sample and correlated with the findings.

PRIOR AND CURRENT PROGRESS

This study was terminated at the 27 March 2001 Human Use Committee meeting for failure to submit and annual progress report.

CONCLUSIONS

This study was terminated at the 27 March 2001 Human Use Committee meeting for failure to submit and annual progress report.

Report Date: 05 April 2001 Work Unit # 2577-98

DETAIL SUMMARY SHEET

TITLE: Influences of Masker Phase on Detection of Brief Signals

KEYWORDS:

PRINCIPAL INVESTIGATOR: Summers, Van Ph.D., DAC
ASSOCIATES:

DEPARTMENT: Surgery
SERVICE: Army Audiology & Speech Center

STATUS: O
INITIAL APPROVAL DATE: 05 May 1998

STUDY OBJECTIVE

Outer hair cells within the cochlea are thought to be the physiological source of an active mechanism which alters the internal representation of an input signal in important ways. In the presence of sensorineural hearing loss, the influence of the active mechanism is reduced or eliminated due to outer hair damage. This experiment involves a signal detection task, which may provide a psychoacoustic means of evaluating active mechanism status in individual listeners.

TECHNICAL APPROACH

Normal-hearing and hearing-impaired listeners are individually tested. The experimental task measures the signal-to-masker detection thresholds for brief tonal signals masked by broadband harmonic complexes which differ only in phase structure ("positive" and "negative" Schroeder phase). Differences in masking effectiveness between the two harmonic complexes and variability in performance based on the temporal position of the probe within each masker are examined.

PRIOR AND CURRENT PROGRESS

Data collection has been completed. The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 17. The total number enrolled study-wide is N/A, if multi-site study.
Presentations describing various aspects of the findings were made at the Joint Meeting of the Acoustical Society of America and European Acoustics Association in Berlin, Germany, March 1999 and at the meeting of the Association for Research in Otolayrngology in St. Petersburg, FL, February 2000. And based on this protocol appeared in the Journal of the Acoustical Society of America in November 2000. There have been no adverse reactions from subjects and there is no benefit to the subjects. Ten subjects served in all of the experimental test conditions. Scheduling constraints required that seven subjects serve in only a subset of the test conditions.

CONCLUSIONS

For normally hearing listeners, the temporal location of the probe signal within the positive-Schroeder masker had a large influence on masking effectiveness. The effect was greatest in testing at moderate presentation levels and diminished at high level. This effect was also greatly reduced in hearing-impaired listeners at all test levels. The results are consistent with active mechanism influences on performance by normal hearing listeners tested at moderate levels with this influence being reduced at high levels in the presence of cochlear damage.

Report Date: 20 July 2001

Work Unit # 2582-98

DETAIL SUMMARY SHEET

TITLE: Effects of Masker Phase Structure on Forward Masking

KEYWORDS: hearing-impaired, forward-masking, masking phase sensitivity

PRINCIPAL INVESTIGATOR: Summers, Van Ph.D. DAC
ASSOCIATES:

DEPARTMENT: Surgery
SERVICE: Army Audiology & Speech Center

STATUS: C
INITIAL APPROVAL DATE: 29 September 1998

STUDY OBJECTIVE

Outer hair cells within the-cochlea are thought to be the physiological source of an active mechanism, which alters the internal representation of an input signal in important ways. In the presence of sensorineural hearing loss, the influence of the active mechanism is reduced or eliminated due to outer hair cell damage. This experiment involves a forward-masking signal detection task, which may provide a psychoacoustic means of evaluating active mechanism status in individual listeners.

TECHNICAL APPROACH

This study involves a forward masking task in which harmonic complexes presented immediately prior to a brief tonal probe influence the ability to detect the probe. Normal-hearing and hearing-impaired subjects are tested.

PRIOR AND CURRENT PROGRESS

Data collection was completed in FY00. The results of the study were presented at the National meeting of the Association for Research in Otolaryngology. A total of twelve subjects have been enrolled in the study, including four subjects enrolled during FY00. None of the subjects have withdrawn from the study. There have been no adverse reactions nor has any subject withdrawn from the study. There is no benefit to the subjects.

CONCLUSIONS

The present forward-masking results agree with earlier findings using simultaneous masking in showing larger effects of masker phase structure on masking effectiveness at moderate levels than at high levels. These results are consistent with suggestions that nonlinear cochlear processing plays an important role in producing these phase effects. Very small phase effects seen for HI listeners are also consistent with this idea. These results provide further evidence that psychoacoustic masking tasks using harmonic complexes similar to those tested here may provide a valuable tool in assessing the degree of nonlinearity present in processing carried out in given listener's cochlea.

Report Date: 8 August 2000

Work Unit # 2583-99

DETAIL SUMMARY SHEET

TITLE: The Laryngeal Mask Airway as an Alternative to Endotracheal Intubation for prolonged Ventilatory Support in a Ferret Model of the Infant Airway

KEYWORDS: ferret, laryngeal mask, subglottic stenosis, prolonged ventilation

PRINCIPAL INVESTIGATOR: Mair, Eric LTC, MC
ASSOCIATES: Brietzke, Scott E. CPT, MC

DEPARTMENT: Surgery
SERVICE: Otolaryngology

STATUS: C
INITIAL APPROVAL DATE: 13 October 1998

STUDY OBJECTIVE

The purpose of this study is to evaluate the incidence and severity of glottic and subglottic injury resulting from prolonged intubation with the endotracheal tube (ETT) versus the LMA using the adult ferret as a model of the neonatal airway.

TECHNICAL APPROACH

A total of twenty-two adult ferrets have been utilized for this protocol. They were randomly intubated under inhalational anesthesia with a 4.0 cuffless ETT or a #1 LMA for a 24-48 hour period. Rigid laryngeal endoscopy was used to evaluate for pharyngeal/glottic injury during the period of intubation and on a routine basis post-extubation.

PRIOR AND CURRENT PROGRESS

A total of 22 ferrets were included in the study to include model development. Sixteen of the 22 animals were euthanized secondary to hyperthermia, aspiration or airway obstruction. Post-mortem analysis has been performed on all ferrets.

CONCLUSIONS

All ferrets in the ETT group developed endoscopically evident subglottic injury with some developing a symptomatic, mature subglottic stenosis. Ferrets in the LMA group had an endoscopically normal larynx. However, all ferrets in the LMA group developed notable tongue cyanosis and edema during the first 24 hours of intubation with multiple of ferrets expiring with respiratory failure due to airway obstruction. The main outcome from this study warns against long term LMA use. The manuscript was presented at the annual meeting of the American Bronchoesophagology Association in May 2000 in Orlando, FL.

Report Date: 22 October 2000 Work Unit # 2584-99

DETAIL SUMMARY SHEET

TITLE: A new treatment for Xerostemia in Postirradiated Head & Neck Cancer Patients

KEYWORDS:

PRINCIPAL INVESTIGATOR: Criswell, Mark MAJ MC
ASSOCIATES: Sinha, Christopher LTC MC

DEPARTMENT: Surgery
SERVICE: Otolaryngology

STATUS: O
INITIAL APPROVAL DATE: 29 October 1998

STUDY OBJECTIVE

To study the benefits of the Vapotherm MT-4000 personal humidifier in patients with xerostemia from radiation treatment of head and neck cancer

TECHNICAL APPROACH

No addenda

PRIOR AND CURRENT PROGRESS

Data collection is complete. Data analysis is ongoing. 12 total subjects were enrolled in the previous year and in total. 3 subjects were withdrawn. 2 of these were at patients' requests because of logistical difficulties in arranging the required 3 clinic visits within the required timeframe, due to their work schedule and commute. 1 patient was disenrolled because his dementia prevented him operating the equipment after several attempts. There have been no adverse consequences for any subjects.

CONCLUSIONS

Preliminary data analysis indicates the Vapotherm device has no significant advantage over a standard bedside humidifier.

Report Date: 04 August 2000 Work Unit # 2585-99

DETAIL SUMMARY SHEET

TITLE: Neuromotor Basis of Stuttering (NIH Grant DC03659 R01)

KEYWORDS: speech, stuttering, orofacial movement, voice

PRINCIPAL INVESTIGATOR: Michael D. McClean PhD
ASSOCIATES: Charles M. Runyan PhD & Stephen M. Tasko PhD

DEPARTMENT: Surgery
SERVICE: Army Audiology & Speech Center

STATUS: O
INITIAL APPROVAL DATE: 27 October 1998

STUDY OBJECTIVE

The goals of the proposed research are an enhanced understanding of the neuromotor basis of stuttering and the development of improved forms of speech therapy for persons who stutter. Given the complexity of this speech production system, it is logical that we develop an improved method for evaluating speech pattern generating function while controlling for different sources of input such as phonetic patterning and emotional response. This approach is taken in the present research through analyses of speech structure movements and voice acoustics. A central issue concerns how different muscle systems (e.g. tongue and jaw) are controlled and coordinated. A general hypothesis underlying much of the work is that there are subgroups of individuals whose pattern generating function for speech reflects different motor strategies, and these strategies have varying levels of instability. Specific hypotheses will address the association of orofacial and respiratory movements, and voice acoustic measures in normal speakers and persons who stutter, the effects of speech therapy on speech motor output, and the temporal-spatial characteristics of orofacial and respiratory movement, and voice acoustics during disfluency. The research should provide an improved basis for clinical categorization of persons who stutter and better understanding of changes in motor performance related to speech therapy.

TECHNICAL APPROACH

The above issues and hypotheses are being studied through analysis of lip, tongue, jaw, rib cage, and thoracic movements, and voice acoustics in individuals with a history of stuttering and a group of normal speakers. Electromagnetic and inductive plethysmographic systems are used to record speech structure movements while subjects produce a small set of speech utterances at varying rates and vocal intensities, a reading passage, and monologue. Wide ranges of clinical-behavioral measures of speech performance are obtained in stutter subjects. Persons who stutter will be tested prior to and following an intensive program of stuttering therapy.

PRIOR AND CURRENT PROGRESS

During the past year the basic experimental procedure was finalized, and data acquired on a total of 12 normal control subjects and 12 who stutter. This included repeated testing on 16 subjects. There have been no adverse reactions, and no subjects have withdrawn from the study. The major portion of the software required for measurement and analysis of physiologic data was developed. Data measurement and analysis has been carried out on a subset of the speech sample in 20 subjects.

CONCLUSIONS

Data from this protocol has been combined with that from previous and other ongoing protocols (WU # 2546 and 2550). The collective results of this work support the following conclusions: (1) more severe stutterers show elevated ratios of lower lip and tongue to jaw speed, (2) when increasing speech rate, stutterers show greater increases in upper lip and jaw speed compared to normal speakers, and (3) individuals with the greatest reductions in stuttering severity following treatment show greater reductions in orofacial speed, particularly in the jaw near the initiation of utterances.

Report Date: 11 October 2000 Work Unit #2586-99

DETAIL SUMMARY SHEET

TITLE: The Effects of Hearing Loss, Visual Acuity, and Aging on Speech Recognition

KEYWORDS:

PRINCIPAL INVESTIGATOR: Grant, Kenneth PhD
ASSOCIATES:

DEPARTMENT: Surgery STATUS: C
SERVICE: Army Audiology & Speech Center INITIAL APPROVAL DATE: 15 December 1998

STUDY OBJECTIVE:
The purpose of this study is to determine whether degree and type of hearing loss, visual, acuity, and/or aging have significant effects on the integration and recognition of auditory and visual (speechreading,) speech information.

TECHNICAL APPROACH
Frequency-band weights are obtained by correlating subject responses to vowel-consonant-vowel presentations when each of four separate and discrete frequency bands of speech are subjected to random amounts of noise on a trial-by-trial basis. A separate correlation is obtained for each band and the correlations across bands are normalized to obtain the frequency weighting function. Weights obtained in auditory and auditory-visual conditions will reveal if modality of presentation alters the way listeners attend to speech. Furthermore, measures of hearing and visual acuity, as well as age will be considered as potentially important factors in interpreting weighting results.

PRIOR AND CURRENT PROGRESS
This multi-year, multi-project protocol was a VA/DOD grant application that was not funded. There have been no subjects recruited and no studies run under this DCI work unit number.

CONCLUSIONS
None.

Report Date: 14 November 2000 Work Unit # 2587-99

DETAIL SUMMARY SHEET

TITLE: Spectral Shape Discrimination by Normal-Hearing and Hearing Impaired Listeners

KEYWORDS: spectral shape, hearing loss, complex sounds

PRINCIPAL INVESTIGATOR: Lentz, Jennifer Ph.D.
ASSOCIATES: Leek, Marjorie Ph.D.

DEPARTMENT: Surgery
SERVICE: Army Audiology & Speech

STATUS: O
INITIAL APPROVAL DATE: 12 January 1999

STUDY OBJECTIVE:
The perception of sounds with different spectral characteristics is one of several important auditory cues to the accurate understanding of speech. These spectral characteristics may be distorted by damage to the inner ear (cochlea), which produces a loss in auditor sensitivity. The role that this damage plays in the discrimination of sounds with different spectra is evaluated in normal-hearing and hearing-impaired listeners. A second part of the protocol is concerned with hearing aids, which can amplify different regions of the spectrum depending on a person's hearing loss. We also will assess whether listeners place more emphasis on amplified spectral regions after wearing a hearing aid for several months.

TECHNICAL APPROACH:
Listeners will hear two short, multi-tonal masking stimuli presented consecutively over headphones. These sounds will have similar spectral characteristics, but a signal tone will be added in-phase to a single component of one of the sounds. The listener is asked to indicate on a touch-screen terminal which sound included the signal. The intensity of the signal necessary for detection will be determined for several combinations of masking frequencies. Weighting analysis techniques will be used to evaluate whether a listener uses frequency region distant from the signal to aid in its detection.

PRIOR AND CURRENT PROGRESS
Data collection and analysis are ongoing. Preliminary results have been presented at national meetings in February 2000 and August 2000. 7 normal-hearing and 10 hearing-impaired have been enrolled in this study. There have been no adverse reactions, and one subject has withdrawn from the study because they chose not to continue. There is no direct benefit to the subjects.

CONCLUSIONS
Preliminary data suggest that both normal-hearing and hearing-impaired listeners are able to use spectral information across a wide-frequency range. Despite reduced sensory information, it appears that hearing-impaired listeners do no rely on frequency regions differently from normal-hearing listeners regardless of their degree of hearing loss. These results have an impact on the development of hearing-aids and medical technologies to restore hearing loss because the central auditory system remains able to use information in the event of peripheral damage to the cochlea.

Report Date: 23 April 2001 Work Unit # 2588-99

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: Variations in Orofacial Reflexes with Stuttering Severity

KEYWORDS: orofacial reflexes, stuttering, lip, jaw, speech

PRINCIPAL INVESTIGATOR: McClean, Michael Ph.D.
ASSOCIATES:

DEPARTMENT: Medicine STATUS: O
SERVICE: Army Audiology & Speech Center INITIAL APPROVAL DATE: 29 June 1999

STUDY OBJECTIVE:
Short-latency reflexes can be evoked in lip and jaw muscle by innocuous mechanical stimulation at the corner of the mouth during static posturing of the lips, tongue and jaw. The goal of this research is to determine whether the relative excitability of these reflexes varies systematically across individuals showing different levels of stuttering severity.

TECHNICAL APPROACH:
Subjects will include 44 adults divided into four groups of approximately 11 according to stuttering severity (nonstutterers, mild, moderate, severe). Surface electromyographic (EMG) recordings will be obtained of lip and jaw muscle while subjects maintain static postures within the orofacial system. A servo-controlled motor operating under position feedback will be used to apply small amplitude (0.8 mm) mechanical stretches at that point in the postero-lateral direction. Signal averages of lip and jaw muscle EMG will be generated using stimulus onset as a trigger. Reflex amplitudes first will be quantified as percent modulation of prestimulus EMG. Percent modulation of EMG on individual muscles will be used to calculated ratios of lip to jaw EMG for both excitatory and suppression responses.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE:
Prior kinematic and reflex studies of the PI suggest that more severe stutterers are likely to show elevated rations relating lip-to-jaw excitatory reflexes and lower ratios relating lip-to-jaw inhibitory reflexes. Work during the past year has continued to focus on refinement and development of the experimental setup. No subjects have yet been run on this protocol in this or previous years. Thus, there have been no adverse reactions, and no subjects have withdrawn from the study.
The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 0.

CONCLUSIONS:
None at this time.

Report Date: 14 July 2001 Work Unit # 2589-99

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: Treatment of Snoring with Palatal Stiffening Injection Sclerotherapy Using Sotradectol – A Pilot Study

KEYWORDS: Snoring, Palatal Stiffening, Sotradecol, Sclerotherapy

PRINCIPAL INVESTIGATOR: Mair, Eric LTC MC
ASSOCIATES: Brietzke, Scott CPT MC USA

DEPARTMENT: Surgery
SERVICE: Otolaryngology

STATUS: C
INITIAL APPROVAL DATE: 27 July 1999

STUDY OBJECTIVE

The purpose of this project is to perform a pilot study to investigate the potential use of Sotradecol (a commonly used sclerotherapy agent) palatal injection sclerotherapy ("injection Snoraplasty") as a primary treatment for palatal flutter-based snoring.

TECHNICAL APPROACH

This study is designed to be a pilot study to investigate the use of Sotradecol in the new indication of palatal sclerotherapy for snoring. A single group of 27 patients has been used to investigate the proper dose and duration of palatal sclerotherapy. The dose and treatment interval may be altered from patient to patient based on serial physical exams nothing ulceration, healing, stiffening, etc. to identify a well-tolerated, safe, effective dose and interval. Treatment endpoints consist of subjective improvement in snoring per sleeping partner and/or objectivity evidence of palatal stiffening as measured by an increase in the palatal flutter frequency per videostroboscopy. Patients are asked to complete a standardized survey reporting pain levels using a visual analog score, analgesic usage, changes in diet and duration of convalescence resulting from treatment.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

This pilot study has been completed. The results have been presented and published in a peer-review journal. The number of subjects enrolled to the study since last APR at WRAMC is 27 and the total enrolled to date at WRAMC is 27.

CONCLUSIONS

Palatal sclerotherapy is a safe, effective and well-tolerated treatment for palatal flutter snoring.

Report Date: 2 July 2001 Work Unit # 2590-99

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: The Effects of Speech reading on Auditory Detection of Spoken Sentences II: The Role of Envelop-Peak Location

KEYWORDS:

PRINCIPAL INVESTIGATOR: Grant, Kenneth Ph.D.
ASSOCIATES: Cord, Mary, M.A.

DEPARTMENT: Medicine
SERVICE: Army Audiology & Speech Center

STATUS: C
INITIAL APPROVAL DATE: 3 August 1999

STUDY OBJECTIVE

To determine whether specific manipulations of the amplitude envelope of spoken sentences affect the amount of masking for sentences detected with and without speech reading. The purpose is to determine if correlated acoustic/visual information obtained during face-to-face communication can serve to partially immunize the acoustic speech signal from the deleterious effects of background noise.

TECHNICAL APPROACH

Subjects will be tested binaurally under headphones in a sound-treated booth using an adaptive two-interval forced-choice (2IFC) procedure. Masked thresholds for detecting speech will be obtained under auditory and auditory-visual conditions. The amplitude-envelope of the speech waveforms will be altered to either increase or decrease the correlation between lip movement and acoustic speech signal. For audiovisual conditions, video speech information will be available equally in both observation intervals. Video signals will be displayed on a 19-inch color monitor positioned approximately 1.5 meters from the subject. The subject's task will be to identify the interval containing the speech plus noise. The intensity of the noise will vary adaptively depending on the subject's response. Threshold estimates for each interleaved track are computed as the mean of the noise levels for each of the last six reversals in the direction of the track. Final threshold values for each of the target sentences in each of audio and audiovisual conditions are the average of at least three separate threshold estimates per subject.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Six normal-hearing subjects have completed the phase of the study pertaining to filtered speech. Pilot tests on a pertaining to direct amplitude manipulation of the speech amplitude envelope were aborted due to methodological difficulties. This phase of the study was subsequently abandoned. Speech detection thresholds in noise were obtained for sentences filtered containing either low- or mid-frequency energy. Post-hoc analyses of the energy envelope of the filtered target sentences and the function describing the area of mouth opening were conducted to determine the degree of correlation between visible movements of the speech articulators and the resulting energy envelope of the produced speech.
The number of subjects enrolled to the study since last APR at WRAMC is _0_and the total enrolled to date at WRAMC is 6.

CONCLUSIONS

Speechreading offers greater masking protection for mid-frequency acoustic speech signals than for low-frequency speech signals. This may be due to the greater degree of correlation between lip movement (visible via speechreading) and acoustic amplitude envelope in the mid frequencies than between lip movement and acoustic amplitude envelope in the low frequencies. These data have implication for theories of auditory-visual integration for speech and for the design of speech processing algorithms that seek to make use of visual speech cues for noise reduction.

Report Date: 11 July 2001

Work Unit # 2591-99

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: Complex Sound Analysis by Persons with Impaired Hearing (Application for NIH NRSA Post Doctoral Fellowship)

KEYWORDS: hearing loss, complex sounds, sound segregation

PRINCIPAL INVESTIGATOR: Lentz, Jennifer PhD DAC
ASSOCIATES: Leek, Marjorie PhD DAC

DEPARTMENT: Surgery
SERVICE: Army Audiology & Speech Center

STATUS: O
INITIAL APPROVAL DATE: 14 September 1999

STUDY OBJECTIVE

The perception of specific sounds in a complex background of sounds is an important aspect to communication. Often times we communicate in the midst of a rich acoustic environment in which many sounds are present with vastly different temporal and spectral characteristics. It is well-known that a healthy auditory system has the ability to distinguish different sound sources from one another and attend to a particular sound source amid multiple sound sources, but less is known regarding the abilities of a damaged auditory system to make use of the prevalent cues in a complex acoustic scene. The main goal of this research protocol is to assess the abilities of hearing-impaired listeners to segregate sounds in a 2-source environment and compare their abilities with those of normal-hearing listeners. We will assess whether hearing-impaired listeners or whether the damage to their cochlea limits their ability to distinguish one sound from another can use certain cues.

TECHNICAL APPROACH

Listeners will hear four short, multi-tonal stimuli presented over headphones. The first two sounds will be played simultaneously. Next, the two sounds will be played again, but one of those sounds will have different spectral characteristics. The listener is asked to indicate on a touch-screen terminal which sound (the third sound or the fourth sound) was changed. Depending on the characteristics of the sounds, listeners will hear the first two simultaneously-presented sounds as either one sound or two sounds. If the listeners hear the two sounds as if they were one, the task will be extremely difficult to do. However, if the listeners hear the two sounds separately, they will easily distinguish which sound changes across the presentations. Different aspects of the sounds will be changed to evaluate when the two sounds are heard as a single sound or heard as two sounds. In some experiments, the onset times of the two sounds will be varied. Sensitivity will be measured as a function of onset time different. In other experiments, the sounds will be modulated at different rates, and sensitivity will be measured as a function of modulation rate difference.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

An addendum to the original protocol was approved 20 September 2000, which provided a new source of funding (NIH RO1 00626; PI: Marjorie Leek, DCI work unit #2570). The number of subjects enrolled to the study since last APR at WRAMC is 2 and the total enrolled to date at WRAMC is 2.

CONCLUSIONS

The preliminary data obtained from only two research subjects suggests that temporal changes in stimulus waveforms do not degrade the abilities of hearing-impaired listeners to perceive changes in the spectrum of sound. These conclusions are only tentative, however, due to the small population tested to date.

Report Date: 10 October 2000

Work Unit # 2592-99

DETAIL SUMMARY SHEET

TITLE: The expression if Vascular Endothelial Growth Factor (VEGF), VEFGR-1 Receptor (FLT-1) and VEGFR-2 Receptor (FLK-1) in Adenoid Cystic Carcinoma of the Salivary Gland: Correlation with Clinical Behavior

KEYWORDS: VEGF, VEGFR-1, VEGFR-2, Adenoid Cystic Carcinoma

PRINCIPAL INVESTIGATOR: MAJ Elizabeth A. Blair, MC
ASSOCIATES: Ifeoplumipo O. Sofola

DEPARTMENT: Surgery
SERVICE: Otolaryngology-Head & Neck Surgery

STATUS: C
INITIAL APPROVAL DATE: 14 September 1999

STUDY OBJECTIVE

To evaluate tissue staining of adenoid cystic carcinoma of the salivary gland obtained from WRAMC, NNMC, and MAMC tissue banks using VEGF, VEGFR-1 and VEGFR-2 and correlate intensity/pattern of staining with clinical outcome of the patients retrospectively by reviewing their tumor records. The purpose was to evaluate if there was any correlation between the pattern and intensity of staining with clinical outcome.

TECHNICAL APPROACH

Tissue blocks of the adenoid cystic carcinoma of the salivary gland were obtained from the WRAMC, NNMC, and MAMC tumor registeries, diagnosis was confirmed by Dr. Adair (pathologist). Tissues were de-paraffinized, mounted and stained as per protocol using VEGF, VEGFR-1 and VEGFR-2. Staining pattern and intensity were scored as outlined in the protocol. Tumor records from tumor registry, otolaryngology, tumor registry, radiation oncology and medical oncology were reviewed as per protocol. Data obtained was analyzed as per protocol.

PRIOR AND CURRENT PROGRESS

Results obtained have been analyzed and presented as a poster at the 5th international conference of Head and Neck Cancer. Currently, we are in the process of further refining our data and writing a manuscript for submission for publication.

CONCLUSIONS

Final conclusions are pending refinement of our data. It appears that there is a correlation between intensity of VEGF and VEGFR-2 staining and prognosis of adenoid cystic carcinoma. Larger series of cases would be needed to confirm our preliminary findings.

Report Date: 20 April 2001 Work Unit # 2635-99

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: Monitoring for Donor-Specific Hyporesponsiveness Following Renal and Pancreatic Allotransplantation

KEYWORDS: Kidney Transplant

PRINCIPAL INVESTIGATOR: Kirk Allan CDR MC
ASSOCIATES:

DEPARTMENT: Surgery STATUS: O
SERVICE: Organ Transplant INITIAL APPROVAL DATE: 22 June 1999

STUDY OBJECTIVE:
Primary Protocol Objective
The primary objective of this protocol is to develop methods of evaluating patients after transplantation that detect donor-specific immune hypo-responsiveness or tolerance.

Secondary protocol objectives include:
1. To monitor patients clinically and generate base-line data on donor specific immune responses that occur following transplantation with conventional immunosuppression. These observations will be used as a comparison for future trials using novel immunomodulatory regimens
2. To correlate long-term patients and graft outcome with findings from the techniques developed. While this study is not powered to clinically correlate these techniques, it is hoped that pilot data can be obtained during assay development indicating that immune hypo-responsiveness to donor antigen results in improved graft survival. Formal study of this will involve subsequent protocol development.

TECHNICAL APPROACH:
Up to 80 transplant patients will be enrolled over a three-year period. In addition, up to 20 normal, non-uremic volunteers will be enrolled to establish a normal baseline for peripheral blood assays. Samples received from transplant patients prior to transplant will serve as uremic controls.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE:
The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 0. The total number enrolled study-wide is 152, if multi-site study.
Expected serious adverse events were submitted to the NIDDK IRB during this review period.

CONCLUSIONS:
Protocol 99-DK-0019, Monitoring for Donor-Specific Hyporesponsiveness Following Renal and Pancreatic Allotransplantation, is currently open for accrual. A total of 116 patients have been enrolled in this protocol. Eighty-eight of the 116 were healthy volunteers. Nine were long-term post transplant patients. Fifteen patients have undergone renal transplantation under this protocol since last review. One graft was lost secondary to rejection in December 2000.

The protocol needs to be maintained to correlate long-term graft outcome with the number of possible indicators such as phenotypic changes in peripheral blood lymphocytes, donor reactivity and presence of donor antibodies. It is also necessary to extend this protocol to examine the functional effects of the certain gene polymorphisms as they relate to graft outcome. This will allow us to investigate the role of various cell types in their functional significant for graft rejection/acceptance.

Report Date: 20 April 2001

Work Unit # 2636-99

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: Live Donor Renal Donation for Allotransportation

KEYWORDS: Kidney Donor

PRINCIPAL INVESTIGATOR: Kirk-Allan CDR MC
ASSOCIATES:

DEPARTMENT: Surgery
SERVICE: Organ Transplant

STATUS: O
INITIAL APPROVAL DATE: 22 June 1999

STUDY OBJECTIVE:
This protocol is designed to identify candidates for renal donation and provide donor kidneys for patients undergoing renal transplantation as part of protocol related studies at the NIH Clinical Center. This protocol will also be used to facilitate the procurement of donor blood and bone marrow in support of transplant studies involving the evaluation of donor specific immune reactivity.

TECHNICAL APPROACH:
The eligible population will be adults without preexisting renal disease who are willing to donate a kidney to a family member or close friend who is enrolled in a clinical transplant protocol at the NIH Clinical Center. Patients will be considered providing they are in good general health. While each patient is evaluated individually, symptomatic cardiac disease, cerebrovascular disease, or peripheral vascular disease will generally lead to the exclusion of the candidate. Also, most contagious infectious diseases contraindicate donation, although this is dependent in large part on the infectious status of the recipient. For example, an individual with Hepatitis C would not be acceptable for general donation but might be able to donate to another individual with the same strain of hepatitis C virus.
Patients will not be selected according to race and gender. However, because some of the disorders under study have different demographic characteristics, the patient populations will not be expected to be evenly balanced (e.g. refractory hypertension). By international convention, children are not allowed to be used as living organ donors regardless of whether their guardians consent. For this reason, only adults will be considered for donation.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE:
The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 0. The total number enrolled study-wide is 38, if multi-site study. One adverse event was submitted on 11 August 2000 reporting a reaction to gadolinium during a standard of care donor evaluation. The IRB concurred that the event was unrelated to the research intervention. A separate procedural consent is signed in the MRI department prior to the MRI being performed, which contains the risks of adverse reactions related to gadolinium.

CONCLUSIONS:
Protocol 99-DK-0107, Live Donor Renal Donation, is currently open to accrual. Under this protocol, a total of ten new patients have been considered for potential renal donation in support of the various transplant protocol since last review. Sixteen patients have been actual donors some of which were enrolled in the previous review period. Approximately, 56 additional patients have been evaluated under the screening protocol for potential renal donation. The patients have all done well post-operatively with only the expected types of complication. All grafts had immediate function and continue to do well.
The protocol needs to be maintained as it is the source of organs for several of the tolerance protocols which are based now on living donor kidneys. Living related and unrelated kidney donation also now provides 50% of the organs for our program in general. Living donation is the preferred treatment for End Stage Renal Disease and must be provided by any full-service transplant program.

Report Date: 21 November 2000

Work Unit #00-2801

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: Mentor Saline Filled Testicular Prosthesis Adjunct Study

KEYWORDS:

PRINCIPAL INVESTIGATOR: McLeod, David COL MC
ASSOCIATES:

DEPARTMENT: Surgery
SERVICE: Urology

STATUS: O
INITIAL APPROVAL DATE: 18 January 2000

STUDY OBJECTIVE

To provide access to this device while the core study data are submitted and reviewed by the Food and Drug Administration (FDA). Once the Mentor Saline filled testicular Prosthesis is cleared for market via the Pre-market Approval (PMA) process, enrollment of subjects into the Adjunct Study will be halted. This control study will collect tracking information on subjects enrolled into the study and information on the incidence and severity of adverse events.

TECHNICAL APPROACH

Enrollment is done through patient screening in the Urology Clinic or referred to us from other urology departments in the military. Male military health care beneficiaries age 18 years of age or older who are indicated for testicular prosthesis implantation (in cases of testicular agenesis or following surgical removal of the testis) either unilaterally or bilaterally are enrolled.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

The protocol was approved January 2000. There are 10 patients enrolled to date at WRAMC and 112 study wide. Enrollment is continuing at this time. All adverse events have been reported.

CONCLUSIONS

None at this time.

Report Date: 02 January 2001 Work Unit #00-2802

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: A Phase II Randomized-Discontinuation Study of Oral CEP-701 in Prostate Cancer Patients Who Have Failed First-Line Hormonal Therapy

KEYWORDS: hormonal, CEP-701, prostate, cancer

PRINCIPAL INVESTIGATOR: McLeod, David COL MC
ASSOCIATES: Moul, Judd COL MC, Spevak, Marianne; Esther, Thomas

DEPARTMENT: Surgery STATUS: C
SERVICE: Urology INITIAL APPROVAL DATE: 25 April 2000

STUDY OBJECTIVE
The objective of this study is to determine the safety and efficacy of CEP-701 as compared to placebo in prostate cancer patients who have failed first-line hormonal therapy.

TECHNICAL APPROACH
Approximately 30 sites are expected to enroll at least 285 eligible male patients. Up to 10 patients will enroll in this study from the Urology clinic at WRAMC. Patients must be at least 18 years of age and have been diagnosed with adenocarcinoma of the prostate for which he has been treated with hormonal androgen suppression or castration.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 0. The total number enrolled study-wide is 80, if multi-site study. Per the sponsor's request, the study will be closed due to lack of efficacy from the 80 patients enrolled. As of this date, no patients were screened for the protocol. Investigational drug was just recently received at this site. A study closeout visit is scheduled in January 2001 with the sponsor.

CONCLUSIONS
CEP-701 showed no apparent benefit. Eighty patients were enrolled in this study and suggested there was a lack of efficacy. The study will be closed at WRAMC effective this date.

Report Date: 2 January 2001 Work Unit #01-2801

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: A Phase II, Long Term, Open-Label Extension Study of Oral CEP-701 in Patients Previously Receiving CEP-701 for Treatment of Prostate Cancer

KEYWORDS:

PRINCIPAL INVESTIGATOR: McLeod, David COL MC
ASSOCIATES:

DEPARTMENT: Surgery
SERVICE: Urology

STATUS: W
INITIAL APPROVAL DATE: 21 November 2000

STUDY OBJECTIVE
The PI before final DCI approval withdrew this protocol.

TECHNICAL APPROACH
The PI before final DCI approval withdrew this protocol.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
The PI before final DCI approval withdrew this protocol.

CONCLUSIONS
The PI before final DCI approval withdrew this protocol.

Report Date: 31 October 2000 Work Unit # 2801

DETAIL SUMMARY SHEET

TITLE: Establishment of a Serum Bank for the Future Detection of New Prostate Cancer Markers in Serum of Patients with Prostate Cancer, Benign Prostate Conditions and No Prostate Disease

KEYWORDS: serum, prostate, future

PRINCIPAL INVESTIGATOR: McLeod, David COL MC
ASSOCIATES: Moul, Judd COL MC

DEPARTMENT: Surgery STATUS: O
SERVICE: Urology INITIAL APPROVAL DATE: 06 December 1994

STUDY OBJECTIVE
Primarily to establish a serum bank. Serum will be obtained from patients with prostate cancer, benign prostate disorders and no prostate disease to use in the evaluation of new markers of disease.

TECHNICAL APPROACH
Thirty cc's of blood will be drawn and spun down, and the serum will be frozen for use in the future.

PRIOR AND CURRENT PROGRESS
At the last APR, there were 822 patients enrolled into the serum bank. Since the last APR, there have been 488 additional patients enrolled, bringing the total to date to 1310 patients enrolled. There have been no adverse reactions reported from this protocol. This protocol will continue to enroll patients.

CONCLUSIONS
None at this time.

Report Date: 23 November 2000

Work Unit # 2802

DETAIL SUMMARY SHEET

TITLE: Center for Prostate Disease Research Prostate Cancer Radical Prostatectomy Follow-Up Questionnaire

KEYWORDS: prostate cancer, survey, outcomes

PRINCIPAL INVESTIGATOR: Moul, Judd COL MC
ASSOCIATES: McLeod, David COL MC

DEPARTMENT: Surgery
SERVICE: Urology

STATUS: O
INITIAL APPROVAL DATE: 13 December 1994

STUDY OBJECTIVE

To conduct a large patient self-reporting questionnaire study of urinary, sexual and quality-of-life morbidity after radical prostatectomy for prostate cancer in the military health care system.

TECHNICAL APPROACH

Researchers will: 1) design and validate a questionnaire to assess incontinence, impotence, urinary stricture, quality-of-life and recurrence in radical prostatectomy patients; 2) generate an accurate list of radical prostatectomy patients from military hospitals; 3) mail questionnaires; and 4) tabulate data and analyze results.

PRIOR AND CURRENT PROGRESS

Due to lack of personnel and priority being put into converting a database (WU#2857) into the ACCESS database format. This protocol has not been actively pursued since last APR. At the present time, the ACCESS database installation has been completed and is currently in operation. We will submit a protocol addendum and the exception to protocol memo since the protocol was approved in 1994 and has reached the five-year time frame for protocols. The amendment for this protocol will be submitted in January 2001. No questionnaires have been collected since the last APR, nor will any be collected until the new amendment has been approved.

CONCLUSIONS

None at this time.

Report Date: 28 November 2000 Work Unit # 2804

DETAIL SUMMARY SHEET

TITLE: Medical Therapy in Benign Prostate Hyperplasia: Full-Scale Trial

KEYWORDS: prostate, medical therapy, BPH

PRINCIPAL INVESTIGATOR: Schenkman, Noah MC.
ASSOCIATES:

DEPARTMENT: Surgery STATUS: O
SERVICE: Urology INITIAL APPROVAL DATE: 31 January 1995

STUDY OBJECTIVE:
To determine the effectiveness of medical therapy (finasteride and/or doxazosin) to treat, delay or prevent the symptomatic progression of benign protstatic hyperplasia (BPH) and to assess differences over time between treatment groups. To investigate prognostic indicators and biologic parameters regarding response to therapy. To gain insight into biologic and physiologic natural history of prostate growth.

TECHNICAL APPROACH:
The study is multi-center, placebo-controlled, double-masked clinical trial in which patients who have been diagnosed with symptomatic BPH are randomly assigned to either of three drug treatment arms or a placebo control once all entrance criteria have been fulfilled. All patients are monitored closely and will undergo follow-up evaluation quarterly for efficacy, adverse events and overall mortality. The protocol was approved 5 May 1995 and addenda were approved 28 June 1995, 29 October 1996, 28 October 1997m 5 February 1998 and 28 April 1998. The third edition of the protocol was last amended on 13 October 2000 and is waiting approval. Change of PI from Dr. Zorn to Dr. Schenkman was submitted in October but not accepted.

PRIOR AND CURRENT PROGRESS
Enrollment started December 1995 and ended January 1998. A total of 166 patients were randomized in the full-scale trial and 24 in the pilot study at WRAMC. Enrollment study-wide is 3047. The following is a breakdown in status of the enrolled WRAMC patients:
13 inactive patients, 4 patients have died
1 patient off doxazosin, 2 patients off finasteride
21 patients off both cardua/finasteride
11 with progression of BPH
15 with prostate/bladder cancer, 11 of these have crossed over to invasive therapy
10 patients had serious adverse events in 2000. None were drug related. The data for study wide serious adverse events will not be available until January 2001. Patients continue to benefit from the relaxation or shrinkage of the prostate and may benefit from the future conclusion of this study. The full-scale trial will continue until 30 November 2001.

CONCLUSIONS
Baseline data has been presented at the American Urological Society meetings and then will be presented at future meetings. Ancillary studies are being submitted for use of tissue accrued from the biopsy subset and after review of submissions these will be prioritized and approved. There are no conclusions to date.

Report Date: 5 July 2001

Work Unit # 2809

DETAIL SUMMARY SHEET

TITLE: Multicenter Prospective Cohort Study to Evaluate the Safety and Effectiveness of the American Medical Systems (AMS) Ambicore TM Inflatable Penile Prostheses

KEYWORDS: Ambicore, implant, prostheses

PRINCIPAL INVESTIGATOR: McLeod, David COL MC
ASSOCIATES:

DEPARTMENT: Surgery
SERVICE: Urology

STATUS: O
INITIAL APPROVAL DATE: 29 August 1995

STUDY OBJECTIVE

To evaluate the ability of the AMS penile prosthesis to provide an erection suitable for sexual intercourse (device function) as determined by PE and patients self report. Safety will be evaluated by measuring rates of complications and the occurrence of medical conditions associated with the device.

TECHNICAL APPROACH

After patients have made a decision to have an Ambicore implant, they are informed about the study. Prestudy/screening lab work must be completed prior to surgery. After surgery, the patient cannot use the device for sexual intercourse for 6 weeks. Follow-up exams will be at 6 weeks, 6 months, 1 year, 18 months, 2 years, and 5 years post-implant. Patients will complete questionnaires at these visits. Complications, associated medical conditions, and other adverse effects will be followed for 5 years.

PRIOR AND CURRENT PROGRESS

The number of subjects enrolled to the study since last APR at WRAMC is 1 and the total enrolled to date at WRAMC is 18. The total number enrolled study-wide is 127, if multi-site study. No adverse events have been reported. Enrollment is still continuing.

CONCLUSIONS

None at this time.

Report Date: 26 September 2000 Work Unit # 2812

DETAIL SUMMARY SHEET

TITLE: A Randomized, Double-Blind Comparative Trial of Bicalutamide (Casodex) vs. Placebo in Patients with Early Prostate Cancer

KEYWORDS: prostate cancer, Casodex

PRINCIPAL INVESTIGATOR: McLeod, David COL MC
ASSOCIATES: Moul, Judd COL MC

DEPARTMENT: Surgery
SERVICE: Urology

STATUS: O
INITIAL APPROVAL DATE: 28 November 1995

STUDY OBJECTIVE

The primary objective is to compare 2 years of adjuvant bicalutamide 150 mg monotherapy with placebo in terms of clinical progression and overall survival. The secondary objectives are to compare 2 years of adjuvant bicalutamide 150 mg monotherapy with placebo in terms of time to treatment failure and tolerability and to investigate the association of serial measurement of serum PSA and treatment outcome following 2 years of adjuvant bicalutamide therapy vs. placebo.

TECHNICAL APPROACH

This is a double blind, randomized clinical trial evaluating bicalutamide (Casodex) 150 mg monotherapy vs. placebo as adjuvant therapy with early prostate cancer.

PRIOR AND CURRENT PROGRESS

Enrollment was completed in 8/97. 3,292 patients were enrolled in this study nationwide. Twenty-four (24) patients were enrolled at WRAMC. We have received no new adverse reports from other sites. All serious and unexpected from WRAMC have been reported. Twenty-two (22) patients have completed the active part of the study are being followed for survival and disease progression per protocol. Four (4) patients have started on second line therapy as a result of disease progression.

CONCLUSIONS

Study is ongoing therefore, no conclusions have been formulated at this time.

Report Date: 02 January 2001

Work Unit # 2813

DETAIL SUMMARY SHEET (Human Use Protocol)

TTTLE: A Phase II Study to Determine the Effects of Finasteride and Flutamide on Patients with Rising PSA's Who Have Had Radical Prostatectomy, Radiation or Cryoblation Treatment for Localized Primary Prostate Cancer.

KEYWORDS: finasteride, flutamide, prostate

PRINCIPAL INVESTIGATOR: Moul, Judd MC
ASSOCIATES: McLeod, David COL MC

DEPARTMENT: Surgery
SERVICE: Urology

STATUS: O
INITIAL APPROVAL DATE: 27 February 1996

STUDY OBJECTIVE

To determine in patients with Stage A, B, C or D1 cancer of the prostate: 1) the likelihood of response in order to assess whether daily finasteride and daily flutamide should be advanced to other studies; 2) toxicity of daily finasteride with daily finasteride; and 3) the likelihood of potency maintenance in patients who were potent before the study.

TECHNICAL APPROACH

Patients will receive flutamide and finasteride daily and will be followed for 2 years. If the patient remains responsive to the study drugs, they will remain on the lower dose and be followed for 5 years. If a patient has three consecutive rises in the PSA, the flutamide will be increased to full dose and the patient will be followed for survival data for 5 years.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Enrollment was completed in August 1997. Of the 39 patients who were enrolled into this study, 36 were evaluable. All patients have completed the 2-year trial and are in the survival arm of the study.

- 15 Patients who continue to respond to low dose hormone therapy
- 1 Patients who continue to respond to full dose hormone therapy
- 8 Patients who have discontinued therapy due to inability to tolerate drug for expected side effects.
- 12 Patients who have discontinued due to progression with rising PSA, or other medically required issue
- 1 Patients who are lost to follow-up (moved to Texas)
- 2 Patients who are deceased

All adverse events have been reported.

CONCLUSIONS

Combination flutamide and finasteride appears to be well-tolerated and effective in short-term reduction of serum PSA for a majority of men with erologic recurrence after prior local therapy. Further study is needed to determine long-term efficacy of this combination low dose hormonal therapy.

Report Date: 28 September 2000 Work Unit # 2822

DETAIL SUMMARY SHEET

TITLE: Prostate Cancer Markers in Young Caucasian and African-American Men Age 20-49

KEYWORDS: CaP marker, Caucasian, African-American

PRINCIPAL INVESTIGATOR: McLeod, David COL MC
ASSOCIATES:

DEPARTMENT: Surgery
SERVICE: Urology

STATUS: C
INITIAL APPROVAL DATE: 19 November 1996

STUDY OBJECTIVE

To evaluate serum prostate specific antigen (PSA), prostate specific member antigen, and free PSA in young men ages 20-49 without prostate disease. In addition, evaluate these same tumor markers in a group of men with prostate cancer.

TECHNICAL APPROACH

Using computer searched of Individual Patient Data Systems (IPDS) at Ft. Sam Houston, Texas, a group of subjects was selected for exclusion if they were found to have other benign prostate conditions that would falsely elevate these markers. Serum (which remains from HIV screening) was then selected from ANSR (Army Navy Serum Repository) for analysis. This phase of the study is performed to establish normal ranges of these markers in young men. Identical methods were used to select a group of prostate cancer patients that has banked serum pre-dating the diagnosis of prostate cancer. Their specimens were collected as well and 4 controls were selected for each subject with prostate cancer. All patients are identified by specimen number only.

PRIOR AND CURRENT PROGRESS

Specimens have been collected and analyzed.

CONCLUSIONS

Results suggest that although African-American men age 20-45 have higher baseline serum PSA levels than Caucasian men of the same age, PSA velocity is greater in young Caucasian men when compared to young African-American men.

Report Date: 15 December 2000

Work Unit # 2827

DETAIL SUMMARY SHEET

TITLE: A Phase II Study to Determine the Effects of Flutamide on Patients with Rising PSA's Who Have Had Radical Prostatectomy, Radiation or Cryoblation Treatment for Localized Primary Prostate Cancer

KEYWORDS: prostate, cancer, flutamide

PRINCIPAL INVESTIGATOR: Moul, Judd COL MC
ASSOCIATES:

DEPARTMENT: Surgery
SERVICE: Urology

STATUS: O
INITIAL APPROVAL DATE: 28 January 1997

STUDY OBJECTIVE

To determine whether or not the use of low dose flutamide alone in patients with PSA – only recurrent prostate cancer should be advanced to the other studies; mainly a phase III randomized trial. This study is also designed to determine the toxicity of 250 mg flutamide and to determine the likelihood of those patients who were potent upon enrolling into the study to maintain their potency.

TECHNICAL APPROACH

Patients receive flutamide daily and are followed for two years.

PRIOR AND CURRENT PROGRESS

Twenty-two patients have been enrolled in this study at WRAMC. All adverse events have been reported. A total of 12 patients have been dropped from the study: five (5) patients for diarrhea (an expected side effect), four (4) had progression of disease and were advanced to full hormonal therapy, one for anxiety, one died and one moved. All patients have experienced gynecomastia (also an anticipated side effect). The 8 patients remaining on study are tolerating the drug and continue to respond. Two (2) patients have completed the two-year study period and will be followed for survival for five (5) years per protocol. Average nadir for this study is 0.9 (2 of 20 reached <0.1) at 3 months. This study remains open to enrollment.

CONCLUSIONS

None to date.

Report Date: 27 September 2000 Work Unit # 2832

DETAIL SUMMARY SHEET

TITLE: Retrospective Study of CPDR Multicenter Database to Develop Nomograms Based on Sextant Positive Biopsy Cores, Gleason Sum and Pre-Biopsy PSA to Predict Pathologic Stage In Radical Prostatectomy Patients

KEYWORDS: prostate cancer, nomograms, pathology

PRINCIPAL INVESTIGATOR: Moul, Judd COL MC
ASSOCIATES: McLeod, David COL MC

DEPARTMENT: Surgery
SERVICE: Urology

STATUS: O
INITIAL APPROVAL DATE: 19 November 1997

STUDY OBJECTIVE

The goal of this study is to develop predictive nomograms based on number of sextant biopsies positive for prostate cancer, highest biopsy Gleason sum, and pre-treatment (or pre-biopsy) PSA to predict final pathological stage variables in men who have undergone radical prostatectomy and whose data has been maintained in the CPDR database.

Secondary goals will be to recreate CPDR nomograms identical to the methodology of Partin et al using their three prognostic factors and to determine how well the Partin, et.al. nomograms predicted our CPDR cases.

TECHNICAL APPROACH

The CPDR prostate cancer database is being used to perform the retrospective study. Patients who have had radical prostatectomy and who have the known preoperative variables of PSA value, biopsy Gleason sum (worst), clinical stage category, and sextant biopsy numbers of cores positive and post-operative pathologic stage are the study subjects. Multivariable logic regression is used to construct nomograms of these factors to predict final stage.

PRIOR AND CURRENT PROGRESS

Approximately 800 patients have been identified who have the needed information in the database. This is an addition 100 from last year. Data collection is continuing at this time.

CONCLUSIONS

Collection of data continues for this project at this time. It still appears that the preoperative factors of PSA, Gleason sum on biopsy and number of sextant cores positive for cancer can be used to construct meaningful nomograms to predict pathologic stage. Final results are still pending.

Report Date: 27 September 2000 Work Unit # 2834

DETAIL SUMMARY SHEET

TITLE: Retrospective Review of Three-Dimensional (3D) Computerized Tumor Volume Determination in Radical Prostatectomy Specimens From Black and White Patients

KEYWORDS: prostate, computerized, tumor volume

PRINCIPAL INVESTIGATOR: Moul, Judd COL MC
ASSOCIATES: McLeod, David COL MC, Bauer John MAJ MC

DEPARTMENT: Surgery
SERVICE: Urology

STATUS: O
INITIAL APPROVAL DATE: 24 November 1997

STUDY OBJECTIVE

The goal of this study is to compare tumor volume and characteristics of whole-mount radical prostatectomy specimens between black and white prostate cancer patients.

TECHNICAL APPROACH

This is a retrospective study of the CPDR Prostate Cancer Database examining the tumor volume measurements and tumor locations derived from our whole-mount radical prostatectomies performed by AFIP since April 1993.

PRIOR AND CURRENT PROGRESS

The database of 3-D prostate models was increased to 280 models during this reporting period. Multiple abstracts and publications have been submitted over the year to disseminate the information obtained from the dataset (see below). The actual comparison of AA and Caucasian tumor locations and positive biopsy results are still pending.

CONCLUSIONS

The analysis to date has shown that the location of positive simulated biopsies is highest in the lateral peripheral regions of the prostate. There did not seem to be statistical difference between black and white patients in the earlier data on 200 models. Frequencies of tumor location in various regions of the prostate are continuing and comparisons between the races will be made.

Report Date: 27 September 2000 Work Unit # 2835

DETAIL SUMMARY SHEET

TITLE: The evaluation of Seminal Leukocytes and Cytokine Function in Infertile Males

KEYWORDS: leukocyte, germ cell, cytokine, infertility

PRINCIPAL INVESTIGATOR: McLeod, David COL MC
ASSOCIATES: Spevak, Marianne

DEPARTMENT: Surgery
SERVICE: Urology

STATUS: C
INITIAL APPROVAL DATE: 25 November 1997

STUDY OBJECTIVE

The purpose of this study is to evaluate leukocyte function in infertile males and fertile controls

TECHNICAL APPROACH

Patients seen in infertility clinic have a semen analysis as part of their routine evaluation. An aliquot of this semen analysis will be cryopreserved in liquid N2 for Immunohistochemical and microscopic analysis for leucocyte, cytokine and germ cell composition and cataloging. Semen analysis from vasectomy patients will be analyzed before and after vasectomy to establish mean population of seminal leucocyte in healthy "normal" males.

PRIOR AND CURRENT PROGRESS

We have received final approval for this protocol on February 10, 1998 and approval for the addendum on April 15, 1998. Four patients have been enrolled in this protocol. No side effects have been reported for this study. Enrollment was slowed due to change in PI and reduced lab space required to conduct this study. Due to lack of space and personnel to conduct this study at this time, we wish to close the study.

CONCLUSIONS

There are none at this time. The specimens collected (4) have been destroyed and the protocol will be closed at this time due to lack of space and personnel. Once the space issue has been resolved and the required staffing is adequate, we may wish to open the protocol again at that time. If we re-open the protocol, we will submit a new protocol at that time.

Report Date: 25 September 2000

Work Unit # 2836

DETAIL SUMMARY SHEET

TITLE: Three-Dimensional Ultrasonic Visualization Prostate Cancer

KEYWORDS: ultrasound, 3-D modeling, prostate

PRINCIPAL INVESTIGATOR: Moul; Judd COL MC
ASSOCIATES: Spevak, Marianne; Zorn, Burkhardt LTC MC; McLeod, David COL MC

DEPARTMENT: Surgery
SERVICE: Urology

STATUS: O
INITIAL APPROVAL DATE: 25 November 1997

STUDY OBJECTIVE

The general objective is to validate current, biopsy-based results indicating that power spectrum analysis of radio-frequency (RF) ultrasonic echo signals from the prostate can distinguish cancerous from non-cancerous prostate tissue in three dimensions (3-D) over the full volume of the prostate. The specific objective is to correlate whole-mount histology obtained from radical prostatectomy specimens with 3-D tissue-typing images derived from RF echo signals obtained immediately prior to prostatectomy.

TECHNICAL APPROACH

Patients enrolled in this study will already be scheduled for radical prostatectomy. These examinations will use standard TRUS instrumentation and procedures to acquire RF-echo signal data within a week of surgery. RF echo-signal data will be acquired using a currently available B&K Medical systems transrectal prostate scanner. This scanner will be interfaced with a data-acquisition computer using an interface module and digital hardware identical to current units currently utilized in Riverside Research Institutes' (RRI) collaborative study with MSKCC. The examining urologist will acquire RF data from approximately 20, evenly spaced, parallel transverse scan planes for each patient. Sectioning of prostatectomy specimens will be performed by pathologists at AFIP in planes corresponding to the scan planes of the pre-surgical TRUS examination. The pathologist will demonstrate lesion boundaries directly on digital images of each whole-mount section using available image-manipulation software. RRI will process RF data using RRIs current off-line method to generate color-encoded, volume renderings of the prostate. The volume renderings will be compared with whole-mount histology performed on excised glands. Comparisons will be made between computer-generated depictions of lesions and lesion properties determined from histology. This comparison will be based on tumor borders demarcated by the pathologist on images of each section and will assess tumor shape, volume, number of foci, etc. In addition, staging based on lesion features depicted by the 3-D images will be compared to clinical and pathological staging; relative performance will be expressed as ROC curves.

PRIOR AND CURRENT PROGRESS

At this time, we have not enrolled any patients on the study. All of the hardware and software has been installed and training has been initiated. Protocol amendment was submitted to DCI on 12 July 00 to include funding for this study. The informed consent was also updated and data collection forms submitted to DCI at that time. Enrollment is expected to start in October 2000 or once approval is given for amendment.

CONCLUSIONS

None at this time

Report Date: 02 January 2001 Work Unit # 2837

DETAIL SUMMARY SHEET (Human Use Protocol)

TTTLE: NPCP 2200: A Comparison of Leuprolide with Leuprolide and Flutamide in Previously Untreated Patients with Clinical Stage D2 Cancer of the Prostate

KEYWORDS: leuprolide, flutamide, prostate cancer

PRINCIPAL INVESTIGATOR: McLeod, David COL MC
ASSOCIATES:

DEPARTMENT: Surgery STATUS: O
SERVICE: Urology INITIAL APPROVAL DATE: 26 February 1985

STUDY OBJECTIVE
To try to determine if the antiandrogen flutamide will increase the efficacy of leuprolide.

TECHNICAL APPROACH
Patients are randomized to receive leuprolide and flutamide or leuprolide and placebo. At the time of progression, the blind is broken, and patients not receiving flutamide will be given drug.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
Although this study was permanently closed on 07/01/87, we continue to follow 2 patients for survival. One patients remains in leuprolide and remains stable without adverse events. The other patient is followed by phone contact and he is reported to be stable and without complaints.

CONCLUSIONS
None. The two patients will continue to be followed for survival.

Report Date: 24 November 2000

Work Unit # 2839-98

DETAIL SUMMARY SHEET

TITLE: Retrospective Review of the Association of p53, MIB-1, and Bel-2 Immunohistochemistry in Needle Prostate Biopsies with Recurrence of Prostate Cancer

KEYWORDS: prostate, cancer, markers

PRINCIPAL INVESTIGATOR: Stackhouse, George MAJ MC
ASSOCIATES: Moul, Judd COL MC

DEPARTMENT: Surgery
SERVICE: Urology

STATUS: C
INITIAL APPROVAL DATE: 13 January 1998

STUDY OBJECTIVE

To determine whether immunohistochemical (IHC) staining of prostate biopsies for p53, Ki-67, and bcl-2 proteins will provide prognostic information regarding recurrence of prostate cancer (clinical recurrence or elevated serum PSA).

TECHNICAL APPROACH

Archival blocks from the diagnostic biopsies of 215 patients will be cut and immunohistochemically stained for p53, MIB-1 (Ki-a67) and bcl-2 at AFIP per standard method. Data will be correlated with date regarding recurrence from the database (WU#2898/2857-98). Life table and Kaplan-Meier survival methodology will be used to analyze the predictive ability of positive staining for recurrence after radical prostatectomy.

PRIOR AND CURRENT PROGRESS

The study is completed with the exception of publication of the MIB-1 (Ki-67) portion of the study.

CONCLUSIONS

Although p53 and bcl-2 are useful biomarkers of prostate cancer recurrence in radical prostatectomy specimens, these biomarkers could not predict recurrence in the needle biopsy specimens. The MIB-1 (Ki-67) staining of needle biopsies was also performed and also did not predict recurrence. These results are being evaluated and will hopefully be written up under a separate manuscript that will be submitted to DCI for approval within the next few months.

Report Date: 15 February 2001 Work Unit # 2840-98

DETAIL SUMMARY SHEET (Human Use Protocol)

TTTLE: Agent Orange Exposure in Vietnam Veterans and the Risks of Prostate Cancer

KEYWORDS: agent orange, prostate, cancer, Vietnam

PRINCIPAL INVESTIGATOR: McLeod, David COL MC
ASSOCIATES:

DEPARTMENT: Surgery STATUS: O
SERVICE: Urology INITIAL APPROVAL DATE: 10 February 1998

STUDY OBJECTIVE
Using a case control design, this study will evaluate the relationship between exposure to Agent Orange and other herbicides and the risk of prostate cancer among the Vietnam veterans who served in the Army. This study also will be able to determine risk based on the level of exposure to Agent Orange.

TECHNICAL APPROACH
This is a case controlled study – Subjects will be identified through the CPDR multi-center database (those patients with prostate cancer) and a registry of Vietnam vets maintained at the DVA (controls). Once the study questionnaire will be mailed to those individuals who complete the telephone survey.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
Interviews began in August 1999. Prior to this APR 962 have been completed, 214 cases and 748 controls. 800 dietary questionnaires have been mailed, approximately 400 have been returned completed to date. As of this date, approximately 500 dietary questionnaires have been received back from patients. The statistician and associate investigator are in the process or analyzing the data. No new patients will be enrolled until the data is evaluated.

CONCLUSIONS
None at this time

Report Date: 02 January 2001

Work Unit # 2841-98

DETAIL SUMMARY SHEET (Human Use Protocol)

TTTLE: Association of 6q Allelic Losses in A Subset of Primary Human Prostate Cancer

KEYWORDS: prostate, cancer, chromosome

PRINCIPAL INVESTIGATOR: Dean, Robert MAJ (P) MC
ASSOCIATES: Moul, Judd COL MC; McLeod, David COL MC

DEPARTMENT: Surgery
SERVICE: Urology

STATUS: O
INITIAL APPROVAL DATE: 10 February 1998

STUDY OBJECTIVE

To examine human prostate tumor cell for loss of heterozygosity (LOH) on Chromosome 6q and its role as a possible marker of prostatic cancer recurrence after radical prostatectomy.

TECHNICAL APPROACH

A retrospective review of 200 patients who underwent a radical prostatectomy at WRAMC between 1986 and 1994 will have prostate tissue analyzed for loss of heterozygosity on chromosome 6q 16.3 – 6q21. A retrospective analysis will be performed to uncover statistical correlations with LOH chromosome 6q and demographic information, path stage and grade as well as recurrence using the CPDR database (WU#2898/2894).

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Genomic DNA from tumor and normal prostate tissues form radical prostatectomy specimens of 38 patients were analyzed by polymerase chain reaction (PCR) for thirteen polymorphic microsatellite loci on 6q. Allelic losses of one or more polymorphic loci were detected in 11 of 38 patients (29%). Six of 11 tumors showing any 6q deletion were found to have allelic losses at D6S300 and D6S1056 loci.

CONCLUSIONS

This study revealed a 1.5 megabase interval between D6S300 and D6S1045 at 6q 16.3 – 6q21 as the minimal region of deletion, which may contain the putative tumor suppressor gene involved in prostate tumorigenesis. One of the tumor samples demonstrated homozygous deletion at a distal location D6S314 (6q23-6q24) suggesting another locus potentially associated with CaP. Although the relationship of 6q loss of heterozygosity (LOH) with various clinicopathologic variables, i.e., cancer recurrence or pathologic stage, did not reveal a statistically significant association, the risk of 6q LOH to non-organ confined (pT3) disease was five fold higher than for organ confined disease. An additional Manuscript/Abstract is being worked on at this time.

Report Date: 01 August 2000

Work Unit # 2843

DETAIL SUMMARY SHEET

TITLE: ECOG EST 1887: A Phase III Trial of Cystectomy Alone vs. Neoadjuvant M-VAC+Cystectomy in Patients with Locally Advanced Bladder Cancer

KEYWORDS: cisplatin, cystectomy, bladder cancer

PRINCIPAL INVESTIGATOR: McLeod, David COL MC
ASSOCIATES:

DEPARTMENT: Surgery
SERVICE: Urology

STATUS: O
INITIAL APPROVAL DATE: 25 October 1988

STUDY OBJECTIVE

To compare the survival in patients with locally advanced bladder cancer who are treated with cystectomy alone to those who are treated with M-VAC (methotrexate/vinblastine/adriamycin/cisplatin) followed by cystectomy in a randomized Phase III neoadjuvant trial, and to qualify the "tumor downstaging" effect of neoadjuvant M-VAC.

TECHNICAL APPROACH

This is a randomized, multicenter, Phase III trial for patients with T2-T4a, NO, MO transitional cell carcinoma of the bladder with or without squamous differentiation. Patients are randomized to radical cystectomy or M-VAC plus radical cystectomy.

PRIOR AND CURRENT PROGRESS

WRAMC is no longer enrolling patients into this study. No patients have been enrolled since 1995. We are following one patient for survival and he remains with no evidence of disease.

CONCLUSIONS

None.

Report Date: 10 January 2001

Work Unit # 2843-98

DETAIL SUMMARY SHEET (Human Use Protocol)

TTTLE: Statistical Modeling Using Pre-Operative Prognostic Variables in Predicting Extrascapsular Extension, Positive Margins and Outcome After Radical Prostatectomy for Prostate Cancer: Retrospective Study Using the CPDR Database

KEYWORDS: prostate, cancer, survival

PRINCIPAL INVESTIGATOR: Moul, Judd COL MC
ASSOCIATES: Bauer, John MAJ MC

DEPARTMENT: Surgery
SERVICE: Urology

STATUS: O
INITIAL APPROVAL DATE: 02 February 1998

STUDY OBJECTIVE

The objective of this study is to perform statistical analysis on a group of patients who have undergone radical prostatectomy for prostate cancer. The outcome of this analysis will establish the important preoperative variables that predict disease-free survival after surgery. These variables will then be used to develop a simple equation to predict outcomes after radical prostatectomy, capsular penetration and probability of positive margins.

TECHNICAL APPROACH

We will query the CPDR Database for those patients who underwent radical prostatectomies at WRAMC between 1985-1995. 573 patients and their data are currently available, only those that have accurate clinical follow-up and variable data will be included in this study. The variables that will be studied are: age, race, pre-treatment PSA, pre-treatment PAP, clinical stage, highest biopsy Gleason sum, highest biopsy glandular differentiation, and highest biopsy nuclear grade. A separate model that employs the number of positive biopsies in place of clinical stage will be performed. Cox proportional hazards model will be used to assess the simultaneous influence of possible predictor variables on the time to disease recurrence after radical prostatectomy.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

The study is on going and we are still conducting statistical testing on the dataset to refine the prognostic ability as the follow-up of the patient cohort matures. We plan to submit an addendum to allow us to include patients who have had surgery between 1996-2000.

CONCLUSIONS

With ongoing analysis, pretreatment PSA, Gleason tumor grade, clinical stage, race and number of positive biopsy cores remain as independent predictors of pathologic stage and recurrence.

Report Date: 25 January 2001 Work Unit #2846-98

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: Assisting the Predictive Accuracy of Prostate Cancer Prognostic Factors Using Traditional Statistical Methods and Artificial Neural Networks

KEYWORDS: prostate cancer, neural network analysis

PRINCIPAL INVESTIGATOR: Moul, Judd COL MC
ASSOCIATES:

DEPARTMENT: Surgery
SERVICE: Urology

STATUS: O
INITIAL APPROVAL DATE: 12 March 1998

STUDY OBJECTIVE

The purpose of this study is to assess the accuracy of prostate cancer prognostic factors in predicting response to therapy and post-therapy recurrence using traditional statistical methods and artificial neural networks.

TECHNICAL APPROACH

Predicting natural history, therapy and post-therapy response require that natural history, therapy-dependent, and post-therapy prognostic factors to be identified and assessed by a statistical model. Our group has examined both anatomic-cellular putative prognostic factors, for example, stage, grade, angiogenesis, Ki-67, PSA and molecular-genetic putative prognostic factors, for instance, p53, bcl-2 and CD-34. The goal of this study is to assess these factors in terms of their utility as natural history, therapy and post-therapy prognostic factor using both traditional statistical methods, for example, logistic regression and proportional hazards methods and artificial neural networks.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Preliminary analysis of 130 subjects shows that p53 tumor suppressor protein expression in the primary tumor of radical prostatectomy patients is an important prognostic indicator in neural network analysis.
In this early detected population the variables of age, PSA, stage and Gleason score were not accurate predictors of recurrence. Of the molecular genetic factors, neither Bcl-2 or MIB 1 were significant. This project is still underway to determine additional prognostic markers in neural network analysis. P53 expression would appear to be a clinically useful prognostic marker in localized cancer. Over the past year, work has been done to complete holes in the database for this project by reviewing all the data for the patients enrolled. The number of subjects enrolled to the study since the last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 2715. There have been no adverse events since this is a database related protocol.

CONCLUSIONS

This project is still ongoing and no conclusions have been made as of this time.

Report Date: 30 March 2001 Work Unit # 2852-98

DETAIL SUMMARY SHEET

TITLE: Comparisons of Disease Progression in pT3 Prostate Cancer. Receiving Adjuvant or Salvage Radiotherapy Following Radical Prostatectomy

KEYWORDS: pT3, prostate cancer, radiotherapy

PRINCIPAL INVESTIGATOR: Petroski, Rayford CPT MC USA
ASSOCIATES:

DEPARTMENT: Surgery
SERVICE: Urology

STATUS: O
INITIAL APPROVAL DATE: 05 May 1998

STUDY OBJECTIVE

To assess the outcomes of men undergoing external beam radiation therapy (XRT) after having radical prostatectomy (RP). To determine whether patients receiving radiation therapy prior to developing a detectable PSA post –operatively have a longer time to PSA recurrence that those patients receiving radiation therapy after developing a detectable PSA.

TECHNICAL APPROACH

Retrospective chart review using the CPDR database (WU3 2857 and 2898). We will query to find those patients with pT3 disease who have been treated with XRT, assessing the outcome based on immediate (adjuvant) or delayed (salvage) radiotherapy.

PRIOR AND CURRENT PROGRESS

A total of 619 patients who underwent RP between 1 January 1989 and 30 June 1996 were identified through the WRAMC database. Of these, 2398 were pT3 patients, 82 of whim received XRT. Data was available on 26 patients receiving adjuvant XRT and 35 patients receiving salvage XRT. Kaplan-Meier Product Limit Estimates (KMPL) was used to assess the time to biochemical (PSA) recurrence. Data has been collected from NNMC. Currently, the data and results have been sent to the statistician to analyze.

CONCLUSIONS

Results are still pending.

Report Date: 02 January 2001

Work Unit # 2854-98

DETAIL SUMMARY SHEET (Human Use Protocol)

TTTLE: ECOG EST 3886: Randomized Phase III Evaluation of Hormonal Therapy vs. Observation in Patients with Stage D1 Adenocarcinoma of the Prostate Following Pelvic Lymphadenectomy and Radical Prostatectomy

KEYWORDS: zoladex, orchietectomy, adenocarcinoma/prostate

PRINCIPAL INVESTIGATOR: McLeod, David COL MC
ASSOCIATES:

DEPARTMENT: Surgery
SERVICE: Urology

STATUS: O
INITIAL APPROVAL DATE: 05 February 1998

STUDY OBJECTIVE
To determine the time to progression and survival in patients with histologically confirmed Stage D1 prostate cancer following radical prostatectomy and pelvic lymphadenectomy treated with no immediate hormonal therapy compared to those treated immediately with hormonal therapy.

TECHNICAL APPROACH
This is a multicenter randomized Phase III trial. Patients can be randomized to hormonal therapy or observation. Those patients randomized to observation may be registered to receive hormonal therapy if their disease progresses. All patients that progress on hormonal therapy will be followed off study drug. This study was closed to enrollment in 1993.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
One patient was randomized to the hormone therapy (zolodex). We continue to follow one patient for survival. This is an ECOG protocol and ECOG no longer provides drug for this study. The patient has experienced no side effects.

CONCLUSIONS
None.

Report Date: 05 May 2001 Work Unit # 2856-98

DETAIL SUMMARY SHEET

TITLE: A Multicenter Randomized Open-Label Trial to Compare Mineral Density and Fat Free Mass in Men Given Either Gosereline Acetate (ZOLADEXTM) 10.8-MG Depot or Bicalutamide (CASODEXTM) 150MG for Treatment of Prostate Cancer

KEYWORDS: casodex, prostate cancer, osteoporosis

PRINCIPAL INVESTIGATOR: McLeod, David COL MC
ASSOCIATES:

DEPARTMENT: Surgery STATUS: C
SERVICE: Urology INITIAL APPROVAL DATE: 26 May 1998

STUDY OBJECTIVE
Primary: To measure change over time compared with baseline measurement of bone mineral density and fat free mass within each treatment group and to compare the 2 groups. Secondary: follow changes in blood lipid levels and assessing the safety and tolerability of goserelin acetate treatment and bicalutamide treatment.

TECHNICAL APPROACH
Multi-center, Randomized, open label, parallel-group trial

PRIOR AND CURRENT PROGRESS
The number of subjects enrolled to the study since the last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 4. The total number enrolled study-wide is 103. Enrollment was closed for this study on 26 April 1999. This study is now closed by the sponsor. The study has been completed. The sponsor's closeout visit for this study is scheduled for 15 May 2001.

CONCLUSIONS
None at this time. Data is still be analyzed by the sponsor.

Report Date: 08 March 2001 Work Unit # 2857-98

DETAIL SUMMARY SHEET

TITLE: Multicenter Prostate Cancer Database for the Center for Prostate Disease Research (CPDR) with Patterns of Care, Outcome and Prognostic Analysis

KEYWORDS: CPDR, prostate, cancer

PRINCIPAL INVESTIGATOR: Moul, Judd COL MC
ASSOCIATES:

DEPARTMENT: Surgery STATUS: O
SERVICE: Urology INITIAL APPROVAL DATE: 26 May 1998

STUDY OBJECTIVE

1) To maintain an accurate, reliable, secure relational database so as to demonstrate and coordinate longitudinal prostate cancer data collection as part of a multi-center DOD prostate cancer repository at USUHS.
2) To use the database to analyze patterns of care, prognostic factors and intermediate and long-term outcomes for prostate cancer.
3) The CPDR database is suitable for analyzing epidemiological features of prostate cancer and treatment efficacy, and monitoring the quality of life of our patients. Our long-term goal is to have 20,000 patients followed for 20 years.

TECHNICAL APPROACH – Our goals and objectives will be achieved by:

1) Retrospectively collecting standardized data on all prostate cancer patients treated at specified military medical centers during the period 1960-1997 (under WU#2898)
2) Prospectively by colleting standardized date on all prostate cancer patients treated at specified military centers beginning in 1998. Prospective data collection will be with consent.

PRIOR AND CURRENT PROGRESS - As of 2/2001, the WRAMC database has archived 113.624 clinical records on 4428 men. 2291 of these men have full consent. CPDR database with all 9 sites has archived 256962 clinical records on 12,004 men. 6476 of these men have full consent. Consenting continues as patients return for follow-up, and as new patients are enrolled in the study. Mean number of follow-up visits per patient is presently 8.02 (91248 total follow-up visits). Currently in our database, frequency of treatment modality is as follows: radical prostatectomy > external beam radiation > total hormonal therapy > branchtherapy > cryotherapy. The ratio of death due to prostate cancer vs. death due to other cause is about 1 to 3. Over the course, there have been a total 24 protocol addenda to this protocol and consequently these investigations have begun. The number of subjects enrolled to the study since the last APR at WRAMC is 586 and the total enrolled to date at WRAMC is 4,428. The total number enrolled study-wide is 12,004.

CONCLUSIONS – This is an ongoing retrospective and prospective prostate cancer and disease research database. It is serving as a platform for many ongoing projects. We have documented a general improvement in disease severity, as the PSA screening test has been more widely used in the military heath care system. The number of patients $\leq$ 60 years of age increased from 1991 to 2000. The ratio of the two ethnic groups (Caucasian vs. African-American) was not changed significantly. Pretreatment PSAs between 4-10 increased from 1990 to 1996, and were stable thereafter. The percentage of biopsy core ratio >50% positive dropped from 1991 to 2000. Detection rates of clinical stages changed from 1990 to 2000, with percentage of T1 disease increasing and percentage of T2 disease decreasing. The overall age at diagnosis has decreased. The trend of younger diagnostic age, lower pretreatment PSA level and T stage, and less cases with > 50% positive core ratio indicate an earlier detection of the prostate cancer.

Report Date: 02 April 2001

Work Unit # 2858-98

DETAIL SUMMARY SHEET

TITLE: An Ultrasound-Based System for Examination and Diagnosis of Prostate and Urinary Conditions – A Phase I Clinical Study

KEYWORDS: ultrasound, prostate cancer, transrectal, transurethral

PRINCIPAL INVESTIGATOR: McLeod, David COL MC
ASSOCIATES: Spevak, Marianne CCRC

DEPARTMENT: Surgery
SERVICE: Urology

STATUS: O
INITIAL APPROVAL DATE: 26 May 1998

STUDY OBJECTIVE

The objective of this study is to evaluate the safety and efficacy of a new device called UROTECH in the detection of prostate cancer. The objective of this phase I study will be to compare whole-amount histology obtained from radical prostatectomy specimens with images derived from this device obtained prior to the prostatectomy.

TECHNICAL APPROACH

Approximately 50 patients will be enrolled in this protocol. Patient will have standard of care TRUS and biopsy performed. Prior to surgery, patients will be studied with the UROTECH device. The device will carefully map the prostate through the utilization of transrectal and transurethral transducers to develop a preoperative map of designated areas of the prostate. After surgery, the whole amount of specimens prepared at AFIP with 3-D reconstruction will be compared to the images obtained with the UROTECH device.

PRIOR AND CURRENT PROGRESS

The number of subjects enrolled to the study since last APR at WRAMC is 4 and the total enrolled to date at WRAMC is 4. Enrollment is continuing at this time. There has been some difficulty with the sponsor to obtain the urethral catheter, but this is expected to resolve shortly. There have been no adverse events to date.

CONCLUSIONS

None at this time.

Report Date: 02 January 2001

Work Unit # 2859-98

DETAIL SUMMARY SHEET (Human Use Protocol)

TTTLE: SWOG 8894 A Comparison of Bilateral Orchiectomy With or Without Flutamide for the Treatment of Patients with Histologically Confirmed Stage D2 Prostate Cancer

KEYWORDS: cancer, prostate, orchiectomy

PRINCIPAL INVESTIGATOR: McLeod, David COL MC
ASSOCIATES:

DEPARTMENT: Surgery
SERVICE: Urology

STATUS: O
INITIAL APPROVAL DATE: 05 February 1998

STUDY OBJECTIVE
To test the hypothesis that total androgen blockade (orchiectomy plus flutamide) may be better than orchiectomy alone.

TECHNICAL APPROACH
This is a prospective, randomized, double blind, placebo controlled study.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
35 patients were enrolled into this protocol at WRAMC. Enrollment was completed in September 1994. We are following 3 patients for survival, all of whom are stable with no evidence of disease. This is an ECOG protocol.

CONCLUSIONS
None at this time.

Report Date: 02 January 2001 Work Unit # 2861-98

DETAIL SUMMARY SHEET (Human Use Protocol)

TTTLE: ECOG P-Z887 A Phase I Study of Intravesical Tumor Necrosis Factor in the Treatment if Superficial Bladder Cancer

KEYWORDS: intravesical, tumor necrosis factor (TNF), bladder cancer

PRINCIPAL INVESTIGATOR: McLeod, David COL MC
ASSOCIATES:

DEPARTMENT: Surgery STATUS: O
SERVICE: Urology INITIAL APPROVAL DATE: 05 February 1998

STUDY OBJECTIVE
To determine: 1) safety of TNF instilled into the bladder as an intravesical form of therapy for superficial bladder cancer; 2) the scope and severity of toxicity of the TNF in patients with bladder cancer; 3) the dose limiting toxicities and maximum tolerated dose of TNF; 4) any systematic effects of the TNF on other organ systems and to determine systemic pharmacokinetics.

TECHNICAL APPROACH
Three patients will be treated at each dose level (200-250 mcg.) Each patient will receive all treatments of TNF in a single dose level. If DLT is seen in more than one patient, an additional three patients will be entered at this dose level. If a total of three of these six patients exhibit a DLT, then dose escalation will end all subsequent patient will be entered at this dose level.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
This study was terminated by ECOG in 1991. We are following two patients for survival at this time. Both patients show no evidence of disease.

CONCLUSIONS
None at this time.

Report Date: 02 January 2001 Work Unit # 2864-98

DETAIL SUMMARY SHEET (Human Use Protocol)

TTTLE: ECOG EST 9887 A Phase III Trial of Treatment of Pathologic Stage C Carcinoma of the Prostate with Adjuvant Radiotherapy

KEYWORDS: prostate, cancer, adjuvant radiotherapy

PRINCIPAL INVESTIGATOR: Moul, Judd COL MC
ASSOCIATES: McLeod, David COL MC

DEPARTMENT: Surgery
SERVICE: Urology

STATUS: O
INITIAL APPROVAL DATE: 05 February 1998

STUDY OBJECTIVE
To compare in a randomized study, the disease-free survival rates in completely resected patients with pathologic Stage C (T3Noh10) carcinoma of the prostate assigned to be treated with adjuvant external beam radiotherapy to that in patients assigned to receive no adjuvant therapy. To assess the qualitative and quantitative toxicities of patients with pathologic Stage C carcinoma of the prostate when treated with eternal beam radiotherapy.

TECHNICAL APPROACH
After prostatectomy with pelvic lymphadenectomy and no evidence of regional lymph node or metastatic disease, the patient is randomized to receive adjuvant radiation therapy or no adjuvant therapy. All patients are off treatment 1 year after randomized or at disease progression.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
Four patients were enrolled in this study. This patient had been closed to enrollment since 1993. We are following three patients for survival. One patient is lost to follow-up. This is an ECOG protocol.

CONCLUSIONS
None at this time.

Report Date: 7 August 2001 Work Unit # 2865-98

DETAIL SUMMARY SHEET

TITLE: Evaluation of Agents that Work Through the Cyclic GMP System on Prostatic Smooth Muscle Function

KEYWORDS: smooth muscle, cyclic GMP, prostate

PRINCIPAL INVESTIGATOR: Dean, Robert LTC MC
ASSOCIATES: Gancarczyk, Kevin CPT MC

DEPARTMENT: Surgery
SERVICE: Urology

STATUS: C
INITIAL APPROVAL DATE: 16 June 1998

STUDY OBJECTIVE

To determine the effect of various agents that work through he nitric Oxide/cyclic GMP system to mediate function of human prostatic smooth muscle in organ bath studies.

TECHNICAL APPROACH

Prostate tissue obtained preoperatively will be evaluated with various phosphodiestaerase inhibitors after contraction with endothelin. The amount of contraction expresses a percent of control will be compared.

PRIOR AND CURRENT PROGRESS

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 16. The total number enrolled study-wide is N/A, if multi-site study. Since the change of PI in 2000 and the change of research residents, no additional work has been done on this protocol since the last APR (2000). At this time, we are requesting to close this protocol. If in the future there is a research resident that is interested in conducting this study or a similar study, we will submit a new protocol.

CONCLUSIONS

The protocol was not completed. No new results are available to report since the initial results reported in last years APR.

Report Date: 20 August 2001 Work Unit # 2867-98

DETAIL SUMMARY SHEET

TITLE: Advanced Computer Algorithms for Assessing Prognostic and Treatment Variable in Prostate Cancer

KEYWORDS: prostate cancer algorithms

PRINCIPAL INVESTIGATOR: McLëod, David COL MC
ASSOCIATES:

DEPARTMENT: Surgery STATUS: O
SERVICE: Urology INITIAL APPROVAL DATE: 22 June 1998

STUDY OBJECTIVE
To ascertain whether patterns exist in the CPDR database at WRAMC that permit accurate diagnosis of the disease in a retrospective and subsequently prospective manner.

TECHNICAL APPROACH
Using specific variable, a number of artificial neural networks and fuzzy logic systems of artificial intelligence will attempt to find underlying patterns. Examples of these patterns are predicting stage given biopsy and clinical information and predicting recurrence given surgical pathology information.

PRIOR AND CURRENT PROGRESS
Johns Hopkins and Georgetown University have joined WRAMC in providing this data to the Institute of Clinical Research in order to provide a substantial database for the algorithms. No WRAMC data has been released this year or the previous year. We are completing the data holes for the patients that we plan to analyze for this study. We plan on looking at 2921 patient records for this protocol.

CONCLUSIONS
None at this time.

Report Date: 16 February 2001 Work Unit # 2868

DETAIL SUMMARY SHEET

TITLE: Randomized Prospective Study Comparing Radical Prostatectomy Alone Versus Radical Prostatectomy Preceded by Androgen Blockade in Clinical B2 (Y2bNxMo) Prostate Cancer

KEYWORDS: androgen blockade, prostate cancer, stage 2b

PRINCIPAL INVESTIGATOR: McLeod, David COL MC
ASSOCIATES: Moul, Judd COL MC

DEPARTMENT: Surgery STATUS: C
SERVICE: Urology INITIAL APPROVAL DATE: 24 September 1991

STUDY OBJECTIVE

To evaluate the safety and efficacy of a combination of leuprolide and flutamide prior to radical prostatectomy in the clinical stage B2 prostate cancer as compared to no therapy before radical prostatectomy.

TECHNICAL APPROACH

This is a randomized multi-center study that will compare the safety and efficacy of leuprolide and flutamide prior to radical prostatectomy versus no therapy prior to surgery. Patients are currently followed twice a year, every six (6) months for survival data. This data includes laboratory values for PSA and testosterone, changes in medical history or physical status, performance status or death.

PRIOR AND CURRENT PROGRESS

Prior to September 2000, we were following six patients for the ten-year survival period. In September 2000, the sponsor closed the study due to conclusions that indicated that there was no significant difference between the treatment and non-treatment groups.

CONCLUSIONS

Study conclusions indicate that there is no significant difference between the treatment and no-treatment groups. The sponsor has decided not to proceed with the study due to theses findings. A final report has been requested from the sponsor and will be forwarded when available.

Report Date: 30 May 2001 Work Unit # 2871-98

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: Creation of a Tissue Library for the Molecular Biologic Study of Patients with Prostate Cancer

KEYWORDS: prostate, cancer, tissue

PRINCIPAL INVESTIGATOR: McLeod, David COL MC
ASSOCIATES:

DEPARTMENT: Surgery STATUS: O
SERVICE: Urology INITIAL APPROVAL DATE: 21 July 1998

STUDY OBJECTIVE

1) To create a tissue library for the molecular biologic study of prostate cancer.
2) Develop a primary and immortalized cell cultures from prostate cancer specimens.
3) Define the role that oncogenes and tumor suppressor genes play in the progression of prostate cancer.
4) Analyze genetic susceptibility factors for prostate cancer such as androgen receptor CAG repeats and HPCI mutations.
5) Correlate RNA and DNA molecular biology assays to the ongoing clinical database (WU # 2898). Create a 3-dimensional reconstruction of the prostate gland to assess the volume of all individual tumors, their locations within the prostate gland, their molecular pedigree and any extracapsular extension of the neoplasm.

TECHNICAL APPROACH

Samples will be obtained from TURP and radical prostatectomy specimens which will include cancerous and normal tissue. Informed consent will allow inter-operative collection of blood, bone marrow, and tissue biopsies of the excised organ. It will allow the use of these specimens as well as the retrieval and use of their original archival biopsy tissue. Blood samples will be used to measure specific molecular markers and will be compared to clinical features. All samples will be processed by AFIP using SOP, and sent to the CPDR lab as required.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

The number of subjects enrolled to the study since last APR at WRAMC is 120 and the total enrolled to date at WRAMC is 271. (There are also 187 consented from WU#2894 – bringing the total to 458 consented in the tissue bank.) There have been no AE's on this study.

CONCLUSIONS

None at this time

Report Date: 30 May 2001

Work Unit #01-2871-98a

DETAIL SUMMARY SHEET (Human Use Protocol)

TTTLE: Characterization of Novel Prostate Specific Gene, PCGEM1

KEYWORDS: tissue, prostate, cancer

PRINCIPAL INVESTIGATOR: McLeod, David COL MC

DEPARTMENT: Surgery
SERVICE: Urology

STATUS: O
INITIAL APPROVAL DATE: 20 February 2001
MASTER PROTOCOL APPROVAL: 21 July 1998

STUDY OBJECTIVE

1. Characterization of PCGEM1 Structure and Function
2. Mechanisms of Regulation of PCGEM1 Expression
3. Analysis of PCGEM1 Expression in Prostate Cancer

TECHNICAL APPROACH

1. Characterization of PCGEM1 Structure and Function: A comprehensive analysis of PCGEM1 cDNA clones ha revealed that PCGEM1 represents a novel cDNA sequence, which may belong to the emerging group of functional non-coding mRNAs. PCGEM1 cDNA as well as the native PCGEM1 mRNA will be analyzed to determine if PCGEM1 functions as a non-coding RNA or one of the short ORFs of the PCGEM1 cDNA encode PCGEM1 protein. PCGEM1 mRNA will be analyzed for its subcellular localization e.g., nuclear localization of PCGEM1 mRNA or absence of PCGEM1 mRNA in polyribosomes will further support its non-coding nature. Anti-peptide antibodies will be raised against PCGEM1 ORFs to detect PCGEM1 encoded protein, if any. The short ORFs derived from the PCGEM1 cDNA will be expressed in NIH3T3 cells as observed with the full length PCGEM1 cDNA. Cell growth regulating functions of the PCGEM1 will be characterized by over expression of PCGEM1 in NIH3T3 cells or immortalized normal prostate epithelial cells and by inhibiting the expression of PCGEM1 sequence LNCaP prostate cancer cells. Deletion mutagenesis will define the regions in PCGEM1 sequence critical for PCGEM1 biologic functions. The cDNA sequence of PCGEM1 homologs from non-human species will determine conserved regions of PCGEM1.

2. Mechanisms of Regulation of PCGEM1 Expression: The prostate tissue specificity and androgen regulation of PCGEM1 suggests for normal functions of PCGEM1 in development and/or maintenance of the prostate gland. Genomic clones of PCGEMI1 will be characterized by DNA sequencing. The PCGEM1 promoter sequence will be identified and characterized by DNA sequencing. The PCGEM1 promoter sequence will be identified and characterized by transfecting PCGEM1 reporter-reporter constructs in LNCap cells treated with or without androgens. Once the PCGEM1 promoter is identified, it will be analyzed for the sequence elements for the presence of androgen response elements (ARE). Deletion mutagenesis of the promoter sequence followed by reporter gene assays will be performed to define the sequences that confer prostate tissue specificity or androgen regulation. Using in situ hybridization assays, the cell type specificity of the PCGEM1 expression will be established in frozen OCT embedded and paraffin embedded tissue sections of the normal and tumor regions of the human prostate.

3. Analysis of PCGEM1 Expression in Prostate Cancer: Preliminary analysis of paired normal and tumor specimens revealed PCGEM1 over expression in tumor specimens of about half of CaP patients. Role of PCGEM1 expression in prostate cancer progression will be evaluated in CWR22 xenograft model derived tumors representing androgen sensitive and androgen refractory tumors. PCGEM1 expression will also be analyzed in matched normal and tumor tissue of 100 prostate cancer patients using laser capture micro dissection (LCM) and quantitative RT-PCR. Analysis of PCGEM1 expression by in situ RNA hybridization in representative specimens will complement the RT-PCR assays. We will examine whether

PCGEM1 over expression is associated with specific pathologic stage, cancer recurrence after radical prostatectomy and the clinical stage of the disease. To address the PCGEM1 expression in the context of multifocal CaP, PCGEM1 expression will be analyzed in the sections of the whole-mounted prostate from cancer patients.

PRIOR AND CURRENT PROGRESS

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 0. This protocol was approved on 04/18/01 and approved at USUHS on 05/18/01. Work has not yet started on this protocol.

CONCLUSIONS

None at this time

Report Date: 31 May 2001 Work Unit #01-2871-98b

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: The Use of Transformed Prostate Cell Lines CPDR7, CPDR8, CPDR9, to evaluate the Capacity of T Lymphocytes to Recognized Prostate-Derived Antigens

KEYWORDS:

PRINCIPAL INVESTIGATOR: McLeod, David COL MC
ASSOCIATES:

DEPARTMENT: Surgery
SERVICE: Urology

STATUS: O
INITIAL APPROVAL DATE: 10 April 2001
MASTER PROTOCOL APPROVAL: 21 July 1998

STUDY OBJECTIVE

The CPDR7, CPDR8 and CPDR9 cell lines will be used as target cells in cytoxicity *in vitro* assays to determine whether peptide-specific CTL can recognize naturally processed antigen.

TECHNICAL APPROACH

CPDR7, CPDR8, CPDR9 immortalized prostate cancer cell lines will be used as targets in the cytoxicity assys in addition to t2 cells. This will specifically help to demonstrate that naturally processed antigens can be lysed by CTL to peptides.

***Day 0** Generation of Dendritic Cells (DC):* Monocytes are purified by plating 10 X 10^6 PBMC in 3 ml of complete medium (RPMI-1640 plus 5% AB hum serum, non-essential AA sodium pyruvate, L-glutamine and gentamycin) in each well of a 6-well plate. After 2 hours at 37° C, the non-adherent cells are removed by gently shaking the plates and aspirating the supernatants with a Pasteur pipette and vacuum. The wells are washed for a total of three times with medium (3 ml) to remove most of the non-adherent and loosely adherent cells. Check the plates in the inverted microscope and if contaminating T cells are still present, remove them by gently flushing medium onto the bottom of the wells with a transfer pipette and removing one more time the supernatants. Add 3 ml of complete medium to each well containing 50 ng/ml of GM-CSF and 1,000 U/ml of IL-4. These DC will be ready to use for CTL induction cultures after 6-7 days. IF the cell cultures become too yellow, remove ½ of medium and feed with fresh medium containing cytokines. On day 6, DC can be induced to maturate by adding fresh medium containing poly I:C (Sigma) to a final concentration of 20 µg/ml.

***Day 7 (part A)** Induction of CTL with DC and peptide:* The DC are harvested and washed 1X with PBS-HAS (human serum albumin) and resuspended in PBS with 1% HSA. The DC are counted and pulsed with 40 µg/ml of synthetic peptides corresponding to prostate antigens (PSA, PSMA, etc...) at a cell concentration of 1~2x 10^6/ml in PBS-HSA in the presence of 3 µg/ml β_2 microglobulin for four hours at 20°C (room temperature) with constant mixing in rocking platform. While the DC are bring pulsed, $CD8^+$T-cells are purified with Miltenyi immunomagnetic beads by positive selection as described above for CD14+cells and will be used for as responders. CD8-depleted cells can be re-frozen for used as monocytes for restimulation with antigen (day 14). Typically to obtain enough cells for one 48-well plate culture, 200 to 250x10^6 PBMC are processed to obtain 24x10^6 CD8+cells. Resuspend the CD8 positive cells after washing them, at 2x10^6 cells/ml and keep at 4°C until further use. After the 4 hr peptide pulsing incubation, the DC are irradiated (4,200 rads), washed 1 time with RPMI-HS medium (RPMI + 5% human AB serum) and diluted at 1 X 10^5 cells/ml.

***Day 7 (part B)** Setting up T-cell priming cultures:* 0.25 ml cytokine-generated DC (@1x10^5 cells/ml) are co-cultured with 0.25 ml of CD8 T-cells (@ 20x10^5 cells/ml) in each well of a 48-well plate in RPMI-HS and in the presence of 10 ng/ml of rIL-7.

Day 8 Add rIL-10 to a final concentration of 10 ng/ml.
Day 14*Restimulate the induction cultures with peptide pulsed adherent cells in individual wells of the 48-well plate:* Plate $2x10^6$ PBMC (washed with DNAse and irradiated ~4,200 rads) in 0.5 ml of the complete medium per well. Incubate for 2 hours at 37°C to allow monocytes to adhere to bottom of plates. Wash off non-adherent cells by gently flushing the cells with PBS 2% FCS and pulse adherent cells with 10 μg/ml of peptide in the presence of 3μg/ml β_2 microglobulin (in 0.25 ml of PBS-FCS per well) for 2 hours at room temperature in rocking platform. The peptide solution from each well is aspirated. One-half of the media is aspirated from the CD8+ cells and fresh media. The cells are resuspended individually and transferred to the wells containing the "dry" peptide-pulsed adherent cells.

Day 15 Add 100 μl of medium containing rIL-10 and rIL-4 (1:100) so final concentration of cytokines is 10 ng/ml and 2000 U/ml.

Day 16 or 17 Add 100 100 μl fresh medium containing rIl-2/ml (final of 50 IU) to each well.

Day 21 Restimulate the entire cultures again. Repeat procedures from day 7 to 17/

Day 28-29 Perform either a cytoxicity (5 hr Cr^{51} release) assay or ELISA for individual wells using a single E/T ratio (use 75% of the cells from each well, and do not count the effectors). Targets used are: T2, T2-pulsed with peptide (10μg/ml the night before). In addition, the CTL will be tested for activity against the CPDR7, CPDR8 and CPDR9 cell lines to demonstrate that these cells can recognize naturally processed antigens. CPDR 7, CPDR 8 and CPDR 9 cell lines will be used as targets in cytoxicity assays, by labeling with 51Cr.

**To continue growing positive wells, the cultures must be restimulated with peptide and APC every 7 days as described above or expanded by REM.

NOTE: Peptides have been provided to you diluted in 100% DMSO plus 0.1%TFA at 20 mg/ml. A total of 5 mg are in each vial, sufficient for several experiments. Dilute in medium for pulsing APC or targets only the amount required. You can store peptide stocks at –20°C and freeze-thaw several times (up to 10) w/o problem.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
The number of subjects enrolled to the study since the last APR at WRAMC is 0. This protocol was just approved 03 May 2001. The enrollment will be accrued under the master protocol 2871-98.

CONCLUSIONS
None at this time

Report Date: 5 July 2001

Work Unit # 2873-98

DETAIL SUMMARY SHEET

TITLE: Macroscopic and Microscopic Anatomy of the Arterial Supply to the Human Vas Deferens

KEYWORDS: arterial supply, vas deferens, cadaver

PRINCIPAL INVESTIGATOR: Marianne Spevak, CCRC
ASSOCIATES:

DEPARTMENT: Surgery
SERVICE: Urology

STATUS: O
INITIAL APPROVAL DATE: 11 August 1998

STUDY OBJECTIVE

The objective is to describe the gross and microscopic blood supply to the vas deferens. Additional objectives are to assess the variability of the arterial and venous structures, assess collateral blood supply to the vas deferens, and to utilize the new understanding of the vascular supply to improve operations on the spermatic cord, scrotal adnexa and vas deferens.

TECHNICAL APPROACH

The gross dissection of the deferential blood supply will be to perform gross dissection of cadaveric and autopsy specimens, dissection of en bloc spermatic cord specimens from formalin preserved and frozen cadavers, and microdissections on cadaveric specimens and autopsy specimens and recording of finding using photos and drawings. The microscopic description of deferential blood supply will include injection studies spermatic artery. Specimens will also be injected with resin, and the surrounding soft tissue treated with acidifying agent to create coasts of the deferential artery and its branches. Histologic sections will be performed using a dissecting microscope in the straight and convoluted portions of the vas deferens sagittally and transversely. These sections will be recorded using photomicrographs and drawings from medical illustrators. The donated cadavers/autopsy will be provided by USUHS. The dissection will be conducted in the Anatomical Teaching Laboratory at USUHS.

PRIOR AND CURRENT PROGRESS

There has been a change in PI since the protocol has been approved. We anticipate to resume working on this protocol immediately. There has been no progress since the last APR.

CONCLUSIONS

None at this time.

Report Date: 1 August 2001 Work Unit # 2877-98

DETAIL SUMMARY SHEET

TITLE: Study of the Safety and Effectiveness of the Mentor Saline-Filled Testicular Prosthesis

KEYWORDS: prosthesis, testicular, implant

PRINCIPAL INVESTIGATOR: Dean, Robert C. MAJ, MC
ASSOCIATES: Peppas, Dennis S., LTC, MC; Marianne Spevak, CCRC

DEPARTMENT: Surgery
SERVICE: Urology

STATUS: O
INITIAL APPROVAL DATE: 1 September 1998

STUDY OBJECTIVE

The objectives of the study are to assess the safety and effectiveness of the Mentor saline-filled testicular prosthesis. We will also look at the rates of and time to explanation, revision and other resurgery of the prosthesis.

TECHNICAL APPROACH

This is a multi-center open label study. Patients are stratified into four groups: adult males who are missing their testicle at baseline; adult males who are not missing their testicle at baseline; pediatric males who are missing their testicles at baseline. Patients will be followed for five years. Patients complete quality of life questionnaires and satisfaction questionnaires throughout the length of the study.

PRIOR AND CURRENT PROGRESS

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 9. The total number enrolled study-wide is 149, if multi-site study. Enrollment ended August 1999. Two patients have retired from the military and are lost to follow-up. The seven remaining patients continue to be followed per protocol. No new adverse events have been reported.

CONCLUSIONS

None at this time.

Report Date: 16 August 2000

Work Unit # 2879-99

DETAIL SUMMARY SHEET

TITLE: A Randomized, Double-Blind Comparative Trial of Bicalutamide (CASODEX™) 150mg Monotherapy Versus Placebo in Patients with a Rising PSA After Radical Prostatectomy for Prostate Cancer

KEYWORDS: prostate, monotherapy, radical prostatectomy

PRINCIPAL INVESTIGATOR: McLeod, David COL MC
ASSOCIATES: Moul, Judd LTC MC, Spevak Marianne

DEPARTMENT: Surgery
SERVICE: Urology

STATUS: O
INITIAL APPROVAL DATE: 06 October 1998

STUDY OBJECTIVE

The primary objective is to compare Bicalutamide 150mg with placebo for time to treatment failure. Time to treatment failure is defined as the time from randomization to the time of any of the following: AE leading to withdrawal of randomized therapy, objective disease progression, imitation of systemic treatment or radiotherapy, or withdraw from the study for any reason. The secondary objective includes QOL questionnaire including a PSA anxiety questionnaire (MAX-PC) and the FACT-P instrument, time to objective disease progression, PSA response and time to PSA progression.

TECHNICAL APPROACH

This is a multi-center, randomized, double blind, parallel-group trail. The patients must be at least one year out from radical prostatectomy and have a rising PSA of greater than or equal to 0.4ng/ml confirmed on two occasions at least one week apart. Patients must have a negative CT scan and bone scan to be eligible for the study. Patients are then randomized to receive placebo or Bicalutamide 150mg. Patient visits are every twelve weeks. They may continue on the study for up to 2 years if they respond to treatment.

PRIOR AND CURRENT PROGRESS

We have screened a total of four patients and enrolled 2 of the four patients at the present time. One screen failure was not enrolled due to his PSA level was not high enough, and the second screen failure was found to have bone metastases on work-up and was not eligible for the study. Enrollment is still continuing at this time. A total of 102 patients have been enrolled study wide. All AE's have been reported to DCI (no new AE's since last APR). Enrollment has been slower than expected all sites.

CONCLUSIONS

None at this time.

Report Date: 25 August 2000 Work Unit # 2881-99

DETAIL SUMMARY SHEET

TITLE: Retrospective Study of the CPDR Prostate Cancer Database to Perform Statistical Modeling Using Pre-Treatment Prognostic Variables in Predicting Disease Progression After Radiotherapy for Clinically Localized Prostate Cancer

KEYWORDS: statistical modeling, dišease progression, prostate cancer

PRINCIPAL INVESTIGATOR: Moul, Judd W. COL MC
ASSOCIATES: Petroski, Raymond CPT MC

DEPARTMENT: Surgery
SERVICE: Urology

STATUS: O
INITIAL APPROVAL DATE: 29 October 1998

STUDY OBJECTIVE

1) To use pre-treatment prognostic variables to predict disease progression in men who have received primary external beam radiotherapy (XRT) using regression analysis 2) Validate a regression equation to predict disease recurrence in men who have received primary external beam radiotherapy in localized prostate cancer

TECHNICAL APPROACH

Retrospective chart review using the CPDR database WU#2857 of all men treated with XRT at WRAMC between 01 January 1989-30 June 1996. The Cox proportional hazards model will be used to assess the simultaneous influence of possible predictor variables on time to disease recurrence after treatment with XRT. Patients will be placed into age, race and stage matched cohorts, with 70% of the patients being used to create the model and the remaining 30% used to validate the model. A backward stepwise elimination procedure will be used to remove the covariates from the model if they are not correlated to the risk of recurrence.

PRIOR AND CURRENT PROGRESS

At this time, data is being reviewed and then will be sent for statistical analysis. We currently have a medical student assisting us with this protocol. We hope to complete the study within the next 12-18 months. There has been a change of PI and DCI was notified of this change.

CONCLUSIONS

None at this time.

Report Date: 27 September 2000

Work Unit # 2883-99

DETAIL SUMMARY SHEET

TITLE: Cyclosporine Treatment and the Effect on Post Vasovasostomy Semen Parameters in the Lewis Rat

KEYWORDS: vasectomy, anti-sperm antibodies,

PRINCIPAL INVESTIGATOR: Siegel, Timothy MAJ MC
ASSOCIATES: Marianne Spevak, CCRC; Petroski, Rayford CPT MC

DEPARTMENT: Surgery
SERVICE: Urology

STATUS: O
INITIAL APPROVAL DATE: 3 November 1998

STUDY OBJECTIVE

The study objective is to study the effect of cyclosporine therapy on semen parameters after vasovasotomy and the correlation between semen parameters and levels of antisperm antibodies.
The hypothesis is that the use of cyclosporine in conjunction with Vasovasostomy will improve semen parameters in previously vasectomized rat. This will be directly correlated with decrease in antisperm antibodies in cyclosporine treated rats.

TECHNICAL APPROACH

Using Lewis rats we will create individual groups to include treated and untreated rats with cyclosporine. These groups will initially undergo vasectomy and then vasovasotomy with pre and post semen analysis to determine improved semen parameters in the treated groups. These parameters will be correlated with pre and post antisperm serologic and semen antibodies. A control group of nonvasectomized rats will be used to determine baseline antisperm antibodies and normal semen parameters. These groups will consist of approximately ten animals. Cyclosporine will be dose at 10mg/kg in the treated groups.

PRIOR AND CURRENT PROGRESS

The research experiment/procedures have been completed. Data is being collected and sent for statistical analysis at this time. Results are pending.

CONCLUSIONS

Pending at this time.

Report Date: 03 April 2001 Work Unit #2884-99

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: Randomized Prospective Study of Adjuvant Androgen Ablation in Radical Prostatectomy Patients at High Risk for Disease Recurrence

KEYWORDS: prostate, cancer, lupron, casodex

PRINCIPAL INVESTIGATOR: COL David G. McLeod MC
ASSOCIATES: COL Judd W. Moul MC

DEPARTMENT: Surgery
SERVICE: Urology

STATUS: C
INITIAL APPROVAL DATE: 16 March 1999

STUDY OBJECTIVE

The objectives of this study are to determine if one-year (48 weeks) of adjuvant androgen ablation in lymph node-negative-post-radical prostatectomy patients at high risk for disease recurrence results in a significant improvement over no immediate adjuvant treatment in the interval to biochemical (PSA) disease progression (primary objective) as well as significant improvement in disease-specific survival and the clinical disease-free interval.

TECHNICAL APPROACH

Patients with high risk of recurrence, defined as a) Gleason score of ≥ 8, b) seminal vesicle invasion, or c) extracapsular extension of cancer, following radical retropubic prostatectomy will be elgible for the study. These patients will be randomized to receive total androgen ablation with lupron depot plus casodex or no immediate medication. They will be followed every 3 months for the first three years and every 6 months for an additional five years. Biochemical and/or clinical progression will be noted on each patients, defined as a) detectable PSA on two consecutive visits, b) locally detectable induration or biopsy proven recurrence, c) radiographic evidence of metastatic disease. Patients will be followed for the duration of the study regardless of whether biochemical or clinical disease progression occurs. Patients who have prematurely terminated from the study will be followed for survival for the duration of the study.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

No modifications have been made in this protocol since the last review. No patients have been enrolled in the study at WRAMC. Therefore, no adverse events have been reported at WRAMC. No serious adverse event reports have been received from the sponsor.

The number of subjects enrolled to the study since the last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 0. The total number enrolled study-wide us 144, if multi-site study.

CONCLUSIONS

This study has been terminated by the sponsor due to an overall inadequate patient accession rate. Based on the patient accession rate up to this point, and the rate that would be required over the next year as a result of the initial slow accession, the sponsor would not have a sufficient number of patients to have meaningful analyses.

Report Date: 12 February 2001 Work Unit # 2886-99

DETAIL SUMMARY SHEET

TITLE: Prostate Cancer: A Patient Education Intervention

KEYWORDS: prostate cancer education

PRINCIPAL INVESTIGATOR: Moul, Judd COL MC

DEPARTMENT: Surgery
SERVICE: Urology

STATUS: C
INITIAL APPROVAL DATE: 18 May 1998

STUDY OBJECTIVE

A. To what extent have the videotape and brochure changed the attitudes and behaviors of recently diagnosed prostate cancer patients.
B. To what extent have the videotape and brochure changed the knowledge of the study participant.
C. Are there significant differences in the impact of the materials depending on the patient age, marital situation, education, income, or race/ethnicity?
D. Are there significant differences in the impact of the materials depending on the stage at which a patient is diagnosed?

TECHNICAL APPROACH

This is a multi-center, randomized study. Following informed consent, information will be communicated to the sponsor for randomization to experimental and control groups. An interview will be conducted on the telephone for patients in both groups. Shortly after this interview, a videotape and educational materials will be mailed to the patients in the experimental group. This group will review the materials in their home. Six weeks after viewing the materials, the patients in the experimental group will be interviewed for a second time. Six weeks after the first interview, patients randomized to the control group will receive their second interview.

PRIOR AND CURRENT PROGRESS

A total of twenty-three (23) patients have been enrolled at WRAMC. Seventy-two (72) patients were enrolled from a total of eight (8) sites. This study was closed to enrollment July 14, 2000. No adverse events have been reported in this data collection.

CONCLUSIONS

1. In combination, the educational materials significantly increased patients' knowledge regarding prostate cancer and its' treatment.
2. In combination, the educational materials significantly improved the ability of patients to deal with their diagnosis;
3. In combination, the videotape and brochure significantly improved the actions taken by patients to address their prostate cancer diagnosis and treatment;
4. Patients assessment of the usefulness of the videotape was mixed. Patients assessed the videotape as more useful in helping them in what they were doing or planning to do to deal with their condition and in increasing their knowledge about prostate cancer than it was in improving their outlook about their condition. The videotape was assessed as helpful by patients irrespective of their age, marital status, race and stage at the time of diagnosis. Patients with less than a college degree and patients whose annual family income was less that $60,000 rated the videotape as significantly more helpful that did patients who had earned at least a college degree and/or had an annual family income of $60,00 or more.
5. Patients assessed all sections of the brochure as useful, with the Glossary, and "Choosing the Right Treatment for You" rated as most useful. The brochure was assessed as useful by patients irrespective of their age, marital status, race, educational attainment, and stage at the time of diagnosis. Patients whose family income was less than $60,000 a year rated the brochure as significantly more useful than did patients who had family incomes of $60,000 a year or above.

Report Date: 14 April 2001

Work Unit # 2887-99

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: ALZA Overactive Bladder Registry Design Document

KEYWORDS: overactive bladder, incontinence

PRINCIPAL INVESTIGATOR: Dean, Robert C. MAJ MC
ASSOCIATES: Michael J. Danier DO CAPT MC USN; Marianne Spevak CCRC

DEPARTMENT: Surgery
SERVICE: Urology

STATUS: O
INITIAL APPROVAL DATE: 08 June 1999

STUDY OBJECTIVE:
The principle objective of this study is to provide comparative outcome information on the effectiveness, tolerability, and quality of life associated with different types of treatments, both pharmacological and behavioral for overactive bladder. The secondary objectives of this study are to: estimate resource utilization of health care services attributable to overactive bladder, provide physician-specific information to enhance patient care, and identify areas for possible further study.

TECHNICAL APPROACH:
Patients were enrolled from the urology clinic. Patients with a newly diagnosed overactive bladder or patients with overactive bladder that have been off medication for at least 12 months were asked to participate. Patients completed the required diaries and questionnaires and will be followed up via telephone calls from the Overactive Bladder Registry at 3 months, 6 months and then every 6 months until up to 3 years. Patients may withdraw at any time.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE:
The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 15. The total number enrolled study-wide is 217. Enrollment is now complete for the pilot portion of the program and each site was allowed to enroll up to 15 patients. WRAMC met the enrollment requirement. Patients are continuing to be followed at this time. No adverse events were reported during this time period.

CONCLUSIONS:
Pending at this time.

Report Date: 14 May 2001

Work Unit # 2888-99

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: An Open-Label, Randomized, Parallel Group Study Comparing the Perioperative Administration of Procrit (Epoetin Alfa) Plus Iron Versus Iron Alone in Patients Undergoing Radical Retropubic Prostatectomy for the Treatment of Prostate Cancer

KEYWORDS: prostate, cancer, procrit

PRINCIPAL INVESTIGATOR: McLeod, David COL MC
ASSOCIATES:

DEPARTMENT: Surgery
SERVICE: Urology

STATUS: O
INITIAL APPROVAL DATE: 22 June 1999

STUDY OBJECTIVE

The objectives of this study are:
1) To study the efficacy and safety of a 2-dose PROCIT regimen [on days –7(+ or – 2), and the day of surgery] in patients with prostate cancer undergoing radical prostatectomy 2) to examine the number of patients who require allogenic blood transfusion 3) to examine the changes in hematological parameters.

TECHNICAL APPROACH

This is a pilot study being conducted only at WRAMC. It is a randomized, open-label, parallel group study. Following informed consent and evaluation for eligibility, patients will be randomized to receive either procrit plus iron or iron alone. The initial dose of procrit will be given subcutaneously seven days (+ or -2 days) prior to scheduled radical prostatectomy. They will receive a second dose of procrit following surgery in the recovery room. All patients will start an iron supplement after screening laboratory evaluations are obtained. Study laboratory evaluations will be performed on post-op day 1, on day of discharge from the hospital, and post-op week 1 and week 2.
There have not been any addenda to the original protocol

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

The number of subjects enrolled to the study since last APR at WRAMC is 10 and the total enrolled to date at WRAMC is 10. At the last APR 5 of the 10 were currently in the screening process. Five patients have received Procrit and 5 patients have received the standard of care. Enrollment is continuing at this time. There have been no adverse events reported at this time.

CONCLUSIONS

None at this time

Report Date: 31 May 2001

Work Unit # 2889-99

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: Radical Prostatectomy of Prostate Cancer Patients and Circulating Cancer Cell Test (CCCT)

KEYWORDS: Circulating, Cancer cell, Prostate

PRINCIPAL INVESTIGATOR: Moul, Judd COL MC
ASSOCIATES:

DEPARTMENT: Surgery
SERVICE: Urology

STATUS: O
INITIAL APPROVAL DATE: 27 July 1999

STUDY OBJECTIVE

To use the CCCT to determine the incidence of circulating prostate cancer cells: 1) before, during and after radical prostatectomy (RRP) and correlate the positive detection of circulating cancer cells to disease recurrence after surgery 2) to correlate the relationship of CCCT and RRP surgical path findings.

TECHNICAL APPROACH

CCCT is drawn within 10 days of RRP, within 10 minutes after the prostate is removed, on discharge from WRAMC and 3-4 weeks after the surgery. These patients are followed every 6 months for 2 years.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

The number of subjects enrolled to the study since last APR at WRAMC is 2 and the total enrolled to date at WRAMC is 11. From February to September 2000, 43 samples from 11 different patients were tested with the Cell Works Circulating Cancer Cell Test. All samples were negative for epithelial cells. In October 2000, Cell Works moved to a larger and more modern facility (the former Guilford Pharmaceuticals Plant) requiring recertification of certain equipment and revalidation of the prostate circulating cancer cell test, which interrupted patient enrollment for approximately 6 months. These requirements have been completed and the company began accepting samples at its new facility in April 2001. From April 16-20, 2001, five samples from five different patients were processed. All samples came from patients who had previously tested negative for circulating cancer cells. Three samples had no epithelial cells. One sample had a single cell epithelial cell with increased DNA content suggestive of cancer. One sample had six cells, but their DNA content was in the normal range. The finding of cells in patients previously testing negative may be an early indication of metastasis, however, longer follow up processing at the new facility. The study is ongoing and no conclusions are permitted.

CONCLUSIONS

None at this time.

Report Date: 5 July 2001

Work Unit # 2890-99

DETAIL SUMMARY SHEET

TITLE: Creation of a Prospective and Retrospective Database of Patients Evaluated and Treated for Urinary Incontinence

KEYWORDS: database, incontinence, therapy

PRINCIPAL INVESTIGATOR: Dean, Robert MAJ MC
ASSOCIATES: Siegal, Timothy MAJ, MC; Dainer, Michael, CAPT MC USN; Spevak, Marianne CCRC

DEPARTMENT: Surgery
SERVICE: Urology

STATUS: O
INITIAL APPROVAL DATE: 24 August 1999

STUDY OBJECTIVE

To collect retrospective and prospective data beginning 1 May, 1994 on all patients age 18 years or older, who present to the Urology and Urogynecology Clinics at Walter Reed Army Medical Center (WRAMC) with the complaint of urinary incontinence. Analysis will include, but not be limited to: risk of development of urinary incontinence; risk of recurrent incontinence; therapy failure; therapy durability; complications of therapy; efficacy of therapy as based on type of incontinence; and comparison of therapy modalities.

TECHNICAL APPROACH

To prospectively and retrospectively collect data on patients seen in the Urology and Urogynecology Clinics at WRAMC complaining of urinary incontinence. Information collected will be those data points included on Database Forms. The procedures and tests in this protocol are standard of care for urinary incontinence. Separate consent forms will be obtained for the standard of care testing and procedures. The only thing that is not standard of care is the questionnaires. Patients participating in the study will be given additional questionnaires to complete. The history, physical examination, and testing will be the same for the patients that participate on this study as it would for patients that do not participate on this study. All patients will undergo complete History and Physical based on gender, American Urologic Association symptom score questionnaire, urodynamics study, quality of life questionnaire, three day voiding diary, one hour pad test, and sexual function questionnaire. Patients will then be offered therapy based on current practice. Patients will undergo repeat evaluation (the same type of an evaluation as the initial evaluation), 6 months-1 year following onset of any therapy received. In addition to the initial and the 6 months to one-year evaluations any additional follow ups, examinations or tests, pertaining to incontinence, required throughout patient's treatment will be recorded.

PRIOR AND CURRENT PROGRESS

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 1. The total number enrolled study-wide is N/A, if multi-site study. Enrollment ended August 1999. Enrollment was not active due to personnel shortage during the last APR. Since staff has increased during the past, enrollment is expected to restart immediately.

CONCLUSIONS

None at this time.

Report Date: 1 July 2001

Work Unit # 2891-99

DETAIL SUMMARY SHEET

TITLE: Uretal Stenting After Distal Uretoroscopy and Stone Retrieval: A Prospective Randomized Study

KEYWORDS: kidney stone, stent, ureteral

PRINCIPAL INVESTIGATOR: Schnēkman, Noah, LTC MC
ASSOCIATES: Spevak, Marianne

DEPARTMENT: Surgery
SERVICE: Urology

STATUS: O
INITIAL APPROVAL DATE: 24 August 1999

STUDY OBJECTIVE

Use of prospective, randomized, unblended protocol to determine is a difference can be demonstrated in postoperative pain, stone free rates, and complications between stented and unstented ureters after distal uretoscopic removal of calculi.

TECHNICAL APPROACH

Patients with distal ureteral calculi as demonstrated by intravenous pyeloureterogram (IVP) or non-contrast CT of the abdomen and pelvis, amendable to ureteroscopic removal, will be eligible to be enrolled in this study. Patients will be randomized to either the stented or unstented group. Preoperative lab evaluation will include UA< urine culture, and serum creatinine. Preoperatively the patient will fill out the pain questionnaire, which will serve as an internal control. The calculus will be removed using standard ureteroscopic techniques Ah operative data sheet will be filled out at the time of surgery by the surgeon. Patients will complete the pain questionnaire and narcotic count sheet at 48 hours post-op, 7-10 days post –op and 4 weeks post-op. Thos patients with ureteral stents in place will have them removed cystoscopically or via urethral string in the clinic on the 7-10 day post-op visit. The patient will return again at 4 weeks after the day of surgery. Post-op UA, urine culture, and serum creatinine will e checked at this time. An IVP will be checked to assess stone-free status and ureteral patience.

PRIOR AND CURRENT PROGRESS

The number of subject enrolled to the study since last APR at WRAMC is 3 and the total enrolled to date at WRAMC is 16. The total number enrolled study-wide is 100.
Is continuing at our site at the present time.

CONCLUSIONS

Enrollment has ended at both sites. Data is currently being analyzed at this time. Results are pending.

Report Date: 15 December 2000

Work Unit # 2892-99

DETAIL SUMMARY SHEET

TITLE: #VCL 1102-202: Phase II Study Evaluating the Safety and Efficacy of Neoadjuvant Leuvectin Immunotherapy for the Treatment of Prostate Cancer (and Amendment 1)

KEYWORDS: prostate, cancer, immunotherapy

PRINCIPAL INVESTIGATOR: Moul, Judd COL, MC
ASSOCIATES: David McLeod, COL, MC; Thomas Esther, PA; Marianne Spevak, CCRC; Gary Blake

DEPARTMENT: Surgery
SERVICE: Urology

STATUS: O
INITIAL APPROVAL DATE: 31 August 1999
(6 month review)

STUDY OBJECTIVE

Further investigate the toxicity and tolerability of Leuvectin in patients scheduled for retropubic prostatectomy. Evaluate the efficacy of Leuvectin in preventing or delaying manifestation of prostate cancer progression as demonstrated by biochemical failure or clinical recurrence.

TECHNICAL APPROACH

This is an open label, multicenter study for patients with clinically organ confined prostate cancer. Patients will receive two injections of the IL-2 plasmid DNA-Lipid complex, followed by a prostatectomy. Patients will receive follow-up visits for 5 years with no additional treatment.

PRIOR AND CURRENT PROGRESS

This protocol received final approval on April 27, 2000. The protocol was submitted to USUHS IRB for review at their June 29, 2000 meeting. Several minor changes to the consent form were requested by the USUHS IRB. These changes were submitted to DCI on August 2, 2000 and approved on August 11, 2000.

A report of an adverse event of pancreatitis at another clinical site was submitted to DCI in May 2000. Subsequent to a review and clarification, the Board requested the inclusion of "pancreatitis" in the risks section of the consent form. This was provided October 20, 20000.

CONCLUSIONS

No patients are enrolled in this study as yet. Screening has just begun.

Report Date: 1 July 2001 Work Unit # 2892-99

DETAIL SUMMARY SHEET

TITLE: #VCL 1102-202: Phase II Study Evaluating the Safety and Efficacy of Neoadjuvant Leuvectin Immunotherapy for the Treatment of Prostate Cancer (and Amendment 1)

KEYWORDS: prostate, cancer, immunotherapy

PRINCIPAL INVESTIGATOR: Moul, Judd COL, MC
ASSOCIATES: David McLeod, COL, MC; Thomas Esther, PA; Marianne Spevak, CCRC; Gary Blake

DEPARTMENT: Surgery STATUS: O
SERVICE: Urology INITIAL APPROVAL DATE: 31 August 1999
(6 month review)

STUDY OBJECTIVE
Further investigate the toxicity and tolerability of Leuvectin in patients scheduled for retropubic prostatectomy. Evaluate the efficacy of Leuvectin in preventing or delaying manifestation of prostate cancer progression as demonstrated by biochemical failure or clinical recurrence.

TECHNICAL APPROACH
This is an open label, multicenter study for patients with clinically organ confined prostate cancer. Patients will receive two injections of the IL-2 plasmid DNA-Lipid complex, followed by a prostatectomy. Patients will receive follow-up visits for 5 years with no additional treatment.
An amendment (#2.02) was submitted and reviewed at the 6/21/00 RYC Meeting which changed the inclusion criteria to allow patients with a minimum PSA of >5.0ng/ml to enroll in the study to adhere more closely to the standard of care. This amendment was approved.

PRIOR AND CURRENT PROGRESS
The number of subject enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 0. The total number enrolled study-wide is 13, if multi-site study.
A report of an adverse event of pancreatitis at another clinical site was submitted to DCI in May 2000. This has been the only adverse event reported. Subsequent to a review and clarification, the Board requested the inclusion of "pancreatitis" in the risks section of the consent form. This was provided October 20, 20000. Screening is continuing at our site at the present time.

CONCLUSIONS
None at this time.

Report Date: 15 December 2000

Work Unit # 2893-99

DETAIL SUMMARY SHEET

TITLE: #VCL 1102-203: Phase II study Evaluating the Safety and Efficacy of Leuvectin Immunotherapy for the Treatment of Locally Recurrent Prostate Cancer Following Radiation Therapy (and Amendment 1)

KEYWORDS: prostate, cancer, immunotherapy

PRINCIPAL INVESTIGATOR: Moul, Judd COL, MC
ASSOCIATES:

DEPARTMENT: Surgery
SERVICE: Urology

STATUS: O
INITIAL APPROVAL DATE: 31 August 1999
(6 month review)

STUDY OBJECTIVE

Further investigate the toxicity and tolerability of Leuvectin in this patient population.
Collect a database of PSA values, slope over time and clinical assessment to estimate the effect of Leuvectin in preventing or delaying manifestations of prostate cancer progression.

TECHNICAL APPROACH

This is an open label, multicenter study of patients with evidence of locally recurring prostate cancer following radiation therapy. Patients will receive up to three series of 2 intraprostate injections of Leuvectin followed by one year of follow-up visits every three months with no additional treatment.

PRIOR AND CURRENT PROGRESS

This protocol received final approval on April 27, 2000. The protocol was submitted to USUHS IRB for review at their June 29, 2000 Meeting. Several minor changes to the consent form were requested by the USUHS IRB. These changes were submitted to DCI on August 2, 20000 and approved on August 11, 2000.

A report of an adverse event of pancreatitis at another clinical site was submitted to DCI in May 2000. Subsequent to a review and clarification, the Board requested the inclusion of "Pancreatitis" in the risks section of the consent form. This was provided October 20, 2000.

A request for Advertisement for Research Subjects was submitted in June 2000 and received final approval on August 10, 2000.

CONCLUSIONS

No patients have been enrolled as yet. Screening has just begun.

Report Date: 1 July 2001

Work Unit # 2893-99

DETAIL SUMMARY SHEET

TITLE: #VCL 1102-203: Phase II study Evaluating the Safety and Efficacy of Leuvectin Immunotherapy for the Treatment of Locally Recurrent Prostate Cancer Following Radiation Therapy (and Amendment 1)

KEYWORDS: prostate, cancer, immunotherapy

PRINCIPAL INVESTIGATOR: Moul, Judd COL, MC
ASSOCIATES:

DEPARTMENT: Surgery
SERVICE: Urology

STATUS: O
INITIAL APPROVAL DATE: 31 August 1999
(6 month review)

STUDY OBJECTIVE
Further investigate the toxicity and tolerability of Leuvectin in this patient population. Collect a database of PSA values, slope over time and clinical assessment to estimate the effect of Leuvectin in preventing or delaying manifestations of prostate cancer progression.

TECHNICAL APPROACH
This is an open label, multicenter study of patients with evidence of locally recurring prostate cancer following radiation therapy. Patients will receive up to three series of 2 intraprostate injections of Leuvectin followed by one year of follow-up visits every three months with no additional treatment. An amendment (#1.02) was submitted and reviewed at the 6/21/00 RUC Meeting which changed the inclusion criteria to lower the PSA value from 1Ong.mil over a6 month period to > 1.9ng/ml over a 3 month period to adhere more closely with the standard of care. The area code for the sponsor was also changed. Approval pending.
An amendment (#1.03) was submitted and reviewed at the 6/21/00 RUC Meeting which changed the exclusion criteria to include patients who have had meoadjuvant hormonal therapy prior to radiation therapy. Approval pending.

PRIOR AND CURRENT PROGRESS
The number of subject enrolled to the study since last APR at WRAMC is 1 and the total enrolled to date at WRAMC is 1. The total number enrolled study-wide 14, if multi-site study. The first patient enrolled at WRAMC was enrolled –6/01.

A report of an adverse event of pancreatitis at another clinical site was submitted to DCI in May 2000. Subsequent to a review and clarification, the Board requested the inclusion of "Pancreatitis" in the risks section of the consent form. This was provided October 20, 2000. A request for Advertisement for Research Subjects was submitted in June 2000 and received final approval on August 10, 2000. Screening and enrollment is continuing at this time.

CONCLUSIONS
None at this time.

Report Date: 01 August 2001

Work Unit # 2894-99

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: Database of Urinary Stone Patients

KEYWORDS: database, kidney stone, outcomes

PRINCIPAL, INVESTIGATOR: Schenkman, Noah LTC MC
ASSOCIATES: Spevak, Marianne CCRC

DEPARTMENT: Surgery
SERVICE: Urology

STATUS: O
INITIAL APPROVAL DATE: 07 September 1999

STUDY ORTECTIVE

The goals of this study are to accumulate long-term data on all kidney stone formers in our clinic. This information will be used to provide needed epidemiologic information on urolithiasis. The information provided will answer questions such as the impact of kidney stones on military readiness, effectiveness of medical treatment regimens and the true recurrence rate of kidney stones in the modem era. With the exception of the completion of patient questionnaires, all other testing, procedures, and patient history are standard of care.

TECHNICAL APPROACH

Male and female patients with confirmed urinary stone disease by either radiographic imagining or passage of calculi will be included in this study. Patients that do not have confirmed stone disease by either of those two methods will be excluded. A clinical suspicion of stone disease does not warrant inclusion - it must be confirmed urinary stone disease. After the diagnosis of urolithiasis is made, the patients will be given information about the database. The patients will then be asked to sign an informed consent if they wish to participate. An initial evaluation will 'include a complete history and focused physical examination. The patient will be asked to fill out the stone database questionnaire. The following results will be recorded, if available: initial laboratory work including serum electrolytes, uric acid, calcium, phosphorus and parathyroid hormone; stone analysis; and radiographic and imaging exams; twenty-four hour urine analysis. The patient's clinical course and condition will dictate follow up. Data of each follow-up, including surgical procedures, will be recorded.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

The number of subjects enrolled to the study since last APR at WRAMC is 23 and the total enrolled to date at WRAMC is 52. Enrollment is continuing at this time. There have been no adverse events on this protocol.

CONCLUSIONS

None at this time.

Report Date: 3 July 2001 Work Unit # 00-3002

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: Noninvasive Screening for Coronary Artery Disease Using A Digital Electronic Stethoscope

KEYWORDS:

PRINCIPAL INVESTIGATOR: Popa, Christian MAJ MC
ASSOCIATES: Allen, Taylor LTC MC, Gorman, Patrick LTC MC

DEPARTMENT: Surgery
SERVICE: Critical Care Medicine

STATUS: O
INITIAL APPROVAL DATE: 1 August 2000

STUDY OBJECTIVE

A. Primary objective: To define the relationship between digital electronic stethoscope signals and the presence of angiographic coronary artery disease.
B. Secondary objective: To numerically evaluate the presence of angiographically proven CAD stenosis with the output from the DES.

TECHNICAL APPROACH

1. Methodology:

Heart sound recordings will be performed by sonographers blinded to all clinical data. Immediately prior to cardiac catheterization (in either the cardiac catheterization laboratory or in the Cardiology Short Stay Observation Center) a foam acoustic chamber will be placed on the subject's chest using the xyphoid process as a reference marker. The purpose of this device is to standardize sound acquisition with the DES and dampen extraneous sounds. The acoustic chamber contains *nine* recording positions which correspond to the following anatomic locations: RSB_1, RSB_2, RSB_3, LSB_1, LSB_2, LSB_3, S_1, S_2, S_3.

Once the acoustic chamber has been correctly placed on the subject, the digital electronic stethoscope will be placed at each listening position, the acoustic chamber lid closed, and 20 seconds of sound data collected. Recordings will be made with the subject in a semirecumbent position at 30 degrees. A simultaneous EKG will be taken for integration into the sonospectrographic recording. It is anticipated that the entire data set acquisition will take approximately 15 minutes per patient. Following heart sound data collection, elective coronary angiography will proceed as planned.

2. Data Collection:

Following informed consent, a cardiac history (history of coronary artery disease, peripheral vascular disease, smoking, hypertension, hypercholesterolemia, diabetes mellitus and current medications) will be collected for the purpose of descriptive reporting. Supine blood pressure will be measured using an automated blood pressure cuff. Sonographic data will be collected as described above using the nine designated listening positions of the acoustic chamber with 20 second recordings at each position. Left and right coronary cineangiograms will be obtained at the discretion of the angiographer.

3. Sample Size/Data Analysis:

Endpoints: Coronary angiographic data will be analyzed by Dr. Gorman, without knowledge of the DES data. The primary variable of interest is the worst angiographic stenosis in a major epicardial coronary artery measured with an automated edge detection system for quantitative coronary angiographic analysis. Signal data from DES will be forwarded to Randy Ford, PhD at SonoMedica for analysis. Signal data are stored as an electronic file on Write Once Read Many (WORM) unrewritable CDROM's which will be provide a permanent record of the acoustic data. Copies of these unalterable CDROM's will be coded and provided to Walter Reed as a record of the acoustic tests to assure that there is no bias in the correlation of the data comparison between angio and acoustic records. Patient confidentiality will be preserved by labeling each study with an anonymous identifier (study enrollment number). The optimal

measurement from DES for correlation with coronary angiography is unknown. Two values will be used: 1. The threshold presenting signal and 2. The maximal observed acoustic frequency. Signal data results will be provided to the Principal Investigator for further analysis as described below.

Secondary analysis: Agreement between the 2 methods (angiography and DES) will be further described using ROC curve analysis. An ROC curve will be constructed for the sensitivity and specificity of the diagnosis of angiographic stenosis by DES.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

To our knowledge, there have not been new developments or publications which would impact on this study. We have currently enrolled 56 patients into the study and are analyzing our current results. The initial results with our first 32 patients are promising (see conclusions). There have been no adverse effects for this minimal risk protocol. We have submitted and had accepted an amendment to establish a CRDA with Sonomedica LLC, the manufacturer of the digital electronic stethoscope we are evaluating. A copy of the amendment and proposed budget is included.

The number of subjects enrolled to the study since last APR at WRAMC is 56 and the total enrolled to date at WRAMC is 56.

CONCLUSIONS

Twenty of the first 32 (62.5%) patients enrolled had a $\geq 25\%$ coronary stenosis by coronary angiography. This group had a significantly higher DES (digital electronic stethoscope) signal than patients with $< 25\%$ stenosis (12.2 ± 12 vs 23 ± 14; $P = .018$). Additionally, we found a modest positive correlation between the severity of the single worst coronary stenosis and the DES score ($r=.37$;$P=.038$). Based on this preliminary data, high frequency coronary acoustic signals, particularly recorded from the mid-sternal location, can predict the presence of a mild to moderate coronary stenosis with moderately high accuracy. Thus, further evaluation of the DES as a non-invasive marker of atherosclerosis is warranted.

Report Date: 1 June 2001 Work Unit # 3000

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: Characterization of the Cytokines Mediating Different Phases of Inflammation Following Controlled Abdominal Trauma

KEYWORDS: cytokine, tumor necrosis factor, interleukins, abdominal trauma, inflammation, hemicolectomy and inguinal hernia

PRINCIPAL INVESTIGATOR: Blanchard, Jeremy MAJ MC
ASSOCIATES: Armstrong, John, LTC, MC, Ling, Geoffrey, LTC, MC, Hadro, Neal, MAJ, MC, Maniscalco-Theberge, Mary, COL, MC, Otchi, Daniel, COL(ret), MC, Calkins, M. MD

DEPARTMENT: Surgery
SERVICE: Critical Care Medicine

STATUS: O
INITIAL APPROVAL DATE: 29 July 1997

STUDY OBJECTIVE

The objective of this study is to characterize the serum levels of several inflammatory cytokines at serial time points after controlled abdominal trauma. Our hypotheses are: 1. Following traumatic injury to bowel, proinflammatory cytokines (TNF-a, interleukin-1B, and interleukin-6) are released at specific times after injury. 2. Subsequent to the initial inflammatory response, anti-inflammatory cytokines (interleukin-10 and interleukin-1 receptor antagonist) are released. 3. A percentage of elective preoperative patients have elevated cytokine levels at baseline (as per our addendum, approved 8 April 1999).

TECHNICAL APPROACH

We are conducting a prospective controlled observational study. 30 consenting adult patients receiving an elective hemicolectomy and 30 consenting adults receiving a laparoscopic inguinal hernia repair will be enrolled. 3 mL blood samples will be collected in heparinized blood collection tubes: preoperatively, 15, 30 minutes, and 1, 1.5, 2, 4, 6, 8, 12, 24, 96 (only hemicolectomy have a 96 hour time point) hours after hernia incision and hemicoletomy. The samples are centrifuged and the supernatant drawn off and frozen at -70C. Serum levels of the proinflammatory cytokines, a-TNF, IL-1B, and IL-6, and anti-inflammatory cytokines, IL-10 and IL-1 receptor antagonist are quantified using electrochemiluminescence (ECM) assays. All excess blood collected from study a participant is discarded. An addendum was approved to allow the 96-hour blood sample in the hemicolectomy patients and CBC's in both groups of patients.
We also are working on the addendum study (approved 8 April 1999) looking at preoperative cytokine levels. 100 consecutive APPC pre-operative patients, already having their blood drawn, were enrolled to evaluate their a-TNF, IL-I beta, IL-6, IL-10 and IL-1 receptor antagonist levels prior to their surgery. We collected a 3 ml sample of blood and processed it as above. The preliminary results are presented below on 30 of the patients.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

At the time of last years APR 12 controls and 9 study patients had been enrolled. Unfortunately over the last year, no further patients have been enrolled. I met with Dr Fant 29 May and we have begun to process the data to evaluate if further enrollment is required to show statistical significant difference between the pro-inflammatory cytokine levels in the study patients and in the laproscopic inguinal hernia patients. Recruitment for the protocol has been very difficult secondary to changes in surgical staff, etc. On preliminary t-testing there appears to be statistically significant difference between the IL-6 in the two groups.
The anti-inflammatory cytokines (IL-10, IL-1ra), will not be run secondary to the loss of samples with a freezer malfunction.
The 100 consecutive patients for preoperative cytokine evaluation were enrolled (per addendum for WU#3000) and samples were obtained, but unfortunately these samples were stored in the same freezer as the above-mentioned samples and were lost to thawing with only the first 30 (as reported last year) having TNF alpha and IL-6 as described last year.

Also of note, an audit was done this spring and with review of my administrative files it was noted a consent form was missing. The HUC decided to allow me to contact the study patient and ask them if they remembered signing a consent form, and if so having them resign a consent form. Unfortunately without the consent forms I have no way of identifying the individual. I review all of the above surgery records for missing consent forms, but was unsuccessful, thus this patient's cytokine results will not be used and he/she will be dropped from the study.

In 2000 and 2001 new literature in this area has been limited. There was a review on ruptured abdominal aneurysms, an evaluation of the cytokine response to depressed patients, and growth hormones effects on cytokines.

The number of subjects enrolled to the study since last APR at WRAMC is _0___ and the total enrolled to date at WRAMC is __20*_____. The total number enrolled study-wide is ___n/a____, if multi-site study.
*one was dropped from the study, because of the missing consent form.

CONCLUSIONS

In conclusion, on preliminary evaluation the cytokine comparison of the pro-inflammatory cytokines (TNF, IL-1B, and IL-6) show a heightened response of IL-6 to hemicolectomies. The TNF is physiologically zero in both group and the IL-1 beta is mildly elevated in both groups.

Report Date: 16 May 2001

Work Unit # 3001-98

DETAIL SUMMARY SHEET (Human Use Protocol)

TTTLE: International Study of Mechanical Ventilation

KEYWORDS: international, mechanical, ventilator

PRINCIPAL INVESTIGATOR: Fitzpatrick, Thomas LTC MC
ASSOCIATES:

DEPARTMENT: Surgery
SERVICE: Critical Care Medicine

STATUS: C
INITIAL APPROVAL DATE: 24 February 1998

STUDY OBJECTIVE

The objective of this study was to study the prevalence and nature of mechanical ventilation that are used in intensive care units worldwide.

TECHNICAL APPROACH

The modes of ventilation and methods of weaning were evaluated throughout the world during specific one-month period. Four questionnaires were filled out on each patient that required prolong ventilation. Data were collected and forwarded to Dr. Andres Esteban for consolidation and evaluation.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Data were collected over a one-month period (4 March-31 March 1998). There were 12 subjects enrolled. No adverse reactions occurred. No patients withdrew form the study.

CONCLUSIONS

Data was analyzed by Dr. Andres Esteban and was presented at the American Thoracic Society Meeting in May 2000.

Report Date: 24 August 2000 Work Unit # 3002-99

DETAIL SUMMARY SHEET

TITLE: Characterization of the Cytokines Mediating Different Phases of Inflammation Following Controlled Head Trauma

KEYWORDS: cytokines, transphenoidal hypophysectormy, temporal lobectomy

PRINCIPAL INVESTIGATOR: Popa, Christian MAJ MC
ASSOCIATES: Calkins, Mark MAJ MC; Ling, Geoffrey LTC MC; Blanchard, Jeremy, MAJ MC; Fitzpatrick, Thomas COL MC

DEPARTMENT: Surgery
SERVICE: Critical Care Medicine

STATUS: O
INITIAL APPROVAL DATE: 27 October 1998

STUDY OBJECTIVE

To characterize the serum and cerebrospinal fluid level of several inflammatory Cytokines at serial time points following controlled head trauma. We hypothesize that both pro-inflammatory and anti-inflammatory cytokines are released.

TECHNICAL APPROACH

Transphenoidal Hypophysectomy patients and patients undergoing temporal lobectomy for refractory seizures will serve as controls and surgical models of head trauma respectively. There have been no addenda to this protocol.

PRIOR AND CURRENT PROGRESS

We have enrolled and collected data on a total of 4 subjects, all of who underwent transphenoidal hypophysectomy with lumbar drain placement. These four patients did well and there were no study related adverse effects. We have analyzed this data for TNF-a, IL-1, and Il-6 by chemiluminescence and noted a rise in CSF TNF-a as well as a bimodal elevation of CSF IL-6 which was mirrored by a smaller rise in blood IL-6. One of the cases was complicated by a dural tear, the others were not. The greater elevation in CSF cytokine levels suggests that the brain is not a protected site as previously thought, and though these procedures were extradural and did not violate brain parenchyma (minus the one dural tear), the brain did mount an inflammatory response. We feel this is an important finding and plan to recruit several additional patients before publishing this. We have not been able to recruit patients for the temporal lobectomy arm of the study, thus we plan to concentrate on transphenoidal hypophysectomy patients

CONCLUSIONS

We would like to extend this study, and recruit additional transphenoidal hypophysectomy patients to study the rise in CSF cytokine levels which occurs with extradural but intracranial trauma. We tentatively plan to publish this as a case series.

Report Date: 11 June 2001

Work Unit # 01-32004

DETAIL SUMMARY SHEET

TITLE: Treatment of Snoring with Palatal Stiffening Injection Sclerotherapy Using Ethanol

KEYWORDS: Sclerotherapy, snoring, Ethanol, Palatal injection

PRINCIPAL INVESTIGATOR: Scott E. Brietzke, CPT MC
ASSOCIATES: Eric A. Mair, Local, USAF, and MC

DEPARTMENT: Surgery
SERVICE: Otolaryngology

STATUS: O
INITIAL APPROVAL DATE: 27 February 2001
(6 month review)

STUDY OBJECTIVE

The objective of this prospective, non-randomized study is to investigate the efficacy of palatal ethanol (Dehydrated Alcohol) injection as a primary treatment for palatal flutter snoring.

TECHNICAL APPROACH

This study is designed to be a prospective, non-protocol to investigate the use palatal Ethanol injection as the primary treatment for palatal flutter snoring. A single cohort of patients (goal = 30 patients) will be prospectively followed after treatment each patient will server as his/her own control with the primary data being the pre-treatment versus post-treatment polysomnogram parameters measured with a standardized polysomnogram device, called the SNAP test. As a conservative precaution, we will start this protocol using ethanol by scheduling and treating only 3 patients one week apart at first and then closely follow their recovery. If two of these three patients experience discomfort greater than what has been observed with Sotradecol, i.e., convalescence for >48 hours, significant diet alteration for greater than 24 hours, the protocol will be stopped.

PRIOR AND CURRENT PROGRESS

This protocol was very recently approved (14 May 2001). We have treated 5 patients to date. One has had pain in excess of what we have observed with sotradecol but was easily controlled with oral rinses and narcotic analgesics. No patient is yet far enough out to confidently measure the snoring results, although improvements have been reported. Further follow-up is planned before more patients are enrolled.

The number of subjects enrolled to the study since last APR at WRAMC is 5 and the total enrolled to date at WRAMC is 5. The total number enrolled study-wide is 5, if multi-site study.

CONCLUSIONS

Adequate progress has been observed. More time is needed to accurately assess the efficacy of the procedure. There is no significant concern for ethanol palatal injection having pain significantly out of proportion with that observed from Sotradecol.

Report Date: 02 April 2001

Work Unit # 3369

DETAIL SUMMARY SHEET

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

KEYWORDS: pollen, aeroallergens, fungal

PRINCIPAL INVESTIGATOR: Kosisky, Susan
ASSOCIATES:

DEPARTMENT: Allergy-Immunology
SERVICE:

STATUS: O
INITIAL APPROVAL DATE: 11 May 1993

STUDY OBJECTIVE

The objective of this protocol is to identify the predominant aeroallergens in the Washington DC area. Identification of prevalent trees, weeds, grasses are essential to the effective treatment and diagnosis of the allergic patient. Daily volumetric samples will reveal peak concentration and pollination periods for area allergenic aeroallergens. Seasonal definition of pollination periods for trees, weeds, grasses and molds will allow for development of a better patient treatment regimen.

TECHNICAL APPROACH

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

PRIOR AND CURRENT PROGRESS

The pollen and spore counts are submitted to the National Allergy Bureau, local and national media networks and various websites for data dissemination. CNN and our local Channel 9 News in the DC area report our counts to the public. A public information group for the daily pollen and mold spore report continues to serve the Walter Reed community and DOD Region 1 through CHCS and Outlook. Data and pictures of area allergenic plants are published through the Academy of Allergy, Asthma and Immunology's Pollen and Spore Report and other informative pamphlets and handouts. The analysis of pollen and spore data continues as well as the correlation with meteorological variables. Our aerobiologcal center for the Washington DC area continues to support area allergists by providing data used for various study protocols. There has been no modification to the research study since the last review.

CONCLUSIONS

The study is ongoing. Data collected over a greater period of time allows for us to see trends in the prevalence and seasonal distribution of predominant are allergens. Year to year variations occur with respect to aeroallergens concentrations. Data analysis will allow for correlations with meteorological variables to provide for a predictive model. The data has been utilized in devising a regional skin-testing panel to be used in DOD Region 1 as well as nationwide. Consistent with the new skin-testing panel our inventory of allergen extract biologicals continues to be refined and reduced saving money and time. Many predominant area pollens and molds which reach significant atmospheric concentrations are not available for skin testing making it difficult to assess the atopic patient. Various allergen extract manufacturers have utilized our Washington DC data to supply extracts of predominant molds and pollens for the testing and treatment of the atopic patient.

Report Date: 03 November 2000 Work Unit # 3372

DETAIL SUMMARY SHEET

TITLE: Mosquito Hypersensitivity: Immunology and Value of Skin Testing with Whole Body Mosquito Extracts

KEYWORDS: skin testing, mosquito, hypersensitivity

PRINCIPAL INVESTIGATOR: Engler, Renata COL MC
ASSOCIATES:

DEPARTMENT: Allergy-Immunology
SERVICE:

STATUS: O
INITIAL APPROVAL DATE: 21 December 1993

STUDY OBJECTIVE

To: 1) determine the sensitivity, specificity and predicative value of prick and intradermal skin tests at different dilutions to mosquito whole body extracts; 2) measure the total mosquito-specific IgE and IgG and IgG subclasses in patients with no reactions, minor reactions, large local reactions, and systemic anaphylaxis to mosquito bites.

TECHNICAL APPROACH

A total of 60 clinically negative subjects (with no adverse reactions to mosquito bites) and 60 clinically positive subjects will be enrolled. Prick and intradermal skin tests with Aedes egypti and Culex pipiens mosquito extracts in five dilutions will be administered. A permanent imprint of the wheal and flare will be measured. Blood will be drawn before and 3 weeks after skin testing to evaluate mosquito-specific IgG, IgG subclasses and IgE.

PRIOR AND CURRENT PROGRESS

A total of 36 subjects have been enrolled since this study began. Only five subjects have had positive reactions and thirty-one had negative reactions. The adverse reactions were neither serious nor unexpected. Upon a DCI audit, five subjects, in addition to the two index cases, had missing consent forms. One has been re-consented, one has declined to consent and others are outstanding. Data and serum will be dealt with appropriately when the final report is made to the Human Use Committee on 12 December 2000. While the subjects may not benefit personally from the study, the medical community will gain an enhanced knowledge of the efficacy of prick and intradermal skin testing to treat mosquito bite anaphylaxis. No cases of mosquito bite anaphylaxis were seen this year and thus no further subjects were enrolled. We would like to keep this protocol open so that subjects can be enrolled as they present.

CONCLUSIONS

To date, no strong correlation has been shown between dilution strength of whole body extracts and reaction history of the subjects enrolled in this study. Not surprisingly, 100% of the subjects with a history of large local or anaphylactic reactions responded positively to mosquito whole body extract skin tests. Of those subjects with a history of minimal to no reaction, 65% responded positively.

Report Date: 03 November 2000 Work Unit # 3385

DETAIL SUMMARY SHEET

TITLE: Adverse Reactions with Intravenous Immunoglobulin Therapy

KEYWORDS: adverse reactions, intravenous immunoglobulin

PRINCIPAL INVESTIGATOR: Englĕr, Renata COL MC
ASSOCIATES:

DEPARTMENT: Allergy-Immunology
SERVICE:

STATUS: O
INITIAL APPROVAL DATE: 10 December1996

STUDY OBJECTIVE

To review, retrospectively and prospectively the quality assurance monitor data collected for the IVIG subcommittee of the WRAMC Pharmacy and Therapeutics Committee. To determine the incidence and demographics of adverse reactions to IVIG between 1991 and 1995 using the CHCS pharmacy register of administrations, laboratory clinical results and individual patient chart reviews. To monitor, prospectively the adverse reactions associated with both intra muscular and IVIG therapy at WRAMC and to develop a database registry. To establish a serum bank and to determine if proteinuria is a "normal" side effect of IVIG therapy.

TECHNICAL APPROACH

The Department of Allergy and Immunology provides all adult immunizations including IVIG therapy. A database of immunizations exists back to 1992 so that subjects have received IVIG therapy can be identified. The actual work of this protocol includes: monthly monitoring of patients receiving IVIG, entering adverse reactions into database, tabulating QA questionnaires from IVIG patients, monthly reviews of IVIG doses and volumes given establishment of a serum bank of patients receiving IVIG and gammaglobulin used at WRAMC, quantifying the level of proteinuria and microhematuria associated with the administration of IVIG by urine dipstick test before and after IVIG. A patient questionnaire filled out at the time of IVIG administration will be kept on file at the Allergy Clinic.

PRIOR AND CURRENT PROGRESS

Twenty-five patients have been prospectively enrolled in this study and are being continuously monitored. Monthly reporting on immunoglobulin prescriptions established with WRAMC pharmacy tracking of IVIG use has provided additional subjects for prospective enrollment and a means of retrospectively identifying prior adverse effects. No patients have been withdrawn from the study. No adverse reactions have occurred as a result of study enrollment. The study is designed to observe adverse reactions during clinically indicated immunoglobulin administration independent of study participation. Recent proposals of mechanisms responsible for adverse reaction such as renal disease caused by excessive sucrose exposure illustrate the continued need for adverse monitoring.

CONCLUSIONS

Adverse reactions are infrequent, but when present, range widely in severity and type. There is a need for continued prospective enrollment of patients to provide additional unbiased prospective data.

Report Date: 11 May 2001 Work Unit # 3390-99

DETAIL SUMMARY SHEET

TITLE: A Phase 3 Study to Determine the Efficacy and Safety of C1-Inhibitor (HUMAN) Vapor Heated, Immuno in Subjects of Hereditary Angioedema (HAE)

KEYWORDS:

PRINCIPAL INVESTIGATOR: Carregal, Valerie MAJ MC
ASSOCIATES:

DEPARTMENT: Allergy-Immunology STATUS: O
SERVICE: INITIAL APPROVAL DATE: 25 May 1999

STUDY OBJECTIVE

The purpose of this study is to provide effective documentation to support an application to the Food and Drug Administration for the C1-Inhibitor (HUMAN) drug to be licensed in the United States to treat Hereditary Angioedema (HAE). This drug is in the final stage of testing. This drug will be given to a large number of patients (adults, children and pregnant adults) to find out its safety and effectiveness.

HAE is caused by a lack of an adequate amount of a blood substance called C 1-Inhibitor. C1 concentrates can be made from human blood to replace this missing substance. This kind of therapy may reduce the swelling associated with attacks of HAE, as well as the associated pain and discomfort.

TECHNICAL APPROACH

This study is divided into 4 parts.

In part 1, the-patients will receive two treatments for an acute attack of HAE. They will be randomly assigned to treatment with either C1-Inhibitor or placebo. At one hour from the beginning of their first treatment, they will receive the other product (i.e., if the patient receives C1-Inhibitor first, the placebo will be received second; if the patient receives the placebo first, the C 1-Inhibitor will be received second). The doctor will not know whether the patients are receiving C1-Inhibitor or the placebo. However, if needed, the doctor can find out from the pharmacy which treatment the patients are receiving.

In part 2, the patients will receive open label active C1-Inhibitor (HUMAN) for acute attacks of HAE.

In part 3, the patients will receive active CI-Inhibitor (HUMAN) to prevent an attack should they require surgery.

In part 4, females who are pregnant will be able to receive active C1 -Inhibitor (HUMAN) under a separate, consent form.

Part 1 of the study should continue for approximately 1 year. Subjects who have completed part 1 may continue into part 2, or 3. After 60 subjects have completed part 1, new eligible subjects will enter part 2, or 3 without the need to complete part 1.

Parts 2, 3 and 4 will continue until licensure of the product.

An addendum to the protocol dated January 4, 2001 increased the number of enrollees allowed nationwide to 200. The number needed to complete the randomization (part 1) did not change from 60.

PRIOR AND CURRENT PROGRESS

The number of subjects enrolled to the study since last APR at WRAMC is 1 and the total enrolled to date at WRAMC is 3. The total number enrolled study-wide is 200. Nationwide, 60 subjects have completed part 1(randomization). Subjects presenting with attacks may now proceed directly to open-label treatment (part 2, 3, or 4). No more subjects will be enrolled. One serious adverse was reported last year. A subject at another site died on January 9, 2000, thirty days after last receiving the drug. The subject had received the medication on three previous occasions. Results from an autopsy were inconclusive and no further report has been disseminated. The principal investigator at the site involved does not feel that the death was related to the study drug. No adverse reactions have been reported since then.

CONCLUSIONS

This is an ongoing study. Data analysis will be performed at a later date.

Report Date: 6 June 2001 Work Unit #00-3601

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: Stability of Cisplatin, Doxorubicin, and Mitomycin Combined with Ioversol for Chemoembolization

KEYWORDS: Cisplatin, Doxorubicin, Mitomycin, Ioversol, Chemoembolization, Stability

PRINCIPAL INVESTIGATOR: LTC Ricke J. Weickum, Pharm.D., MS
ASSOCIATES: CPT Michael I. Mayer, Pharm.D., MS; Dr. Gregory Fant, Ph.D., DAC; Dr. Diarmuid Nicholson, Ph.D., DAC; Mr. Bader Fileta, DAC; Mr. Maged M. Abdel-Rahim, M.S., DAC; Mr. Dominic Solimando, Jr., M.A

DEPARTMENT: Pharmacy
SERVICE: Hematology-Oncology

STATUS: C
INITIAL APPROVAL DATE: 11 April 2000

STUDY OBJECTIVE:
To evaluate the chemical stability of a mixture of cisplatin 10mg/ml, doxorubicin 5mg/ml, and mitomycin 1mg/ml in 0.9% NaCl, and the same preparation mixed with ioversol 16% in plastic syringes at 4 degrees C, 25 degrees C, and 37 degrees C.

TECHNICAL APPROACH:
Laboratory experiment – drug stability study utilizing HPLC.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE:
HPLC reference ranges were re-verified for each drug and complete HPLC procedure was added to the manuscript submitted to Annals of Pharmacotherapy. We do not anticipate any further requirement to keep this protocol open.

CONCLUSIONS:
Experiment was conducted as described in the protocol. Triplicate HPLC measurements were conducted on each sample for each temperature and at time 0, 4 hrs, 12 hrs, 24 hrs, 72 hrs and 120 hrs post mixture preparation. Solutions were also inspected for visual changes. The results of the experiment demonstrated that the 3-drug mixture was stable in 0.9% NaCl for up to 12 hrs at 4 degrees C, and in 0.9% NaCl plus ioversol up to 72 hrs at 4 degrees C. Study is complete. Based on this study, we have now changed our procedures for preparing this combination chemotherapy for the WRAMC Interventional Radiology Service. Manuscript was submitted for publication, has been reviewed and edited, and resubmitted.

Report Date: 29 September 2000 Work Unit # 3612-98

DETAIL SUMMARY SHEET

TITLE: A Prospective, Randomized, Double-Blind, Placebo-Controlled Trial to Determine the Efficacy of Amiloride in Preventing Amphotericin-B Induced Hypokalemia in Neutropenic Patients

KEYWORDS: amiloride, amphotericin-B, hypokalemia, neutropenia

PRINCIPAL INVESTIGATOR: Timothy J. Murphy, CPT MC
ASSOCIATES: Stephen M. Ford, MAJ MS; Joseph J. Drabick, LTC MC; Ricke J. Weickum, LTC MS; Audrey S. Chang, PhD, DAC

DEPARTMENT: Pharmacy
SERVICE: Hematology-Oncology

STATUS: C
INITIAL APPROVAL DATE: 28 April 1998

STUDY OBJECTIVES

1. To assess the efficacy of the potassium-sparing diuretic amiloride in preventing the hypokalemia induced by amphotericin B in neutropenic patients.
2. To assess the efficacy of amiloride in preventing magnesium wasting in amphotericin B treated neutropenic patients.

TECHNICAL APPROACH

Prospective, Randomized, Double-Blind, Placebo-Controlled Trial

PRIOR AND CURRENT PROGRESS

No patients have been enrolled since the last APR. PI relocated to BAMC and associate investigators are not interested in continuing this protocol; therefore we elect to close it. A decline in the number of potentially eligible patients and a change in antifungal therapy, with the adoption of lipid formulations of amphotericin-B as preferred antifungal therapy in neutropenic patients, reduced eligible patient enrollment and the need for intervention.

CONCLUSIONS

Protocol closed.

Report Date: 19 April 2001

Work Unit #3614-99

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: Feasibility Study of Shortened Administration Schedule of Rituximab

KEYWORDS: Rituximab, monoclonal antibody, non-Hodgkin's lymphoma

PRINCIPAL INVESTIGATOR: Weickum, Ricke LTC MS
ASSOCIATES: Wagner, Keith CPT MS; McGrail, Lisa CPT MC; Murphy, Timothy CPT MC; Drabick, Joseph LTC MC

DEPARTMENT: Pharmacy
SERVICE:

STATUS: C
INITIAL APPROVAL DATE: 20 April 1999

STUDY OBJECTIVE

1. To assess the feasibility of administering Rituximab over 60 minutes after its first infusion.
2. To assess the frequency of infusion related symptoms utilizing a 60 minutes infusion schedule.

TECHNICAL APPROACH

1. Eligible patients with B-cell lymphoma expressing CD20 (low grade and intermediate grade) will be enrolled.
2. All enrolled patients will be given Rituximab based on inclusion criteria. Study participants. researchers and clinic physicians will not be blinded.
3. Pre-treatment immunoplienotyping on peripheral blood will be performed Day 1 and Day 3.
4. Criteria for Stopping Study Treatment:
   Patients will come off study if they experience grade 3 or greater infusion-related toxicity with the second or subsequent infusion. Furthermore, given the nature of this study, if one patient experiences grade 3 dyspnea, bronchospasm, or hypotension, the study will be terminated or the design modified. The medical monitor will review each patient's results on days 1 and 3 to ensure patient safety.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE:

Due to experience from other trials, which has partially duplicated this work, there is no desire to pursue any further research on this study. The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 1. The total number enrolled study-wide is n/a, if multi-site study.

CONCLUSIONS:

Study is closed.

Report Date: 28 December 2000

Work Unit # 00-3701

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: Early Signaling Events in Lupus B Cells

KEYWORDS:B Lymphocytes, systemic lupus erythematosus, signaling events

PRINCIPAL INVESTIGATOR: Jeanne P. Mitchell MD CPT (P) MC
ASSOCIATES: George Tsokos MD COL MC

DEPARTMENT: Medicine
SERVICE: Rheumatology

STATUS: O
INITIAL APPROVAL DATE: 15 February 2000

STUDY OBJECTIVE

To study early signaling events in B lymphocytes of patients with systemic lupus erythematosus (SLE). More specifically, to quantify the B cell receptor mediated free intracytoplasmic calcium response after cross-linking the Fc-gamma and CR2 receptors with various ligands in B cells from patients with SLE and from patients with other systemic connective tissue diseases, and to quantify the degree of protein tyrosine residue phosphorylation after cross-linking these B-cell receptors with the same ligands. Lastly, to correlate the obtained free intracytoplasmic calcium responses with the degree of protein tyrosine residue phosphorylation for each receptor-ligand interaction.

TECHNICAL APPROACH

Patients with a diagnosis of systemic lupus erythematosus, in accordance with the ACR classification criteria, will be asked to participate and will have blood drawn, consisting of a 25 cc sample, at the hospital laboratory. B cells will be separated from the peripheral blood sample using the standard Ficoll-Hypaque gradient centrifugation method and then will be negatively selected by staining the samples with sell surface marker labeled antibodies. Intracellular calcium measurements will be performed using the flow cytometry and will be obtained at each sample's baseline and after simulation with anti-sIg mAb's and Fc-gamma and CR2 ligands. Lysates of the B cell enriched populations will be separated by gel electrophoresis and the resolved proteins will be immunoblotted with anti-phosphotyrosine Ab. Densitometric readings will be obtained for the molecular regions of 30-70kD. An age and sex-matched control sample will run in each experiment. Addenda: (1) The surface expression of the CR2 and FcγRIIB receptors on the B cells was determined by flow cytometry.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Study findings: Analysis thus far for N = 12 (SLE), N = 14 (Disease Controls) (1) The ratio of $F(ab)'_2$ fragment to anti-sIgM stimulation (as measured by intracellular calcium response) was significantly lower in the B cells of patients with systemic lupus. (2) The intracellular calcium response for the CR2 ligand (anti-sIgD-gp350) was similar for patients with systemic lupus and for patients with other systemic connective tissue diseases. (3) The surface expression of FcγRIIB was similar in patients with SLE and in the disease control group. (4) The surface expression of CR2 on SLE B cells was decreased compared to the disease control patients. Number of subjects enrolled last year: 35 SLE, 25 Disease Controls; Total Enrollment to Date: 60 (Combined SLE and disease controls); Adverse reactions: None
Patients Withdrawn from the Study:
A. 12 SLE (1 patient did not have blood drawn at the specified time required in order for processing of the cells to be done; for the other 11 SLE samples, there were not enough peripheral blood mononuclear cells harvested from the peripheral blood sample in order to initiate the experiments).
B. 3 Disease Controls (For each of these three samples, there were not enough peripheral mononuclear cells harvested from the peripheral blood samples in order to initiate the experiments.

CONCLUSIONS

One result listed under prior and current progress (above) indicated that both deficient FcγRIIB mediated suppression and increased CR2 mediated enhancement are involved in the augmented intracellular cytoplasmic calcium responses of B cells from patients with systemic lupus erythematosus. The detection of abnormal regulatory events that are initiated by B cell surface membrane molecules will contribute to our understanding of basic defects contributing to the pathogenesis of this prototype autoimmune disease. Therapeutic interventions designed to target specific biologic processes may be developed as a result of having more specific information in this regard.

Report Date: 2 February 2001 Work Unit # 00-3702

DETAIL SUMMARY SHEET

TITLE: Aberrant T Cell Receptors in Systemic Lupus Erythematosus

KEYWORDS:

PRINCIPAL INVESTIGATOR: Gregory J. Dennis COL, MC
COLLABORATING PERSONNEL: William N. Fishbein, MD, PhD

DEPARTMENT: Medicine
SERVICE: Rheumatology

STATUS: O
INITIAL APPROVAL DATE: 7 March 2000

STUDY OBJECTIVE

Compare the percentage of aberrant T cell receptors in patients with systemic lupus erythematosus to that of rheumatoid arthritis.

TECHNICAL APPROACH

Using the chromosome 7 inversion assay blood samples of patients with these diseases will be analyzed for the presence of Vγ-Jβ1 hybrid T-cell receptors and quantified as the number of inversions per ug DNA.

PRIOR AND CURRENT PROGRESS

Since the initiation of the study in Aug 2000 collection of patients with the diagnoses of rheumatoid arthritis and systemic lupus erythematosus has been underway. A total of 40 patients were determined to be necessary in order to make an appropriate statistical comparison (20 patients with SLE and 20 patients with RA). To date, 20 patient samples with SLE have and 15 patient samples with RA have been collection. Extractions on each of these individuals have been carried out.

CONCLUSIONS

Sample collection is close to completion. Will obtain samples from 5 additional patients with RA and will then begin the inversion assays in order to perform the analysis.

Report Date: 1 June 2001

Work Unit # 3724

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: Immunogenetic Factors During the Clinical Evolution of Systemic Lupus Erythematosus

KEYWORDS: Systemic lupus erythematosus, lupus, SLE, connective tissue disease, autoimmunity

PRINCIPAL INVESTIGATOR: Dennis, Gregory COL MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Rheumatology

STATUS: O
INITIAL APPROVAL DATE: 30 July 1997

STUDY OBJECTIVE

Identify a cohort of military service members who meet the American College of Rheumatology Criteria for a diagnosis of systemic lupus erythematosus (SLE) to be followed longitudinally. Compare the frequency of Epstein Barr Virus seroconversion of patients with systemic lupus erythematosus in the military to a group of patients without autoimmunity. Characterize the maturation of the humoral autoimmune response before clinical presentation and diagnosis and relate these findings to the later clinical and serologic expression of disease.

TECHNICAL APPROACH

Retrieve sera from the Army/Navy serum repository on active duty or previously active duty military who have a confirmed diagnosis of systemic lupus erythematosus and from age and sex matched controls. Each serum sample received is evaluated for the presence of defined autoantibodies and antibodies to EBV.

PRIOR AND CURRENT PROGRESS

After appreciating that the prevalence of positive EBV serologies is likely low enough only in the Caucasian and Hispanic male populations to reasonably test the hypothesis that EBV exposure precedes the development of SLE using our current approach, we have attempted to focus our identification on cases on these particular ethnic groups. In the past year we have identified an additional 22 subjects in whom a diagnosis of lupus has been confirmed throughout the military system with samples available for testing in the serum repository.

REVIEW OF RECENT LITERATURE

There have been two publications in the past year concerning the potential role that EBV has in the immuno-pathogenesis of SLE. Both of these published in 2001 concluded with disparate conclusions. That is, one concluded that the serological profiles present in patients with lupus were likely a consequence of immune dys-regulation secondary to SLE or its therapy rather than rampant infection with EBV. This, however, has not altered our view. We are continuing to retrieve serum samples frequently greater than five years prior to their initial presentation of lupus and have previously demonstrated the presence EBV exposure prior to the onset of lupus. To date, unfortunately, we have not collected a sufficient of cases to allow us to draw a statistically significant conclusion at this time.

The number of subjects enrolled to the study since last APR at WRAMC is __6__ and the total enrolled to date at WRAMC is ___66____. The total number enrolled study-wide is ___205____, if multi-site study.

CONCLUSIONS

The prevalence of positive EBV serologies is only low enough in the target population of Caucasian and Hispanic males to test the hypothesis that EBV exposure precedes the development of SLE. We are continuing to identify cases to increase out total number of subjects which will allow statistical comparisons to be made.

Report Date: 25 June 2001 Work Unit # 3726-98

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: Prevalence and Impact of Cyclical Mastalgia in Rheumatology Clinic Patients

KEYWORDS: Mastalgia, Fibromyalgia Syndrome

PRINCIPAL INVESTIGATOR: Jeanne P. Mitchell MAJ MC
ASSOCIATES: Deborah Ader PhD

DEPARTMENT: Medicine
SERVICE: Rheumatology

STATUS: O
INITIAL APPROVAL DATE: 10 March 1998

STUDY OBJECTIVE

(1) Identify the prevalence and impact of cyclical mastalgia in military and DEERS-eligible women with fibromyalgia and rheumatoid arthritis, and (2) compare the prevalence of mastalgia in these groups with existing data from women without rheumatologic disorders. In addition, we propose to examine the relationship between functional status of patients with these rheumatologic disorders and their reports of cyclical mastalgia.

TECHNICAL APPROACH

Addendum to original protocol: We wish to implement the following in regard to obtaining information from the above selected patients: (1) Identification of patients with either fibromyalgia or rheumatoid arthritis by chart review, (2) Verbal consent for participation in this study via telephonic contact. and (3) Participant receipt and completion of study questionnaire via mail.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Thus far, 31 patients with rheumatoid arthritis and 23 matched controls with fibromyalgia have been studied.
The number of subjects enrolled to the study since last APR at WRAMC is __0__ and the total enrolled to date at WRAMC is ___54____.

CONCLUSIONS

We have made no conclusions regarding the collected data as of this date.

Report Date: 08 May 2001

Work Unit # 3727 -98

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: Lymphocyte Signaling Defects in Patients with Lupus

KEYWORDS: autoimmunity, cell signaling, immune cells, humans

PRINCIPAL INVESTIGATOR: Tsokos, Gregory COL MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Rheumatology

STATUS: O
INITIAL APPROVAL DATE: 21 July 1998

STUDY OBJECTIVE

Characterize signaling abnormalities in human autoimmune cells. Specifically, study the antigen-mediated signaling events including activation of kinases, phosphatases, calcium mobilization and transcription factor activation in lymphocytes from patients with systemic autoimmune diseases (lupus).

TECHNICAL APPROACH

Isolate lymphocytes from peripheral blood; perform calcium mobilization studies; measure kinase and phosphatase activity using biochemical assays, measure transcription factor activity using shift assays.

PRIOR AND CURRENT PROGRESS

During the last year, experiments were continued to understand the causes and effects of abnormal T-cell signaling in SLE. We were able to show that the decreased TCR chain is functionally replaced by the gamma chain of the Fc epsilon receptor type 1. The downstream associations of this molecule may well explain some of the signaling defects. We were also able to show that small doses of prednisone, the drug most commonly used to treat patients with SLE, upregulates the transcription of the zeta chain gene. Additional experiments showed that increased ubiquitanation is partially responsible for the decreased levels of zeta chain in lupus patients.
The number of subjects enrolled to the study since last APR at WRAMC is 22 and the total enrolled to date at WRAMC is 82. The total number enrolled study-wide is n/a, if multi-site study.

CONCLUSIONS

Zeta chain is decreased in SLE patients because it undergoes increased ubiquitination and in its absence it is replaced by the gamma chain of the Fc receptor. Prednisone helps lupus patients because, among other things, it increases the levels of zeta chain.

Report Date: 27 March 2001 Work Unit #3728-99

DETAIL SUMMARY SHEET

TITLE: Rheumatoid Arthritis of the Robust Reaction Type

KEYWORDS:

PRINCIPAL INVESTIGATOR: CPT Thomas Rennie, MC
ASSOCIATES:

DEPARTMENT: Medicine STATUS: T
SERVICE: Rheumatology INITIAL APPROVAL DATE: 19 January 1999

STUDY OBJECTIVE

1. To identify a cohort of patients who have the arthritis robustus phenotype of rheumatoid arthritis.
2. Compare the clinical characteristics of those with the arthritis robustus phenotype to a matched control group of rheumatoid arthritis.

TECHNICAL APPROACH

1. Each patient is to complete the following questionnaires:
    a. Health Assessment Questionnaire (HAQ)
    b. Arthritis Self0efficacy Scale (ASES)
2. Physical Examination indices
    a. Hand grip
    b. Global Severity index
    c. ESR
    d. Joint Count
    e. Pain Scale
    f. Functional Disability Ranking
    g. DIP pain threshold
    h. Subcutaneous nodule documentation
3. Laboratory Data
    a. ESR
    b. RF
    c. CBC
    d. ANA
    e. CRP
4. Radiographic Evaluation
5. Occupational Therapy Evaluation

PRIOR AND CURRENT PROGRESS

This study was terminated by the 27 March 2001 Human Use Committee because a completed Annual Progress Report was not submitted.

CONCLUSIONS

This study was terminated by the 27 March 2001 Human Use Committee because a completed Annual Progress Report was not submitted.

Report Date: 04 January 2001

Work Unit # 3729-99

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: The Clinical Efficacy and Tolerability of Moderate-Dose Oral Compared to Subcutaneous Methotrexate in Rheumatoid Arthritis: A Prospective Crossover Trial

KEYWORDS:

PRINCIPAL INVESTIGATOR: Downs, Walter LCDR, MC
ASSOCIATES: Christopher Parker CPT, MC; LTC William Gilliland, MC; Elizabeth Mewshaw RN, MSN; COL Gregory J. Dennis, MC

DEPARTMENT: Medicine
SERVICE: Rheumatology

STATUS: O
INITIAL APPROVAL DATE: 16 February 1998

STUDY OBJECTIVE

To evaluate the effectiveness of switching from oral to subcutaneous methotrexate at the upper limit of the recommended oral dose range

TECHNICAL APPROACH

A prospective, open label, examiner blinded, randomized cross over trial

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

To date eight patients have met the inclusion criteria and have been enrolled. All eight patients have completed the trial and none have withdrawn or suffered adverse reactions. Both the oral and subcutaneous methotrexate administrations were well tolerated. Two of eight patients significantly responded by American College Rheumatology criteria while on the subcutaneous route of administration. One patient achieved an ACR 20 response. The other patient achieved an ACR 50 response. The average percent improvement in pain scores of these two was 68%. No significant improvement was observed with oral administration.
There is no new literature on methotrexate in this regard either by abstract (last meeting) or print.

CONCLUSIONS

The study design and subcutaneous route of administration is well tolerated by this patient population. The trial statistical analysis that quantifies benefit (the study is designed to quantitate response) is ongoing. Augmentation of methotrexate from 20 mg to 25 mg per week may improve active rheumatoid arthritis in some patients if the route of administration is changed to subcutaneous injection. Further study is warranted

Report Date: 24 May 2001

Work Unit # 00-4301

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: GOG 178 Phase III Randomized Trial of 12 Months vs. Months of Paclitaxel in Patients with Advanced Ovarian, Fallopian Tube or Primary Peritoneal Cancer Who Attain a Clinically Defined Complete Response (CR) Following Platinum/Paclitaxel-Based Chemotherapy

KEYWORDS:

PRINCIPAL INVESTIGATOR: Maxwell, G. Larry MAJ MC
ASSOCIATES:

DEPARTMENT: Obstetrics & Gynecology
SERVICE: Gynecologic Oncology Group

STATUS: O
INITIAL APPROVAL DATE: 25 July 2000

STUDY OBJECTIVE

To assess whether the continuation of paclitaxel, a cycle specific antineoplastic agent, for 12 months following the attainment of a clinically-defined complete response (CR) to initial platinum (carboplatinum or cisplatin)/paclitaxel-based chemotherapy can significantly increase progression-free survival and overall survival when compared to a 3-month continuation in women with advanced ovarian, fallopian tube or primary peritoneal cancer. To assess the toxicities associated with prolonged paclitaxel.

TECHNICAL APPROACH

This is a Phase III study. Patients on this study will be receiving paclitaxel either for a 12-month cycle (12 courses) or over a 3-month cycle (3 courses). Patients are followed for progression-free survival and overall survival and toxicities.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

This is the first APR for this protocol and we have no publications to report from studies similar in design. The number of subjects enrolled to the study since last APR at WRAMC is _0_ and the total enrolled to date at WRAMC is __2_. The total number enrolled study-wide is _ 58_, if multi-site study. Grade 4 toxicities include 1 hematologic, and 1 lung (2 unknown). One of 21 patients evaluated for toxicity on the 12-course arm had grade 4 dyspnea. One of 20 patients evaluated for toxicity on the 3-course arm had grade 4 neutropenia/granulocytopenia.
Ref: Jan 01 GOG Statistical Report

CONCLUSIONS

Too early.

Report Date: 19 June 2001

Work Unit # 00-4302

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: GOG 9901 Comparison of Quality of Life for Ovarian Germ Cell Cancer Survivors

KEYWORDS:

PRINCIPAL INVESTIGATOR: Maxwell, G. Larry MAJ MC
ASSOCIATES:

DEPARTMENT: Obstetrics and Gynecology
SERVICE: Gynecologic Oncology Group

STATUS: O
INITIAL APPROVAL DATE: 15 August 2000

STUDY OBJECTIVE

To compare germ cell tumor survivors with a matched control group of well females on the quality of life variables of health status and sexual functioning. Psychological and emotional well-being and social functioning will be compared as secondary end points.

TECHNICAL APPROACH

Patients with early and advanced ovarian germ cell tumors who have previously been enrolled on GOG protocols 45, 78, 90, and 116. Patients and control individuals will complete a self-administered questionnaire. They will also be administered a variety of instruments that will assess physical and sexual functioning, social networks, and psychological functioning. A detailed statistical analysis will be done to compare patients and controls for these variables.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

This is the first APR for this study at WRAMC. There have been a couple of publications reporting data for this study. The objectives of this investigation have not been fulfilled by prior studies.
The number of subjects enrolled to the study since last APR at WRAMC is _0_ and the total enrolled to date at WRAMC is __0__. The total number enrolled study-wide is _90_, if multi-site study.
Ref: Jan 01 GOG Statistical Report

CONCLUSIONS

Too early.

Report Date: 20 June 2001 Work Unit # 00-4303

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: GOG 175: A Randomized Phase III Trial of IV Carboplatin (AUC 6) and Paclitaxel 175 mg/m^2 Q 21 Days x 3 Courses Plus Low Dose Paclitaxel 40 mg/m^2/wk vs. IV Carboplatin (AUC 6) and Paclitaxel 175 mg/m^2 q 21 Days x 3 Courses Plus Observation in Patients with Early Stage Ovarian Carcinoma

KEYWORDS:

PRINCIPAL INVESTIGATOR: Maxwell, G. Larry MAJ MC
ASSOCIATES:

DEPARTMENT: Obstetrics and Gynecology STATUS: O
SERVICE: Gynecologic Oncology Group INITIAL APPROVAL DATE: 15 August 2000

STUDY OBJECTIVE
To compare the progression-free interval and overall survival in the two treatment arms. To assess the frequency and severity of toxicities due to the continued low dose paclitaxel regimen. To investigate markers of angiogenesis and metastasis as prognostic indicators for early stage epithelial ovarian cancer.

TECHNICAL APPROACH
All patients must have a histopathologic diagnosis of epithelial ovarian cancer. Patients with sufficient tumor tissue must have tissue specimen(s) sent to the GOG Tissue Bank.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
This is the first APR for this study at WRAMC. There have been no publications reporting data from studies with similar study design in literature. The number of subjects enrolled to the study since last APR at WRAMC is _0_ and the total enrolled to date at WRAMC is __0_. The total number enrolled study-wide is _182, if multi-site study. Grade 4 toxicities include 1 WBC, 2 platelets, 73 granulocytes, 1 cardiovascular, 1 gastrointestinal, and 1 neurologic.
Ref: Jan 01 GOG Statistical Report

CONCLUSIONS
Too early.

Report Date: 12 January 2001 Work Unit #00-4304

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: GOG 172 A Phase III Randomized Phase III Trial of Intravenous Paclitaxel and Cisplatin Versus Intravenous Paclitaxel, Intraperitoneal Cisplatin and Intraperitoneal Paclitaxel in Patients with Optimal Stage III Epithelial Ovarian Carcinoma of Primary Peritoneal Carcinoma

KEYWORDS:

PRINCIPAL INVESTIGATOR: Maxwell, G. Larry MAJ MC
ASSOCIATES:

DEPARTMENT: Obstetrics and Gynecology STATUS: W
SERVICE: Gynecologic Oncology Group INITIAL APPROVAL DATE: 19 September 2000

STUDY OBJECTIVE
This protocol was withdrawn, effective 12 January 2001.

TECHNICAL APPROACH
This protocol was withdrawn, effective 12 January 2001.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
This protocol was withdrawn, effective 12 January 2001.

CONCLUSIONS
This protocol was withdrawn, effective 12 January 2001.

Report Date: 26 July 2001 Work Unit # 00-4305

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: GOG 171: Expression of the MN Protein in Atypical Glandular Cells of Undetermined Significance (AGUS or AGCUS) as Potential Diagnostic Biomarkers of Cervical Dysplasia / Neoplasia

KEYWORDS:

PRINCIPAL INVESTIGATOR: Maxwell, G. Larry MAJ MC
ASSOCIATES:

DEPARTMENT: Obstetrics and Gynecology
SERVICE: Gynecologic Oncology Group

STATUS: O
INITIAL APPROVAL DATE: 26 September 2000

STUDY OBJECTIVE
To evaluate the utility of a novel tumor-associated antigen termed "MN" as a potential diagnostic biomarker for cervical glandular and/or squamous neoplasia in patients with cytologic diagnosis of atypical glandular cells of undetermined significance (AGUS). To measure the frequency and type of cervical pathology associated with AGUS diagnosis.

TECHNICAL APPROACH
Patients with cytologic diagnosis of AGUS, in whom complete histological examination of cervix (cone or LEEP biopsy) is planned will be eligible for this protocol.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
This is the first APR for this study here at WR. There have been no publications reporting data from studies with similar study design in literature. The number of subjects enrolled to the study since last APR at WRAMC is _n/a_ and the total enrolled to date at WRAMC is __12_. The total number enrolled study-wide is _231_, if multi-site study. No toxicities reported.
Ref: Jul 01 GOG Statistical Report

CONCLUSIONS
Too early.

Report Date: 13 November 2000 Work Unit # 00-4401

DETAIL SUMMARY SHEET

TITLE: Phase III Clinical Study of MX6 (Adapalene Gel/Collagen Sponge) vs. Placebo in Subjects with Cervical Intraepithelial Neoplasia Level II, III or Carcinoma In Situ (CIN II, III or CIS)

KEYWORDS: MX6, Cervical Intraepithelial Neoplasia

PRINCIPAL INVESTIGATOR: LTC Mary F. Parker, MC
ASSOCIATE INVESTIGOR: LTC Jay Carlson, MC

DEPARTMENT: Obstetrics and Gynecology STATUS: C
SERVICE: Gynecologic Oncology INITIAL APPROVAL DATE: 25 January 2000

STUDY OBJECTIVES:
A. The first objective of this Phase III multicenter clinical study is to compare the response rate for MX6 (adapalene gel/collagen sponge) to placebo in subjects with biopsy proven cervical intraepithelial neoplasia level II, III, or carcinoma *in situ* (CIN II, III or CIS).
The primary efficacy endpoint of this study is the proportion of patients with any response (complete or partial response). The null statistical hypothesis to be tested is that the proportion of subjects receiving MX6 with any response equals the proportion of subjects receiving placebo with any response.
B. The second objective is to determine the local and general tolerability of MX6 in this subject population.

TECHNICAL APPROACH:
There have been no addenda to original protocol.
Randomization
In the total study population of at least 180 subjects, 90 subjects will be randomly assigned to receive active drug while 90 will be assigned to receive placebo. Randomization will be stratified by investigational site and disease level (CIN II or III/CIS) at enrollment. When a study material kit is dispensed to a subject, the subject's assigned study number is pre-printed on the kit label and label extension. Subjects with CIN II will be assigned low kit numbers, starting with the lowest number provided and counting forward. Those with CIN III/CIS will be assigned high kit numbers, starting with the highest number provided and counting backward.
Length of Treatment and Follow-Up
MX6 or placebo will be administered once daily for 14 consecutive days. Each day the cervical cap with collagen sponge and MX6 or placebo gel will remain in place for 8 ± 2 hours. Upon completion of the 90 day treatment and evaluation period, subjects who received MX6 or placebo with no response or progression of disease will receive standard treatment at the investigator's discretion, while MX6 and placebo subjects with partial or complete response will receive long-term follow-up evaluation.
Administration
For administration of MX6 or placebo, a collagen sponge is placed in the bottom of the cervical cap, and the contents of two tubes are applied to the sponge. Both tubes must be completely emptied. For subjects assigned to receive MX6, the daily dose of adapalene will be 4.0mg (contents of two tubes). The cap is then inserted high into the vaginal vault and applied to the cervix. On the day that each subject is enrolled into the study, the investigator or an experienced nurse will train the subject to prepare and insert the device.

Patient Encounters
The study consists of the following evaluations: Baseline/First Treatment Day, During Treatment (Day 8), End of Treatment (Day 15) and Post-treatment Follow-up (Days 21 and 90). A summary of the study procedure is on page 13 of the sponsor's protocol.

Sample Size/Data Analysis

All statistical tests will be two-tailed and performed at the 0.05 level. All analyses will be performed using SAS software (SAS Institute, Cary, NC) . Analyses will be done both on an intent-to-treat basis and for evaluable subjects only. The proportion of subjects with any response (partial or complete) will be calculated for the MX6 and placebo groups, as well as for subgroups classified on the basis of severity of dysplasia, smoking status, type of contraception and Vitamin A intake. Equality of the proportions will be tested with Fisher's exact test. Exact binomial confidence intervals for each group (95%) will be presented. Fisher's exact tests will also be performed to test equality of complete response rates and of partial response rates between the MX6 and placebo groups. Log-linear analyses will be performed to identify interaction effects due to level of disease at enrollment. A sample size of 180 subjects (90 subjects in each treatment group) is sufficient to detect a difference of 20%, (25% - 45%) with a Fisher's exact test, with a power of 80%, a 5% significance level, and a 15% drop-out rate. An interim efficacy analysis will be performed for administrative purposes. Analyses will be performed for the entire study population (intent-to-treat) and the evaluable population, using the primary efficacy variable, the results of cervical biopsies. The interim analysis will take place after 90 patients (half the planned population) have completed all study evaluations. Adjustment of p-values will be by the method of O'Brien and Fleming (8). According to this method, significance levels will be p=0.0051 for the interim analysis and p=0.0475 for the final analysis. Because of the involvement of unblinded data, the interim analysis will be confidential. Results of the analysis will determine whether the study will continue. These results will be available only to the statistical consultant and to the President and Vice President/Drug Development of MAXIA Pharmaceuticals, Inc. The study sponsor, Maxia Pharmaceuticals, will use an independent analysis group for the interim analysis. There will not be an independent safety-monitoring group for this study. A complete report of adverse effects in the phase I/II cervical dysplasia trial preceding this study is detailed in the Clinical Investigator's Brochure for Topical MX6 (on file with the Research Review Service, Department of Clinical Investigation). A biopsy diagnosis of CIN 3 following a previous diagnosis of CIN 2 is not considered progression of disease, as these conditions are clinically treated in the same fashion and can be difficult to distinguish on pathologic interpretation. A biopsy diagnosis of CIN 2 following a previous diagnosis of CIN 3 is likewise not considered regression of disease.

PRIOR AND CURRENT PROGRESS:

Three patients total were enrolled at this site in the last year, with a total of 3 to date. There have been 207 total patients enrolled from all sites. Patient enrollment has been closed. Data analysis is currently ongoing.

An interim report of adverse events from all study sites is attached to this report.

Because data analysis has not yet been completed, the benefit to patients is not yet known.

CONCLUSIONS:

Data analysis is currently ongoing. There are not conclusions to report at this time.

Report Date: 10 January 2001 Work Unit #00-4402

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: Long-Term Follow-up Evaluation of Subjects Participating in Phase III Clinical Studies of MX6 (Adapalene Gel/Collagen Sponge) in Cervical Intraepithelial Neoplasia Level II, III or Carcinoma in situ (CIN II, III or CIS)

PRINCIPAL INVESTIGATOR: Parker, Mary F. LTC MC
ASSOCIATES: Carlson, Jay LTC MC

DEPARTMENT: Obstetrics & Gynecology STATUS: C
SERVICE: Gynecologic Oncology INITIAL APPROVAL DATE: 21 March 1999

STUDY OBJECTIVE: The objective of this study is to verify the long-term effect (180 and 360 days) of MX6 (adapalene gel/collagen sponge) after treatment with MX6 for biopsy-proven cervical intraepithelial neoplasia level II, III, or carcinoma *in situ* (CIN II, III, or CIS). Results after long-term follow-up will be compared to results for subjects receiving placebo in previous studies (MX6-02 (USA); MX6-05 (Europe)).

TECHNICAL APPROACH: There have been no addenda to original protocol. This study is intended for follow-up of subjects participating in WRAMC protocol #00-4401 (MX6-02 (USA), MX6-03, and MX6-05 (Europe)) of the efficacy, uptake and tolerability of MX6 in cervical intraepithelial neoplasia level II, III, or carcinoma *in situ* (CIN II, III, or CIS). Subjects with a complete or partial response 90 days after treatment with MX6 or placebo will be evaluated by colposcopy, colpophotography and Papanicolaou smear at 180 and 360 days after the start of treatment in the previous study. Cervical biopsy will be performed if indicated by colposcopic and/or cytologic findings. Results will be compared to those obtained at 90 days after treatment.

Subjects are evaluable in this study if they have had a cervical biopsy at 90 days after the first day of MX6 or placebo treatment, and if they undergo gynecologic examinations (pelvic examination, Papanicolaou smear, colposcopy, colpophotography, cervical biopsy if indicated) at 180 and 360 days after the first treatment day.

Cytologic, colposcopic and colpophotographic findings, and cervical biopsy if indicated, at 180 and 360 days after the first dose of MX6 or placebo, will provide the endpoints for evaluation. All colposcopic, colpophotographic, cytologic and histologic findings will be reviewed and classified. Histologic findings will also be reviewed by an independent reviewer. The independent reviewer will visit all study sites and make judgments of efficacy. In case of disagreement between the investigator and the independent reviewer, the independent reviewer's decision will prevail. The independent reviewer will be masked to all subject treatment assignments. Response will be determined and recorded at 180 and 360 days after the first day of MX6 treatment as follows: complete response – findings are normal; partial response - mild dysplasia (CIN I; low-grade squamous intraepithelial lesion) is present; and progression - CIN II (moderate dysplasia; high-grade squamous intraepithelial lesion), CIN III (severe dysplasia; carcinoma *in situ*; high-grade squamous intraepithelial lesion) or invasive cancer is present. All analyses will be performed using SAS software. The proportions of subjects with continuing complete and partial response, and disease progression will be calculated.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE: The number of subjects enrolled to the study since last APR at WRAMC is _0___ and the total enrolled to date at WRAMC is __0_____. The total number enrolled study-wide is ___49____. To date, no serious or non-serious adverse events have been reported from any study site, and 5 patients have been withdrawn from the study prematurely (3 patients required LEEP and 2 were lost to follow-up). Enrollment to the study and follow-up at other sites continues. Until further data analysis is completed, and the study is unblinded, it is unknown whether or not any patient benefit has occurred at this time. There have been no modifications to the research study.

CONCLUSIONS: Data analysis is currently ongoing. There are not conclusions to report at this time.

Report Date: 16 February 2001

Work Unit #00-4403

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: A Trial of Vitamin B Complex for the Treatment of Chemotherapy Induced Peripheral Neuropathy

KEYWORDS: Vitamin B Complex, Neuropathy

PRINCIPAL INVESTIGATOR: Parker, Mary F. LTC MC
ASSOCIATES: Rogers, Stacey J. LCDR MC; Aylesworth, Cheryl, MD; Giroux, Donna, RN, BSN; Petrov, Jean, RN, MS

DEPARTMENT: Obstetrics & Gynecology
SERVICE: Gynecologic Oncology

STATUS: O
INITIAL APPROVAL DATE: 18 April 2000

STUDY OBJECTIVES

To determine if vitamin B complex is effective in the treatment of chemotherapy induced neuropathy and to determine the side effects of such treatment.

TECHNICAL APPROACH

There have been no modifications since the protocol was approved. Subjects receiving chemotherapy with a Taxol-containing regimen who develop peripheral neuropathy are given vitamin B complex twice a day for 6 weeks. Subjects are queried at baseline (prior to starting the vitamin B complex), weekly during the study, and at the conclusion of the study regarding their neurologic symptoms and any changes that occur during the course of the vitamin treatment. A brief neurologic examination is performed at baseline and at the completion of the 6 weeks of treatment. Based on the questionnaires and neurologic examinations, grades of peripheral neuropathy are assigned. Response is defined as an improvement in peripheral neuropathy by at least one grade. After 25 evaluable subjects have been accrued, statistical analysis will be performed to determine if further study is warranted.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

There have been no modifications since the protocol was approved.
This is the initial APR for this study. There have been 11 subjects enrolled to date. There has been one subject withdrawn from the study due to facial flushing associated with the vitamin B complex. The flushing resolved upon discontinuation of the vitamin B complex. This adverse event was not serious. As noted in the consent form, facial flushing is usually seen at higher dosages than given in this study. All subjects have reported the expected color change and/or odor in their urine.
Summary of findings to date: Of the 11 subjects enrolled, 1 subject was withdrawn prior to the completion of 6 weeks of vitamin B complex treatment. Of the remaining 10 subjects, there have been 4 responders, 4 non-responders (3 subjects with unchanged neuropathy, 1 subject with worsening neuropathy), and 2 subjects with final analysis pending.

CONCLUSIONS

Based on the number of responses seen to date, and the parameters set forth in the data analysis portion of the protocol, continuation of the study is warranted. If found to significantly decrease the severity of chemotherapy induced peripheral neuropathy, this treatment could significantly impact the quality of life of these patients and potentially allow for dose escalation of chemotherapeutic agents. Further study via randomized trial would be recommended to compare the vitamin B complex to placebo, as well as to ensure the vitamin treatment does not adversely affect patient survival (currently unknown).

Report Date: 16 July 2000 Work Unit # 00-4404

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: The Creation of a Blood and Tissue Bank and the Collection of Clinical Data From Patients Undergoing In Vitro Fertilization

KEYWORDS: In Vitro Fertilization, Tissue Bank, Blood

PRINCIPAL INVESTIGATOR: Mark P. Leondires, MD
ASSOCIATES: Lynette Scott, PhD

DEPARTMENT: Obstetrics and Gynecology STATUS: O
SERVICE: Reproductive Endocrinology INITIAL APPROVAL DATE: 27 June 2000

STUDY OBJECTIVE

- To collect prospective clinical data on patients aged 18 years and over being treated for infertility using in vitro fertilization at WRAMC.
- To accomplish the collection and storage of human blood, granulosa cells, and follicular fluid from *in vitro fertilization* patients which would otherwise be discarded.
- To make available normally discarded human blood, granulosa cells, and follicular fluid for proposed projects in the Pediatric and Reproductive Endocrinology Branch and the Endocrinology and Reproduction Branch of the National Institute of Child Health and Human Development.

TECHNICAL APPROACH

This is an observational study with no active intervention. The technical approach is to prospectively collect clinical data using a computerized database. Furthermore, we have been saving blood samples to provide a repository for clinical specimens to include blood, follicular fluid, and granulosa cells from patients participating in the study.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE:

There have been no major modifications in the practice of in vitro fertilization over the past year. Overall pregnancy rates have continued to climb likely secondary to changes in laboratory systems and quality control. To date no NIH researchers have requested use of the specimens. This is secondary to changes in project design at that institution and somewhat related to the length of time it took for this researcher to get this protocol approved. In addition the restriction of genetic studies even in an anonymous fashion has been a problem. Since the main goal of the protocol is to generate a computerized database and this process is ongoing the major intent of the protocol is progressing adequately. To date a total of 153 women have been recruited for this study. There have been no adverse events which have been related to this observation study.

The number of subjects enrolled to the study since last APR at WRAMC is 153 and the total enrolled to date at WRAMC is 153. This is not a multi-site study. Ethnicity is not known. I will modify the database to capture this information in the future.

CONCLUSIONS

This continues to be an active protocol which serves to inform patients of the potential uses of their clinical data and is providing an excellent resource for continued retrospective studies within our department.

Report Date: 28 April 2001 Work Unit # 00-4405

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: A Prospective, Randomized, Double-Blind, Placebo Controlled Study of Oral Misoprostol Prior to Operative Hysteroscopy

PRINCIPAL INVESTIGATOR: Alvero, Ruben LTC MC
ASSOCIATES: Preen, Amy CPT MC

DEPARTMENT: Obstetrics and Gynecology
SERVICE: Reproductive Endocrinology

STATUS: O
INITIAL APPROVAL DATE: 27 June 2000

STUDY OBJECTIVE: Null hypothesis: Oral misoprostol prior to hysteroscopy, will not enhance cervical dilation or decrease operating time. We will investigate the time needed for cervical dilation, time needed for hysterescopy and the ease at which hysterscopy is performed with preoperative administration of misoprostol. If oral misoprostol is effective in softening the uterine cervix, we expect that operative time; complication rate and patient post-operative discomfort will all be reduced. Primarily, we plan to measure length of dilation, length of surgery, and the first noted cervical dilator with resistance. Secondarily, we plan to subjectively assess ease of procedure and the patient's symptoms prior to surgery and post-operative pain. We will assess the incidence of complication such as uterine perforation.

TECHNICAL APPROACH: 1. Patients will have been already been scheduled for an indicated operative hysteroscopy at WRAMC will be advised of the study. All patients will have urine hCG the day of surgery.
2. At their scheduled pre-operative visit patients will be counseled as to the risks, benefits, and alternatives and then sign the consent to participate in the study. Once they have signed the consent they will be given an opaque coded sealed envelope that will contain a misoprostol 400 microgram capsule or placebo. Factors (menopausal status, parity, and use of estrogen replacement therapy) that may affect the outcome measure (i.e. time needed for cervical dilation) will be determined for stratification. Patients within each stratum will be randomized to either misoprostol or placebo with equal number. The pharmacy will have a copy of the randomization scheme. Patients will be given a pre-questionnaire to fill out the time and date the capsule was taken and any side effect experienced.
3. They will take the capsule approximately 12 hours prior to the procedure.
4. When they arrive for surgery they will finish the pre-questionnaire regarding any noted discomforts or symptoms they experienced after taking the capsule. This questionnaire will be completely filled out prior to the procedure and collected by the operating surgeon.
5. The surgeon will fill out a questionnaire to include basic information about the surgery (secondary outcomes): the procedure performed (for example: myomectomy, polypectomy, septum resection; adhesiolysis), media used (sorbitol, saline, hyskon, mannitol or CO2), and the total media deficit. The questionnaire will also include primary endpoints: time at start of dilation, time at finish of dilation (largest dilator needed to place operative hysteroscope), first cervical dilator with noted resistance, start time and finish time of hysteroscopy. Secondary endpoints will also be recorded: ease of procedure (visual analogue scale) and any complications that occurred.
6. The day after the procedure the patient will be called by a department secretary to remind them to fill out the post-procedure questionnaire. The patient will be asked to rate post-operative discomfort on a visual analogue scale along with any side-effects they have felt regarding the medicine and the procedure. They will record these on a post- questionnaire given to them prior to discharge from the hospital.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE: No recent literature in this area has been published since the last update. The number of subjects enrolled to the study since last APR at WRAMC is 18 and the total enrolled to date at WRAMC is 18.

CONCLUSIONS: As this blinded study is still ongoing, there is no way that any conclusions can be reached at this time.

Report Date: 24 September 2001 Work Unit # 00-4406

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: Characterization of Peritoneal Fluid in Differentiating Benign from Malignant Adnexal Masses

KEYWORDS:

PRINCIPAL INVESTIGATOR: McBroom, John MAJ MC
ASSOCIATES:

DEPARTMENT: Obstetrics and Gynecology STATUS: O
SERVICE: Gynecology Oncology INITIAL APPROVAL DATE: 05 July 2000

STUDY OBJECTIVE
If peritoneal fluid LDH, cholesterol, or interleukin-6 levels can discriminate between benign and malignant adnexal masses. We will also compare the serum: peritoneal fluid ratios to determine if this augments the ability to discriminate.
To determine if these chemistry values are significantly different between women with an adnexal mass and those without an adnexal mass.

TECHNICAL APPROACH
This research study involves patients who are schedules to undergo surgery in the gynecology department. They will evaluate the fluid in the patient's peritoneal cavity and their blood for chemical markers. These markers may have the ability to determine if a patient with a mass has cancer or not. If they are undergoing gynecologic surgery and do not have a mass the patients participation is needed in order to compare their values to those women with a mass.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
This is the first APR for this study and there have bee no publications reporting data from this study.
The number of subjects enrolled to the study since last APR at WRAMC is N/A and the total enrolled to date at WRAMC is __15___. The total number enrolled study-wide is _N/A__, if multi-site study. No toxicities to report.

CONCLUSIONS
Too early.

Report Date: 13 November 2000

Work Unit # 4113

DETAIL SUMMARY SHEET

TITLE: Cooperative Gynecologic Oncology Group

KEYWORDS: gynecologic, oncology, group

PRINCIPAL INVESTIGATOR: Rose, G. Scott LTC MC
ASSOCIATES:

DEPARTMENT: Obstetrics & Gynecology
SERVICE: Gynecologic Oncology Group

STATUS: O
INITIAL APPROVAL DATE: 31 January 1974

STUDY OBJECTIVE

Walter Reed Army Medical Center section of Gynecologic Oncology is involved with the nationally organized Gynecologic Oncology Group, consisting of 40 major medical centers in the country who are interested in the area of gynecologic tumors and the treatment of gynecologic cancer. The GOG is recognized and funded through the National Cancer Institute.

TECHNICAL APPROACH

Walter Reed is active in approximately 40 GOG protocols. Presently, there are 60 protocols that are either active or continue to provide significant data. These protocols involve treatment of ovarian carcinoma, cervical carcinoma, adenocarcinoma of the endometrium, uterine sarcoma, vulvar carcinoma, and gestational trophoblastic disease.

PRIOR AND CURRENT PROGRESS

Approximately 1116 patients have been entered into GOG Protocols from Walter Reed Army Medical Center; 30 during this year.

CONCLUSIONS

Detailed in individual reports.

Report Date: 26 February 2001 Work Unit #4229

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: GOG 86A: Master Protocol for Phase II Drug Studies in Treatment of Advanced or Recurrent Carcinoma of the Endometrium

KEYWORDS: advanced, carcinoma, endometrium

PRINCIPAL INVESTIGATOR: Maxwell, G. Larry MAJ MC
ASSOCIATES:

DEPARTMENT: Obstetrics & Gynecology STATUS: O
SERVICE: Gynecologic Oncology Group INITIAL APPROVAL DATE: 29 April 1986

STUDY OBJECTIVE
To identify additional active agents for treating advanced or recurrent endometrial adenocarcinoma by studying single new drugs in patients with this disease who have not been previously exposed to chemotherapy.

TECHNICAL APPROACH
Patients must have histologically confirmed advanced, persistent, or recurrent endometrial carcinoma with documented disease progression after local therapy. All patients must have measurable disease. Patients must have failed local therapeutic measures or must be considered incurable with local therapy.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
This is a master protocol. Please see individual protocols for further information.

CONCLUSIONS
See individual protocols for further information

Report Date: 20 March 2001

Work Unit # 4231

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: GOG 87A: Master Protocol for Phase II Drug Studies in the Treatment of Recurrent or Advanced Uterine Sarcomas

KEYWORDS: advanced, uterus, sarcoma

PRINCIPAL INVESTIGATOR: Maxwell, G. Larry MAJ MC
ASSOCIATES:

DEPARTMENT: Obstetrics & Gynecology
SERVICE: Gynecologic Oncology Group

STATUS: O
INITIAL APPROVAL DATE: 27 May 1986

STUDY OBJECTIVE
To allow the best possible chance for a new cytotoxic agent to demonstrate activity, this study constitutes a Phase II design in a population of patients who have had no prior drug therapy.

TECHNICAL APPROACH
To treat an average sample size of 30 patients per drug studied for each of the following cell categories: mixed mesodermal tumor, leiomyosarcoma, and other sarcomas. Patients will have histological confirmed advanced, persistent, or recurrent uterine sarcoma with documented disease progression after appropriate local therapy. Each patient will receive a chemotherapeutic regimen as outlined in each segment of the protocol.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
This is a master protocol. Please see individual protocols for further information.

CONCLUSIONS
See individual protocols for further information.

Report Date: 29 January 2001 Work Unit #4244

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: GOG 90: Evaluation of Cisplatin, Etoposide, and Bleomycin (BEP) Induction Followed by Vincristine, Dactinomycin, and Cyclophosphamide (VAC) Consolidation in Advanced Ovarian Germ Cell Tumors, Phase II

KEYWORDS: ovarian, germ cell, tumors

PRINCIPAL INVESTIGATOR: Rose, G. Scott LTC MC
ASSOCIATES:

DEPARTMENT: Obstetrics & Gynecology
SERVICE: Gynecologic Oncology Group

STATUS: O
INITIAL APPROVAL DATE: 31 March 1987

STUDY OBJECTIVE

To evaluate the effect of induction chemotherapy with cisplatin plus etoposide plus bleomycin (BEP), followed by consolidation with vincristine plus dactinomycin plus cyclophosphamide (VAC) in previously untreated patients with advanced ovarian germ cell tumors.

TECHNICAL APPROACH

Eligible patients include those with histologically confirmed malignant germ cell tumors of the ovary who have incompletely resected Stage II, III, or IV disease. Patients who have previously received pelvic radiation therapy will be eligible, but the initial dose of etoposide will be reduced 20%.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

The number of subjects enrolled to the study since last APR at WRAMC is __0__ and the total enrolled to date at WRAMC is _2. The total number enrolled study-wide is _131_, if multi-site study. Grade IV toxicities include 45 leukopenia, 15 thrombocytopenia, 76 granulocytopenia, 5 GI, 2 fever, 4 anemia, 1 pulmonary, 1 allergic reaction, 1 hepatic, 1 metabolic, 1 sepsis, 1 leukemia/death. This protocol was closed to patient entry effective 7/27/98.
Since this protocol's review a year ago, there has been no additional literature, amendments or modifications that have not been mentioned before on this report. See enclosure #3.

Ref: Jan 01 GOG Statistical Report

CONCLUSIONS

It is too early to draw final conclusions to the therapeutic aspects of this protocol. Data from this and other studies have identified patients that should and should not undergo second look laparotomy. Patients with advanced dysgerminoma have a very high response rate to chemotherapy.

Report Date: 20 March 2001

Work Unit # 4247

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: GOG 95: Randomized Clinical Trial for the Treatment of Women with Selected Stage IC and II (A, B, C) and Selected Stage IAi and IBi and IAii and IBii Ovarian Cancer, Phase III

KEYWORDS: randomized, ovarian, cancer

PRINCIPAL INVESTIGATOR: Maxwell, G. Larry MC.
ASSOCIATES:

DEPARTMENT: Obstetrics & Gynecology
SERVICE: Gynecologic Oncology Group

STATUS: O
INITIAL APPROVAL DATE: 26 May 1987

STUDY OBJECTIVE

This study seeks to compare the progression-free interval and overall survival between p32 and a combination of cyclophosphamide and cisplatin for patients with early ovarian cancer and to determine the patterns of relapse for each form of therapy.

TECHNICAL APPROACH

All patients must have a histopathologic diagnosis of epithelial ovarian cancer of each histologic cell type: serous mucinous; others include endometrioid, transitional mesonephroid (clear cell), adenocarcinoma (endometrioid with squamous metaplasia), mixed epithelial, and unclassifiable (undifferentiated).

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Since this protocol's last years review there have been no additional publications reporting data from studies with similar study design in the literature.
The number of subjects enrolled to the study since last APR at WRAMC is _0_ and the total enrolled to date at WRAMC is _6_. The total number enrolled study-wide is _251_, if multi-site study.
Walter Reed has enrolled 6 patients (1 now deceased). There have been no adverse reactions or serious toxicities. There have been 86 Grade IV neutropenic episodes, 4 thrombocyopenias, and 1 GI. Two patients experienced small bowel perforation during p32 administration. There have been two treatment related deaths. This protocol was closed to patient entry March 14, 1994.
Ref: Jan 01 GOG Statistical Report

CONCLUSIONS

After adjusting for stage and histologic grade, the recurrence rate on the cisplatin regimen is 34% lower than the p32 regimen. Estimated relative risk is 0.665 (90% confidence interval: 0.440-1.006).

Report Date: 24 May 2001 Work Unit # 4254

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: GOG 93: Evaluation of Intraperitoneal Chromic Phosphate Suspension Therapy Following Negative Second-Look Laparotomy for Epithelial Ovarian Carcinoma, Stage III, Phase III

KEYWORDS: chromic phosphate, ovarian, carcinoma

PRINCIPAL INVESTIGATOR: Maxwell, G. Larry MAJ MC
ASSOCIATES:

DEPARTMENT: Obstetrics and Gynecology
SERVICE: Gynecologic Oncology Group

STATUS: O
INITIAL APPROVAL DATE: 28 July 1987

STUDY OBJECTIVE
To evaluate the role of intraperitoneal chromic phosphate suspension therapy in patients with Stage III epithelial ovarian carcinoma who have no detectable evidence of disease at the second-look laparotomy.

TECHNICAL APPROACH
Patients will be given Topotecan *.5 mg/m□ IV over 24 hours every 3 weeks until progression of disease or adverse effects prohibit further therapy.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
Since this protocol's review a year ago, there have been no publications reported.
The number of subjects enrolled to the study since last APR at WRAMC is _0_ and the total enrolled to date at WRAMC is _2_. The total number enrolled study-wide is _267_, if multi-site study. Grade 4 toxicities are 1 hematologic, and 3 GI. Protocol was closed to patient entry 10/28/96. Protocol can be closed here at Walter Reed.

Ref: Jan 01 GOG Statistical Report

CONCLUSIONS
Too early.

Report Date: 26 July 2001

Work Unit # 4255

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: GOG 78: Evaluation of Adjuvant Vinblastine, Bleomycin and Cisplatin Therapy in Totally Reducing Choriocarcinoma, Endodermal Sinus Tumor or Embryonal Carcinoma of the Ovary, Pure and Mixed with Other Elements, Phase II

KEYWORDS: VP-16, bleomycin, cisplatin

PRINCIPAL INVESTIGATOR: Maxwell, G. Larry MAJ MC
ASSOCIATES:

DEPARTMENT: Obstetrics and Gynecology
SERVICE: Gynecologic Oncology Group

STATUS: O
INITIAL APPROVAL DATE: 29 September 1987

STUDY OBJECTIVE

To evaluate the effect of adjuvant VP-16, bleomycin, and cisplatin chemotherapy in patients with endodermal sinus tumor, choriocarcinoma, embryonal carcinoma, and grades 2 and 3 immature teratoma of the ovary after removal of all gross tumors.

TECHNICAL APPROACH

Eligible patients include those with histologically confirmed Stage I choriocarcinoma, endodermal sinus tumor, embryonal carcinoma, and grades 2 and 3 immature teratoma. Patients with Stage II and III disease are also eligible if all gross tumor is removed. Serum AFP and beta-HCG levels should be normal.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Since this protocol's review one year ago, there have been no publications reporting data from studies with similar study design in the literature.
The number of subjects enrolled to the study since last APR at WRAMC is _0___ and the total enrolled to date at WRAMC is __2___. The total number enrolled study-wide is _117_, if multi-site study. Grade 4 toxicities include 8 leukopenia, 3 thrombocytopenia, 39 granulocytopenia, 2 GI, 1 dermatologic, and 2 anemia. This study was closed to patient accrual 2/10/92.

Ref: Jul 01 GOG Statistical Report

CONCLUSIONS

This trial has confirmed the effectiveness of BEP in patients with ovarian germ cell tumors who have been initially completely resected. Nearly all patients treated this way will survive free of cancer. Short and long term morbidity is acceptable.

Report Date: 29 August 2000 Work Unit # 4257

DETAIL SUMMARY SHEET

TITLE: GOG 99: A Phase III Randomized Study of Adjunctive Radiation Therapy in Intermediate Risk Endometrial Adenocarcinoma

KEYWORDS: radiation, endometrial, adenocarcinoma

PRINCIPAL INVESTIGATOR: Rose, G. Scott MAJ (P) MC
ASSOCIATES:

DEPARTMENT: Obstetrics & Gynecology
SERVICE: Gynecologic Oncology Group

STATUS: O
INITIAL APPROVAL DATE: 27 October 1987

STUDY OBJECTIVE

1) To determine if patients with intermediate-risk endometrial adenocarcinoma who have no spread of disease to their lymph nodes benefit from postoperative pelvic radiotherapy, and 2) evaluate how the addition of pelvic radiotherapy will alter the site and rate of cancer recurrence in these intermediate-risk patients.

TECHNICAL APPROACH

Patients with primary histologically confirmed grades 2 and 3 endometrial adenocarcinoma are eligible. Patients must have had a total abdominal hysterectomy, bilateral salpingo-oophorectomy, pelvic and para-aortic lymph node sampling, pelvic washings, and found to be surgical Stage I. Patients must have myometrial invasion.

PRIOR AND CURRENT PROGRESS

The GOG has entered 448 patients nationally. WRAMC has entered 9 patients (still living). Grade IV toxicities include 4 GI, 5GI obstruction, 1 cutaneous, and 1 pulmonary. This protocol was closed to patient entry July 3, 1995.

Ref: Jul 00 GOG Statistical Report

CONCLUSIONS

The use of adjuvant RT, in women with intermediate risk endometrial cancer, decreases the risk of recurrences but has an inappreciable effect on overall survival.

Report Date: 26 March 2001 Work Unit # 4262

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: A Multicenter Randomized Trial of Adjuvant Cisplatin/Bleomycin Plus Whole Pelvis Irradiation vs. Cisplatin/Bleomycin Alone in High-Risk Stage IB and IIA Carcinoma of the Cervix

KEYWORDS: carcinoma, cervix

PRINCIPAL INVESTIGATOR: Rose, G. Scott LTC MC
ASSOCIATES:

DEPARTMENT: Obstetrics & Gynecology STATUS: C
SERVICE: Gynecologic Oncology Group INITIAL APPROVAL DATE: 31 May 1988

STUDY OBJECTIVE
A) To evaluate the effect of adjunctive pelvic irradiation added to adjunctive chemotherapy for high-risk Stage IB and IIA cervical cancer as measured by progression-free interval and survival; and b) To compare the relative toxicities of two regimens with respect to serious complications and/or side effects.

TECHNICAL APPROACH
To be eligible, patients must have had radical hysterectomy with pelvic and para-aortic lymphadenectomy for Stage IB or IIA cervical carcinoma. They must have one or more of the following poor prognostic signs: nodal metastasis, parametrial involvement, positive surgical margin, tumor diameter greater than 4 cm, deep cervical invasion, adenocarcinoma, adenosquamous carcinoma, or small-cell histologic type. Patients are randomized to receive postoperative chemotherapy alone or chemotherapy plus pelvic irradiation.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
There have been no publications reporting data from studies with similar study design.
The number of subjects enrolled to the study since last APR at WRAMC is _0__ and the total enrolled to date at WRAMC is _8_. The total number enrolled study-wide is _72_, if multi-site study. No significant toxicity has been reported thus far. Patients on this study continue to be followed clinically. No new subjects have been enrolled since FY 94. Protocol is closed to patient entry. This study can be closed here at WRAMC.

CONCLUSIONS
Both arms showed statistically similar survivals and equal toxicity. Addition of radiation therapy does not improve survival.

Report Date: 24 May 2001 Work Unit # 4266

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: GOG 76A: Master Protocol for Phase II Drug Studies in the Treatment of Advanced or Recurrent Squamous Cell Carcinoma of the Cervix

KEYWORDS: advanced, squamous cell carcinoma, cervix

PRINCIPAL INVESTIGATOR: Maxwell, G. Larry MAJ MC
ASSOCIATES:

DEPARTMENT: Obstetrics & Gynecology STATUS: O
SERVICE: Gynecologic Oncology Group INITIAL APPROVAL DATE: 26 July 1988

STUDY OBJECTIVE
To continue identification of new active drugs in the treatment of advanced or recurrent squamous cell carcinoma of the cervix so that combinations of cytotoxic drugs can be formed which might lead to an improved complete remission rate.

TECHNICAL APPROACH
Patients enrolled in individual protocols under this Master Protocol will have histologically confirmed, advanced, persistent, or recurrent squamous cell carcinoma of the cervix with documented disease progression after local therapy.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
This is a master protocol. Please see individual protocols for further information.

Ref: Jan 01 GOG Statistical Report

CONCLUSIONS
See individual protocols.

Report Date: 13 November 2000 Work Unit # 4274

DETAIL SUMMARY SHEET

TITLE: GOG 104: Intraperitoneal Cisplatinum/Intravenous Cyclophosphamide Vs. Intravenous Cisplatinum/Intravenous Cyclophosphamide in Patients with Nonmeasureable Disease Stage III Ovarian Cancer, Phase III

KEYWORDS: cisplatinum, cyclophosphamide, ovary

PRINCIPAL INVESTIGATOR: Rose, G. Scott LTC MC
ASSOCIATES:

DEPARTMENT: Obstetrics & Gynecology STATUS: O
SERVICE: Gynecologic Oncology Group INITIAL APPROVAL DATE: 31 January 1989

STUDY OBJECTIVE

To carry out a Phase III randomized trial of intermediate dose intraperitoneal cisplatinum plus intravenous cyclophosphamide versus intermediate dose intravenous cisplatinum plus intravenous cyclophosphamide for optimal Stage III ovarian cancer.

TECHNICAL APPROACH

Patients will be randomized to receive on of the two regimens listed above. Eligible patients must have a histologically confirmed pure epithelial ovarian carcinoma. Those with a borderline tumor will be excluded.

PRIOR AND CURRENT PROGRESS

The GOG has entered 649 patients; WRAMC has entered 4 patients (still living). Grade 4 toxicities include 1 abdominal pain, 20 anemia, 5 anorexia, 1 anxiety/depression, 1 clinical hearing loss, 3 creatinine, 1 dehydration, 2 infection, 1 edema, 189 granulocytopenia, 5 hepatic-bilirubin, 1 hypotension, 53 leukopenia, 2 nausea/vomiting, 2 pulmonary, 1 renal cr. Clearance, 1 renal-other, 1 sepsis, 1 stomatitis, 15 thrombocytopenia, and 1 vision. Protocol was closed to patient enrollment effective July 15, 1992.

Ref: Jul 00 GOG Statistical Report

CONCLUSIONS

The ovarian cancer patients with optimally debulked (less than 2cm residual tumor mass) Stage III disease, IP administration of cisplatin is associated with statistically significant prolongation of survival and fewer incidences of clinical hearing loss, tinnitus, granulocytopenia, leukopenia, and thrombocytopenia. The IV administration has fewer incidences of abdominal pain and cramping. The IP administration is recommended for cisplatin treatment of this patient population.

Report Date: 20 March 2001 Work Unit # 4277

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: GOG 108: Ifosfamide and the Uroprotector, Mesna, with or without Cisplatin in Patients with Advanced or Recurrent Mixed Mesodermal Tumors of the Uterus, Phase III

KEYWORDS: ifosfamide, uterine, sarcoma

PRINCIPAL INVESTIGATOR: Maxwell, G. Larry MAJ MC
ASSOCIATES:

DEPARTMENT: Obstetrics & Gynecology STATUS: O
SERVICE: Gynecologic Oncology Group INITIAL APPROVAL DATE: 23 May 1989

STUDY OBJECTIVE

To confirm reported high response rates of advanced or recurrent mixed mesodermal tumors of the uterus to ifosfamide/Mesna. To determine whether the addition of cisplatin to ifosfamide/Mesna improves response rates or survival in patients with these tumors.

TECHNICAL APPROACH

Eligible patients include those with primary, histologically confirmed, heterologous or homologous (carcinosarcoma) mixed mesodermal tumors of the uterus. All patients must have measureable disease. Patients who have received prior chemotherapy are not eligible.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

There have been no additional publications this year that were not reported on the last APR for this study or with similar study design.
The number of subjects enrolled to the study since last APR at WRAMC is _0_ and the total enrolled to date at WRAMC is _3_. The total number enrolled study-wide is _224_, if multi-site study. Walter Reed has 3 patients (2 now deceased) and is still following 1 patient. Within WR, one patient experienced disease progression and died from disease. There was one Grade IV hematologic toxicity, 68 neutropenic episodes, 36 thrombocytopenias, and 4 GI. This protocol was closed to patient entry July 29, 1996.
Ref: Jan 01 GOG Statistical Report

CONCLUSIONS

Combination therapy results in a higher response rate, greater toxicity, and no improvement in survival when compared with ifosfamide alone. To study comparing Ifosfamide versus Ifosfamidel/Taxol is currently ongoing.

Report Date: 13 November 2000

Work Unit # 4281

DETAIL SUMMARY SHEET

TITLE: GOG 8801 A Phase I Evaluation of Multiple Daily Fraction Radiation and Hydroxurea in Patients with Stage IIB, III, and IVA Carcinoma of the Cervix with Negative Para-aortic Nodes

KEYWORDS: radiation, hydroxyurea, cervix

PRINCIPAL INVESTIGATOR: Rose, G. Scott LTC MC
ASSOCIATES:

DEPARTMENT: Obstetrics & Gynecology
SERVICE: Gynecologic Oncology Group

STATUS: O
INITIAL APPROVAL DATE: 30 January 1990

STUDY OBJECTIVE

To determine the toxicity of accelerated hyperfractionated radiation plus hydroxyurea in patients with cancer of the cervix. To determine the optimal tolerated dose of hyperfractionated radiation when combined with hydroxyurea and intracavitary radiation.

TECHNICAL APPROACH

Patients must have primary previously untreated histologically confirmed carcinoma of the cervix; squamous cell carcinoma, adenocarcinoma, and adenosquamous carcinoma are eligible. Patients must have FIGO Stage IIB, IIIA, IIIB, or IV disease with negative para-aortic nodes. Patients must have a para-aortic lymphadenectomy and intraperitoneal exploration with cytologic washings as outlined in the protocol.

PRIOR AND CURRENT PROGRESS

The entire GOG has accrued 39 patients; WRAMC has entered 5 patients (all still living). Last APR 1 patient was reported deceased which was incorrect. There have been 4 Grade 3 GI toxicities, otherwise minimal toxicity. This protocol was closed to patient entry 14 Feb 94. The protocol was terminated 11 Aug 97.

Ref: Jul 00 GOG Statistical Report

CONCLUSIONS

Dose level 3 appears to be intolerable in terms of chronic reactions. A fourth dose level is not planned.

Report Date: 13 November 2000 Work Unit # 4282

DETAIL SUMMARY SHEET

TITLE: GOG 8901: A Phase I Evaluation of Multiple Daily Fraction Radiation and 5FU Plus Cisplatin in Stage IIB, III, IVA Carcinoma of the Cervix with Negative Para-aortic Nodes

KEYWORDS: radiation, 5FU, cisplatin

PRINCIPAL INVESTIGATOR: Rose, G. Scott LTC MC
ASSOCIATES:

DEPARTMENT: Obstetrics & Gynecology STATUS: O
SERVICE: Gynecologic Oncology Group INITIAL APPROVAL DATE: 30 January 1990

STUDY OBJECTIVE

To determine the toxicity of accelerated hyperfractionated radiation plus 5-fluorouracil (5-FU) and cisplatin in patients with cancer of the cervix. To determine the optimal tolerated dose of hyperfractionated radiation when combined with 5-FU, cisplatin, and intracavitary radiation.

TECHNICAL APPROACH

Patients must have primary previously untreated histologically confirmed carcinoma of the cervix. Squamous cell carcinoma, adenocarcinoma, and adenosquamous carcinoma are eligible. Patients must have FIGO Stage IIB, IIIB, or IVA disease with negative para-aortic nodes. Patients must have a para-aortic lymphadenectomy and intraperitoneal exploration with cytologic washings as outlined in the protocol.

PRIOR AND CURRENT PROGRESS

The GOG has entered 34 patients nationally; WRAMC has entered 4 patients (3 still living, 1 now deceased). There were 3 Grade 3-4 toxicities at dose level 3, 1 vault necrosis, and 1 rectovaginal fistual. Dose levels 1 and 2 had no treatment related complications. This protocol was closed to patient entry on November 8, 1993. The protocol was terminated August 11, 1997.

Ref: Jul 00 GOG Statistical Report

CONCLUSIONS

This chemotherapy regimen appears less toxic than hydroxyurea as given on GOG 8801. Dose level 3 appears to be tolerable both in terms of acute and chronic reactions. Data are maturing for acute/chronic reactions.

Report Date: 26 April 2001

Work Unit # 4309

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: GOG 120: A Randomized Comparison of Hydroxyurea vs. Hydroxyurea, 5-FU Infusion and Cisplatin vs. Weekly Cisplatin as Adjunct to Radiation Therapy in Patients with Stages II-B, III, or IV-A Carcinoma of the Cervix and Negative Para-Aortic Nodes

KEYWORDS: cervix, carcinoma, Phase III

PRINCIPAL INVESTIGATOR: Maxwell, G. Larry MAJ MC
ASSOCIATES:

DEPARTMENT: Obstetrics and Gynecology
SERVICE: Gynecologic Oncology

STATUS: O
INITIAL APPROVAL DATE: 30 June 1992

STUDY OBJECTIVE

To determine whether hydroxyurea; hydroxyurea, 5-FU infusion plus bolus cisplatin; or weekly cisplatin is superior as a potentiator of radiation therapy in locally advanced cervical carcinoma.

TECHNICAL APPROACH

Patients with cervical carcinoma (Stages IIB, IIA, IIIB, or IVA) will undergo extraperitoneal staging surgery. Those patients with negative para-aortic nodes will then be randomized to receive radiotherapy plus either: 1) cisplatin; 2) cisplatin, 5FU, and hydroxyurea; or 3) hydroxyurea. Following the completion of therapy, the patients will be followed clinically.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Since this protocol's review a year ago, there have been no publications reporting data from studies with similar study design in the literature.
The number of subjects enrolled to the study since last APR at WRAMC is _0___ and the total enrolled to date at WRAMC is __5_. The total number enrolled study-wide is _575_, if multi-site study. Grade IV toxicities reported are 36 hemotologic, 30 GI, 8 GU, 1 neurologic, 6 cutaneous, 1 fever, 2 hypomagnesemia. Protocol was closed to patient entry April 21, 1997.

Ref: Jan 01 GOG Statistical Report

CONCLUSIONS

Cisplatin based chemotherapy and radiation is more effective than chemotherapy and radiation with hydroxyurea. The weekly cisplatin regimen is less toxic than the three-drug cisplatin containing regimen.

Report Date: 19 June 2001 Work Unit # 4310

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: GOG 136: Acquisition of Human Ovarian and Other Tissue Specimens and Serum to be Used in Studying the Causes, Diagnosis, Prevention and Treatment of Cancer

KEYWORDS: ovarian, tissue, collection

PRINCIPAL INVESTIGATOR: Maxwell, G. Larry MAJ MC
ASSOCIATES:

DEPARTMENT: Obstetrics & Gynecology STATUS: O
SERVICE: Gynecologic Oncology Group INITIAL APPROVAL DATE: 25 August 1992

STUDY OBJECTIVE
To: 1) accomplish the collection of human ovarian tissue specimens and serum within GOG participating institutions; and 2) provide a long-term storage repository for ovarian tumors and serum. The material will be used in studies to better understand the molecular biology of ovarian tumors.

TECHNICAL APPROACH
All patients who have had ovarian tumor tissue or extra-ovarian peritoneal serous carcinoma tissue removed are eligible. All patients who have had ovaries removed because of a family history of ovarian cancer are eligible. The tissue, when removed, is shipped along with serum specimens to the GOG repository facility.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
Since this protocol's review one year ago, there have been no publications reporting data from studies with similar study design in the literature.
The number of subjects enrolled to the study since last APR at WRAMC is _0_ and the total enrolled to date at WRAMC is _82__. The total number enrolled study-wide is _3675_, if multi-site study. No toxicities were reported.

Ref: Jan 01 GOG Statistical Report

CONCLUSIONS
None

Report Date: 26 July 2001 Work Unit # 4311

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: GOG 134: A Phase III Trial of Taxol at Three Dose Levels and G-CSF at Two Dose Levels in Platinum-Resistant Ovarian Carcinoma

KEYWORDS: taxol, ovarian, G-CSF

PRINCIPAL INVESTIGATOR: Maxwell, G. Larry MAJ MC
ASSOCIATES:

DEPARTMENT: Obstetrics and Gynecology STATUS: O
SERVICE: Gynecologic Oncology Group INITIAL APPROVAL DATE: 29 September 1992

STUDY OBJECTIVE

To: 1) determine if taxol at different dose levels affects response rate, progression-free interval, or survival in patients with platinum-resistant ovarian cancer; 2) compare toxicities of the regimens; and 3) compare the efficacy and toxicity of G-CSF in patients receiving high-dose taxol.

TECHNICAL APPROACH

Patients with platinum-resistant ovarian epithelial cancer with clinically measurable disease will be randomized to receive taxol at three different dose levels. Patients at the highest dose level will also receive G-CSF at one of two dose levels. Patients are then followed clinically to assess response.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Since this protocol's last review there have been no new publications reporting data.
The number of subjects enrolled to the study since last APR at WRAMC is __0_ and the total enrolled to date at WRAMC is 6 (5 deceased). The total number enrolled study-wide is 449, if multi-site study. Grade 4 toxicities include 1 pulmonary, 1 renal, and 3 infections. This study was closed to patient accrual 2/6/95.

Ref: Jul 01 GOG Statistical Report

CONCLUSIONS

Prognostic factors associated with survival and PFS include prior platinum resistance measurable disease mucinous or clear cell histology and poor performance score.
Doubling the dose of G-CSF did not reduce the frequency of neutropenic fever following the first course of treatment.

Report Date: 29 August 2000 Work Unit # 4312

DETAIL SUMMARY SHEET

TITLE: GOG 122: Whole Abdominal Radiotherapy vs. Combination Doxorubicin-Cisplatin Chemotherapy in Advanced Endometrial Carcinoma

KEYWORDS: radiation, endometrial, chemotherapy

PRINCIPAL INVESTIGATOR: Rose, G. Scott, MAJ (P) MC
ASSOCIATES:

DEPARTMENT: Obstetrics & Gynecology STATUS: O
SERVICE: Gynecologic Oncology Group INITIAL APPROVAL DATE: 27 October 1992

STUDY OBJECTIVE

1) To assess treatment outcomes (survival and progression-free interval) and failure patterns for advanced Stages III and IV endometrial adenocarcinoma patients using adjuvant, whole, abdominal radiation therapy vs. combination intravenous chemotherapy, and 2) treatment toxicities of either therapy.

TECHNICAL APPROACH

All patients with endometrial carcinoma undergo surgical staging (TAH, BSO, LNS) and in advanced stage disease are randomized to adjuvant whole abdominal radiation (tele-therapy) vs. combination intravenous doxorubicin-cisplatin chemotherapy every 3 weeks for eight courses.

PRIOR AND CURRENT PROGRESS

The GOG has enrolled 422 patients nationally. WRAMC has enrolled 3 patients (still living). Grade IV toxicities included 126 hematologic, 2 GU, 14 GI, 2 hepatic, 1 vascular, 6 cardiac, 2 neurologic, 3 fever, 1 fatigue, 1 cutaneous, and 6 sepsis/infection. This protocol was closed to patient entry February 25, 2000.

Ref: Jul 00 GOG Statistical Report

CONCLUSIONS

Too early.

Report Date: 21 September 2000 Work Unit # 4319

DETAIL SUMMARY SHEET

TITLE: GOG 118: Evaluation of the Predicted Value of Antineoplastic Drug Resistance Determined by In Vitro Assay

KEYWORDS: carcinoma, ovarian, drug

PRINCIPAL INVESTIGATOR: Rose, G. Scott MAJ MC
ASSOCIATES:

DEPARTMENT: Obstetrics and Gynecology STATUS: O
SERVICE: Gynecologic Oncology Group INITIAL APPROVAL DATE: 30 November 1993

STUDY OBJECTIVE
To evaluate the correlation between response to chemotherapy and in vitro drug resistance assays. To correlate lab results with clinical responses, both complete (CR) and partial (PR).

TECHNICAL APPROACH
Patients with Stage III/IV ovarian epithelial carcinoma treated with taxol/CDDP will be eligible for entry into this study.

PRIOR AND CURRENT PROGRESS
The GOG has entered 106 patients nationally. WRAMC has entered 4 patients (2 alive, 2 deceased). No toxicities reported. This study was closed to patient entry 8/5/96 and terminated 10/28/96.

Ref: Jul 00 GOG Statistical Report

CONCLUSIONS
Too early.

Report Date: 21 September 2000

Work Unit # 4320

DETAIL SUMMARY SHEET

TITLE: GOG 140: An Assessment of Age and Other Factors Influencing Protocol vs. Alternative Treatments for Patients with Epithelial Ovarian Cancer Referred to Gynecologic Oncology Group Institutions

KEYWORDS: familial, carcinoma, genetics

PRINCIPAL INVESTIGATOR: Rose, G. Scott MAJ MC
ASSOCIATES:

DEPARTMENT: Obstetrics and Gynecology
SERVICE: Gynecologic Oncology Group

STATUS: O
INITIAL APPROVAL DATE: 30 November 1993

STUDY OBJECTIVE

To assess the frequency at which patients with ovarian cancer enroll in prospective clinical studies. To assess whether age effects enrollment vs. other demographic or clinicopathological factors.

TECHNICAL APPROACH

All patients with primary ovarian carcinoma, including low malignant potential tumors, will fill out a patient questionnaire.

PRIOR AND CURRENT PROGRESS

The GOG has entered 982 patients nationally. WRAMC has entered 24 patients (4 deceased). There were no toxicities. The protocol was closed to patient entry 2/5/96.

Ref: Jul 00 GOG Statistical Report

CONCLUSIONS

Among patients entered on this protocol there is a significant relationship between age at diagnosis and stage of disease at diagnosis. In fact older patients tend to present with more advanced disease than younger patients.

This preliminary analysis suggests that among early stage patients, few are enrolled on GOG studies and this does not vary by age. However, among advanced stage patients entered on this survey study, 36% of younger patients compared to 26% of older patients were enrolled on GOG clinical studies. Further analysis is underway to investigate whether the relationship of age to planned treatment among advanced stage patients can be explained by other coexisting medical conditions related to the aging process.

The validity of this study depends upon the extent to which patients were "captured" for this study at each participating institution. Information is being collected from tumor registries to assess the number of patients missed and the reasons for failing to capture these patients.

Report Date: 26 October 2000 Work Unit #4323

DETAIL SUMMARY SHEET

TITLE: GOG 26LL: A Phase II Trial of Prolonged Oral Etoposide (VP-16) in Patients with Advanced Pelvic Malignancies

KEYWORDS: carcinoma, chemotherapy, pelvic

PRINCIPAL INVESTIGATOR: Rose, G. Scott LTC MC
ASSOCIATES:

DEPARTMENT: Obstetrics and Gynecology STATUS: O
SERVICE: Gynecologic Oncology Group INITIAL APPROVAL DATE: 21 December 1993

STUDY OBJECTIVE
To determine the efficacy of oral etoposide in patients with advanced pelvic malignancies.

TECHNICAL APPROACH
Patients with histologically confirmed recurrent or metastatic gynecologic cancer refractory to standard therapy with measurable disease receive oral VP-16 on days 1-21 monthly. Treatment continues until response or toxicity occurs.

PRIOR AND CURRENT PROGRESS
The GOG has entered 145 patients nationally; WRAMC has entered 6 patients (5 now deceased, 1 still living). Grade 4 toxicities reported include 6 leukopenia, 2 thrombocytopenia, 8 neutropenia, 1 GI, and 2 anemia. Study met accrual goal and is closed to patient entry effective 5 Sept 00.

Ref: Jul 00 GOG Statistical Report

CONCLUSIONS
There is evidence of activity with this regimen in patients with recurrent epithelial ovarian carcinoma. Phase I studies of dose escalating oral Etoposide in combination are being conducted in untreated and previously treated ovarian carcinoma.

Report Date: 31 October 2000

Work Unit #4324

DETAIL SUMMARY SHEET

TITLE: GOG 109: A Randomized Comparison of 5-FU Infusion and Bolus Cisplatin as an Adjunct to Radiation Therapy Alone in Selected Patients with Stages I-A2, I-B, and II-A Carcinoma of the Cervix Following Radical Hysterectomy and Node Dissection Phase III Inter

KEYWORDS: cisplatin, radiation, cervix

PRINCIPAL INVESTIGATOR: Rose, G. Scott LTC MC
ASSOCIATES:

DEPARTMENT: Obstetrics and Gynecology
SERVICE: Gynecologic Oncology Group

STATUS: O
INITIAL APPROVAL DATE: 21 December 1993

STUDY OBJECTIVE

To determine whether the combination of 5-fluorouracil (5FU) and cisplatin used as an adjunct to radiation therapy will improve survival rate or progression-free survival and decrease extra pelvic failure compared to radiation therapy alone in patients with positive parametrial involvement or positive surgical margins following radical hysterectomy and lymph node dissection for Stages I-A2, IB, and IIA carcinoma of the cervix.

TECHNICAL APPROACH

Patients with Stage IA2, IB, and IIA invasive squamous, adeno or adenosquamous carcinoma of the cervix, status post radical hysterectomy with histologically-positive lymph nodes, parametria, or surgical margins will be enrolled. Patients will receive standard whole pelvic radiation with or without chemosensitization.

PRIOR AND CURRENT PROGRESS

The GOG has entered 226 patients nationally; WRAMC has entered 1 patient (still living). Grade 4 toxicities are 1 anemia, 1 cardiac, 5 diarrhea, 2 dyspenea, 12 granulocytopenia, 1 infection, 3 leukopenia, 1 skin ulceration (non-local), 2 small bowel obstruction, 1 stomatitis, and 3 vomiting. The protocol was closed to patient entry effective 12/15/96.

Ref: Jul 00 GOG Statistical Report

CONCLUSIONS

It was concluded that the addition of chemotherapy to radiation therapy significantly improves progression-free and overall survival for high-risk, stages I-A2 through II-A patients who undergo radical hysterectomy and pelvic lymphadenectomy for carcinoma of the cervix.

Report Date: 31 October 2000 Work Unit #4325

DETAIL SUMMARY SHEET

TITLE: GOG 123: A Randomized Comparison of Radiation Therapy and Adjuvant Hysterectomy vs. Radiation Therapy and Weekly Cisplatin and Adjuvant Hysterectomy in Patients with Bulky Stage IB Carcinoma of the Cervix (Phase III)

KEYWORDS: carcinoma, cervix, radiation

PRINCIPAL INVESTIGATOR: Rose, G. Scott LTC MC
ASSOCIATES:

DEPARTMENT: Obstetrics and Gynecology STATUS: O
SERVICE: Gynecologic Oncology Group INITIAL APPROVAL DATE: 21December 1993

STUDY OBJECTIVE
To determine if weekly cisplatin infusion improves local-regional control and survival when added to radiation therapy and extrafascial hysterectomy, also, to determine the toxicities of these two treatments.

TECHNICAL APPROACH
Patients with bulky IB and barrel-shaped cervical invasive squamous, adeno, or adenosquamous carcinomas who have surgically negative pelvic/para-aortic nodes receive either whole pelvic radiation with or without cisplatin chemosensitization followed by extrafascial hysterectomy.

PRIOR AND CURRENT PROGRESS
The GOG has entered 374 patients; WRAMC has entered 2 patients (still living). Grade IV toxicities are 6 hematologic, 14 GI, 3 GU, 1 cardiovascular, and 1 cutaneous. This study was closed 7 Apr 97 to patient accrual.

Ref: Jul 00 GOG Statistical Report

CONCLUSIONS
The addition of weekly cisplatin during irradiation was associated with a reduction in risk of recurrence of 49% and a risk of death 46%. Both statistics were highly significant.

Report Date: 14 November 2000

Work Unit # 4327

DETAIL SUMMARY SHEET

TITLE: Acquisition of Human Uterine Tissue Specimens and Peripheral Blood to be used in Studying the Causes, Diagnosis, Prevention, and Treatment of Cancer

KEYWORDS: tissue, uterus, blood

PRINCIPAL INVESTIGATOR: Rose, G. Scott LTC MC
ASSOCIATES:

DEPARTMENT: Obstetrics & Gynecology
SERVICE: Gynecologic Oncology Group

STATUS: C
INITIAL APPROVAL DATE: 25 January 1994

STUDY OBJECTIVE

To collect tissue and blood that will be stored in anticipation of developing a new and more effective therapy for patients with uterine cancer.

TECHNICAL APPROACH

This study involves taking uterine (endometrial) tissue obtained during routine abdominal surgery and submitting that tissue to the Gynecologic Oncology Tissue Bank at the National Cancer Institute. Additionally, 50 cc of blood will be collected simultaneously. These specimens will be stored and made available for researchers at the National Cancer Institute.

PRIOR AND CURRENT PROGRESS

Walter Reed has enrolled 4 patients in this tissue procurement protocol. Effective 6 Jun 00 this protocol was closed to patient enrollment. Per Dr. G. Scott Rose this protocol can be closed here at WR.

CONCLUSIONS

Too early.

Report Date: 14 November 2000 Work Unit # 4328

DETAIL SUMMARY SHEET

TITLE: Acquisition of Human Uterine Cervical Tissue Specimens and Peripheral Blood to be used in Studying the Causes, Diagnosis, Prevention and Treatment of Cancer

KEYWORDS: cervix, carcinoma, tissue

PRINCIPAL INVESTIGATOR: Rose, G. Scott LTC MC
ASSOCIATES:

DEPARTMENT: Obstetrics & Gynecology STATUS: C
SERVICE: Gynecologic Oncology Group INITIAL APPROVAL DATE: 25 January 1994

STUDY OBJECTIVE
To collect tissue and blood that will be stored in anticipation of developing a new and more effective therapy for patients with cervical cancer.

TECHNICAL APPROACH
This study involves collecting uterine cervical tissue obtained during routine abdominal surgery and submitting that tissue to the Gynecologic Oncology Tissue Bank at the National Cancer Institute. Additionally, 50 cc of blood will be collected simultaneously. These specimens will be stored and made available for researchers at the National Cancer Institute.

PRIOR AND CURRENT PROGRESS
Walter Reed has entered one patient on this tissue protocol with no toxicity. Effective 6 Jun 00 this protocol was closed to patient enrollment. Per Dr. G. Scott Rose this protocol can be closed here at WR.

CONCLUSIONS
Too early.

Report Date: 14 November 2000

Work Unit # 4329

DETAIL SUMMARY SHEET

TITLE: GOG 149: A Randomized Study of Cisplatin Plus Ifosfamide and Mesna Versus Cisplatin, Bleomycin, Ifosfamide, and Mesna in Stage IV-B, Recurrent or Persistent Squamous Cell Carcinoma of the Cervix

KEYWORDS: cervix, carcinoma, chemotherapy

PRINCIPAL INVESTIGATOR: Rose, G. Scott LTC MC
ASSOCIATES:

DEPARTMENT: Obstetrics & Gynecology
SERVICE: Gynecologic Oncology Group

STATUS: O
INITIAL APPROVAL DATE: 25 January 1994

STUDY OBJECTIVE

To determine if bleomycin plus ifosfamide/mesna plus cisplatin (BIP) improves response rate, response duration, and survival in advanced squamous cervical cancer compared to treatment with cisplatin plus ifosfamide/mesna, also, to compare toxicities of these regimens.

TECHNICAL APPROACH

Patients with histologically proven Stage IVB, recurrent or persistent squamous cell cervical carcinoma with measurable disease are treated with either chemotherapy regimen.

PRIOR AND CURRENT PROGRESS

The entire GOG has entered 303 patients; WRAMC has entered two patients (1 still living, 1 now deceased). Grade 4 toxicities include 136 leukopenia, 22 thrombocytopenia, 167 neutropenia, 7 anemia, 18 nausea/vomiting, 6 GI, 2 renal, 1 cardiac, 1 peripheral neurotoxicity, 3 central neurotoxicity, 2 hematuria, 1 pulmonary, 1 hepatic, 4 sepsis, 1 allergy reaction, and 1 infection. This protocol was closed to patient entry 28 Apr 97.

Ref: Jul 00 GOG Statistical Report

CONCLUSIONS

Response rate, progression free survival and survival were essentially identical between the two arms

Report Date: 14 November 2000

Work Unit # 4333

DETAIL SUMMARY SHEET

TITLE: GOG #150 A Phase III Randomized Study of Whole Abdominal Radiotherapy (WAR) versus Combination Ifosfamide-Mensa with Cisplatin in Optimally Debulked Stage I, II, III or IV Carcinosarcoma (CS) of the Uterus

KEYWORDS: uterine, sarcoma, therapy

PRINCIPAL INVESTIGATOR: Rose, G. Scott LTC MC
ASSOCIATES:

DEPARTMENT: Obstetrics & Gynecology
SERVICE: Gynecologic Oncology Group

STATUS: O
INITIAL APPROVAL DATE: 25 January 1994

STUDY OBJECTIVE

To compare outcomes and failure patterns in patients with Stage I-IV uterine carcinosarcoma treated with whole abdominal radiotherapy vs. combination chemotherapy with cisplatin/ifosfamide/mesna, also, to compare toxicities of two regimens.

TECHNICAL APPROACH

All eligible patients will be enrolled who have had surgical Stage I-IV disease, s/o TAH, BSO, and maximal resection of macroscopic abdomino-pelvic lesions (including lymph nodes) to greater than 1 cm disease. All patients less than 8 weeks postop will be randomized to either program.

PRIOR AND CURRENT PROGRESS

The entire GOG has entered 130 patients; WRAMC has entered two patients (1 now deceased). Grade 4 toxicities are 1 anemia, 5 GI, 1 hepatic, 2 cardiovascular and 2 hepatic.

Ref: Jul 00 GOG Statistical Report

CONCLUSIONS

Too early.

Report Date: 29 January 2001 Work Unit #4337

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: GOG 128-B: Evaluation of Paclitaxel (TAXOL) in Persistent or Recurrent Non-Squamous Cell Carcinoma of the Cervix and Vagina

KEYWORDS: cervix, carcinoma, chemotherapy

PRINCIPAL INVESTIGATOR: Rose, G. Scott LTC MC
ASSOCIATES:

DEPARTMENT: Obstetrics & Gynecology STATUS: C
SERVICE: Gynecologic Oncology Group INITIAL APPROVAL DATE: 29 March 1994

STUDY OBJECTIVE
To: 1) study the efficacy of Paclitaxel (taxol) in patients with persistent or recurrent nonsquamous-cell carcinoma of the cervix and vagina; and 2) evaluate the toxicity of this therapy.

TECHNICAL APPROACH
All patients with persistent or recurrent non squamous-cell carcinoma of the cervix or vagina, and who failed local therapy and have measurable disease, will be asked to enroll. Patients will receive Paclitaxel (taxol) intravenously over 24 hours every 3 weeks until disease is resolved or progresses, or drug toxicity is experienced.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
The number of subjects enrolled to the study since last APR at WRAMC is _0___ and the total enrolled to date at WRAMC is __3. The total number enrolled study-wide is __54__, if multi-site study. Grade IV toxicities include 28 neutropenia, and 1 GI. This protocol was closed to patient entry 12/13/94 and reactivated 5/1/95 for the very rare DES associated clear cell carcinomas. Now the protocol was closed to patient entry 5/8/00. This protocol can be closed here at WRAMC because all patients enrolled are now deceased.
As the study is closed (5/8/00) no amendments or modifications to this study will be performed because of the recent literature named on this report.

Ref: Jan 01 GOG Statistical Report

CONCLUSIONS
Taxol has demonstrated a response rate in nonsquamous cancer of the cervix in patients who have received prior chemotherapy, which may justify further exploration of this agent in various populations with this type of cancer.

Report Date: 23 March 2001 Work Unit # 4339

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: GOG 152: A Phase II Randomized Study of Cisplatin (NSC #119875) and TAXOL (Paclitaxel) (NSC #12973) with Interval Secondary Cytoreduction Versus Cisplatin and Paclitaxel in Patients with Suboptimal Stage III & IV Epithelial Ovarian Carcinoma

KEYWORDS: ovary, cancer, chemotherapy

PRINCIPAL INVESTIGATOR: Maxwell, G. Larry MAJ MC.
ASSOCIATES:

DEPARTMENT: Obstetrics & Gynecology STATUS: O
SERVICE: Gynecologic Oncology Group INITIAL APPROVAL DATE: 31 May 1994

STUDY OBJECTIVE
To determine if secondary cytoreduction contributes to progression-free interval and survival in patients with suboptimally debulked Stage III and IV epithelial ovarian cancer, also, to determine the morbidity of the cytoreduction surgery.

TECHNICAL APPROACH
Suboptimal debulked Stage III and IV ovarian epithelial cancer patients receive three courses of taxol/cisplatinum intravenously. Patients who respond are randomized to an interim cytoreduction followed by three additional courses of taxol/cisplatinum versus no surgery but three courses of taxol/cisplatinum.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
Since this protocol's review one year ago there have been no publications reporting data from studies with similar study design in the literature.
The number of subjects enrolled to the study since last APR at WRAMC is _0_ and the total enrolled to date at WRAMC is _7_. The total number enrolled study-wide is _542_, if multi-site study. WR has enrolled 7 patients (4 now deceased, 3 still following). Grade IV toxicities include 21 leukopenia, 279 granulocytopenia, 1 thrombocytopenia, 21 GI, 2 pulmonary, 3 cardiac, 1 neurologic, 1 infection, and 3 metabolic. This study is closed to patient accrual effective January 29, 2001.
Ref: Jan 01 GOG Statistical Report

CONCLUSIONS
Too early.

Report Date: 24 May 2001 Work Unit # 4344

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: Acquisition of Human Ovarian Tissue Specimens and Peripheral Blood to be Used in Studying the Causes, Diagnosis, Prevention, and Treatment of Cancer

KEYWORDS: ovary, carcinoma, diagnosis

PRINCIPAL INVESTIGATOR: Rose, G. Scott LTC MC
ASSOCIATES:

DEPARTMENT: Obstetrics and Gynecology STATUS: C
SERVICE: INITIAL APPROVAL DATE: 26 July 1994

STUDY OBJECTIVE
To obtain malignant and non-malignant ovarian tissue. These tissues are stored at the Cooperative Human Tissue Network and are available for approved research on the cause, diagnosis, prevention, and treatment of ovarian cancer.

TECHNICAL APPROACH
Eligible patients must have tissue removed.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
Since this protocol's review one year ago, there have been no publications reporting data from studies with similar design in literature.
This is a tissue specimen protocol. WRAMC has 22 patients with no new patients enrolled since last reported. Effective 6 Jun 00 this protocol was closed to patient enrollment. Per Dr. Rose this protocol can be closed here at Walter Reed. No toxicities have been reported.

CONCLUSIONS
Too early.

Report Date: 29 August 2000 Work Unit # 4349

DETAIL SUMMARY SHEET

TITLE: GOG 145: A Randomized Study of Surgery vs. Surgery plus Vulvar Radiation in the Management of Poor Prognosis Primary Vulvar Cancer, and of Radiation vs. Radiation and Chemotherapy for Positive Inguinal Nodes

KEYWORDS: vulva, radiation, chemotherapy

PRINCIPAL INVESTIGATOR: Rose, G. Scott MAJ (P) MC
ASSOCIATES:

DEPARTMENT: Obstetrics and Gynecology STATUS: C
SERVICE: Gynecologic Oncology Group INITIAL APPROVAL DATE: 25 October 1994

STUDY OBJECTIVE
To assess the value of adding chemotherapy to radiation therapy in women having node-positive vulvar carcinoma.

TECHNICAL APPROACH
Patients with surgically staged squamous-cell carcinoma of the vulva are to be stratified into high and low-risk groups based on lesion size and nodal metastases. High-risk patients will be randomized to radiation vs. radiation plus chemotherapy.

PRIOR AND CURRENT PROGRESS
The GOG enrolled 18 patients nationally. WRAMC enrolled 1 patient (still living). No Grade IV toxicities reported. This protocol was closed to patient entry August 11, 1997. This protocol was terminated October 27, 1997.

Ref: Jul 00 GOG Statistical Report

CONCLUSIONS
None reported

Report Date: 24 August 2000 Work Unit #4356

DETAIL SUMMARY SHEET

TITLE: The Role of the p53 and RAS Oncogenes in the Development of Female Genital Tract Malignancy

KEYWORDS: oncogene, gynecologic, cancer

PRINCIPAL INVESTIGATOR: Rose, G. Scott MAJ(P) MC
ASSOCIATES:

DEPARTMENT: Obstetrics & Gynecology STATUS: C
SERVICE: Gynecologic Oncology Group INITIAL APPROVAL DATE: 06 December 1994

STUDY OBJECTIVE
To describe the oncogene genotype of gynecologic malignancies.

TECHNICAL APPROACH
Archived paraffin-embedded tissue blocks are temporarily borrowed, section made, and DNA analysis performed using molecular biologic techniques.

PRIOR AND CURRENT PROGRESS
To date 350 tissue blocks have been examined. Metastatic sites from endometrial, epithelial ovarian and LMP tumors are currently being analyzed. There are no toxicities to report. This protocol can be closed here at Walter Reed.

CONCLUSIONS
Too early.

Report Date: 14 November 2000

Work Unit # 4360

DETAIL SUMMARY SHEET

TITLE: Acquisition of Human Tissue Samples from the Lower Genital Tract for Assessment of Tumor Markers in Ovarian Cancer

KEYWORDS: ovary, cancer, diagnosis

PRINCIPAL INVESTIGATOR: Rose, G. Scott LTC MC
ASSOCIATES:

DEPARTMENT: Obstetrics & Gynecology
SERVICE: Gynecologic Oncology Service

STATUS: C
INITIAL APPROVAL DATE: 31 January 1995

STUDY OBJECTIVE

To ascertain if molecular markers of ovarian cancer are present in the lower genital tract.

TECHNICAL APPROACH

Patients with clinically apparent ovarian cancer are asked to allow Pap smear and endometrial biopsy immediately prior to surgery. These tissue samples are probed for molecular markers at malignancy.

PRIOR AND CURRENT PROGRESS

Seven patients have been entered on this protocol at WRAMC. There have been no adverse outcomes from obtaining this tissue. Effective 6 Jun 00 this protocol has been closed to enrollment. Per Dr. G. Scott Rose this protocol can be closed here at WRAMC.

CONCLUSIONS

Too early.

Report Date: 31 January 2001 Work Unit #4365

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: GOG 157: A Randomized Phase II Trial of Carboplatin (AUC 7.5) and Paclitaxel 175 mg/m2 q 21 Days X Three Courses vs. the Same Regimen X Six Courses, in Patients with Selected Stage IC and II (A,B,C) and Selected IA and IB Ovarian Cancer

KEYWORDS:

PRINCIPAL INVESTIGATOR: Rose, G. Scott LTC MC
ASSOCIATES:

DEPARTMENT: Obstetrics & Gynecology STATUS: O
SERVICE: Gynecologic Oncology Group INITIAL APPROVAL DATE: 28 March 1995

STUDY OBJECTIVE
To evaluate any chemotherapy schedule dependence in the treatment of early-stage ovarian cancer.

TECHNICAL APPROACH
This is a Phase III protocol studying the difference between three vs. six cycles of taxol and carboplatin in patients having early-stage ovarian cancer.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
The number of subjects enrolled to the study since last APR at WRAMC is _0___ and the total enrolled to date at WRAMC is __8. The total number enrolled study-wide is __457__, if multi-site study. Grade IV toxicities include 9 leukopenia, 192 granulocytopenia, 41 thrombocytopenia, 1 anemia, 9 GI, 1 infection, and 3 allergy. This study was closed to patient entry effective 5/28/98.
Since this protocol's review one year ago there have been no publications reporting data from studies with similar study design in the literature. The objectives of this investigation have not been fulfilled by prior studies.

Ref: Jan 01 GOG Statistical Report

CONCLUSIONS
Too early.

Report Date: 26 February 2001

Work Unit #4366

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: GOG 9404: p53 Mutation and c-erB-2 Expression in Advanced Stage Epithelial Ovarian Carcinoma and Correlation with Prognostic Factors and Treatment Outcomes

KEYWORDS: ovary, p53, c-erB-2

PRINCIPAL INVESTIGATOR: Maxwell, G. Larry MAJ MC
ASSOCIATES:

DEPARTMENT: Obstetrics & Gynecology
SERVICE: Gynecologic Oncology Group

STATUS: O
INITIAL APPROVAL DATE: 18 April 1995

STUDY OBJECTIVE
To determine the incidence of p53 and c-erB-2 mutations in advanced epithelial ovarian carcinoma.

TECHNICAL APPROACH
Molecular analysis is performed on archived tissue blocks from patients previously enrolled on GOG 111. DNA is extracted from slices of these blocks and probed for oncogene mutations.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 4. The total number enrolled study-wide is 145. This protocol was closed to patient enrollment effective 5/18/98.
Since this protocol's review one year ago, there has been one abstract, but for the most part analysis is still in progress.

Ref: Jan 01 GOG Statistical Report

CONCLUSIONS
Analysis in progress.

Report Date: 26 February 2001 Work Unit #4368

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: GOG 156 Phase III Randomized Trial of Pelvic Radiation Versus Doxorubicin Plus Cisplatin in Stage IB, Stage IC, IIA and IIB Endometrial Carcinoma

KEYWORDS: endometrial, radiation, chemotherapy

PRINCIPAL INVESTIGATOR: Maxwell, G. Larry MAJ MC
ASSOCIATES:

DEPARTMENT: Obstetrics & Gynecology
SERVICE: Gynecologic Oncology Group

STATUS: C
INITIAL APPROVAL DATE: 25 April 1995

STUDY OBJECTIVE

To compare the recurrence, incidence, progression-free survival, and overall survival rates in women with high-risk endometrial carcinomas confined to the uterus who receive postoperative adjuvant therapy with either pelvic irradiation or systemic chemotherapy consisting of doxorubicin and cisplatin.

TECHNICAL APPROACH

This is a Phase III trial comparing adjuvant pelvic radiation therapy to combination chemotherapy. Eligible patients are those having risk factors for recurrent disease as determined by surgical staging and complete pathologic review.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 2. The total number enrolled study-wide is 64. Grade IV toxicities are 8 neutropenia, and 1 GI. This protocol was closed to patient entry effective 11/3/97. This protocol was terminated effective 11/8/99.

Since this protocol's review one year ago, there have been no publications reporting data from studies with similar study design in the literature. The objectives of this investigation have not been fulfilled by prior studies.

Ref: Jan 01 GOG Statistical Report

CONCLUSIONS

Too early.

Report Date: 20 June 2001

Work Unit # 4370

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: GOG 158: A Phase III Randomized Study of Cisplatin and Paclitaxel (24-Hour Infusion) vs. Carboplatin and Paclitaxel (3-Hour Infusion) in Optimal Stage III Epithelial Ovarian Carcinoma

KEYWORDS: cisplatin, paclitaxel, ovarian

PRINCIPAL INVESTIGATOR: Maxwell, G. Larry MAJ
ASSOCIATES:

DEPARTMENT: Obstetrics & Gynecology
SERVICE: Gynecologic Oncology Group

STATUS: O
INITIAL APPROVAL DATE: 29 August 1995

STUDY OBJECTIVE

To compare recurrence-free interval and survival in patients with less than or equal to 1 cm residual Stage III epithelial ovarian cancer receiving cisplatin and paclitaxel administered by a 24-hour infusion vs. carboplatin plus paclitaxel administered by a 3-hour infusion.

TECHNICAL APPROACH

This is a Phase III study. Patients must have histologic diagnosis of epithelial ovarian cancer Stage III with less than or equal to 1 cm residual disease. All patients must have appropriate surgery for ovarian carcinoma.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Since this protocol's review one year ago, there has been one additional abstract awaiting first draft of manuscript. The objectives of this investigation have not been fulfilled by prior studies.
The number of subjects enrolled to the study since last APR at WRAMC is _0_ and the total enrolled to date at WRAMC is 3 (1 now deceased). The total number enrolled study-wide is _850_, if multi-site study. Grade 4 toxicities include 72 leukopenia, 89 thrombocytopenia, 596 other hematologic, 54 GI, 1 GU, 2 pulmonary, 6 cardiovascular, 2 neurologic, 3 fever, 9 allergic, 2 fatigue, 8 infection, 10 metabolic, 2 pain, 1 hepatic, and 1 lymphatic. This protocol was closed to patient accrual January 26, 1998.

Ref: Jan 01 GOG Statistical Report

CONCLUSIONS

Too early.

Report Date: 31 October 2000 Work Unit #4372

DETAIL SUMMARY SHEET

TITLE: GOG #LAPI - Orientation and Evaluation Study in Performing in GOG Standardized Procedure for Laparoscopic FIGO Staging in Adenocarcinoma of the Endometrium

KEYWORDS: endometrium, cancer, laparoscopy

PRINCIPAL INVESTIGATOR: Rose, G. Scott LTC MC
ASSOCIATES: Gynecologic Oncology Group

DEPARTMENT: Obstetrics and Gynecology STATUS: O
SERVICE: Gynecologic Oncology Group INITIAL APPROVAL DATE: 19 December 1995

STUDY OBJECTIVE
To determine the feasibility of laparoscopic surgery in managing patients with clinical Stage I endometrial cancer.

TECHNICAL APPROACH
Laparoscopic-assisted transvaginal hysterectomy with pelvic and para-aortic lymph node sampling. This procedure is videotaped to document safety and adequacy of the surgery.

PRIOR AND CURRENT PROGRESS
The GOG has entered 62 patients; WRAMC entered 4 patients (still living). No grade 4 toxicities have been reported. Protocol was closed to patient entry 1/26/98.

Ref: Jul 00 GOG Statistical Report

CONCLUSIONS
Too early.

Report Date: 23 March 2001 Work Unit # 4378

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: GOG 162: A Phase III Randomized Trial of Cisplatin (NSC #119875) with Paclitaxel (NSC #125973) Administered by Either 24-Hour Infusion or 96-Hour Infusion in Patients with Selected Stage III and Stage IV Epithelial Ovarian Cancer

KEYWORDS: ovary, neoplasm, taxol

PRINCIPAL INVESTIGATOR: Maxwell, G. Larry MAJ MC
ASSOCIATES:

DEPARTMENT: Obstetrics & Gynecology STATUS: O
SERVICE: Gynecologic Oncology Group INITIAL APPROVAL DATE: 28 May 1996

STUDY OBJECTIVE
To compare progression-free survival, overall survival and frequency of response of 24-hour vs. 96-hour paclitaxel (Taxol) infusions, each combined with cisplatin, in the treatments of selected stage III and stage IV epithelial ovarian cancer. To determine the incidence and severity of adverse events, including catheter complications and chemotherapy toxicity, for 96-hour infusions of paclitaxel. To examine the relationship between plasma paclitaxel concentrations and measures of drug toxicity and response in both 24-hour and 96- hour infusion schedules.

TECHNICAL APPROACH
This is a Phase III trial randomizing between 24-hour and 96-hour taxol infusions in patients with advanced ovarian carcinoma.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
Since this protocol's review one year ago, it is still too early for any publications reporting any data. The number of subjects enrolled to the study since last APR at WRAMC is _1_ and the total enrolled to date at WRAMC is _7_. The total number enrolled study-wide is _293_, if multi-site study. WRAMC has enrolled 7 patients (5 now deceased, 2 still following). Grade IV toxicities include 49 leukopenia, 10 thrombocytopenia, 185 granulocytopenia, 1 anemia, 30 GI, 1 GU, 1 renal, 1 hepatic, 4 pulmonary, 5 cardiac, 10 infection, 1 pain, 2 central neurologic, 2 allergy, and 8 metabolic. WRAMC has reported 1 patient with adverse reaction. Patient admitted for anticoagulation. This study was closed to patient entry August 2, 2000.
Ref: Jan 01 GOG Statistical Report

CONCLUSIONS
Too early.

Report Date: 24 May 2001 Work Unit # 4380

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: GOG #LAP2: A Phase III Randomized Clinical Trial of Laparoscopic Pelvic and Para-Aortic Node Sampling with Vaginal Hysterectomy and BSO vs. Open Laparotomy with Pelvic and Para-Aortic Node Sampling and Abdominal Hysterectomy and BSO in Endometrial Adenocarcinoma, Clinical Stages I, IIA, Grades I, II, and III

KEYWORDS: laparoscopy, lymphadenectomy, endometrium

PRINCIPAL INVESTIGATOR: Maxwell, G. Larry MAJ MC
ASSOCIATES:

DEPARTMENT: Obstetrics & Gynecology STATUS: O
SERVICE: Gynecologic Oncology Group INITIAL APPROVAL DATE: 30 July 1996

STUDY OBJECTIVE
To measure surgical outcomes in patients with early-stage endometrial cancer to open laparotomy vs. laparoscopic procedures.

TECHNICAL APPROACH
This is a Phase III study.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
Since this protocol's review one year ago, there have been no publications reporting data from studies with similar study design in the literature. The objectives of this investigation have not been fulfilled by prior studies.
The number of subjects enrolled to the study since last APR at WRAMC is _8__ and the total enrolled to date at WRAMC is __13__. The total number enrolled study-wide is _709__, if multi-site study. Grade 4 toxicities include 1 urinary tract infection, 2 fever, 1 pelvic cellulitis, 2 abscess, 6 pulmonary embolus, 1 bowel obstruction, 2 ileus, 2 pneumonia, and 1 bowel fistula.
Ref: Jan 01 GOG Statistical Report

CONCLUSIONS
Too early.

Report Date: 31 October 2000 Work Unit #4382

DETAIL SUMMARY SHEET

TITLE: GOG #9302 – Laparoscopic Staging in Patients with Incompletely Staged Cancer of the Ovary, Primary Fallopian Tube Carcinoma and Primary Peritoneal Carcinoma

KEYWORDS:

PRINCIPAL INVESTIGATOR: Rose, G. Scott LTC MC
ASSOCIATES: Gynecologic Oncology Group

DEPARTMENT: Obstetrics & Gynecology
SERVICE: Gynecologic Oncology Group

STATUS: O
INITIAL APPROVAL DATE: 17 December 1996

STUDY OBJECTIVE
To determine the feasibility of performing laparoscopic staging in those patients incompletely staged by laparotomy. To evaluate the adverse effects related to laparoscopic staging.

TECHNICAL APPROACH
Laparoscopy will replace a second laparotomy in those patients incompletely staged with ovarian, fallopian tube, or peritoneal cancers.

PRIOR AND CURRENT PROGRESS
The GOG has entered 70 patients; WRAMC has entered 7 patients (1 this year), with one disqualified. No Grade 4 toxicities. Study met its accrual goal; and closed to patient entry effective August 28, 2000.

Ref: Jul 00 GOG Statistical Report

CONCLUSIONS
Too early.

Report Date: 15 November 2000 Work Unit # 4384

DETAIL SUMMARY SHEET

TITLE: GOG 163: A Randomized Study of Doxorubicin Plus Cisplatin vs. Doxorubicin Plus 24-Hr. Paclitaxel Plus C-CSF in Patients with Primary Stage III & IV or Recurrent Endometrial Carcinoma

KEYWORDS:

PRINCIPAL INVESTIGATOR: Rose, G. Scott LTC MC
ASSOCIATES:

DEPARTMENT: Obstetrics & Gynecology STATUS: C
SERVICE: Gynecologic Oncology Group INITIAL APPROVAL DATE: 28 January 1997

STUDY OBJECTIVE
Does a 24-hour infusion of taxol with doxorubicin improve survival compared to doxorubicin cisplatin in advanced endometrial cancer?

TECHNICAL APPROACH
This is a randomized phase III protocol.

PRIOR AND CURRENT PROGRESS
The entire GOG has enrolled 328 patients; WRAMC has enrolled 2 patients (both now deceased). Grade 4 toxicities are 77 leukopenia, 4 thrombocytopenia, 161 granulocytopenia, 3 anemia, 1 stomatitis, 21 GI, 2 GU/renal, 2 neurologic, 3 infection, 4 metabolic, 2 fever, 2 cardiac, and 1 AML. This protocol was closed to patient entry 11/30/98. This protocol can be closed here at WR.

Ref: Jul 00 GOG Statistical Report

CONCLUSIONS
There was no significant difference in response rate or survival between the two arms of Doxorubicin plus Cisplatin vs Doxorubicin plus 24-Hour Paclitaxel plus G-CSF.

Report Date: 26 February 2001 Work Unit #4389

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: GOG #164 Randomized, Controlled Trial of Salvage TX w/Paclitaxel & Carboplatin vs. Salvage TX w/Stem Cell Supported High-Dose Carboplatin, Mitoxantrone & Cyclophosphamide in Patients w/Persistent Low Volume Ovarian CA

KEYWORDS: ovarian, chemotherapy, bone marrow

PRINCIPAL INVESTIGATOR: Maxwell, G. Larry MAJ MC
ASSOCIATES:

DEPARTMENT: Obstetrics & Gynecology STATUS: O
SERVICE: Gynecologic Oncology Group INITIAL APPROVAL DATE: 24 April 1997

STUDY OBJECTIVE
1) To compare outcomes of salvage therapy with either standard dose chemo or bone marrow reconstitution following high dose chemo in patients with drug sensitive, low volume persistent ovarian cancer after standard therapy; 2) to compare the toxicities of these two salvage regimens; 3) to compare selected health related dimensions of quality of life in these two patient populations.

TECHNICAL APPROACH
This is a phase III trial design of the above. Parameters to be measured include overall survival, progressive free survival, toxicities, and selected quality of life issues.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 1. The total number enrolled study-wide is 24, if multi-site study. No Grade IV toxicities have been reported to date. This study was closed to patient entry 5/10/99. This protocol was terminated effective 2/7/00 due to insufficient accrual rate.
Since this protocol's review one year ago, there have been no publications reporting data from studies with similar study design in the literature. The objectives of this investigation have not been fulfilled by prior studies.

Ref: Jan 01 GOG Statistical Report

CONCLUSIONS
Study closed due to insufficient accrual rate.

Report Date: 26 July 2001 Work Unit # 4400

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: GOG 137 - A Randomized Double-Blinded Trial of Estrogen Replacement Therapy Versus Placebo in Women with Stage I or II Endometrial Adenocarcinoma.

KEYWORDS:

PRINCIPAL INVESTIGATOR: Maxwell, G. Larry MAJ MC
ASSOCIATES:

DEPARTMENT: Obstetrics and Gynecology STATUS: O
SERVICE: Gynecologic Oncology Group INITIAL APPROVAL DATE: 30 September 1997

STUDY OBJECTIVE
To determine the effect of estrogen replacement therapy on recurrence free and overall survival in women with a history of stage I and II endometrial adenocarcinoma.

TECHNICAL APPROACH
Patients are randomized to either receive ERT for 3 years, or a placebo for 3 years. Both groups are followed for 5 years.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
Since this protocol's review one year ago, there have been no publications reporting data from studies with similar study design in the literature. The objectives of this investigation have not been fulfilled by prior studies.
The number of subjects enrolled to the study since last APR at WRAMC is _2__ and the total enrolled to date at WRAMC is _9__. The total number enrolled study-wide is _946___, if multi-site study. No toxicities reported.

Ref: Jul 01 GOG Statistical Report

CONCLUSIONS
Too early.

Report Date: 31 October 2000 Work Unit #4401-98

DETAIL SUMMARY SHEET

TITLE: GOG 169 - A Randomized Phase III Study of Cisplatin vs. Cisplatin Plus Paclitaxel in Stage IVB, Recurrent or Persistent Squamous Cell Carcinoma of the Cervix

KEYWORDS:

PRINCIPAL INVESTIGATOR: Rose, G. Scott LTC MC
ASSOCIATES:

DEPARTMENT: Obstetrics and Gynecology STATUS: C
SERVICE: Gynecologic Oncology Group INITIAL APPROVAL DATE: 16 December 1997

STUDY OBJECTIVE
To determine if paclitaxel plus cisplatin improves response rate and duration in patients with advanced squamous cell cancer of the cervix compared to single agent cisplatin therapy. To determine if this combination improves progression-free interval and survival over single agent cisplatin.

TECHNICAL APPROACH
Patients with Stage IVB recurrent or persistent squamous cell cancer of the cervix are randomized to receive either Cisplatin @ 50mg/m2 or Paclitaxel @ 135mg/m2 over 24 hours plus Cisplatin @ 50mg/m2. Each regimen is given q 3 weeks x 6 cycles or until progressive disease or adverse effects prohibit further therapy.

PRIOR AND CURRENT PROGRESS
The GOG has entered 280 patients; WRAMC has entered 2 patients (now deceased). Grade 4 toxicities are 24 leukopenia, 4 thrombocytopenia, 60 neutropenia, 12 anemia, 4 nausea/vomiting, 4 GI, 2 neurologic, 1 fever, 1 dermatologic, 1 fatigue, 1 GU, 1 metabolic, 1 lymphocytes and 1 pulmonary. This protocol is closed to patient entry effective 3/8/99. This protocol can be closed here at WR.

Ref: Jul 00 GOG Statistical Report

CONCLUSIONS
Too early.

Report Date: 4 December 2000 Work Unit # 4403-98

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: GOG 141: Treatment of Patients with Suboptimal ("Bulky") Stage IB Carcinoma of the Cervix: A Randomized Comparison of Radical Hysterectomy and Pelvic and Para-Aortic Lymphadenectomy With or Without Neoadjuvant Vincristine and Cisplatin Chemotherapy

KEYWORDS:

PRINCIPAL INVESTIGATOR: Rose, G. Scott LTC MC
ASSOCIATES:

DEPARTMENT: Obstetrics and Gynecology STATUS: O
SERVICE: Gynecologic Oncology Group INITIAL APPROVAL DATE: 5 February 1998

STUDY OBJECTIVE
Determine neoadjuvant cisplatin and vincristine chemotherapy prior to radical hysterectomy and bilateral pelvic and para-aortic lymphadenectomy for patients with suboptimal stage IB carcinoma of the cervix improves progression-free survival.

TECHNICAL APPROACH
This is a Phase III trial for patients with suboptimal (bulky) stage IB carcinoma of the cervix.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
The entire GOG has enrolled 237 patients; WRAMC has entered zero patients. Grade 4 toxicities include 4 hematologic, 7 GI, 1 GU, 1 hepatic, and 2 metabolic. Since this protocol's review one year ago, there have been no publications reporting data from studies with similar study design in the literature. The objectives of this investigation have not been fulfilled by prior studies.

Ref: Jul 00 GOG Statistical Report

CONCLUSIONS
Too early.

Report Date: 4 December 2000 Work Unit # 4404-98

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: GOG 165: A Randomized Comparison of Radiation Plus Weekly Cisplatin vs Radiation Plus PVI (Protracted Venous Infusion) 5FU in Patients with Stage IIB, IIIB, and IVA Carcinoma of the Cervix

KEYWORDS:

PRINCIPAL INVESTIGATOR: Rose, G. Scott LTC MC
ASSOCIATES:

DEPARTMENT: Obstetrics and Gynecology STATUS: O
SERVICE: Gynecologic Oncology Group INITIAL APPROVAL DATE: 5 February 1998

STUDY OBJECTIVE
To compare the progression-free survival of patients with advanced cervical cancer limited to the pelvis receiving radiation only to radiation plus weekly cisplatin. To compare the progression free survival of patients with advanced cervical cancer limited to the pelvis receiving radiation plus prolonged venous infusion (PVI) 5-fluorouracil to radiation plus weekly cisplatin. To determine the relative toxicities of radiation plus chemotherapy (either weekly cisplatin or PVI 5 fluorouracil) compared to radiation alone. To compare the progression-free survival and survival of patients with advanced cervical cancer limited to the pelvis who (a) smoke at the time of diagnosis and (b) smoke during radiation therapy vs. those who quit.

TECHNICAL APPROACH
This study deals with patients with stage II-B, III-B and IV-A carcinoma of the cervix.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
The entire GOG has entered 341 patients on this study; WRAMC has entered 1 patient this year. Grade 4 toxicities include 7 hematologic, 20 GI, 4 GU, 2 metabolic, 2 fatigue, 2 cutaneous, and 1 cardiovascular. Protocol was closed to patient entry effective August 2, 2000. Since this protocol's review one year ago, there have been no publications reporting data from studies with similar study design in the literature. The objectives of this investigation have not been fulfilled by prior studies.

Ref: Jul 00 GOG Statistical Report

CONCLUSIONS
Too early.

Report Date: 4 December 2000 Work Unit # 4406-98

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: GOG 161: A Phase III Trial of Ifosfamide (NSC #109724) vs. Ifosfamide plus Paclitaxel (NSC #125973) in Patients with Advanced, Persistent or Recurrent Carcinosarcoma (Mixed Mesodermal Tumors) of the Uterus

KEYWORDS:

PRINCIPAL INVESTIGATOR: Rose, G. Scott LTC MC
ASSOCIATES:

DEPARTMENT: Obstetrics and Gynecology STATUS: O
SERVICE: Gynecologic Oncology Group INITIAL APPROVAL DATE: 24 February 1998

STUDY OBJECTIVE
To determine whether the addition of paclitaxel improves length of survival, progression-free interval and response rate when compared to ifosfamide alone in previously untreated patients with advanced, persistent or recurrent carcinosarcoma (mixed mesodermal tumors) of the uterus.

TECHNICAL APPROACH
This is a Phase III trial for patients with advanced, persistent or recurrent carcinosarcomas (mixed mesodermal tumors) of the uterus.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
The entire GOG study group has entered 86 patients on this study; WRAMC has enrolled zero patients. Grade 4 toxicities include 5 leukopenia, 18 granulocytopenia, 1 GI, 1 cardiac, 1 neurologic, 1 pulmonary, and 1 methemoglobinemia. Since this protocol's review one year ago, there have been no publications reporting data from studies with similar study design in the literature. The objectives of this investigation have not been fulfilled by prior studies.

Ref: Jul 00 GOG Statistical Report

CONCLUSIONS
Too early.

Report Date: 17 July 2001

Work Unit # 4411-98

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: Randomized Prospective Comparison of Day Three versus Blastocvst Embryo Transfer

KEYWORDS: Blastocyst, In Vitro Fertilization, Pregnancy rates, Multifetal pregnancy rates, Live birth rates, Embryo transfer, Assisted reproductive technology,

PRINCIPAL INVESTIGATOR: Frattarelli, John MAJ MC
ASSOCIATES: Leondires, Mark MAJ MC

DEPARTMENT: Obstetrics & Gynecology
SERVICE: Reproductive Endocrinology

STATUS: C
INITIAL APPROVAL DATE: 11 August 1998

STUDY OBJECTIVE

To randomly and prospectively compare embryo transfer at the day three and day five (blastocyst) stages. We will compare the two arms in respect to implantation rates, miscarriage rates, pregnancy rates, live birth rates, multiple pregnancy rates, and medical health care cost.

TECHNICAL APPROACH

We planned to prospectively enroll a total of 136 WRAMC patients (68 in each group). The number of patients is based on a power analysis assuming a 45% pregnancy rate in the day 3 patients and a 70% pregnancy rate in the day 5 patients. This gives us an 80% chance to detect a difference. Each patient will be randomized to a day 3 or day 5 embryo transfer. The groups will be compared with respect to embryo grade and morphology on day 3, number of embryos or blastocysts transferred, implantation rate, miscarriage rate, pregnancy rate, multiple fetal pregnancy rate, live birth rate, morbidity related to preterm delivery, and health care cost for the subsequent pregnancy or failure.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Fifty-seven patients agreed to be in the study and were originally randomized. Eight patients subsequently withdrew from the study. Four patients were withdrawn for having < 6 high-grade embryos after fertilization, one patient developed severe OHSS and elected to not have an embryo transfer, one patient withdrew stating she had changed her mind and did not wish to be in the study, and two patients had family emergencies necessitating an earlier transfer on day 3. In total, five patients from the day 3 group were removed and 3 patients from the day 5 group were removed. This left 49 patients continuing in the study. With 164 patients initially approached for study randomization and only 34.8 % agreeing to be in the study, the recruitment of patients was difficult. The majority of patients entering an IVF program are knowledgeable about the procedure and have predetermined biases based on the lay literature. As the study progressed, recruitment waned with only 11.9 % of patients (1 of 9) agreeing to participate in the study in the final 2 months of recruitment. Therefore recruitment was ended and the study was closed.

There have been no adverse events. Our study demonstrated a significantly higher multiple pregnancy rate in the day 3 embryo transfer group. A possible explanation for this increased multifetal pregnancy rate lies in the fact that this study specifically evaluated those patients with good reproductive potential; thus, the same patients who are at risk for multiple gestations. In summary, patients randomized to a day 5 embryo transfer had significantly fewer embryos transferred, significantly fewer multiple births, a significantly higher embryo implantation rate, and a greater likelihood of having a live birth.
The number of subjects enrolled to the study since last APR at WRAMC is ____ and the total enrolled to date at WRAMC is ___49__. The total number enrolled study-wide is __NA___, if multi-site study.

CONCLUSIONS

This study is now closed for enrollment and the paper has been sent out for review by Dr. Fratterelli.

Report Date: 31 January 2001

Work Unit #4413-99

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: The Effect of Environmental C02 on Thermotolerance-Associated Heat Shock Protein Synthesis

KEYWORDS:

PRINCIPAL INVESTIGATOR: Rose, G. Scott LTC MC
ASSOCIATES:

DEPARTMENT: Obstetrics & Gynecology
SERVICE:

STATUS: O
INITIAL APPROVAL DATE: 02 March 1999

STUDY OBJECTIVE
To determine if heat shock protein synthesis associated with the development of thermotolerance can be influenced by increasing environmental C02 concentration in-vitro.

TECHNICAL APPROACH
This is a basic service project involving no human subjects. All experiments are derived from established cell line.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
The number of subjects enrolled to the study since last APR at WRAMC is _N/A___ and the total enrolled to date at WRAMC is _N/A_____. The total number enrolled study-wide is _N/A_____, if multi-site study.
This is a WRAMC study which does not involve human subjects. There has bee no progress on this study thus far.

CONCLUSIONS
Too early.

Report Date: 13 April 2001

Work Unit #4415-99

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: A Prospective Assessment of Antral Follicle, Ovarian Volume

KEYWORDS: In-Vitro Fertilization, Ovarian Reserve, Antral Follicle, Ovarian Volume

PRINCIPAL INVESTIGATOR: MAJ Mark Leondires MC
ASSOCIATES: LTC John Frattarelli MC

DEPARTMENT: Obstetrics & Gynecology
SERVICE: Reproductive Endocrinology

STATUS: C
INITIAL APPROVAL DATE: 13 April 1999

STUDY OBJECTIVE

To prospectively determine the predictive value of pretreatment transvaginal ultrasound measurements of estimated ovarian volume and basal antral follicle count in determining the number of ococytes and the incidence of cycle cancellation in patients undergoing in vitro fertilization (NT).

TECHNICAL APPROACH

We plan to prospectively recruit 278 infertility patients age 20 to 43 undergoing IVF at WRAMC in order to measure ovarian volume and number of basal antral follicles prior to starting gonadotropin therapy. All patients will undergo a transvaginal ultrasound prior to beginning their IVF cycle. All IVF patients will be eligible for the protocol. We will evaluate the ovarian volume and antral follicle number to determine if a linear correlation exists. Patients will continue to be followed as per standard of care until the end of the IVF cycle and the following information will be collected: number of ovarian follicles produced, number of ococytes fertilized, ampoules of gonadotropins used, days of stimulation, cycle cancellation rate, miscarriage rate and pregnancy rate.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

There have been two recent publications on this topic both of which found no significant differences. These are all significantly smaller than the current study. Therefore with our sample size being much larger the impact of this study should be great. The number of subjects enrolled to the study since last APR at WRAMC is 278 and the total enrolled to date at WRAMC is 278. The total number enrolled study-wide is 278, if multi-site study. No adverse events occurred. The study is now closed.

CONCLUSIONS

We are in the process of crunching these numbers and the comparison should be complete soon and be presented at a national meeting and for publication. As of yet these data have not been presented.

Report Date: 28 April 2001 Work Unit # 4417-99

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: Evaluation of Metabolic Products of Embryo Culture and Their Correlation with Morphologic Appearance and Pregnancy Outcome

KEYWORDS:

PRINCIPAL INVESTIGATOR: Alvero, Ruben LTC MC
ASSOCIATES:

DEPARTMENT: Obstetrics and Gynecology STATUS: O
SERVICE: Reproductive Endocrinology INITIAL APPROVAL DATE: 6 July 1999

STUDY OBJECTIVE:
Development of a non-invasive methodology for assessing embryos would complement and perhaps supplant current morphologic criteria in the selection of viable embryos for transfer. The objectives of this study are: a) to characterize metabolic changes occurring in developing embryos as reflected in cellular products deposited into the culture media. These metabolic characteristics can be correlated with the current "gold standard' of embryo grading. b) to assess whether metabolic parameters are better predictors of implantation and pregnancy outcome than cellular morphology.

TECHNICAL APPROACH:
a) Subjects: Patients undergoing in-vitro fertilization (IVF) cycles at the Reproductive Science at Walter Reed Army Medical Center. All subjects involved in these cycles are eligible to participate. After 1200 cycles, over 3 years; patients mean age is 34.4, with a standard deviation of 4.8 and a range of 22-43.

b) Inclusion and Exclusion Criteria: All patients involved in IVF cycles at RSC-WRAMC are eligible for inclusion. Patients not going to oocyte retrieval are excluded from the protocol.

c) Study Design: Prospective observational and laboratory assay study

d) Methodology: Oocyte retrieval, embryo culture and embryo transfer will proceed as normal and as outlined in the standard operating procedures of the NT laboratory. All inseminations; embryo scoring and transfer to fresh media will be done at set times.
On day 2, 3, 4 and 5 after embryos are moved from their culture drops, the media will be aspirated from the dish using a fine pulled pipette and placed in Eppendorf tubes. A drop of media from the same dish containing no embryo will be collected and used as a control. All media samples will be coded by cycle number and unique patient identifier known only to the laboratory director. The media will be collected would normally be discarded. Embryos will not be comprised in any way by the collection of this media.

e) Data Collection As has been outlines in the Methodology section; embryos will be cultured in defined media, as is the standard for the Reproductive Science Center. At the conclusion of each 24-hour period of embryo culture, embryos will be moved from one culture dish and placed in the next fresh drop of media. The used media, which is normally discarded, will be used for metabolic assessment. The study will have two objectives. The first objective will be to characterize metabolic products elaborated during the culture period. Changes in the composition of media over a 24-hour time period will be evaluated as appropriate by either High Performance Liquid Chromatography (HPLC). Enzyme-linked immunoassay (ELISA). There will be a systemic approach of analysis in utilizing HPLC and ELISA. HPLC will be used for pyruvate, glucose and amino acid analysis and ELISA for determination of hCG levels. At present, the single most significant discriminator for predicting pregnancy in IVT is maternal age, with embryo morphology second. The aim of this study to is to look at embryonic metabolic factors as they relate to age

and embryo morphology as well as implantation. All age groups qualifying for Assisted Reproductive Technologies (ART) at WRAMC are eligible to participate. Media will be stored on all embryos at all time points. A drop of media from the same dish containing no embryo will be collected and used as control. Analysis of media will be on select embryos determined after embryo transfer. Initially, pronuclear embryos will be scored according to the criteria system already in place in the laboratory. Embryos from groups 1 and 2 have been shown to give highest implantation rates and the greatest conversion to blastocyst and therefore transfer. Embryos will be followed through to day 4 and from day 4 to 5. On day 5, one to three embryos, according to morphology and patient age, will be transferred.
The pyruvate, glucose and amino acid metabolism and hCG production of embryos transferred on day 5 and one to three non-transferred controls will be measured. Pyruvate metabolism at the pronuclear stage on day one will be measured on this same group of embryos.
The implantation of embryos will be correlated with pronuclear, day 3 and blastocyst morphology, pyruvate and glucose metabolism and hCG production. It must be emphasized that, given the variable nature of embryology with regard to number and qualify of embryo products for each patient, it will be up to the Laboratory-Director (Dr. Lynette Scott) to select the embryos used for evaluation. Specific pregnancy outcomes would include: a) chemical pregnancy (P hCG elevation without detection of clinical pregnancy by ultrasound), b) ectopic gestation (pregnancy outside of the uterine cavity), c) clinical pregnancy with spontaneous abortion (detection of an intrauterine gestational sac with subsequent demise), d) ongoing or delivered pregnancy. Statistical procedures used would include unpaired Student's t-test for comparison of individual metabolic products. For evaluation of morphology and pregnancy outcomes once metabolic products are characterized, Fisher's exact test and/or chi-square contingency tables would be used. Other statistical procedures, including non-parametric assessment would be used as indicated.
No addenda have been made to the original protocol.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE:
No recent literature in this area has been published since the last update.
The number of subjects enrolled to the study since the last APR at WRAMC is 56 and the total enrolled to date at WRAMC is 56.

CONCLUSIONS:
Difficulties with the assays have precluded any conclusions at this time. Various different approaches have been tried to date the small volumes required for embryo culture have precluded definitive success with the assay, as it currently exists. We are now focusing on the hCG assay using grouped embryos in an attempt to overcome this problem.

Report Date: 26 July 2001 Work Unit # 4418-99

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: GOG #9902: Quality of Life of Gynecologic Cancer Survivors (NCI 1 RO1 CA 79039-01)

KEYWORDS:

PRINCIPAL INVESTIGATOR: Maxwell, G. Larry MAJ MC
ASSOCIATES:

DEPARTMENT: Obstetrics and Gynecology STATUS: O
SERVICE: Gynecologic Oncology Group INITIAL APPROVAL DATE: 21 September 1999

STUDY OBJECTIVE
To describe the significant quality of life (QOL) concerns and long-term survivorship issues of women who were diagnosed and treated for early-stage ovarian and endometrial cancer five or more years ago.
To identify mechanisms which contribute to a gynecologic cancer survivorship model through comparison and prediction of high versus low QOL associated with long-term adjustment and survivorship.

TECHNICAL APPROACH
This is a QOL phone interview for survivors who completed GOG clinical trial #95 (ovarian), or GOG clinical trial #99 (endometrial) at least 5 years and are without recurrent disease.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
This protocol is fairly new, so there have been no publications reporting definite data as of yet.
The number of subjects enrolled to the study since last APR at WRAMC is _6__ and the total enrolled to date at WRAMC is __6__. The total number enrolled study-wide is _160____, if multi-site study. No toxicities reported.

Ref: Jul 01 GOG Statistical Report

CONCLUSIONS
Too early.

Report Date: 27 July 2001 Work Unit # 4419-99

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: GOG 167: A Two Part Study of the Treatment of Atypical Endometrial Hyperplasia: Part A: A Prospective Study of Immediate Hysterectomy; Part B: A Randomized Phase II Study of Medoroxyprogesterone Acetate Versus Depoprovera

KEYWORDS:

PRINCIPAL INVESTIGATOR: Maxwell, G. Larry MAJ MC
ASSOCIATES:

DEPARTMENT: Obstetrics and Gynecology
SERVICE: Gynecologic Oncology Group

STATUS: O
INITIAL APPROVAL DATE: 21 September 1999

STUDY OBJECTIVE

Part A:

To estimate and compare the frequency of adenocarcinoma in patients diagnosed with atypical hyperplasia (AEH) at initial biopsy in groups defined by the Study Co-Chairs and those not considered AEH by central review. Given favorable results, Part B will be opened to patient accrual.

Part B:

To conduct a randomized phase II trial to determine the frequency of complete remission of atypical endometrial hyperplasia (AEH) in patients treated for three months with oral medroxyprogesterone acetate or depoprovera IM.

TECHNICAL APPROACH

Part A:

Patients diagnosed with atypical endometrial hyperplasia and entry onto the study, patients will receive immediate hysterectomy.

Part B:

Patients with confirmed diagnosed of endometrial hyperplasia will be randomized to:

Regimen 1: Medroxyprogesterone acetate (MPA) 10mg/po/day continuously for three months.
Regimen 2: Depoprovera 150mg IM (gluteal or deltoid muscle) Q months for 3 months.

After 3 months patients will undergo total hysterectomy.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Since this protocol's last review there have been no reported publications for this particular study.
The number of subjects enrolled to the study since last APR at WRAMC is _5__ and the total enrolled to date at WRAMC is __5___. The total number enrolled study-wide is _112__, if multi-site study. Grade 4 toxicities include 1 hemoglobin, 1 other hematologic, and 1 coagulation.

Ref: Jul 01 GOG Statistical Report

CONCLUSIONS

Too early.

Report Date: 24 July 2001 Work Unit # 4420-99

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: Hyperspectral Diagnostic Imaging of the Cervix

KEYWORDS: hyperspectral, imaging

PRINCIPAL INVESTIGATOR: Parker, Mary F. LTC MC
ASSOCIATES: McBroom, John MAJ MC

DEPARTMENT: Obstetrics and Gynecology
SERVICE: Gynecologic Oncology

STATUS: O
INITIAL APPROVAL DATE: 29 September 1999

STUDY OBJECTIVES:
To continue the development of hyperspectral diagnostic imaging (HSDI) for the detection and localization of cervical dysplasia.

TECHNICAL APPROACH
There have been no addenda to the original protocol.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
The number of subjects enrolled to the study since last APR at WRAMC is _9_ and the total enrolled to date at WRAMC is _54_. The TAMC pilot protocol (numbers reported in 7/00 APR) was closed to subject entry and a new protocol submitted with updated clinical findings, at the request of TAMC DCI. The new TAMC protocol has just been approved for accrual of 150 subjects.
There have been no AE or subjects withdrawn from study.
Due to prolonged contract negotiations between the government and private industry since the last APR, data collection activities were limited. Promising results of initial intrapatient and interpatient neural net analysis were summarized in the last APR. Data analysis recently resumed. There are no new findings to report at this time. A recent publication by Ferris et al., describing the use of a contact multimodal cervical imaging device, further suggests the property of tissue fluorescence will be useful for diagnosing cervical dysplasia.

CONCLUSIONS
Initial data analysis is encouraging, but the hyperspectral diagnostic imaging device is not yet ready for validation studies. The device does not currently have a role in patient care.

Report Date: 24 October 2000

Work Unit # 00-4501

DETAIL SUMMARY SHEET

TITLE: Feasibility, Accuracy and Efficiency of an Internet Based Tele-Nuclear Consultation System for the Military, Phase I: Phantom Studies

PRINCIPAL INVESTIGATOR: LTC Thomas W. Allen
ASSOCIATES: Barry Cannon, RN; COL Ana Rodriguez; Eiping Quang, PhD; LTC Poropatich; COL Lenoard Nagorski; MAJ Carlos Jimenez

DEPARTMENT: Radiology
SERVICE: Nuclear Medicine

STATUS: O
INITIAL APPROVAL DATE: 12 October 1999

STUDY OBJECTIVE

1. To determine the feasibility of an Internet based Tele-Nuclear consultation system between Walter Reed Army Medical Center and Fort Knox Department of Radiology. Feasibility is defined as the technical ability to perform this transmission and review using existing technology. Efficiency is defined as the speed of transmission and time of evaluation using the system.
2. To examine the concordance in the image quality between native phantom studies vs. those reviewed using the Internet based Tele-Nuclear system.
3. To examine the concordance in the diagnosis between native phantom studies vs. those reviewed using the Internet based Tele-Nuclear system.

TECHNICAL APPROACH

This is a prospective, concordance trial using similar data from two separate locations. The image phantoms will be filled with appropriate radiopharmaceutical agents, and images will be acquired at Fort Knox Radiology Department using the protocols sent out by the ACNP. These studies will be scored independently by two board certified nuclear medicine physicians at WRAMC using criteria from the ACNP data collection sheet. Rater 1 will review the six phantoms at Fort Knox, while rater 2 will review the data acquired from the six phantoms via the Internet based system at WRAMC. After a one month delay to insure reader blinding, Rater 2 will then review the phantoms at Fort Knox while Rater 1 reviews the phantoms at Walter Reed. A third board certified nuclear medicine physician at Rodrigues Army Health Clinic, Puerto Rico will provide an independent reading of only the transmitted images from Fort Knox for comparison. By having a third reader, we can evaluate the concordance between two readers blinded to the transmitted study. These sets of data will be evaluated for concordance. The phantom images collected will be evaluated using an ANCP data collection sheet.

PRIOR AND CURRENT PROGRESS

This expedited protocol was approved on 08 December 1999. Since that time, installation of the required workstations and software at Fort Knox and WRAMC and installation of a FTP server at WRAMC has been completed. Two test images, one a flood source mage and the other a myocardial perfusion study phantom have been successfully transmitted from Fort Knox via the system in July 2000. Unfortunately, a number of issues have delayed further progress on the protocol. The previous PI on the protocol, departed the Nuclear Medicine Service in July of 2000 requiring that a new PI, be appointed. Sudbury, the vender providing the Internet based Tele-Nuclear medicine system, has repeatedly missed several important milestones required before interpretation of phantom images can actually commence. Missed milestones by the vendor include the provision of a training manual and documentation needed to use the system. This was to have been completed and submitted to WRAMC Telemedicine and Nuclear Medicine for review To date, data has been collected on the ten procedures where FluoraNav was not used and three of the twenty using FluoroNav have been completed and the data recorded.

CONCLUSIONS

The study is in progress and any conclusions would be premature at this time.

Report Date: 25 September 2001 Work Unit # 00-4502

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: Double-Blind Placebo Controlled Study of Samarium Sm-153 Lexidronam (Quadramet) for the Treatment of Asymptomatic Skeletal Metastases in Patients with Hormone-Refractory Prostate Carcinoma

KEYWORDS:

PRINCIPAL INVESTIGATOR: Allen, Thomas LTC MC
ASSOCIATES:

DEPARTMENT: Radiology
SERVICE: Nuclear Medicine

STATUS: C
INITIAL APPROVAL DATE: 19 September 2000

STUDY OBJECTIVE

Primary: To assess the efficacy and safety of 0.5 and 1.0 mCi/kg doses of samarium Sm-153 lexidronam in delaying progression of painful symptoms associated with bone metastases in patients with hormone-refractory prostate cancer.

Secondary: To assess the efficacy of 0.5 and 1.0 mCi/kg doses of samarium Sm-153 lexidronam in delaying progression as assessed by changes in serum prostate-specific antigen (PSA), time to clinical intervention, radionuclide bone scan and survival.

TECHNICAL APPROACH

-Multi-center, randomized, placebo-controlled, double-blind (third party unblended), parallel-group
-Men 18 Years of age or greater with asymptomatic bone scan positive metastases secondary to hormone-refractory prostate carcinoma.
-Patients randomized to:

0.5 mCi/kg samarium Sm 153 lexidronam
1.0 mCi/kg samarium Sm 153 lexidronam
Placebo (^{99M}Tc-MPD or HDP)

-Treatment repeated on 16-week intervals
-Planned total: 318 patients (106) per treatment group
-No modifications or amendments to the original DCI approved protocol have been made

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

The number of subjects enrolled to the study since last APR at WRAMC is one and the total enrolled to date at WRAMC is one. The total number enrolled study-wide is unknown to the investigator. There have been no publications, pertinent study findings and no amendments or modifications to the protocol since final approval to commence patient enrollment was received in December 2000.
There have been no adverse events (AE) at this institution. The only patient enrolled from this institution withdrew from the protocol on 26 April 2001 during the first treatment cycle. The reason for patient withdrawal was because he developed a painful skull lesion and desired to seek other forms of treatment (radiation therapy) for the pain. Per the patient's request, he was withdrawn from the protocol and was placed in the protocol's 8-week follow-up cycle that ended on 21 June 2001.
On May 7, 2001 the study sponsor, Berlex Corporation, sent out correspondence to all investigators that his protocol was being terminated due to slow patient enrollment. Berlex Corporation directed all sites to cease enrolling new patients effective May 25, 2001. A study monitor from Quintiles Corporation performed a site closeout visit for the protocol at WRAMC CPDR ward on September 25, 2001.

CONCLUSIONS

Protocol terminated by sponsor effective May 25, 2001 due to slow patient enrollment. Insufficient patient data accumulated at this institution to draw any conclusions.

Report Date: 18 September 2000

Work Unit # 4544

DETAIL SUMMARY SHEET

TITLE: Technetium 99m Methylene Diphosphonate Blood Pool Imaging to Detect Cancerous Breast Lesions

KEYWORDS:

PRINCIPAL INVESTIGATOR: Stack, Aaron L. MAJ MC
ASSOCIATES:

DEPARTMENT: Radiology
SERVICE: Nuclear Medicine

STATUS: C
INITIAL APPROVAL DATE: 26 November 1996

STUDY OBJECTIVE

To compare the agreement between Technetium 99m blood pool scintimammography and mammography for the detection of breast cancer in a screening population of patients and patients with abnormal mammograms.

TECHNICAL APPROACH

Prospective, observer blinded study comparing blood pool scintimammography and mammogram in a population of patients referred for osseous scintigraphy. Up to 300 patients will be enrolled (200 Group 2, and 100 Group1). The PI has been changed to: Aaron L. Stack MAJ MC. There have been no other modifications to the original protocol during the year.

PRIOR AND CURRENT PROGRESS

There have been no new enrollments during the current or prior year. Given the decreased enrollment and advent of new imaging agents, it is felt that this protocol no longer offers a diagnostic advantage and closure of the protocol is requested.

CONCLUSIONS

Poor enrollment in recent past, coupled with recent advances in other areas of breast cancer detection, eliminate the need for further investigation under this protocol. Closure is requested.

Report Date: 12 March 2001 Work Unit #4546

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: Intravenous Administration of 1311-6-B Iodomethylnorcholesterol (NP-59) for Adrenal Evaluation and Imaging

KEYWORDS:

PRINCIPAL INVESTIGATOR: Allen, Thomas W. LTC MC
ASSOCIATES:

DEPARTMENT: Radiology STATUS: O
SERVICE: Nuclear Medicine INITIAL APPROVAL DATE: 24 April 1997

STUDY OBJECTIVE

Clinical evaluation of NP-59 as a diagnostic agent for the detection of adrenal-cortical disorders.

TECHNICAL APPROACH

This study will be performed in humans of either sex. NP-59 will be administered by slow intravenous injection with a dose of 2mCi in adults, 15 uC8/kg in children. Lugol's solution, 5 drops twice daily starting one day before injection and continuing for two weeks, will be used to block thyroid uptake of radionuclide. Planar and SPECT images will be obtained on the 3rd, 4th and 5th days after injection using the scintillation camera and the on-line microcomputer. The drug to be used in this study, NP-59 is investigational and will be used under IND number 12605, which is held by the University of Michigan.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

The number of subjects enrolled to the study since last APR at WRAMC is zero and the total enrolled to date at WRAMC is 2 (one on 03 Dec 98 and the second on 19 Mar 99). There have been no adverse events (AE) for the two patients enrolled to date in the protocol. This is not a multi-center study. No patient enrolled in the study has withdrawn from it. Both patients previously enrolled in the protocol had studies that were diagnostic for unilateral functioning adrenal adenomas. One of the patients underwent laproscopic surgery for an adrenal mass and had pathological confirmation of a functioning adrenal adenoma.

CONCLUSIONS

NP-59 adrenocortical imaging is useful but infrequently used imaging adjunct in the evaluation of patients with suspected functioning adrenocortical disorders, especially in patients with equivocal clinical presentations and laboratory values. The drug being used as an imaging agent, NP-59 is an investigational new drug (IND number 12605) produced only by the University of Michigan. Patient enrollment in this protocol remains limited because of the infrequency of patients presenting with adrenocortical disorders. The WRAMC Endocrinology service is the primary source of patient referral for this protocol. The Endocrinology Service and Nuclear Medicine Service conduct weekly joint conferences, and during these conferences the management challenging endocrinology patients is discussed. Endocrinology physicians are aware of the NP-59 protocol and both endocrinology and nuclear medicine remain vigilant for new patients to enroll into the protocol.

Report Date: 30 April 2001

Work Unit # 4601

DETAIL SUMMARY SHEET

TITLE: RTOG 94-08: A Phase III Trial of the Study of Endocrine Therapy Used as a Cytoreductive and Cytostatic Agent Prior to Radiation Therapy in Good Prognosis Locally-Confined Adenocarcinoma of the Prostate

KEYWORDS: Zoladex, Flutamide

PRINCIPAL INVESTIGATOR: William B. Warlick, Jr., CPT MC
ASSOCIATES:

DEPARTMENT: Radiology
SERVICE: Radiation Therapy

STATUS: O
INITIAL APPROVAL DATE: 23 May 1995

STUDY OBJECTIVE

To evaluate the potential impact of a combination of Zoladex and Flutamide used as cytoreductive agents prior to undergoing definitive radiation therapy in locally-confined carcinomas of the prostate.

TECHNICAL APPROACH

There are two arms to this randomized study for patients with clinical stages T1b-T2b adenocarcinoma of the prostate. The control arm (Arm 2) is radiation therapy only to the prostate and regional lymphatics. The experimental arm (Arm 1) involves the use of total androgen suppression (Zoladex and Flutamide) for 2 months prior and 2 months during radiation therapy to the prostate and regional lymphatics.

PRIOR AND CURRENT PROGRESS

The multi-institutional trial opened on October 31, 1994. The targeted accrual is 1980 cases. As of October 1, 2000, 1,922 patients have been entered. The study was anticipating completion by January 2001 but we have not received any notification as to stopping accrual. At Walter Reed, eighteen patients were enrolled. The numbers enrolled at each year are as follows: 1995-3, 1996-6, 1997-4, 1998-2, and 1999-3. We have not enrolled any further patients. Fourteen patients continue in follow-up. Three patients developed an elevation in liver function tests and Flutamide was discontinued. One patient developed Grade 3 pancytopenia (1995) for which he received red blood cell transfusions. Flutamide was discontinued in this patient. One patient did have Grade 2 radiation prostatitis for which he received steroid enemas with improvement. This patient also recently suffered a hip fracture following a fall and underwent a hip replacement. He had his other hip replaced several years ago, prior to radiation. This problem was not related to his treatments. Two deaths have occurred (July 1997 and Feb 2000) for causes unrelated to prostate cancer. One patient has terminated participation in the study. One patient has been lost to follow-up.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 18. The total number enrolled study-wide is 1,922, if multi-site study.

CONCLUSIONS

This protocol therapy has been well tolerated. This study will provide information on the appropriate role of hormonal therapy in locally confined prostate cancer primarily treated with radiation.

Report Date: 5 January 2001 Work Unit # 4602

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: RTOG 94-13: A Phase III Trial Comparing Whole Pelvic Irradiation Followed by a Conedown Boost to Boost Irradiation Only and Comparing Neoadjuvant Total Androgen Suppression

KEYWORDS: radiotherapy, prostate cancer

PRINCIPAL INVESTIGATOR: Warlick, William B. MAJ MC
ASSOCIATES: Dullea, Michael D. MAJ MC

DEPARTMENT: Radiology STATUS: O
SERVICE: Radiation Therapy INITIAL APPROVAL DATE: 27 February 1996

STUDY OBJECTIVE

To determine optimal method of delivery of hormonal therapy with radiotherapy in the treatment of localized prostate cancer. A secondary objective is determination of optimal field size in the delivery of radiotherapy.

TECHNICAL APPROACH

There are four arms to the study: Arm 1 delivers neoadjuvant and concurrent hormonal therapy with pelvis radiation. Arm 2 delivers neoadjuvant and concurrent hormonal therapy with prostate-only radiation. Arm 3 delivers concurrent and adjuvant hormonal therapy with pelvis radiation. Arm 4 delivers concurrent and adjuvant hormonal therapy with prostate-only radiation.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Sixteen (16) WRAMC patients were enrolled in this study. Two patients have died of unrelated causes, which have been reported. This leaves fourteen (14) patients actively being followed per protocol. No patients were enrolled within the last year (2000). One (1) patient was enrolled in 1999. Seven (7) patients were enrolled in 1998. Three (3) adverse events have occurred at WRAMC and were reported as per protocol. All patients continue in follow-up and no withdrawals have occurred.

CONCLUSIONS

Protocol closed to accrual effective 30 June 1999. All patients will continue in follow-up as per protocol. It is too early to comment on conclusions/implications from this study.

Report Date: 2 March 2001

Work Unit #4705

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: Proton Magnetic Resonance Spectroscopic Imaging in Patients with Partial Epilepsy

KEYWORDS: spectroscopy, proton, epilepsy

PRINCIPAL INVESTIGATOR: Jabbari, Bahman COL MC
ASSOCIATES:

DEPARTMENT: Radiology
SERVICE: Diagnostic Radiology

STATUS: O
INITIAL APPROVAL DATE: 25 April 1995

STUDY OBJECTIVE

To investigate the yield and clinical utility of Magnetic Resonance Spectroscopy (MRS) in patients with partial epilepsy.

TECHNICAL APPROACH

Fifty subjects with partial epilepsy will undergo MRS, a noninvasive technique which allows focused study of biochemistry within normal and diseased brains. Conventional MRI with additional special equipment and software is utilized to allow spectral analysis.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

The number of subjects enrolled to the study since last APR at WRAMC is four and the total enrolled to date at WRAMC is twenty-four. No side effects were noted.

CONCLUSIONS

This study shows focal abnormalities of MRS (changes of NNA, choline, creatinine) on the side of epileptic EEG abnormality, the finding that can be helpful in surgical management of these patients. Pathology groups are still too small for performing statistical analysis of MRS/pathology correlation.

Report Date: 09 August 2000 Work Unit # 4709

DETAIL SUMMARY SHEET

TITLE: Utility of Electron Beam Computed Tomography in Pediatric Imaging

KEYWORDS:

PRINCIPAL INVESTIGATOR: Statler, John CPT MC
ASSOCIATES: Philip Rogers COL MC, Michael Brazaitis COL MC, Paula Coughlin CPT MC

DEPARTMENT: Radiology
SERVICE: Diagnostic Radiology

STATUS: C
INITIAL APPROVAL DATE: 14 October 1994

STUDY OBJECTIVE

To compare studies obtained on awake pediatric subjects, using the Imatron Electron Beam CT scanner with those obtained on sedated patients using the GE helical scanners. Variables examined include motion artifact, sedation failures, adverse events, and cost.

TECHNICAL APPROACH

All patients presenting to the pediatric sedation unit for CT scans are enrolled (with the exception of those having sinus and/or temporal bone CT's). The patients are then transported to the CT suite, scanned, and released to home.

PRIOR AND CURRENT PROGRESS

No patients were enrolled in the last year. To date, seventeen (17) patients have been enrolled. There have been no adverse reactions and no patients have withdrawn from the study.

CONCLUSIONS

Electron Beam CT is an effective method for imaging pediatric patients without sedation. Due to the heavy load of adult patients undergoing cardiac EBCT, there is little time for scanning pediatric patients at Walter Reed. We continue to image children with a medical contraindication to sedation on the EBCT.

Report Date: 02 February 2001

Work Unit #4710-99

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: Comparison of Electron Beam Computed Virtual Colonoscopy (EBCT-VC) with Visual Colonoscopy, Using Each Patient as Their Own Control

KEYWORDS: Colonoscopy; X-ray computed tomography; Electron beam computed tomography; Colon, Cancer, colon; Polyp; Imaging; Three-dimensional imaging

PRINCIPAL INVESTIGATOR: Irwin M. Feuerstein, MD
ASSOCIATES: COL Michael P. Brazaitis, MC; CPT Roger Polish, MC; CPT Eric Osgard, MC; COL Roy Wong, MC; Corinne Maydonovitch, BS; Audrey Chang, PhD; Gregory N. Bender, MD

DEPARTMENT: Radiology
SERVICE: Diagnostic Radiology

STATUS: O
INITIAL APPROVAL DATE: 23 March 1999

STUDY OBJECTIVE

To determine whether computed tomography (CT) colography, using electron beam computed tomographic virtual colonoscopy (EBCT-VC) methodology, can identify the normal colon with a high degree of predictability. Secondary information of benefit will be to identify the length of CT colography (CTC) examination time relative to the examination time of colonoscopy, to identify the success rate of CTC in visualizing the entire colon relative to the success rate of colonoscopy to do the same, to identify which examination is more preferable to the patient, and to identify if CTC can be relied upon to such a degree that repeat colonoscopy might be necessary if initially negative in the face of a positive CTC examination.

TECHNICAL APPROACH

Patients will receive virtual and fiberoptic colonoscopy on the same day, with the information conveyed via the patient guardian. Fiberoptic colonoscopy will be done in the standard manner, while virtual colonoscopy will be done on the electron beam scanner with Colyte preparation and air insufflations using a standard tip. Images will be reviewed in both 2- and 3-dimensions with fly-through.
Based upon our recent experience and the current literature, several protocol modifications will be made. The barium preparation will be eliminated. The c-arm fluoroscopy will be eliminated. The glucagon will be eliminated. The pre-fiberoptic colonoscopic image analysis will involve two-dimensional axial images and multiplanar reconstructions interpreted on the Scribe workstation. The three-dimensional colonoscopic flythrough images will be interpreted on the AccuImage workstation after the fiberoptic colonoscopy.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Recent literature has debated the use of glucagon during virtual colonoscopy. The preponderance of the published work does not support the use of glucagon, though this result is counterintuitive and has been contested. Nevertheless, since glucagon injection adds potential morbidity and significantly lengthens the examination, in the absence of compelling benefit it has been eliminated from the protocol. Because glucagon has been eliminated, the contraindications relative to its use, including pheochromocytoma and MEN syndromes, have been removed. The use of the barium preparation caused a great deal of consternation amongst our gastroenterology physician's secondary to stool and barium retention, and in one instance resulted in abdominal pain. In addition, despite many centers anecdotally trying various oral contrast regimens, none have come forward as adding substantially to the results. Thus, oral barium has been removed from the protocol. We also found that the oral iodine solutions were so impalatable (to the authors, we never gave it to patients) that it could not be administered. This was eliminated from the protocol as well. The assessment of colonic distension using c-arm fluoroscopy lengthened the procedure, proved impractical, and caused technical failure of the equipment in several cases. Thus, c-arm fluoroscopy has been eliminated from the procedure. Most centers use comfort levels in combination with counting the number of bulb insufflations, and we will revert to this method. Because of some technical aspects of

moving the data from the scanner to the AccuImage workstations, the length of time necessary for this maneuver was impractically long, and the fiberoptic colonoscopy was unacceptably delayed. In addition, it has been shown that assessment of two-dimensional axial images and multiplanar reconstruction is much quicker and provides virtually all of the information needed for accurate diagnosis. In light of these matters, pre-fiberoptic assessment will consist of the much quicker two-dimensional assessment, and the three-dimensional flythrough analysis will be done in blinded fashion after the colonoscopy. The Human Use Committee is already aware of the several minor complications that have transpired during the performance of the protocol in 2000. We voluntarily informed the Committee and offered to suspend the protocol pending modifications. There were two machine failures secondary to problems with the c-arm and the required unusually long table modifications. One patient experienced abdominal pain secondary to the barium, and what may have been insufficient fluid intake concurrent with the barium ingestion. One patient experienced a significant anesthesia reaction during colonoscopy which was likely unrelated to the protocol, but reported nonetheless. Virtually ubiquitous were problems with the barium and colon preparation, and there were questions regarding the glucagon and colonic motility. These were all reported. There were no serious complications attributable to the protocol.

The number of subjects enrolled to the study since last APR at WRAMC is six and the total enrolled to date at WRAMC is six.

Several members of the research team have moved on. Two have made no significant contributions to the protocol and have been removed as collaborators. Two have made large contributions to the protocol and remain as both collaborators and future consultants. One investigator has joined the group.

CONCLUSIONS

The protocol has been voluntarily suspended, but we wish to resurrect the protocol in a modified, simplified, more patient-friendly and physician-friendly format. To that end, protocol modifications have been introduced here and will be submitted as protocol addenda. We still feel that this protocol and this technology has the potential to make a major impact on the field and needs to be pursued in a more efficient and effective manner.

Report Date: 01 August 2001

Work Unit # 4833-98

DETAIL SUMMARY SHEET

TITLE: Determination of Reference Values for Percent Free PSA in Patients for Prostatic Evaluation

KEYWORDS: free PSA, prostate, cancer

PRINCIPAL INVESTIGATOR: Moul, Judd W. COL MC
ASSOCIATES: Ali, Amina MT

DEPARTMENT: Surgery
SERVICE: Urology

STATUS: O
INITIAL APPROVAL DATE: 01 September 1998

STUDY OBJECTIVE

To determine Hybritech Tandem-MP free and total PSA ration values on WRAMC patient population related to age and race. In the men who are diagnosed with prostate cancer: to evaluate the free PSA and correlate it to the pathological stage and tumor stage.

TECHNICAL APPROACH

This is a prospective study, previously frozen, stored serum samples under WU#2801 from patients who have had prostate biopsies will be used for this study. Clinical data will be provided from the CPDR database at WRAMC (WU#2857). For the patients who have a positive biopsy, we will correlate the percent free PSA to stage, grade and number of prostate biopsy cores involved with cancer and see if the percent free PSA is a marker of stage/grade. Specimens with total PSA values in the 2.0-10.0 ng/ml range will be used.

PRIOR AND CURRENT PROGRESS

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 223. There were 232 previously frozen stored specimens from patients who have had prostate biopsies and out of the 232 specimens, 223 were used. The specimens were tested for free PSA and total PSA. The percent of free PSA was also calculated.

CONCLUSIONS

Data collection and data analysis is currently being conducted. Results are still pending at this time, but are expected within the next month from the statistician.

Report Date: 29 October 2000 Work Unit # 00-6501

DETAIL SUMMARY SHEET

TITLE: The Role of Ki-67 Antigen in Differentiated Thyroid Cancers

KEYWORDS: Ki-67, Thyroid, Cancer

PRINCIPAL INVESTIGATOR: Gary L. Francis COL MC
ASSOCIATES: Angela Folstad LT USN

DEPARTMENT: Pediatrics
SERVICE: Pediatric Endocrinology

STATUS: O
INITIAL APPROVAL DATE: 5 October 1999

STUDY OBJECTIVE

This study was designed to examine the number of K1-67 positive (proliferating) cells in a group of benign and malignant archived thyroid tumors and to correlate the number of Ki-67 positive cells with the risks of metastasis and recurrence.

TECHNICAL APPROACH

Archived thyroid tissue blocks were examined for Ki-67 positive cells by immunohistochemistry. The number of positive cells was counted (# /high power field) and correlated with tumor size, metastasis, and recurrence.

PRIOR AND CURRENT PROGRESS

39 papillary thyroid carcinomas (PTC), 9 follicular thyroid carcinomas (FTC), 2 medullary thyroid carcinomas (MTC) and 11 benign lesions were examined. Recurrence developed only in tumors which had no Ki-67 positive cells / power field. In a detailed examination of these tumors, we believe the proliferating cells (ki-67) might be lymphocytes. In an addendum to this protocol, we obtained permission to examine the same tumors for the expression of leukocyte common antigen (LCA). We are currently examining the number of LCA positive cells / high power field for each tumor.

CONCLUSIONS

This study has generated a remarkable finding (recurrence occurs only in Ki-67 negative tumors) which may have profound impact on our understanding of thyroid cancer biology. The study is making excellent progress and we plan to continue to pursue this study.

Report Date: 1 September 2000

Work Unit # 00-6502

DETAIL SUMMARY SHEET

TITLE: Comparative Genomic Hybridization of Differentiated Thyroid Cancer

KEYWORDS: CGH, Thyroid Cancer

PRINCIPAL INVESTIGATOR: Andrew J. Bauer MAJ MC
ASSOCIATES: Cydney Fenton MAJ MC, Gary L. Francis COL MC, Aneeta Patel MSc, Diamuid Nicholson, PhD, Henry Burch LTC MC, Bassem R. Haddad MD, Constantine A. Stratakis MD, R. Michael Tuttle MD

DEPARTMENT: Pediatrics
SERVICE: Pediatric Endocrinology

STATUS: O
INITIAL APPROVAL DATE: 12 October 1999

STUDY OBJECTIVE

To determine if different patterns of gene loss and/or gain exist in childhood and adult thyroid cancers and that those differences explain the heterogeneity of clinical behavior.

TECHNICAL APPROACH

To test this hypothesis, we have been using the powerful technique of comparative genomic hybridization (CGH) to examine the entire genome of papillary thyroid carcinoma from children and adults, and to correlate specific genomic aberrations with the clinical course of the individual.
CGH is a molecular cytogenetic technique which uses quantitative two color fluorescent in situ hybridization (FISH) to simultaneously compare the entire genome from multiple test samples. In a single experiment, CGH can detect genetic imbalance in solid tumors and map the region of chromosomal gain or loss compared to normal reference metaphase chromosomes.

PRIOR AND CURRENT PROGRESS

We have completed CGH analysis on 15 adult PTC samples. The sample population included 83% women with an average age of 42.6 years (range 22-67 years). The average tumor size was 2.6 cm (range 1.0-7.5 cm). There was one tumor of a Grade I morphology, seven of Grade II (47%), four of Grade III (27%), one of Grade IV and two of unknown grade. Three of the 15 adult PTC samples (3/15, 20%) had abnormal CGH profiles (20%). This included one tumor with a loss of 4q (4q-), one tumor with a loss of 4q and gain of 20q (4q-, 20q+) and a one tumor (tall cell variant on histopathology) with a gain of 20q, as well as a loss of 13 (20q+, 15+, 13-). All other samples, to include three normal thyroid controls, demonstrated normal profiles.

CONCLUSIONS

We found that three out of 15(20%) papillary thyroid carcinomas (PTC) exhibit chromosomal gain or loss (unpublished). Of these 3, one cancer was a tall-cell variant, known to be associated with a poor prognosis. Two additional tumors were shown to have a gain of chromosome 20q, a region that contains the gene encoding $G_S\alpha$ (OMIM # 139320). $G_S\alpha$ has been reported to be constitutively activated in a number of differentiated thyroid carcinomas. Based on these observations, we believe PTC with genomic aberrations may have the worst clinical prognosis. Continuation of this protocol is vital for the potential identification of these non-random tumor specific aberrations (i.e. molecular "profiling" of the tumors). Knowledge of that correlation with outcome and prognosis is critical to develop more accurate methods for individualized patient management decisions and improve upon the current morphologically based classification of PTC.

Report Date: 27 November 2000 Work Unit # 00-6503

DETAIL SUMMARY SHEET

TITLE: Role of Thyroid Transcription Factor-1 in Differentiated Thyroid Cancer

KEYWORDS: Thyroid, Transcription Factors, Cancer

PRINCIPAL INVESTIGATOR: Andrew J. Bauer MAJ MC
ASSOCIATES: Gary Francis COL MC

DEPARTMENT: Pediatrics
SERVICE: Endocrinology

STATUS: O
INITIAL APPROVAL DATE: 1 November 1999

STUDY OBJECTIVE:
This study was designed to determine the expression of thyroid transcription factor-1 (TTF-1) in a group of benign and malignant thyroid lesions and to determine if the intensity of expressions is related to the risk of metastasis or recurrence.

TECHNICAL APPROACH:
A group of archived, previously existing thyroid tumors were stained for the expression of TTF-1 using immunohistochemical techniques and antisera specific for TTF-1. The sub-cellular location and intensity of staining were graded by two independent examiners and scored for nuclear or cytoplasmic staining or intensity grade 1-3.

PRIOR AND CURRENT PROGRESS:
To date, 62 thyroid carcinomas, 15 benign lesions and 2 normal thyroid glands have been stained for TTF-1 expression, TTF-1 was found in benign and malignant lesions, but the intensity of nuclear TTF-1 expression was related to the serum TSH activity ($p=0.024$) and patient age ($p=0.035$). In addition, papillary thyroid carcinoma which expressed TTF-1 were more likely to recur or persist despite treatment ($p=0.06$).

CONCLUSIONS:
The study is progressing well and has shown that nuclear TTF-1 expression is important in defining the behavior of papillary thyroid carcinoma. Furthermore, there are potentially important relationships between TTF-1 expression and TSH activity. Further study is required to better define these relationships.

Report Date: 12 September 2000

Work Unit # 00-6504

DETAIL SUMMARY SHEET

TITLE: Role of Focal Matrix Metalloproteinases in Differentiated Thyroid Cancer

KEYWORDS: metalloproteinase, thyroid, cancer

PRINCIPAL INVESTIGATOR: Gary Francis COL MC
ASSOCIATES:

DEPARTMENT: Pediatrics
SERVICE: Endocrinology

STATUS: O
INTIAL APPROVAL DATE: 30 November 1999

STUDY OBJECTIVE:
This study is designed to determine if the expression of matrix metalloproteinases is increased in a group of archived paraffin-embedded thyroid tissue blocks when compared to a similar group of archived benign thyroid lesions. If so, this would provide evidence that metalloproteinases are important in thyroid cancer and would offer a novel therapeutic window of inhibitors of metalloproteinases for this disease.

TECHNICAL APPROACH:
Archived thyroid tissues are deparafinized and stained by immunohistochemistry for matrix metalloproteinase expression. The intensity of staining is graded by two independent examiners and then compared to the rate of recurrence, tumor size, and presence of metastasis.

PRIOR AND CURRENT PROGRESS:
A total of 32 papillary thyroid cancers, 7 follicular thyroid cancers and 12 benign lesions have been stained and scored for malloproteinase expression. MMP-1 is increased in malignant compared to benign tissues. MTI-MMP appears to be directly related to the rate of recurrence, whereas TIMP-1 is inversely related to the risk of recurrence.

CONCLUSIONS:
This study has provided the first evidence that malloproteinases are important in thyroid cancer biology. The study is ongoing and making good progress.

Report Date: 15 July 2001

Work Unit # 00-6601

DETAIL SUMMARY SHEET

TITLE: POG 9900: Aline 17 Classification Protocol – A Pediatric Oncology Group Non-Therapeutic Study

KEYWORDS:

PRINCIPAL INVESTIGATOR: Edward, Glenn LTC MC
ASSOCIATES:

DEPARTMENT: Pediatrics
SERVICE:

STATUS: O
INITIAL APPROVAL DATE: 15 August 2000

STUDY OBJECTIVE

(1) To provide the clinical and laboratory data necessary for placing each patient with ALL onto the proper therapeutic trial. (2) To provide an administrative base to capture classification data for correlative studies in ALL treatment protocols and series of historical protocols.

TECHNICAL APPROACH

This is a non-therapeutic laboratory classification study for subjects with newly diagnosed acute lymphoblastic leukemia, ≤ 21 years of age at the time of diagnosis. Through local and reference laboratories each subject will have there leukemic cells biologically subclassified at the time of diagnosis using a variety of laboratory methods. This information will be used to place each subject onto the proper therapeutic trial.

PRIOR AND CURRENT PROGRESS

This is the first WRAMC APR for this protocol. As of February 1, 2001, groupwide accrual stands at 789. There have been no WRAMC registrations on this protocol. Since this is a non-therapeutic study, there are no toxicity data to report.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 0. The total number enrolled study-wide is 789, if multi-site study. No adverse events have been reported. Enrollment is still continuing.

CONCLUSIONS

Study should remain open.

Report Date: 15 July 2001

Work Unit # 00-6602

DETAIL SUMMARY SHEET

TITLE: POG 9907: Aline 17 Cytogenetics Protocol – A Pediatric Oncology Group No-Therapeutic Study

KEYWORDS:

PRINCIPAL INVESTIGATOR: Edwards, Glenn LTC MC
ASSOCIATES:

DEPARTMENT: Pediatrics
SERVICE:

STATUS: O
INITIAL APPROVAL DATE: 15 August 2000

STUDY OBJECTIVE

Assess the feasibility of obtaining high quality decentralized cytogenetic karyotyping in POG. To continue the POG tradition of having well cytogenetically characterized patients for use in correlative and descriptive cross-protocol studies in POG and in international collaborative analyses.

TECHNICAL APPROACH

Children $\leq$ 21 years of age with newly diagnose acute lymphoblastic leukemia will have their leukemia cells karyotyped at a POG approved cytogenetics laboratory. This information will be compiled and stored in a secure database for use in correlative and descriptive studies of this patient population. In addition, the cytogenetics data, if informative, will be taken into account by the UNM Molecular Reference Laboratory in reporting the DI (including hypodiploidy), FISH 4&10, and molecular detection results for the E2A/PBX-1, t (1;19); the BCR/ABL, (9;22); and MLL(11q23) rearrangements. The cytogenetics data will be considered in any case in which the DNA index, FISH 4&10, or molecular detection results are not straightforward.

PRIOR AND CURRENT PROGRESS

This is the first WRAMC APR for this study. As of 02/01/2001, groupwide accrual stands at 573. There have been no WRAMC registrations on this protocol to date. Initial data evaluation show excellent correlation between the routine karytype results and results obtained from molecular studies (POG 9900) performed at the UNM Molecular Reference Laboratory.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 0. The total number enrolled study-wide is 573, is multi-site study.

CONCLUSIONS

Study should remain open.

Report Date: 22 November 2000 Work Unit # 6121

DETAIL SUMMARY SHEET

TITLE: POG 7799 Rare Tumor Registry

KEYWORDS: rare tumors, tumors, pediatric tumors

PRINCIPAL INVESTIGATOR: Edwards, Glenn LTC MC
ASSOCIATES: Mosijczuk, Askold COL MC; Crouch, Gary LtCol MC

DEPARTMENT: Pediatrics
SERVICE: Pediatric Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 22 January 1980

STUDY OBJECTIVE

To accumulate natural history data on malignancies which occur so rarely that larger series of cases cannot be accumulated at any single institution.

TECHNICAL APPROACH

To build a registry which contains pathology review of patients with rare tumors and annual reporting of status of patients.

PRIOR AND CURRENT PROGRESS

Data are reported in the POG agenda for the previous 5 years. From April 1995 to April 2000 there have been 221 patients registered group-wide; 50 patients were registered group-wide in the last year. There was one WRAMC registration on this protocol since the last APR. WRAMC total registrations are 10. Benefits to patients include participation in the national database, which expedites enrollment in newly developed rare tumor studies.

CONCLUSIONS

Study should remain open.

Report Date: 19 April 2001

Work Unit # 6177

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: POG 8602: Evaluation of Treatment Regimens in Acute Lymphoid Leukemia of Childhood (AlinC #14), A POG Phase III Study

KEYWORDS: lymphocytic leukemia, childhood leukemia, methotrexate

PRINCIPAL INVESTIGATOR: Edwards, Glenn LTC MC
ASSOCIATES: Mosijczuk, Askold COL MC; Hartman, Kip COL MC; Crouch, Gary LTC MC

DEPARTMENT: Pediatrics
SERVICE: Pediatric Hematology-Oncology

STATUS: C
INITIAL APPROVAL DATE: 27 May 1986

STUDY OBJECTIVE

To treat patients with lymphocytic leukemia in order to provide optimal opportunity for possible cure.

TECHNICAL APPROACH

A comparison of regimens to determine if intermediate-dose methotrexate (IDM) and Ara-C in consolidation is superior to IDM + L-asparaginase, and if pulses of IDM/Ara-C at 3-week intervals is superior to pulses at 12-week intervals.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

This study closed to accrual January 1991. Of the 19 patients enrolled on this study at WRAMC 5 transferred to other POG institutions. Of the remaining 14, 6 are followed at WRAMC and remain in CR and 8 have died of their disease. There have been no reports of late effects toxicity. Benefits to patients included the possibility of remission of disease.

CONCLUSIONS

Study should be closed at WRAMC. The last patient was enrolled on this study at WRAMC in December 1990. Patients will continue to receive routine follow-up on an annual basis.

Report Date: 14 May 2001

Work Unit # 6181

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: POG 8625/8626: Combined Therapy and Restaging in the Treatment of Stages I, IIA, IIIA1 Hodgkin's Disease in Pediatric Patients, A Phase II Study

KEYWORDS: Hodgkin's disease, radiation, MOPP/ABVD

PRINCIPAL INVESTIGATOR: Edwards, Glenn LTC MC
ASSOCIATES: Mosijczuk, Askold COL MC; Hartman, Kip COL MC; Crouch, Gary LTC MC

DEPARTMENT: Pediatrics
SERVICE: Pediatric Hematology-Oncology

STATUS: C
INITIAL APPROVAL DATE: 24 June 1986

STUDY OBJECTIVE

To treat Hodgkin's disease in patients staged as I, IIA and IIIA1.

TECHNICAL APPROACH

Effectiveness and toxicities of three cycles of MOPP/ABVD are compared with two cycles of MOPP/ABVD plus radiation.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

This study closed September 1992 with a final total accrual of 247. WRAMC's final total accrual remains at four. All four of the WRAMC registrants remain in CR >10 years off-therapy. Study results: There is insufficient evidence to detect a difference between the treatments as measured by duration of continuous remission. Toxicity was acceptable for this chemotherapy. Benefits to patients included the possibility of remission of disease. There have been no new reports from POG. This 10-year off-therapy follow-up requirement for this study has been met for all 4 WRAMC patients.

CONCLUSIONS

Study is complete at WRAMC and should be closed.

Report Date: 7 August 2000

Work Unit # 6188

DETAIL SUMMARY SHEET

TITLE: POG 8650: National Wilm's Tumor Study: A POG Phase III Study

KEYWORDS: Wilms' tumor, renal tumor, nephroblastoma

PRINCIPAL INVESTIGATOR: Edwards, Glenn LTC MC
ASSOCIATES: Mosijczuk, A. COL MC; Crouch, G. LtCol MC; Hartman, K. LTC MC

DEPARTMENT: Pediatrics
SERVICE: Pediatric Hematology Oncology

STATUS: O
INITIAL APPROVAL DATE: 28 October 1986

STUDY OBJECTIVE

1) To gather data on morphology and correlate it with treatment and clinical outcome; and 2) refine clinical trials to reduce therapy to simpler and shorter regimens.

TECHNICAL APPROACH

To attempt to give the usual 5-day course one day (has been done with other tumors), and to examine in randomized trial with current therapies.

PRIOR AND CURRENT PROGRESS

This study closed to accrual effective 1 September 1994. Final accrual as of last reporting to POG (31 Jan 96) is 3335. There were a total of 14 patients registered at WRAMC; the last WRAMC registration was in July 1993. There were no unexpected toxicities reported. Of the 14 WRAMC registrants 9 are followed at WRAMC and are in remission, 4 transferred to other POG institutions, and 1 died of relapse and progressive disease. Results showed no statistically significant difference in relapse-free survival or survival for patients treated with short versus long treatment regimens. No new outcome analyses have been reported as of the most recent POG report. [Reference Fall 1999 Joint POG/CCG Meeting Agenda and Current Report of Studies]

CONCLUSIONS

Study is closed to accrual but should remain open to complete 10-year follow-up period for patients followed at WRAMC.

Report Date: 19 April 2001 Work Unit # 6217

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: POG 8725: Randomized Study of Intensive Chemotherapy (MOPP/ABVD Plus/Minus Low-Dose Total Nodal Radiation Therapy in the Treatment of Stages IIB, IIIA2, IIIB, IV Hodgkin's Disease in Pediatric Patients, Phase III

KEYWORDS: Hodgkin's disease, nodal radiation, MOPP/ABVD

PRINCIPAL INVESTIGATOR: Edwards, Glenn LTC MC
ASSOCIATES: Mosijczuk, Askold COL MC; Hartman, Kip COL MC; Crouch, Gary LTC MC

DEPARTMENT: Pediatrics STATUS: C
SERVICE: Pediatric Hematology-Oncology INITIAL APPROVAL DATE: 31 May 1988

STUDY OBJECTIVE

To determine in a randomized study whether the addition of low-dose total nodal irradiation to four courses of MOPP/ABVD combination chemotherapy will improve the duration of complete remission and survival when compared with patients who have had chemotherapy only.

TECHNICAL APPROACH

Patients are 21 years old and younger, who have previously untreated histologically-proven Hodgkin's disease (Stage IIB, III2A, IIIB, and IV).

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

This study closed to accrual March 1992. The 5 WRAMC registrants 2 continued to be followed at WRAMC and remain in CR, 3 were transferred to other institutions (1 of the three died of disease at Portsmouth Naval Hospital). There have been no reports of adverse reactions in the past reporting year. There were no new data reported in the last POG Agenda. Benefits to patients included the possibility of remission of disease.

CONCLUSIONS

Study should be closed at WRAMC. The last patient was enrolled on study at WRAMC in January 1991 therefore, the 10 year follow-up requirement has been met on all patients.

Report Date: 14 August 2001

Work Unit # 6221

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: POG 8821: Intensive Multi-agent Therapy vs. Autologous Bone Marrow Transplant Early in First CR for Children with Acute Myelocytic Leukemia - A Phase III Study

KEYWORDS: autologous bone marrow, transplant, acute myelocytic leukemia

PRINCIPAL INVESTIGATOR: Edwards, Glenn LTC MC
ASSOCIATES: Mosijczuk, Askold COL MC; Crouch Gary LTC MC

DEPARTMENT: Pediatrics
SERVICE: Pediatric Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 27 September 1988

STUDY OBJECTIVE

To: 1) determine DFS with intensive chemotherapy using non-cross resistant drug pairs; 2) determine if short-term intensive therapy with autologous bone marrow transplant (with 4-Hydroperoxycyclophosphamide purge) is effective therapy; and 3) compare the two regimens' results and to correlate outcome with clinical and laboratory features.

TECHNICAL APPROACH

Registrants are 21 years of age and younger with previously untreated acute myelocytic leukemia (AML). Induction for both arms uses intrathecal Ara-C, daunomycin, Ara-C, 6-TG, followed by high-dose Ara-C. Patients are then randomized to receive either IT Ara-C, VP-16/5-AZA plus ABMT with 4-HC purge, or to receive IT Ara-C, HDAC/daunomycin, Ara-C/6-TG, and VP-16/5-AZA.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

This study has been closed since 11 March 1993. The 666 group-wide accrual figure remains unchanged. Of the seven patients registered on protocol at WRAMC four have relapsed (three of the relapsed patients have died of their disease and one is in a second remission after ABMT), one transferred to another POG institution, and two are alive, in first CR, off therapy. There have been no late reports of adverse reactions. Benefits to patients included the possibility of remission of disease.
There were no further reports from POG in the last year.
The number of subjects enrolled to the study since last APR at WRAMC is __0__ and the total enrolled to date at WRAMC is ___7____. The total number enrolled study-wide is __666_____, if multi-site study.

CONCLUSIONS

Study should remain open to follow WRAMC registrants.

Report Date: 19 April 2001

Work Unit # 6242

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: POG 8828: Late Effects of Treatment of Hodgkin's Disease: A POG Non-therapeutic Study

KEYWORDS: childhood, Hodgkin's disease, long-term effects

PRINCIPAL INVESTIGATOR: Edwards, Glenn LTC MC
ASSOCIATES: Mosijczuk, Askold COL MC; Hartman, Kip COL MC; Crouch, Gary LTC MC

DEPARTMENT: Pediatrics
SERVICE: Pediatric Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 23 May 1989

STUDY OBJECTIVE

To estimate incidence of late effects following treatment for Hodgkin's disease on current frontline POG studies and to attempt to identify pre-treatment and/or on-treatment factors which predict high risk of specific late effects.

TECHNICAL APPROACH

Registrants are patients on POG frontline Hodgkin's protocols and are followed through completion of late effects study forms every 3 years.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Group wide, 631 patients have accrued to this study; 58 registrations since the last APR. There were no accruals at WRAMC in the past year; WRAMC total is nine. There have been no adverse effects from participation in this non-therapeutic study. Benefits to patients may result from greater awareness of late effects with subsequent earlier treatment intervention as a result completing the late-effects study forms every 3 years.
[Ref: The Children's Oncology Group Current Reports, Vol I, Spring 2001]

CONCLUSIONS

Study should remain open.

Report Date: 15 March 2001

Work Unit # 6261

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: POG 9047: Neuroblastoma Biology Protocol

KEYWORDS: cytogenetics, neuroblastoma

PRINCIPAL INVESTIGATOR: Edwards, Glenn LTC MC
ASSOCIATES: Mosijczuk, Askold COL MC; Crouch, Gary LtCol

DEPARTMENT: Pediatrics
SERVICE: Pediatric Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 27 February 1990

STUDY OBJECTIVE

To analyze cytogenetics of neuroblastoma cells and determine the clinical significance of genetic variations found, compared to conventional clinical, histologic, and biologic variables in predicting response to treatment or outcome. To develop a neuroblastoma serum and tissue bank for future studies, and to collect natural history and lab data on patients with untreated disease (stages A and DS).

TECHNICAL APPROACH

All newly-diagnosed patients 21 years old or less who are registered on POG neuroblastoma treatment protocols, or stage A or DS (favorable risk), will submit discarded biopsy material and serum for cytogenetic studies and banking.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

This study was closed to accrual in February 2001. Since February 1990, 2202 patients have been enrolled in this biological study; 354 since the last APR. WRAMC has had no new registrations since the last APR, so total WRAMC registrations are 15. There have been no reports of adverse events resulting from participation in this study. Benefits to patients include the possibility that the clinical significance of the genetic rearrangements will more accurately predict treatment outcome.
[Ref: Fall 2000 COG Current Reports of Studies]

CONCLUSIONS

Study is closed to accrual.

Report Date: 6 October 2000

Work Unit # 6302

DETAIL SUMMARY SHEET

TITLE: POG: 9151 Intergroup Rhabdomyosarcoma Study IV: Treatment for Stage 2 and 3 Diseases: A Phase III Trial

KEYWORDS: rhabdomyosarcoma, children, chemotherapy

PRINCIPAL INVESTIGATOR: Edwards, Glenn LTC MC
ASSOCIATES: Mosijczuk, Askold COL MC; Crouch, Gary LtCol MC

DEPARTMENT: Pediatrics
SERVICE: Pediatric Hematology-Oncology

STATUS: O
INTIAL APPROVAL DATE: 26 November 1991

STUDY OBJECTIVE

To compare progression-free survival of children with rhabdomyosarcoma treated with chemotherapy, radiation, and surgery per protocol; to collect data on the toxicity of these treatments; to correlate disease features (cell biology, tumor size and location, and cytogenetic features) with treatment outcome and survival. Study will also collect material for a tumor tissue to use in future tumor biology studies.

TECHNICAL APPROACH

Subjects ages 21 years and less with rhabdomyosarcoma or undifferentiated soft tissue sarcoma will be randomized to receive one of three chemotherapy regimens: vincristine, actinomycim-D, cyclophosphamide; vincristine, actinomycim-D, etoposide; or vincristine, etoposide, ifosfamide. Registrants will also be randomized to receive radiation on a once daily or twice daily schedule. Supportive care with G-CSF will be given. Tumor cytogenetics will be evaluated at a central POG laboratory for future correlations with response data. Patients will be followed for relapse.

PRIOR AND CURRENT PROGRESS

This protocol was closed to accrual in Jan 1998. There has been no new data reported since the last APR. The last IRSG report was reported in POG Fall 1998 Report and fails to break down the registrants (stages 1-3) by stage and combines data from the POG 9150/9151 protocols in IRS IV. Total registrants on these intergroup studies was 988. There remains but one WRAMC registrant due to IRB closure of a required companion study (POG 9153). This patient has developed recurrent disease at the primary site. There were no ADR's at WRAMC and group-wide there has been no unexpected toxicity.
[Data from POG Meeting Agenda and Current Report of Studies, October 1998]

CONCLUSIONS

Study should remain open to follow WRAMC registrant.

Report Date: 15 March 2001

Work Unit # 6311

DETAIL SUMMARY SHEET

TITLE: POG 9182: HIV/Malignancy Biology Study: A Pediatric Oncology Group Aids/Malignancy Network Study

KEYWORDS: AIDS, children, malignancy

PRINCIPAL INVESTIGATOR: Edwards, E. Glenn LTC MC
ASSOCIATES: Mosijczuk, Askold COL MC; Crouch, Gary LtCol MC

DEPARTMENT: Pediatrics
SERVICE: Pediatric Hematology-Oncology

STATUS: C
INITIAL APPROVAL DATE: 28 January 1992

STUDY OBJECTIVE

To establish a national registry of HIV-related malignancies in children; to conduct therapeutic trials on these malignancies; and to determine incidence and viral burden of HIV and several other viruses (EBV, CMV, HHV6, HCV) in tumors and body fluids to correlate with other disease and/or treatment information. To study the difference between tumor tissue in HIV positive and HIV negative children.

TECHNICAL APPROACH

Patients 21 years of age or less will be enrolled from three groups: HIV (+) but cancer (-), HIV (-) but cancer (+), and HIV (+) and cancer (+). They will be asked to donate specimens (tumor tissue and body fluids) for the national registry. Cases of HIV-related malignancy will be matched with cases of the same malignancy in a child who does not have HIV. These control cases will be sought from POG registrants in therapeutic trials. So far, studies on viral burden, tumor cytogenetics, and viral incidence are planned for specimens gathered form all three groups. If other factors related to tumor development become uncovered, specimens may be requested from this registry. Chart data will also be collected.

PRIOR AND CURRENT PROGRESS

This study closed to accrual on 22 September 2000. Total accrual groupwide was 171; 1 since the last APR. There were no registrations at WRAMC. Registration breakdown: Stratum 1 (cases) 43; Stratum 2 (malignancy controls) 54; Stratum 3 (non-malignancy controls) 74. There have been no reports of adverse reactions stemming from participation in this protocol. Potential benefit is better understanding of the infectious agents and molecular changes in HIV-related cancer tissue, and the possible therapeutic adjustments which would result.
[Results reported in Fall 2000 COG Current Report of Studies]

CONCLUSIONS

Study is closed to accrual with no registrations at WRAMC. Study should be closed at WRAMC.

Report Date: 15 March 2001 Work Unit #6314

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: POG 9284/85: Barriers to Enrollment on POG Frontline Therapeutic Clinical Trials and Development of Intervention Strategies; A POG Therapeutic Study

KEYWORDS: accrual, oncology treatment

PRINCIPAL INVESTIGATOR: Edwards, Glenn LTC MC
ASSOCIATES: Mosijczuk, Askold COL MC; Crouch, Gary LtCol

DEPARTMENT: Pediatrics
SERVICE: Pediatric Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 31 March 1992

STUDY OBJECTIVE

To: 1) prospectively identify factors leading to non-accrual of eligible patients on POG frontline therapeutic studies; and 2) develop intervention strategies designed to decrease barriers to patient enrollment on POG studies, thus increasing future accrual rates in the POG.

TECHNICAL APPROACH

Patients diagnosed with cancer at POG institutions and their physicians are surveyed within 7 days of their decision whether to participate on POG treatment studies. Survey results from those who decide not to participate (not register on frontline POG study) will be analyzed and compared to the results of those who do register.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Group-wide accrual is 359; 11 since the previous APR. There have been no additional WRAMC accrual. The total WRAMC registrations are 7. There are too few patients in the control groups to do a matched case-controlled analysis. There have been no adverse reactions reported from participation in the study. This is a non-therapeutic study. Benefits to patients include the possibility that participation in this study may lead to enrollment in an appropriate study.
[Ref: Fall 2000 COG Current Report of Studies]

CONCLUSIONS

Study should remain open.

Report Date: 19 April 2001

Work Unit # 6323

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: POG 9233/34: A Phase III Randomized Trial of Standard vs. Dose-Intensified Chemotherapy <3 years of Age with a CNS Malignancy Treated With or Without Radiation Therapy

KEYWORDS: brain tumor, child, pre-school, chemotherapy

PRINCIPAL INVESTIGATOR: Edwards, Glenn LTC MC
ASSOCIATES: Mosijczuk, Askold COL MC; Hartman, Kip COL MC; Crouch, Gary LTC MC

DEPARTMENT:Pediatrics
SERVICE: Pediatric Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 26 May 1992

STUDY OBJECTIVE

To study efficacy and toxicity of dose intensified chemotherapy in children less than 3 years old with selected types of brain tumors by means of a randomized comparison. To relate response to DNA index of tumor. To attempt to observe for disease progression over 1 year, with the option of giving irradiation if tumor relapses during this year.

TECHNICAL APPROACH

Children less than 3 years of age with selected types of brain tumors will be randomized to receive either intensive or standard chemotherapy (POG 9233). If response is adequate, there will be 1 year of close observation, during which time radiation therapy on POG 9234 will be available if the tumor relapses. Patients who have less than adequate response on 9233 will receive irradiation on POG 9234 as soon as possible. The DNA index of diagnostic tumor tissue will be related to the treatment outcome.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

All strata of POG9233 achieved accrual goals and were closed as of 8 May 1998. POG 9234 was closed to accrual on 14 December 2000. The last reported data are from the Children's Oncology Group Current Report of Studies, Spring 2000. Group wide total accrual for both 9233 and 9234 is 391 (338 on 9233 and 53 on 9234); 0 since the previous APR. WRAMC has four registrations; none in the last year. A fifth patient is being followed at WRAMC after being transferred here from MAMC. Of the 5 patients followed at WRAMC 3 remain in CR, 2 have died of disease. Toxicity has been as expected with this therapy with the most common being myelosuppression (detailed toxicity data reported in Children's Oncology Group Current Report of Studies, Vol II, Spring 2000). Early results from 9233 shows 5 year EFS and survival of 21% and 34%, respectively. Data for 9234 are masked. Benefits to patients include the possibility of remission of disease.

CONCLUSIONS

Study should remain open to follow study registrants at WRAMC.

Report Date: 05 October 2000

Work Unit # 6332

DETAIL SUMMARY SHEET

TITLE: The Effect of Profound Hypoglycemia on the Release of Excitatory Amino Acids in the Central Nervous System of the Developing Pig

KEYWORDS: hypoglycemia, excitatory amino acids, brain damage

PRINCIPAL INVESTIGATOR: Darling, Bryan LT MC USNR
ASSOCIATES: O'Neill, Timothy PhD; Payne, Matthew CPT PhD

DEPARTMENT: Pediatrics
SERVICE:

STATUS: C
INITIAL APPROVAL DATE: July 1992

STUDY OBJECTIVE

To determine if acute severe hypoglycemia is associated with the release of aspartate (ASP) and glutamate (GLU) from the newborn piglet brain, if ASP and GLU release differs in older pigs, and if ASP and GLU release is related to brain activity.

TECHNICAL APPROACH

Newborn piglets and adolescent pigs will be anesthetized and ventilated. Femoral arterial and venous lines will be placed for fluid and medications, blood pressure measurements, and blood samples. A sagittal sinus catheter will be placed for blood sampling. A 3mm loop microdialysis probe will be placed in the hippocampus area using stereotaxic surgery, and perfused at 2.5 ul/min with artificial CSF. Six piglets and six pigs will be injected with 200 IU/kg of regular pork insulin, followed by a continuous infusion of 20 IU/kg/hr. All measurements and samples will be collected at baseline, 30 min, 1 hr, 1.5 hr, and 2 hr of severe hypoglycemia. CSF amino acids will be determined by HPLC.

PRIOR AND CURRENT PROGRESS

Eleven of twelve newborn normoglycemic piglets had no detectable baseline levels (0.5 μM) of AA, while pigs had aspartate and glutamate concentrations of $1.78 \pm 0.44\mu M$ and $3.43 \pm 1.14\mu M$ (mean $\pm$ /SEM) respectively. After 2 hours with plasma glucose values $\leq$ 20mg/dl, piglet aspartate and glutamate concentrations reached but did not significantly exceed normoglycemic pig levels. Elevations in EAA were only measured in piglets whose EEG activity ceased. Aspartate and glutamate concentrations did not increase in insulin treated pigs nor control animals.

CONCLUSIONS

We conclude that newborns with blood glucose values approaching the lowest clinically acceptable values (20 mg/dl) may be protected form EAA-associated neuronal damage during acute hypoglycemia. This protection is provided by lower normoglycemic levels of EAA, and that hypoglycemic levels in newborns did not exceed normoglycemic levels in older pigs.

Report Date: 7 March 2001

Work Unit #6351

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: POG 9317: Chemotherapy for Children with Advanced-Stage (III/IV) Diffuse Undifferentiated Burkitt's Lymphoma and B-Cell ALL; A Phase IV Study

KEYWORDS: Burkitt's lymphoma, Cytoxan, Ara-C

PRINCIPAL INVESTIGATOR: Edwards, Glenn LTC MC
ASSOCIATES: Mosijczuk, Askold COL MC; Crouch, Gary LtCol MC

DEPARTMENT: Pediatrics
SERVICE: Pediatric Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 30 March 1993

STUDY OBJECTIVE

To: 1) evaluate the efficacy of adding VP-16/ifosfamide (VP/IFOS) intensification to the treatment of patients with advanced-stage B-cell malignancies (Stages III and IV DU NHL and B-cell ALL), and to compare the toxicity of high doses of Ara-C given by intermittent bolus vs. bolus/continuous infusion.

TECHNICAL APPROACH

Registrants must be 21 years old or younger and have had no previous chemotherapy. Concomitant registration on POG 9000 (biology study) is required. Children with diagnosed advanced-stage (III-IV) diffuse undifferentiated Burkitt's lymphoma and B-cell ALL will receive randomized induction therapy to compare the toxicity of high-dose Ara-C given by intermittent bolus (q 12 hours x 4) vs. bolus/continuous infusion over 48 hours, followed by randomization to receive or not receive VP/IFOS for intensification.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

The number of subjects enrolled to the study since last APR at WRAMC is __0__ and the total enrolled to date at WRAMC is ___2____. The total number enrolled study-wide is _343_, if multi-site study.
Of the 2 patients enrolled at WRAMC, 1 died of progressive disease after relapse and 1 is alive and remains in CR. Early results so far show no significant difference in event-free survival between ARA-C vs ARA-C+VP/IFOS or continuous infusion vs bolus ARA-C. Group-wide reported ADRs and all toxicities are listed in the report cited below. There has been significant absolute neutrophil count, platelet and hemoglobin toxicity as expected for this therapy. Benefits to patients include the possibility of remission of disease.
[Ref: Fall 2000 COG Current Report of Studies]

CONCLUSIONS

This study was closed to accrual in March 1999. Should remain open to follow study registrant.

Report Date: 15 March 2001 Work Unit # 6364

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: POG 9351/CCG 7921 Trial of Doxorubicin, Cisplatin and Methotrexate with and without Ifosfamide, with and without Muramyl Tripeptide Phosphatidyl Ethanolamine (MTP-PE) for Treatment of Osteogenic Sarcoma

KEYWORDS: doxorubicin, osteogenic, sarcoma

PRINCIPAL INVESTIGATOR: Edwards, Glenn LTC MC
ASSOCIATES: Mosijczuk, Askold COL MC; Crouch, Gary LtCol MC

DEPARTMENT: Pediatrics STATUS: O
SERVICE: Pediatric Hematology-Oncology INITIAL APPROVAL DATE: 22 February 1994

STUDY OBJECTIVE

To: 1) improve survival and compare results of two chemotherapeutic regimens; 2) determine whether histologic response assessed after prolonged therapy with more drugs predicts disease-free survival (DFS) with the same power seen in CCG-782, which used fewer drugs over a shorter time; 3) determine whether liposomal muramyl tripeptide-phosphatidyl ethanolamine can improve DFS; and 4) determine whether MDR expression is useful to determine prognosis or assign therapy.

TECHNICAL APPROACH

Patients </= 30 years old will be treated in a Phase III randomized trial of two chemotherapy regimens for the treatment of newly diagnosed, previously untreated osteogenic sarcoma. One regimen calls for the administration of high-dose methotrexate, doxorubicin, and cisplatin. The other regimen calls for the administration of these agents plus ifosfamide. Chemotherapy is administered for 10 weeks prior to surgical resection of primary tumor and any metastatic disease. Patients also are randomly assigned either to receive MTP-PE with maintenance chemotherapy or to receive maintenance chemotherapy alone.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

This protocol was closed to accrual on 25 Nov 1997. Total intergroup enrollment was 679 (CCG 358, POG 321). There have been no additional WRAMC registrations; total remains 4. There were eight toxic deaths on this study: five due to infections during neutropenia, one an intraoperative mortality, and there is insufficient data to characterize the other two. Results to date show no difference in outcome due to MTP in the CDDP/DOX/HDMTX regimen (3yr EFS=69%). There does appear to be a difference in outcome with the four-drug regimen when MTP was added (3yr EFS= 59% without MTP vs 80% with MTP). A detailed discussion of results and toxicity appears in the reference cited below. There have been no toxic deaths at WRAMC. Three of the four WRAMC registrants have died of recurrent or progressive disease. The other WRAMC registrant is alive with no evidence of disease. Benefits to patients include the possibility of remission of their disease.
[Data is from Spring 2000 COG Current Report of Studies]

CONCLUSIONS

Study is closed to accrual. Study should remain open to follow WRAMC registrant.

Report Date: 1 July 2001

Work Unit # 6374

DETAIL SUMMARY SHEET

TITLE: The Role of Nitric Oxide in Cerebrovascular Autoregulation in the Newborn Piglet

KEYWORDS: cerebrovascular, autoregulation, nitric oxide

PRINCIPAL INVESTIGATOR: Mark Thompson, MAJ, MC, USA
ASSOCIATES: J. Timothy O'Neill, Ph.D.

DEPARTMENT: Pediatrics
SERVICE: Neonatology

STATUS: O
INITIAL APPROVAL DATE: August 1994

STUDY OBJECTIVE

To determine 1) the relationship between cerebral perfusion pressure and blood flow during induced hypertension in the newborn piglet: and 2) the role on nitric oxide in the relationship between cerebral perfusion pressure and blood flow.

TECHNICAL APPROACH

Chloralose and urethane anesthetized piglets were catherized and instrumented for the measurement of regional blood flows with radioactive microspheres. Blood gases and pH were maintained in the normal range throughout the experiment. Blood flows were measured before and 30 minutes after 7-NI (25mg/kg i.p.) or peanut oil (the vehicle for the 7-NI,3 cc/kg i.p.). Mean arterial pressure (MAP) was then raised to 100-110 mmHg and 110-125 mmHg with aortic occlusion and/or norepinephrine infusion and blood flow measured in each pressure range.

PRIOR AND CURRENT PROGRESS

We have previously shown that blockade of nitric oxide synthase (NOS) alters the newborn piglet's ability to maintain rCBF during acute hypertension (*Soc Neurosci Abstr 1996,* 22:1103). When NOS was inhibited by N-nitro-L-arginine methyl ester (L-NAME), blood flow to the cerebrum, particularly the cortical gray matter and occipital lobes, did not change when MAP was raised 36%. Whereas this elevation of MAP resulted in a 60-80% increase in blood flow in these structures of untreated animals. The lower brain rCBFs including medulla/pons midbrain/diecephalon and cerebrum were not altered by the blood pressures studied. Since L-NAME inhibits both neuronal and endothelial isoforms of NOS< we sought to determine the role of the neuronal isoform of NOS (nNOS) in the observed response by selectively inhibiting nNOS with 7-Nitroindazole (70-NI) in piglets. 7-NI did not change MAP, as did L-NAME. Baseline rCBFs were also not altered after 7-NI. After 7-NI, we elevated MAP from 83$\pm$ 3 to 103$\pm$2 and 117$\pm$1 sequentially. It appeared that no brain structure was capable of autoregulation after 7-NI. However, statistical analysis did not confirm this conclusion. Oxygen consumption to the cerebrum was monitored and was not elevated by 7-NI nor the elevated MAP.

CONCLUSIONS

Blockade of nNOS with 7-NI does not alter the newborn piglet brain's capability to maintain blood flow when blood pressure is acutely elevated. In light of our previous data, it seems possible that NO of endothelial origin is solely responsible for the upper limit of autoregulation during acute episodes of hypertension.

Report Date: 27 June 2001 Work Unit # 6376

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: Prevalence of Islet Cell Antibodies in Sera of Relatives of Children with IDDM

KEYWORDS: IDDM, Islet, antibodies

PRINCIPAL INVESTIGATOR: Gary, Francis COL MC
ASSOCIATES:

DEPARTMENT: Pediatrics
SERVICE: Pediatric Endocrinology

STATUS: C
INITIAL APPROVAL DATE: 30 August 1994

STUDY OBJECTIVE

To determine the prevalence of islet cell antibodies in the mixed ethnic and geographically derived population of the Department of Defense

TECHNICAL APPROACH

Sera were obtained from relatives of patients with IDDM and sent to Stanford CA for islet cell antibody determination.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

The national Diabetes Prevention Trial I is currently collecting data on this topic from all investigators throughout the U.S. No publication has yet been generated from this data.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date is 181.

CONCLUSIONS

This study is ready to be closed. A total of 181 samples have been sent for determination and due to the outdated nature of the consent form, protocol and method of data analysis, we request the study be closed. It is our intention to replace this with a new and updated version in the near future.

Report Date: 20 November 2000

Work Unit #6383

DETAIL SUMMARY SHEET

TITLE: POG 9405: ALinC16; Protocol for Patients with Newly Diagnosed Standard-Risk Acute Lymphoblastic Leukemia - POG Phase III Study

KEYWORDS: leukemia, lymphoblastic, children

PRINCIPAL INVESTIGATOR: Edwards, Glenn LTC
ASSOCIATES: Mosijczuk, Askold COL MC; Crouch, Gary LTC MC

DEPARTMENT: Pediatrics
SERVICE: Pediatric Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 20 December 1994

STUDY OBJECTIVE

To: 1) determine the efficacy of a higher vs. standard dose MTX infusion during consolidation; 2) describe the incidence of adverse reactions occurring with administration of higher dose MTX; 3) determine the efficacy of delivering oral 6 MP on a once vs. twice daily schedule during continuation.

TECHNICAL APPROACH

Newly diagnosed B-Precursor ALL patients (including B-ALL that is not L3 morphology) will be enrolled prior to registration on POG 9400. Patients will be randomized to compare the efficacy of a higher vs. standard dose MTX infusion during consolidation.

PRIOR AND CURRENT PROGRESS

This study was closed to accrual in December 1995 due to excessive acute neurotoxicity. A total of 299 patients were registered on the protocol group-wide, with 285 non-Down patients achieving remission. One patient has been registered at WRAMC and continues to do well in complete remission without evidence of neurotoxicity. Reported toxicity was similar to that seen historically with methotrexate, including slurred speech, staring, ataxia and other gross motor findings, behavioral disorders, seizures, somnolence, and loss of milestones. Of concern was that, if actuarial projections continued, the incidence of neurotoxicity would approach 30%, compared with 3-12% historically. The protocol therapy was amended in January 1996 to minimize the risk of CNS toxicity in patients already enrolled and was closed early due to predicted neurotoxicity in the protocol. The last report from POG (Joint POG/CCG Fall 1999 Meeting Agenda and Current Report of Studies) was restricted to reporting of CNS toxicity. Of the 285 patients, 70 (25%) had a reportable CNS adverse event; 29 (10%) were seizures. Benefits to patients included the possibility of remission of disease.
[Results reported in Joint POG/CCG Fall 1999 Meeting and Agenda and Current Report of Studies]

CONCLUSIONS

Study is closed to accrual but should remain open to follow WRAMC registrant.

Report Date: 20 November 2000 Work Unit #6384

DETAIL SUMMARY SHEET

TITLE: POG 9406: ALinC16; Protocol for Patients with Newly Diagnosed High-Risk Acute Lymphoblastic Leukemia - A POG Phase III Study

KEYWORDS: newly-diagnosed, high-risk, lymphoblastic leukemia

PRINCIPAL INVESTIGATOR: Edwards, Glenn LTC MC
ASSOCIATES: Mosijczuk, Askold COL MC; Crouch, Gary LtCol MC

DEPARTMENT: Pediatrics
SERVICE: Pediatric Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 20 December 1994

STUDY OBJECTIVE

To: 1) compare, in a randomized trial, the efficacy and toxicity of 12 intensive courses of IV MTX/6-MP vs. 12 intensive courses of alternating chemotherapy pairs; and 2) assess short-term toxicity of modified regimen B (Treatment C) where higher-dose MTX is substituted in first cycle of consolidation.

TECHNICAL APPROACH

Newly diagnosed non-T, non-B ALL patients who fit the following criteria will be enrolled: 1-21 years old, poor prognostic features based on age, ploidy, translocations, and immunophenotypes, and with no history of prior treatment. Two treatments will be compared: 12 intensive courses of IV MTX/6MP vs. 12 intensive courses of alternating chemotherapy pairs (MTX/6-MP, VM-26/Ara-C, daunomycin/Ara-C).

PRIOR AND CURRENT PROGRESS

This study was closed to accrual on 15 Nov 99, having met its accrual goal. Final accrual is 906 groupwide; 73 since the last APR. No patients were registered at WRAMC since the last APR leaving the total at three. All 3 WRAMC patients are in CR. The most significant toxicity has been neurotoxicity which resulted in an amendment to the protocol adding additional leukovorin and changing triple intrathecal chemotherapy to methotrexate alone. The latest actuarial projection is an 11% CNS ADR rate by the end of treatment. There were no adverse reactions at WRAMC since the last report. Results, although early, show an overall response rate (CR) of 97% and a CCR for randomized patients of 81.3% (± 2.2) at 2-3 years. Survival curves are still unstable. Benefits to patients include the possibility of disease remission.
[Results and ADR's reported in COG Fall 2000 Current Report of Studies]

CONCLUSIONS

Study is closed to accrual but should remain open to follow enrolled patients.

Report Date: 7 March 2001

Work Unit #6386

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: POG 9362: A Phase II Study of Alpha Interferon in HIV-Related Malignancies; A Pediatric Oncology Groupwide Study

KEYWORDS: interferon, HIV, malignancies

PRINCIPAL INVESTIGATOR: Edwards, Glenn LTC MC
ASSOCIATES: Mosijczuk, Askold COL MC; Crouch, Gary LtCol MC

DEPARTMENT: Pediatrics
SERVICE: Pediatric Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 28 March 1995

STUDY OBJECTIVE

To: 1) estimate the complete response rate for HIV-related malignancies treated with alpha interferon; 2) estimate the 1-year disease-free survival; and 3) evaluate the toxicity of alpha interferon alone or in combination with anti-retroviral therapy.

TECHNICAL APPROACH

All patients are required to be enrolled in POG 9182, and in compliance with all specimen submission requirements of that protocol. Additional tissue sampling will be minimized, including CSF or blood sampling, except as required for monitoring for toxicity and tumor response. HIV-positive children with refractory or newly diagnosed malignancies will be treated with alpha IFN alone or in combination with other antiretroviral agents.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

The number of subjects enrolled to the study since last APR at WRAMC is __0__ and the total enrolled to date at WRAMC is ___0____. The total number enrolled study-wide is ___8____, if multi-site study. See attached report from Fall 2000 COG Current Report of Studies.

CONCLUSIONS

Study should remain open for patient accrual.

Report Date: 15 March 2001 Work Unit #6387

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: POG 9421: Phase III Evaluation of Standard vs. High-Dose Ara-C Induction Followed by the Randomized Use of Cyclosporin A as an MDR Reversal Agent, Compared to Allogeneic BMT, in Childhood AML

KEYWORDS: allogeneic, BMT, AML

PRINCIPAL INVESTIGATOR: Edwards, Glenn LTC MC
ASSOCIATES: Mosijczuk, Askold COL MC; Crouch, Gary LtCol MC

DEPARTMENT: Pediatrics
SERVICE: Pediatric Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 28 March 1995

STUDY OBJECTIVE

To: 1) determine the effect of high-dose vs. standard-dose Ara-C induction on complete response (CR) and event-free survival (EFS) in childhood AML; 2) compare the EFS in childhood AML after three cycles of consolidation with or without the multi-drug resistance (MDR) modulator cyclosporin A; 3) compare the EFS between patients genetically randomized between allogeneic BMT and chemotherapy.

TECHNICAL APPROACH

To test, in a randomized study, the role of HD Ara-C in military health care beneficiaries who are <21 years of age, presenting with newly-diagnosed acute myeloid leukemia who have had no prior therapy.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

This study achieved its planned accrual and was closed to accrual on 15 August 1999. Final accrual was 654 subjects group-wide, 54 since the last APR. Nineteen patients were ineligible leaving 635 eligible patients. There were no new registrations at WRAMC since the last APR, leaving the total at 5. Two of these patients are still being followed at WRAMC and are in CR; 2 have been transferred to other military POG institutions; 1 patient registered at WRAMC died of progressive disease after a BMT in first CR. The overall remission rate is 89.2%. A minimum of 2 years follow-up is required for EFS and a formal analysis will be performed in the Fall 2001. Myelotoxicity has been significant but as anticipated. ADR's and toxicity details are listed in the reference cited below. Benefits to patients include the possibility of remission of disease.
[Ref: Joint POG/CCG Fall 1999 Meeting Agenda and Current Report of Studies, October 1999]

CONCLUSIONS

Study is closed to accrual. Study should remain open for follow-up of WRAMC registrants.

Report Date: 19 April 2001

Work Unit # 6388

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: POG 9201 ALINC #16: Treatment for Patients with Lesser Risk Acute Lymphoblastic Leukemia - A Pediatric Phase III Study

KEYWORDS: acute, lymphoblastic, leukemia

PRINCIPAL INVESTIGATOR: Edwards, Glenn LTC MC
ASSOCIATES: Mosijczuk, Askold COL MC; Hartman, Kip COL MC; Crouch, Gary LTC MC

DEPARTMENT: Pediatrics
SERVICE: Pediatric Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 23 May 1995

STUDY OBJECTIVE

To: 1) confirm the outstanding results in patients with lesser-risk non-T, non-B acute lymphoblastic leukemia (ALL) treated in a fashion similar to the least intensive arm of POG 8602 (ALinC 14, Arm A); and 2) study laboratory correlates from POG 9400 and clinical correlates with outcome in pooling studies 9201, 9405, and 9406.

TECHNICAL APPROACH

Military health care beneficiaries who are </= 21 years of age with newly-diagnosed ALL will be prospectively identified to be at lowest risk of treatment failure based on the new consensus risk groups and through the use of trisomies 4 and 10 in a trial to confirm the very favorable results of ALinC #14.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

This study was closed to accrual on Nov. 14, 1999 with a final group-wide accrual on the phase III part of this study of 625. There are four WRAMC registrations; no additional registrations since the last APR. One of these four have transferred to another POG institution. WRAMC has accepted two transfer patients on protocol from other POG institutions. Five patients, therefore, are followed on this protocol at WRAMC. Of these 5, four remain in CR and one has relapsed and is now in a second remission. There are no reports of adverse reactions at WRAMC. Group-wide there have been 3 induction deaths, 37 relapses, and two remission deaths (infection) amongst 622 eligible, not too early Phase III patients. Aside from the 3 induction deaths all patients have achieved remission. Event-free survival at 4 years is 91% but the curve past 3 years is still unstable. Benefits to patients include the possibility of remission of disease. [Ref: The Children's Oncology Group Current Reports, Vol I, Spring 2001]

CONCLUSIONS

Study should remain open to follow study registrants at WRAMC.

Report Date: 01 June 2001

Work Unit # 6391

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: The Effect of Sphingomyelinase on Gene Transcription in Steroidogenic Cells

KEYWORDS: sphingomyelinase, StAR, steroid

PRINCIPAL INVESTIGATOR: Francis, Gary COL MC
ASSOCIATES:

DEPARTMENT: Pediatrics
SERVICE: Endocrinology

STATUS: C
INITIAL APPROVAL DATE: 18 July 1995

STUDY OBJECTIVE

The study was designed to determine the effect of sphingomyelinase and ceramide on the transcription of steroidogenic genes using JEG-3 (placental) cells and MA-10 (Leydig) cells.

TECHNICAL APPROACH

JEG-3 and MA-10 cells were grown in the laboratory in serum free media and the MA-10 cells were stimulated with human chorionic gonadotropin (hCG). Total RNA was isolated from control cultures as well as stimulated cells at various times ranging from 30 min-24 hours. Total RNA was reverse – transcribed and specific gene products amplified by semi-quantitative PCR.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

There are no subjects enrolled in this study. The study used tissue culture only. We found a significant up-regulation of StAR gene expression, but no other significant changes in other steroidogenic enzyme gene expression. The results have been published and no further work on this project is planned.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 0. The total number enrolled study-wide is 0, if multi-site study.

CONCLUSIONS

HCG stimulates StAR gene transcription in MA-10 cells, and ceramide stimulates StAR gene transcription in JEG-3 cells.

Report Date: 12 July 2001

Work Unit # 6397

DETAIL SUMMARY SHEET

TITLE: POG 9354/CCG 7932: Phase III Evaluation of Intensified Vincristine, Doxorubicin, Cyclophosphamide, Ifosfamide, and Etoposide in the Treatment of Newly-Diagnosed Ewing's Sarcoma or Primitive Neuroectodermal Tumor of Bone or Soft Tissue

KEYWORDS: newly-diagnosed, Ewing's sarcoma

PRINCIPAL INVESTIGATOR: Edwards, Glenn LTC MC
ASSOCIATES: Mosijszuk, Askold COL MC; Hartman, Kip COL MC; Crouch, Gary LTC MC

DEPARTMENT: Pediatrics
SERVICE: Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 12 July 2001

STUDY OBJECTIVE

To compare the even-free survival, and toxicity in patients with Ewing's sarcoma treated with a 48-week course of standard-dose vincristine, doxorubicin, cyclophosphamide, ifosfamide, MESNA, and etoposide plus G-CSF, with that of patients treated with the same agents given in a 30-week dose-intensified regiment.

TECHNICAL APPROACH

Patients less than 30 years of age with newly-diagnosed Ewing's sarcoma or PNET of bone or soft tissue will be randomized to receive either the 48-week course of standard-dose vincristine, doxorubicin cyclophosphamide, MESNA and etoposide plus G-CSF, or the 30-week dose-intensified regiment using the same agents.

PRIOR AND CURRENT PROGRESS

This study has met accrual goals and was closed to further accrual on 9/15/98. There were 492 group wide registrations. Three patients have been registered at WRAMC and are alive in remission. Myelosuppression and mucositis are the predominant toxicities and two are followed t WRAMC and are alive in remission. Myelosuppression and mucositis are the predominate toxicities and appear to be more severe in Regiment B (intensified regiment) than in Regimen A. There were a total of 7 toxic deaths, 4 were on Regiment. Two of the, seven were due to post-0surgical complications. Adverse drug reactions seem equally distributed between the 2 regimens. Secondary leukemia has been reported in 8 patients (4 in each arm). AT this time, the incidence of secondary leukemia appears to be no greater than that reported in previous studies. Response is masked. Overall even-free survival and survival are 73.0 (SE4.5) and 81.8 (SE 4.0) respectively at 3 years. Benefits to patients include the possibility of remission of disease., (Reference: COG Current Report of Studies, Spring 2001)

The number of subject enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 3. The total number enrolled study-wide is 492, if multi-site study.

CONCLUSIONS

Study should remain open at WRAMC to follow WRAMC registrants.

Report Date: 14 August 2001 Work Unit # 6400

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: An Overview of the Research Protocol Entitled POG 9440/CCG 4941: National Wilms' Tumor Study - 5: Therapeutic Trial and Biology Study

KEYWORDS: Wilms', therapeutic, biology

PRINCIPAL INVESTIGATOR: Edwards, Glenn LTC MC
ASSOCIATES: Mosijczuk, Askold COL MC; Crouch, Gary LTC MC

DEPARTMENT: Pediatrics
SERVICE: Pediatric Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 26 September 1995

STUDY OBJECTIVE

To: 1) increase the survival rate of children with favorable Wilms' tumor and other renal tumors of childhood; 2) determine if loss of heterozygosity for chromosome 16q markers in tumor tissue is associated with a poorer diagnosis for children with favorable histology Wilms' tumor; and 3) determine if loss of heterozygosity for chromosome lp markers in tumor tissue is associated with a poorer prognosis for children with favorable histology Wilms' tumor.

TECHNICAL APPROACH

Pediatric military health care beneficiaries will be registered as either studied, followed, or registered only. Study patients must be less than 16 years of age, not received chemotherapy or radiation therapy, and have a stage I-IV favorable histology Wilms' tumor, stage I-V focal or diffuse anaplastic Wilms' tumor stage I-V clear-cell sarcoma of the kidney or stage I-V rhabdoid tumor of the kidney. Patients must have undergone a nephrectomy.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

The last report from the Renal Tumors Committee of COG (Nov 2000) did not include accrual data. There were no WRAMC registrations in the past year and the total remains 7. One of the patients registered on study at WRAMC was transferred to another POG institution, so there are currently 6 patients followed at WRAMC on this protocol. Relapse-free survival for patients with favorable histology (FH) Stage I-IV tumors is consistent with historical expectations. Notably, all children who relapsed following nephrectomy only, remain alive. Results for Stage I focal and diffuse anaplasia disease may not be equivalent to Stage I favorable as expected. This will be followed closely. Patients with Stages II or III with focal or diffuse anaplasia appear to be faring better on NWTS 5. Stage I CCSK currently has 100% RFS although with small numbers (8 pts). CCSK stages II-IV is also looking good with 85% 2 yr RFS. Patients with stage IV diffuse anaplasia and those with stages I-IV rhabdoid tumor continue to fare poorly despite treatment with new regimens, I and RTK, and will be reviewed for possible closure of these Phase II studies. There have been no AER/ADR's at WRAMC and none were reported by the Renal Tumors Committee. Benefits to patients include the possibility of remission of disease. [Reference: Minutes of Renal Tumors Committee Meeting Nov 4, 2000]

The number of subjects enrolled to the study since last APR at WRAMC is __0__ and the total enrolled to date at WRAMC is ___7____. The total number enrolled study-wide is _(see above)_, if multi-site study.

CONCLUSIONS

Study should remain open.

Report Date: 22 November 2000

Work Unit # 6401

DETAIL SUMMARY SHEET

TITLE: Support of Pediatric Oncology Group Activities, WRAMC

KEYWORDS: cancer, grant, children

PRINCIPAL INVESTIGATOR: Edwards, Glenn LTC MC
ASSOCIATES: Mosijczuk, Askold COL MC; Crouch, Gary LTC MC

DEPARTMENT: Pediatrics
SERVICE: Pediatric Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 30 January 1996

STUDY OBJECTIVE:
The NIH grant application is to bring in the funds in support of the research conducted at WRAMC sponsored by the Pediatric Oncology Group.

TECHNICAL APPROACH:
None.

PRIOR AND CURRENT PROGRESS
Please refer to the individual POG protocols.

CONCLUSIONS
None.

Report Date: 25 May 2001

Work Unit # 6405

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: A Multicenter Study to Determine the Prevalence and Clinical Characteristics of Barrett's Esophagus in Childhood

KEYWORDS: Barrett's Esophagus, esophagitis, gastroesophageal reflux

PRINCIPAL INVESTIGATOR: COL Philip L. Rogers MC
ASSOCIATES:

DEPARTMENT: Pediatrics
SERVICE: Pediatric GI & Nutrition

STATUS: O
INITIAL APPROVAL DATE: 28 May 1996

STUDY OBJECTIVE

To determine the prevalence of short segment Barrett's esophagus in pediatric patients presenting for esophagogastroduodenoscopy (EGD); 2) describe the clinical and histologic findings in patients with Barrett's esophagus; 3) Correlate the clinical and histologic findings in patients with reflux esophagitis; and 4) Validate the use of a gastroesophageal reflux questionnaire in the evaluation of gastroesophageal reflux disease in children.

TECHNICAL APPROACH

The study population will consist of 650 patients consecutively enrolled who are scheduled for routine EGD by the division of Pediatric Gastroenterology and Nutrition at WRAMC and other participating centers. A gastroesophageal reflux questionnaire will be completed prior to the performance of an EGD. A standard EGD with biopsies will be performed. Additionally, a biopsy at the squamocolumnar junction will be obtained. The histologic characteristics of the esophageal biopsies and prevalence of SSBE will be determined. The clinical presentations of the patients, as determined by the questionnaires, will be compared to the histologic findings. The ability to determine esophagitis by the use of questionnaires will be determined.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

307 patients have been enrolled in the study at WRAMC to date. None have been enrolled in the past year. We have stopped enrolling patients (as of 15 April 1999) with the plan to review all of the present data. The questionnaires have been processed for entry into a database and pathology has been reviewed. One paper is in the final stage before submission for publication with the conclusions given below. The data will next be reviewed to evaluate the endoscopic and histologic findings other than Barrett's esophagus. Another abstract is expected to be submitted in this fiscal year. There have been no serious or unexpected adverse reactions. No patients have been withdrawn from the study.

CONCLUSIONS

Our study found one case of SIM-GEJ, and two cases of possible BE in 182 patients who were studied. The prevalence of SIM-GEJ, and of possible BE were 0.55% (0.01-3.02%. 95% confidence interval) and 1.10% (0.13-3.91%, 95% confidence interval) respectively. The patient with SIM-GEJ had no history suggestive of GER, and no endoscopic histologic findings to suggest GER. On the other hand, our patients with possible BE had a history of GER. We did not find any cases of SSBE or LSBE. The prevalence of the variants of BE in childhood appear to be extremely low and certainly much lower than those found in adults. Although the numbers in this study are small, both patients with possible BE had a significant history of GER disease which increased our suspicion for BE. We believe that the rarity of all types of BE and the rarity of adenocarcinoma in children does not warrant biopsy of the SCI for the evaluation of BE during routine EGD.

Report Date: 14 May 2001 Work Unit # 6408

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: POG 9605: AlinC 16; Protocol for Patients with Newly-Diagnosed Standard-Risk Acute Lymphoblastic Leukemia (ALL)

KEYWORDS: pediatrics, lymphoblastic, leukemia

PRINCIPAL INVESTIGATOR: Edwards, Glenn LTC MC
ASSOCIATES: Mosijczuk, Askold COL MC; Hartman, Kip COL MC; Crouch, Gary LTC MC

DEPARTMENT: Pediatrics
SERVICE: Pediatric Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 25 June 1996

STUDY OBJECTIVE

To: 1) determine if EFS can be improved with the addition of 6 months of delayed intensification with divided-dose oral methotrexate plus oral 6 MP as divided, or once a day dose given during intensification and continuation; 2) correlate laboratory and clinical findings from this study, and POG #s 9400, 9201, and 9406; 3) assess significance of marrow findings after 2 weeks of induction; and 4) describe occurrence and prognostic significance of elevated transaminases.

TECHNICAL APPROACH

After induction and consolidation, patients are randomized to one of four late intensification/consolidation arms. Regimen 1: Weekly IM MTX plus once daily oral 6MP intensification followed by daily oral 6MP in continuation. Regimen 2: Divided dose oral MTX plus once daily oral 6MP intensification followed by daily oral 6MP in continuation. Regimen 3: Weekly IM MTX plus divided-dose oral 6MP intensification followed by divided-dose 6MP in continuation. Regimen 4: Divided-dose oral MTX plus divided-dose oral 6MP intensification followed by divided-dose 6MP continuation. All patients will receive vincristine/prednisone pulses and IT MTX/Ara-C/HC during continuation therapy.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

This study was closed to accrual on Nov 15, 1999. Final group-wide accrual was 1087. WRAMC has 3 registrants and two others accepted in transfer from other POG institutions. There have been no new registrations at WRAMC since the last report. Three are currently being followed at WRAMC and remain in CR, and two have been transferred to other POG institutions. There have been 1067 CR's, 7 failed to achieve remission, and 2 are awaiting documentation in patients evaluable for response (3 are not evaluable). So far, 113 randomized patients have failed (107 relapses, 2 infectious death, one toxic death, one remission death, and 2 second malignancy). Event free survival curves are unstable at 2 years. There have been no ADR's at WRAMC. In the previous study 21% of the patients had adverse CNS events. There have been 139 ADR's reported groupwide involving the CNS. The actuarial projections for CNS events are 6.6% by the end of consolidation and 12.3% by the end of therapy. For seizures, it is 2.2% by the end of consolidation and 6.0% by the end of therapy.
[Data from COG Current Report of Studies, April 2001 in which details of ADR's and toxicity may be found]

CONCLUSIONS

Study is closed to patient accrual but should remain open for patient follow-up.

Report Date: 12 July 2001

Work Unit # 6410

DETAIL SUMMARY SHEET

TITLE: POG 9404: T-Cell #4 Protocol - Intensive Treatment for T-Cell Acute Lymphoblastic Leukemia and Advanced-Stage Lymphoblastic Non-Hodgkin's Lymphoma

KEYWORDS: leukemia, T-Cell, chemotherapy

PRINCIPAL INVESTIGATOR: Edwards, Glenn LTC MC
ASSOCIATES: Mosijczuk, Askold COL MC; Hartman, Kip LTC MC; Crouch, Gary LtCol MC

DEPARTMENT: Pediatrics
SERVICE: Hematology-Oncology

STATUS: O
INITIAL APPROVAL DATE: 27 August 1996

STUDY OBJECTIVE

To: 1) determine, in a randomized trial, the effectiveness of high-dose methotrexate (HD MTX) when added to a multi-agent chemotherapy backbone (DFC1 87-001) proven effective in T-Cell acute lymphoblastic leukemias (T-all); 2) determine, in a randomized trial, the role of the cardioprotectant Zinecard (DZR) in preventing cardiotoxicity; and 3) study the biology of T-Cell lymphoid malignancies, including the correlation of minimal residual disease with event-free survival, utilizing the TAL 1 proto-oncogene, p53 and p16 tumor suppressor genes, and drug sensitivity profiles of blast cells to adriamycin, methotrexate and cytarabine.

TECHNICAL APPROACH

Patients with T-ALL (DR-T+) who are <22 years old, and patients with lymphoblastic lymphoma Murphy stage III or IV who are <21 years old (including those <12 months) will be randomized to receive or not receive high-dose methotrexate and Zinecard. Response rates and degree of anthracycline cardiotoxicity will be evaluated and compared.

PRIOR AND CURRENT PROGRESS

A total of 503 patients have been accrued; 123 since the last APR. There have been three WRAMC registrations; no new registrations since the last APR. All three subjects at WRAMC are doing well in remission. On September 27, 2000 Data Monitoring Committee action led to the closure of Arms 1 and 2, due to a sequential analysis demonstrating efficacy of the high dose MTX. The Zinacard randomization remains open. So far, there have been 79 failures reported (30 induction, 43 relapses, 3 remission deaths, and 3 second cancers: AML, Large Cell NHL, Granulocytic Sarcoma). Early EFS results show a 2-year survival of 77.5 (se 3.2) and 85.2(se 4.1) for T-ALL and NHL, respectively. While non-CNS toxicity has been near the expected rate, an apparent excess of CNS events has been observed. As a result of concerns about the excess CNS toxicity the protocol therapy for intrathecal medications was amended in September 1999. It is too early to determine if these treatment changes have significantly altered the incidence of CNS toxicity. There have been no CNS events in the WRAMC patients. Benefits to patients include the possibility of remission of disease. {Reference: COG Current Report of Studies, Spring 2001}

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 3. The total number enrolled study-wide is 503.

CONCLUSIONS

Study should remain open.

Report Date: 29 August 2000

Work Unit # 6414

DETAIL SUMMARY SHEET

TITLE: Oncogene Expression in Thyroid Neoplasia

KEYWORDS: thyroid, cancer, oncogene

PRINCIPAL INVESTIGATOR: Catherine Dinauer MAJ MC
ASSOCIATES: Gary Francis COL MC

DEPARTMENT: Clinical Investigations
SERVICE: Pediatric Endocrine

STATUS: O
INITIAL APPROVAL DATE: 05 October 1999

STUDY OBJECTIVE

This study is designed to examine the expression of various oncogenes in thyroid cancers and to correlate the expression with the risk of metastasis and recurrence.

TECHNICAL APPROACH

Archived thyroid tumors are sectioned and either 1) stained by immunoperoxidase specific for each oncogene or 2) extracted for RNA which is then reverse transcribed and amplified (PCR) for detection of specific mutations and mRNA levels. The intensity of expression is then correlated with the risk of metastasis and recurrence.

PRIOR AND CURRENT PROGRESS

A total of 32 papillary thyroid cancers, 10 follicular thyroid cancers, and 13 benign lesions have been stained for expression of various oncogene protein products, including p53, VEGF, cMET, HGF/SF, and VEGF receptors. In addition, RNA has been extracted and amplified for expression of ras and ret/PTC mutations.

CONCLUSIONS

The techniques for immunohistochemistry and RNA amplification have been optimized with paraffin embedded tissues. Progress has been excellent on this project, and the results have been used to target several specific oncogenes in additional DCI supported protocols.

Report Date: 29 August 2000

Work Unit # 6416

DETAIL SUMMARY SHEET

TITLE: Analysis of Parental Time Allocation in Families where Children with Special Needs Live with their Unaffected Siblings

KEYWORDS:

PRINCIPAL INVESTIGATOR: Levin, Sondra MD
ASSOCIATES:

DEPARTMENT: Pediatrics
SERVICE:

STATUS: O
INITIAL APPROVAL DATE: 19 November 1996

STUDY OBJECTIVE

To determine whether there is a difference in parental time allocation for siblings in families with a disabled child vs. families without a disabled child.

TECHNICAL APPROACH

Data will be compiled by having parents voluntarily complete a study questionnaire. Parents will be recruited from the general pediatrics clinic and the genetics clinic at WRAMC as well as from the University of Maryland, where this study was also approved. Follow-up weekly diaries of time spent with children at home will be solicited as well.

PRIOR AND CURRENT PROGRESS

No new questionnaires completed over the past year.

CONCLUSIONS

No new data obtained so no further conclusions drawn.

Report Date: 30 November 2000

Work Unit # 6421

DETAIL SUMMARY SHEET

TITLE: Transfusion Practice in the Pediatric Critical Care Unit- Variability and Relationship to Outcome

KEYWORDS:

PRINCIPAL INVESTIGATOR: Patterson, Harlan COL MC
ASSOCIATES: Allyson Goodman MD, Murray Pollack MD, Jacqueline Williams MD, Steven Lucking MD, Aaron Zuckerberg MD, Vinay Nadkami MD

DEPARTMENT: Pediatrics
SERVICE: PICU

STATUS: C
INITIAL APPROVAL DATE: 04 November 1997

STUDY OBJECTIVE
(1) To define a relationship that currently exists for blood transfusion and patient outcome at 6 different PICUs.
(2) Propose a more "appropriate" transfusion "trigger" for the pediatric patient if possible.

TECHNICAL APPROACH
60 recent PICU patients with Hgb less than 9.1 mg/dl

PRIOR AND CURRENT PROGRESS
Abstract submitted for presentation at Society for Critical Care Medicine annual meeting.

CONCLUSIONS
RBC transfusions are associated with increased PICU resource use. (This is consistent with the increased mortality seen in adult studies)

Report Date: 22 December 2000 Work Unit # 6423

DETAIL SUMMARY SHEET (Human Use Protocol)

TTTLE: Sphingomyelinase and Ceramide Regulate Steroid Synthesis

KEYWORDS: ceramide, steroid hormone

PRINCIPAL INVESTIGATOR: Francis, Gary COL MC
ASSOCIATES:

DEPARTMENT: Pediatrics
SERVICE:

STATUS: O
INITIAL APPROVAL DATE: 03 February 1998

STUDY OBJECTIVE

To determine if SMAse or Ceramide have effects on the genes which control steroid biosynthesis.

TECHNICAL APPROACH

Messenger RNA will be isolated from MA-10, and IEG-3 cells incubated with either control media, or media containing SMAse or ceramide. The specific sequence encoding steroidogenic enzymes will be reverse transcribed and amplified to determine if the mRNA is increased following SMAse or Ceramide stimulation.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

The specific mRNAs encoding the major steroidogenic enzymes have been reverse transcribed and amplified. There is no change in the steady state mRNA level for any message so far examined. This suggests that a more likely possibility is that SMAse or ceramide activate one or more of these enzymes by a post-transcriptional mechanism. This could include increased enzyme phosphorylation, inhibition of phosphatase activity, or cytoskeletal changes that increase the bioavailability of cholesterol for enzyme activation.

CONCLUSIONS

No changes in mRNA levels have been identified, however, the possibility of a mutant CYP-17 gene product is shown. Further sequence analysis of the CYP-17 mRNA product is underway to better define the possibility of a mutation in CYP-17.

Report Date: 03 April 2001 Work Unit # 6425-98

DETAIL SUMMARY SHEET

TITLE: Power Spectrum Analysis as a Marker of Diabetic Autonomic Neuropathy in Children and Adolescents with Diabetes Mellitus

KEYWORDS: Heart Rate variability

PRINCIPAL INVESTIGATOR: Thomas R. Burklow LTC MC
ASSOCIATES: Merily Poth MD USUHS; James J. Bailey MD NIH

DEPARTMENT: Pediatric
SERVICE: Pediatric Cardiology

STATUS: O
INITIAL APPROVAL DATE: 26 May 1998

STUDY OBJECTIVE

1) To examine the association of heart rate variability in children with clinical symptoms of neuropathy in diabetic children
2) To examine the association of heart rate variability in children with standard clinical testing for neuropathy in diabetic children

TECHNICAL APPROACH

Diabetic children and adolescents are recruited from the pediatric endocrinology clinic. A Holter monitor is applied and the patients are coached through the following maneuvers: 1-Valsalva breathing, 2-metronomic breathing and 3) upright standing. After completion the patient is then disconnected and his or her participation is completed. The Holter monitor recording is then analyzed through a Sun workstation for analysis of heart rate variability through autoregression analysis.

PRIOR AND CURRENT PROGRESS

Since beginning patient enrollment in September 1998, we have performed clinical, laboratory and electrophysiological assessments on 32 patients. An interim data analysis has demonstrated no correlations with the parameters of heart rate variability, biochemical, standard testing for autonomic dysfunction and demographic data. As a result this analysis, no further patients have been enrolled since August 2000. We are currently in the process of reviewing this data further to ascertain whether more subjects are to be enrolled or whether to halt further data collection.
There have been no adverse events recorded during the conduct of this protocol.
The number of subjects enrolled to the study since last APR at WRAMC is 14 and the total enrolled to date at WRAMC is 32. The total number enrolled study-wide is n/a, if multi-site study.

CONCLUSIONS

None.

Report Date: 31 July 2000 Work Unit # 6427-99

DETAIL SUMMARY SHEET

TITLE: Cardiac Repolarization Abnormalities and Cisapride Use in Children

KEYWORDS:

PRINCIPAL INVESTIGATOR: Burklow, Thomas LTC MC
ASSOCIATES: Shmorhum, Daniel LCDR; Sullivan, Carolyn LTC

DEPARTMENT: Pediatrics
SERVICE: Pediatric Cardiology

STATUS: C
INITIAL APPROVAL DATE: 27 October 1998

STUDY OBJECTIVE

a) Determine the incidence of arrhythmias and repolarization abnormalities associated with the routine clinical use of cisapride
b) Correlate the incidence of repolarization abnormalities and arrhythmias with serum cisapride levels

TECHNICAL APPROACH

Infants, children, and adolescents are determined to be candidates for cisapride therapy for gastroesophageal disease are approached regarding enrollment. Once enrolled, a pretreatment EKG is performed. 2-4 weeks after beginning therapy, a repeat EKG is performed and serum is drawn for a serum cisapride level and electrolytes. The EKGs will be separately analyzed by two blinded cardiologists for evidence of repolarization abnormalities. The cisapride level will be correlated with clinical response and EKG finding, if any.

PRIOR AND CURRENT PROGRESS

Since last APR, Janssen Pharmaceuticals has voluntarily withdrawn cisapride from the market because of increasing concerns with possible ventricular arrythmias. There is consideration for a "compassionate use" program for cisapride being considered but this is not instituted yet to my knowledge. Therefore, this protocol is being closed and withdrawn. No patients have been enrolled.

CONCLUSIONS

None

Report Date: 16 January 2001 Work Unit #6428-99

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: Significance of ret/PTC mRNA in Peripheral Blood of Subjects with Diseases of the Thyroid

KEYWORDS: ret/PC, thyroid, cancer

PRINCIPAL INVESTIGATOR: Gary Francis COL MC
ASSOCIATES: Yvonne Lukes, DAC

DEPARTMENT: Pediatrics
SERVICE: Endocrine

STATUS: C
INITIAL APPROVAL DATE: 16 March 1999

STUDY OBJECTIVE

The study was designed to determine if the peripheral blood of patients with papillary thyroid carcinoma (PTC) could be used to detect circulating thyroid cancer by RT-PCR amplification of the PTC specific gene ret/PTC. If so, this test could be used to diagnose PTC without biopsy, and could be used to follow patients for early signs of recurrence.

TECHNICAL APPROACH

Under informed consent, 3 cc's of blood was removed from patients and RNA isolated and amplified by RT-PCR using primer pairs specific for ret/PTC-1, ret/PTC-2 and ret/PTC-3. The internal standard GAPDH was also amplified to ensure RNA integrity.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

To date, 100 peripheral blood samples have been examined, including 14 since 01 February 2000. Of these 100 samples, none has contained ret/PTC sequences. Based on the absence of positive samples, we believe that the probability that this technique could be used diagnostically is too low to warrant further enrollment. There have been no untoward events, and no patient has had any complication from the blood draw procedure.

CONCLUSIONS

Although a promising theory, the amplification of ret/PTC sequences does not appear to be useful for evaluation of patients with PTC. As of this date, patient recruitment has ceased, and we plan to enroll and study no further subjects. We request the protocol be closed.

Report Date: 12 March 2001

Work Unit #6429-99

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: Bone Mineral Density in Survivors of Childhood Thyroid Cancer.

KEYWORDS:

PRINCIPAL INVESTIGATOR: Dinauer, Catherine MAJ MC
ASSOCIATES:

DEPARTMENT: Clinical Investigation
SERVICE: Clinical Studies

STATUS: O
INITIAL APPROVAL DATE: 27 April 1999

STUDY OBJECTIVE

This is a pilot observational study evaluating bone mineral density of patients diagnosed with thyroid cancer at <21 years of age.

TECHNICAL APPROACH

Potential subjects are identified from pre-existing databases of pts diagnosed with thyroid cancer in childhood (databases are under WU #6398 and #6414). After obtaining consent, subjects complete a questionnaire (re: demographics, treatment and status of thyroid cancer, other medical problems, exercise habits, calcium intake, age at puberty, and, for females, menstrual history), undergo a physical exam, have blood drawn for thyroid function tests and thyroglobulin, and undergo a DEXA scan. In addition, subjects' medical records are reviewed.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

The number of subjects enrolled to the study since last APR at WRAMC is _0__ and the total enrolled to date at WRAMC is ____3__. The total number enrolled study-wide is n/a.
There have been no adverse events and no subjects have withdrawn from the study.
Unfortunately, no progress has been made on this study in the past year, due to loss of several of the AIs, other responsibilities of the PI, and the fact that many of the patients diagnosed with thyroid cancer as children are no longer eligible for military care (and are thus not eligible to participate in this research study). Efforts are underway to find a new PI and to reassess how many eligible subjects exist. If a new PI is not found and/or the number of potential subjects appears to be minimal, the study will be closed.

CONCLUSIONS

Progress on this protocol has been slow; the situation is being reassessed and either a new PI will be named or the study will be closed.

Report Date: 5 July 2001 Work Unit #6430-99

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: Acute Pediatric Care in a Pediatric Clinic Versus a General Emergency Department: A Performance Improvement Project Comparing Outcomes and Patient Satisfaction

KEYWORDS: Acute Care, Pediatrics, Outcomes, Patient Satisfaction

PRINCIPAL INVESTIGATOR: Dinauer, Catherine A. MAJ MC
ASSOCIATES: Lucci, Ed LTC MC; Harper, Brenda COL MC

DEPARTMENT: Pediatrics
SERVICE:

STATUS: O
INITIAL APPROVAL DATE: 10 August 1999

STUDY OBJECTIVE

This study is a Performance Improvement project designed to investigate the acute care of pediatric patients at WRAMC in two settings: the Pediatric Clinic (PC) and the Emergency Department (ED). The plan is to examine:

1) clinical outcomes,
2) functional outcomes, and
3) parent satisfaction with care in the two clinical venues.

TECHNICAL APPROACH

The parents of patients seen in either a PC Same Day Appointment or in the ED will be contacted by telephone 7-10 days after the visit and asked to complete a survey. Parents will be informed of the survey at the time of the child's visit through a memo (explaining the study purpose and plan, voluntary nature of their participation, etc). A pilot survey of parents of 20 children (10 PC and 10 ED) will be performed initially. Once reliability and validity of the survey are assessed, quarterly surveys of the parents of 50 patients (25 PC and 25 ED) will be performed.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

A pilot survey of 20 parents was performed; analysis of the survey items by the Nursing Research Service showed high reliability. Two full-fledged surveys were then performed, in October 2000 (n=50) and January 2001 (n=40). 5% of parents contacted declined participation. 11% of the phone numbers attempted were disconnected or incorrect. A preliminary analysis showed that, overall, parents expressed high ratings of satisfaction with care in the PC and ED and that overall satisfaction with pediatric acute care appears to be more highly correlated with ratings of clinical care than with ratings of wait time. Satisfaction scores for the PC were higher than those for the ED on the Jan survey, but were not significantly different on the Oct survey. The reason for this is not clear, but may relate to wait times (which were longer in the ED in the winter). More data need to be collected (in other quarters – e.g. spring and summer) in order to perform an appropriately powered analysis.
No parents have withdrawn from the study and there have been no adverse events.
The number of subjects enrolled to the study since last APR at WRAMC is 110 and the total enrolled to date at WRAMC is 110. The total number enrolled study-wide is __n/a_____, if multi-site study.

CONCLUSIONS

Study should continue so that additional data may be collected in order to perform a valid analysis. The high percentage of invalid telephone numbers is concerning and suggests CHCS registration information is not routinely verified as part of the check-in process.

Report Date: 2 February 2001 Work Unit #00-7102

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: A Randomized Placebo-Controlled Trial of Sertraline for Neurobehavioral Sequelae of Traumatic Brain Injury

KEYWORDS: Traumatic Brain Injury, Head Injury, SSRI

PRINCIPAL INVESTIGATOR: Deborah L. Warden, M.D.
ASSOCIATES: Joan Walter, P.A., James Ecklund, M.D., Bahman Jabbai, M.D., Laurie Ryan, Ph.D., Elisabeth Moy-Martin, RNC, M.A., Mary Coyle, RNCS, M.S.N., Maria Graves, R.N., Molly Sparling, B.A.

DEPARTMENT: Neurology
SERVICE: Traumatic Brain Injury Program

STATUS: O
INITIAL APPROVAL DATE: 21 March 2000

STUDY OBJECTIVE

a. To investigate the efficacy of sertraline, a selective serotonin reuptake inhibitor (SSRI), in treating neurobehavioral sequelae of irritability, depression, frustration, anxiety and other post-concussive symptoms following traumatic brain injury (TBI).
b. To explore possible relationships between anosmia (deficits in smell) and irritability/ aggression.

TECHNICAL APPROACH

As the standard of care for patients with traumatic brain injury (TBI) at Walter Reed, patients receive a multidisciplinary evaluation consisting of neurology exam, neuropsychology, psychiatry, psychosocial, EEG, MRI, phlebotomy, and family interview. Research tests include the smell test, evoked potentials, drawing and storing of the blood sample, and some questionnaires related to the subject's medication response. Blood samples (about two tablespoons) are kept at the DVHIP labeled with the patient's study number for possible future use in studies to understand better aspects of recovery from head injury. An addendum was approved 12/6/00 to use the blood samples for studies of genetic markers potentially related to outcome from TBI. Participants have the option of not consenting to the genetic analyses while still participating in the rest of the protocol. After signing the volunteer informed consent, patients will be randomized into an active drug or placebo group. Patients receive an increasing dose of sertraline or placebo starting at 50mg (1 pill) and increasing to a dose of 200 mg (4 pills) of sertraline. Dose adjustment is considered every 3 weeks and is based on scores on the Clinical Global Improvement Scale. Family members or a close friend of the subject are asked to complete some questionnaires after giving informed consent for their participation.

The medication phase lasts 12 weeks. Patients receive standard TBI care during this period which may include a period of Convalescent Leave Home (CVL) followed by a gradual return to duty. All patients are contacted weekly during the medication phase to assess general condition, current symptoms, and assessment of compliance. If patients require a clinical medical appointment during the 12 weeks, patients are seen at WRAMC if possible. If not possible, study personnel are available to speak with the patient's clinician at a local medical facility. Patients return to WRAMC at 12 weeks for a follow-up evaluation of their symptoms, or are contacted by phone if unable to return to WRAMC for their 12-week evaluation. An addendum was approved 11 Jan 2001 to obtain sertraline blood levels at 12 weeks as a measure of compliance and as a potential correlate to symptom amelioration. After the 12-week evaluation, patients are tapered off sertraline or placebo over 2 weeks.

If subjects have recurrent symptoms following the 12-week evaluation that are distressing to them, or believe they need medication to keep their symptoms from recurring, pharmacologic and nonpharmacologic treatments are discussed with them. Patients are offered appropriate treatment, including sertraline, if medically indicated. The blind is not yet broken, that is, patients are not able to learn if they were being treated with placebo or sertraline. Subjects are contacted by phone or seen at 3, 6, 9, and 12 months following their 12 week follow-up evaluation for an assessment of their symptoms and general level of functioning. If patients are in the area, these follow-up evaluations are done in person.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

As mentioned above, two addendums have been submitted and approved. One involves the use of blood samples for testing for genetic markers. The second allows for sertraline blood levels to be obtained at the end of the treatment period. We feel that both these modifications will greatly enhance the results and potential application of the research. Final approval for this protocol was not obtained until 6/22/00. Mrs. Molly Sparling was hired as research coordinator for

the protocol at that time and started 01 Aug 2000. Because of the delayed approval, change in staffing, and training of new personnel, recruitment for the study did not begin until September 2000. We currently have enrolled two participants who are in their 9th and 11th weeks of the protocol respectively. There are no significant adverse events to report at this time and we feel that the protocol is running smoothly. No patients have withdrawn from the study for any reason. A recent literature search completed 1/29/01 revealed no new research directly relating to this protocol.

CONCLUSIONS

Subject enrollment is currently underway. There have been no adverse events to date.

Report Date: 6 February 2001

Work Unit # 00-7103

DETAIL SUMMARY SHEET

TITLE: Validation of an Instrument to Assess Outcome Following a Severe Brain Injury

KEYWORDS:

PRINCIPAL INVESTIGATOR: Dr. Deborah Warden, M.D., DAC
ASSOCIATES:

DEPARTMENT: Neurology
SERVICE:

STATUS: W
INITIAL APPROVAL DATE: 28 March 2000

STUDY OBJECTIVE
At the request of the PI, this study has been withdrawn.

TECHNICAL APPROACH
This study has been withdrawn.

PRIOR AND CURRENT PROGRESS
This study has been withdrawn.

CONCLUSIONS
This study has been withdrawn.

Report Date: 6 July 2001 Work Unit # 00-7104

DETAIL SUMMARY SHEET

TITLE: A Study for the Use of Telemedicine/Teleradiology in the Initial Management of Acute Stroke

KEYWORDS: Stroke, Cerebrovascular Disease, Telemedicine, Network, and Teleradiology

PRINCIPAL INVESTIGATOR: Choi, John Y. MAJ MC
ASSOCIATES: Rotenberg, Joshua CPT MC, Daniels, Stacey LT USN MC, Ling, Geoffery LTC MC, Labutta, Robert LTC MC, Martin, Albert MAJ MC, Poropatich LTC MC, Baxter, Brian MAJ MC, Depper, Mark MAJ MC, Feolo, Gabriele RN MSN

DEPARTMENT: Neurology STATUS: O
SERVICE: Cerebrovascular Diseases INITIAL APPROVAL DATE: 22 August 2000

STUDY OBJECTIVE

This study seeks to establish the feasibility of telemedicine consultation in the diagnosis of stroke. Telemedicine evaluation of the neurologic examination and brain computed tomography (CT) would be examined.

TECHNICAL APPROACH

This study will assess the logistics of setting up equipment in the emergency department (ED) and the feasibility of implementing a telemedicine consultation from a remote site. For this study the remote site will be within WRAMC, but outside the ED. Neurology personnel (neurology residents, nurse coordinator, and staff) will perform the examinations and handle the equipment for the video presentation. Equipment used will include a color video camera, a portable video teleconference (VTC), and a videocassette recorder.

Up to ten volunteer subjects will be asked to participate in this phase I study. The investigators will obtain a written informed consent from subjects during the subjects' recruitment from the neurology clinic or ward. The volunteers may either have a normal neurological examination, or an abnormal neurological examination related to stroke or nonstroke causes. A subject that has a normal neurological examination might show symptoms unrelated to neurological disease. A stroke subject will have a neurological deficit related to either a brain ischemic or hemorrhagic lesion. A non-stroke subject will have neurological deficits or symptoms not related to brain ischemia or hemorrhagic lesion.

Prior to obtaining consent an investigator will determine the subjects competency using the mini mental status exam. A study coordinator will schedule the volunteer for a study intervention by blinded neurology personnel in the ED. Volunteers may be briefed prior to their ED appointment to recite a scenario during the study intervention. Scenarios will include mock information about onset of signs and symptoms related to neurological or non-neurological causes. These scenarios will be assigned accordingly to the appropriate volunteer groups (normal neurological examination, stroke/abnormal neurological examination or non-stroke/abnormal neurological examination) in an otherwise random order. For example, scenarios that should reflect findings of normal neurological examinations will be randomly dispensed to patients with normal neurological examination. After the subject arrived at the ED, telemetry monitoring will be established. A beeper will then notify the in-person neurology or telemedicine consultant about the subject. Only the neurology resident, neuradiologist, or nurse coordinator will know the volunteer's prior history and physical examination. Other study personnel participating in the volunteer's evaluation will be blinded to this information.

Two consecutive, timed study interventions will occur in the ED. The telemedicine neurology consultant will obtain the subject's history and neurological examination. This timed intervention will be captured on videotape. The intervention's starting time is a VTC equipment activation in the subject's ED examination room. The end time will be the moment the intervention by in-person history and neurological examination. This timed examination will serve as the gold standard. Both the telemedicine and in-person consultants will be advised to complete the history and neurological examination within 30 ± 15 minutes.

The order that the telemedicine and in-person examinations are performed will be altered to minimize the effects of learning by the subject from the previous examinations.
Archived brain CTs without patient identifiers will be recorded on *Impax*. Those CTs will show findings or normal, old strokes or acute strokes. A non-blinded neuroradiologist will instruct the telemedicine consultant to evaluate the CT for the clinical situation. For example, control group subjects will have normal CT scan findings. Stroke subjects may have old strokes or acute stroke findings. Evaluation time will be measured from the moment the scan is loaded on the video screen until the consultant has analyzed the scan under a time restriction of 10 minutes $\pm$ 5 minutes. The in-person neurologist and a blinded neuroradiologist will read the brain CT under the same time restriction. The time it takes the blinded neuroradiologist to read the CT will serve as the gold standard.
Video recordings of the telemedicine consultant's interview and examination will be edited to remove patient identifiers. CT scans for the videotape presentation will be edited as well to remove patient identifiers. The video will then be evaluated in real time by associate investigators serving as telemedicine consultants, to perform a NIH stroke scale assessment and to make a diagnosis. Telemedicine consultants will be blinded to the diagnosis and results of the in-person neurological evaluation. Dr. Lee Schwamm will be involved only for evaluating videotape and brain CT presentations and as a technical advisor.
Any adverse reactions will be reported, in accordance with the required policies and procedures, to the Department of Clinical Investigations (DCI) at WRAMC as well as to USAMRMC Office of Regulatory Compliance and Activity. Serious adverse reactions, as described in the subjects' consent form, include the possibility of falling during transport to the ED, and increased stress from the study intervention which might result in worsening the subject's medical condition. Both of these events are of low risk and incidence. Study personnel will assist with transfers to minimize the potential risk of falling. Subjects may terminate the study at any time if they feel overstressed. Investigators may terminate the study at any time if there is indication the subject's medical condition worsens.

*Modifications made to the methodology section since the initial IRB approval on 22 August 2000.

In the methodology section, the remote site is defined as a location within WRAMC but outside the Emergency Department. Recruitment will be based on referrals and will not involve written advertisements or posters.
The number of volunteers is not a maximum of 10, instead of 12 as proposed initially. We added documentation regarding the availability of assistance to study volunteers during the transfer to the emergency department. We also discussed the necessity for study subjects to recite study case scenarios.
The coordination of the patient interview is outlined in more detail. The study personnel and the nurse coordinator will handle the equipment for the video presentation of the study. Further details about investigators' procedure for subject assessment in this study and specific relevant appendices/data record sheets are discussed. We will include a set of mock laboratory values to further simulate a patient encounter. Study personnel will be with the volunteer at all times after activation of the study intervention to serve as witnesses.
There will be a blinded neuroradiologist, setting the gold standard for the brain CT reading, for comparison versus the telemedicine and in-person neurology consultant. This will be a time evaluation planned for 10 minutes. The possible risk of falls or worsening of medical condition is added. We added to research record review, representatives of the U.S. Army Medical research and Material Command. We discussed preventative measures taken by study personnel to minimize the risk of adverse events to study volunteers.
As outline of necessary follow-up actions was added, if an adverse event should occur.
Two paragraphs were added discussing the security of confidential patient data. Only participating study personnel will have access to patient information. All data collected during the trial period will be handled, stored and discarded in accordance with the USAMRM policies. Data collection, specific details on storage, record upkeep and destruction of data after the required waiting period are mentioned. Data associated with the study volunteers will be entered into the Command's Volunteer Registry Data Base.
Time goals for telemedicine consultation and brain CT readings were redefined.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE:

Additional recent literature has been reviewed and four more references were included for citation to support the protocol regarding assessment of subject competency and recent telemedicine study publication.

No study findings were obtained thus far, since there are no subjects enrolled into this study yet. Modifications to the methodology section of this research study since the last review have been listed in the technical approach section above. The Consent Form was revised as well as an additional consent form for study investigators since they are deemed research subjects. Additional changes made to the protocol since the last review consist of:

1. A change in associate investigators is placed (changes had already been filed to DCI, WRAMC)
2. An addition of the nurse stroke coordinator (Gabriele Geolo, RN), collaborating personnel (Dr. Lee Schwamm; changes had already been filed to DCI, WRAMC) and medical monitor.
3. A statement was added referring to a prior published study showing the feasibility of performing a stroke scale via a telemedicine assessment.
4. The inclusion and exclusion criteria now read: "Subjects who are medically stable will be consented". Vital signs criteria must be met to qualify for inclusion into this study. Inpatients are recruited 48 hours after admission to the ward. Any potential subject with evidence of stroke involving one-half of a cerebral hemisphere as confirmed by neuroimaging will be consented at a minimum of 72 hours after the onset of the stroke. Investigators will confirm a patient's competency via a mini mental status examination (MMSE). Appendix F has been created for a screening guide for subjects. Active duty personnel will have an ombudsman available during the consenting process.
5. The sample size/data analysis, desired mean time goals and the calculation of confidence intervals were refigured. Table 1 was created to discuss percentage of successful trials for planning of the next phase for this project. Appendix E is mentioned, which contains a questionnaire, for the ER staff to evaluate the impact by this study to normal ER operations.
6. A discussion for implications for stopping this study was added. A serious complication rate of > than 5% of the lower limits of the 95% confidence interval, or if two out the first three subjects show complications, will result in cessation of subject enrollment and a reassessment of the methods of this study.
7. Four new reference citations are now included with a change in date of start and funding implications continuing into.
8. Appendix A shows changes to the case report form with respect to the time allotted to complete the exam, and questions directed to the patient.
9. Appendix C contains changes to the format of the data sheet and the date and time of data collection. Appendix C, (page 2), contains a copy of the NIH stroke scale.
10. Appendix D has changes regarding the case report form layout and additional questions assessing the evidence of an acute or an old stroke in volunteers, and evidence of intracerebral hemorrhage.
11. Appendix E contains the emergency department questionnaire for phase I of the study.
12. Appendix F contains a screening questionnaire to be used by investigators during assessment for consent of study subjects.

There have not been any adverse events (AE), since there are no subjects enrolled into this study yet. The number of subjects enrolled to the study since last APR at WRAMC is zero and the total enrolled to date at WRAMC is zero.

CONCLUSIONS

None can be made at this time. Recent review of the literature indicates no known new publications that would make this study a redundant project.

Report Date: 03 August 2001 Work Unit # 00-7105

DETAIL SUMMARY SHEET

TITLE: Effectiveness of Botulinum Toxin Type-A in the Treatment of Migraine Headache: A Randomized Controlled Trial

PRINCIPAL INVESTIGATOR: Sartori, Roberto MAJ MC
ASSOCIATES: Jabbari, Bahman COL MC, Labutta, Robert LTC MC, Murray, Evan MAJ MC

DEPARTMENT: Neurology STATUS: O
SERVICE: INITIAL APPROVAL DATE: 26 September 2000

STUDY OBJECTIVE:
It is hypothesized that patients who receive injections of Botulinum toxin A (BTX-A) into selected pericranial muscles experience a significant reduction in the frequency of headaches and/or the average severity of attacks. We intend to evaluate the efficacy of BTX-A in the treatment of migraine headache.

TECHNICAL APPROACH:
This study is a prospective, randomized double blind placebo-controlled trial comparing the efficacy of BTX-A injections versus placebo in migraine headache prevention. Patients record the frequency and intensity of headaches in a daily diary for a 1-month baseline period, and for 6 months after they receive a single treatment of placebo dose to selected pericranial muscles. The primary outcome measure is the average frequency of headache days measured during 30-day blocks for six months. The secondary outcome measure is the severity of attacks using a visual analog scale (VAS) from 0 to 10 (0=no headache pain; 10 = most severe headache pain experienced)

Two modifications to the protocol and consent form were approved by the WRAMC HUC/IRB on 6 March 01. (1) The Migraine Specific Quality of Life Questionnaire, Version 2.1 (MSQ v. 2.1) was added as a secondary outcome measure. The MSQ is a 14-item, self-administered instrument originally developed to assess the impact of migraine on health related quality of life. A Vaseline MSQ is administered on the day of injection. Patients then repeat the questionnaire at weeks 12 and 24. (2) We have eliminated the assessment and measurement of pericranial muscle tenderness, either before or after injection. All other aspects of the protocol remain unchanged.

PRIOR AND CURRENT PROGRESS:
The total number of 18 subjects has been screened to date. Of these, 7 subjects did not meet all study criteria. 11 subjects have been enrolled. No subjects have withdrawn from the study. Two subjects reported mild, transient muscle tenderness at the injection site (an expected side effect). One subject was recently hospitalized at Walter Reed for a refractory migraine attack. The subject has a history of prior hospitalizations with similar symptoms. The hospitalization was reported to DCI within 24 hours of notification to the PI, in accordance with adverse event reporting instructions.

There has been no new published data regarding the effectiveness of Botulinum toxin-A injections in migraine headache prevention. Mauskop A, and Basdeo R, of the New York Headache Center, recently reported in a poster presentation their results of a retrospective chart review of 38 migraine patients injected with variable doses ranging from 10 to 100 units. 71% (27) of patients reported over a 50% reduction in frequency or pain severity after 1 to 5 treatment sessions. Mean duration of relief was 2.8 months (range 2-5 months).

CONCLUSIONS
No conclusions have been obtained to date. Interim data analysis will be carried out once a total of 40 patients have completed the study.

Report Date: 03 August 2001 Work Unit # 00-7106

DETAIL SUMMARY SHEET

TITLE: Effectiveness of Botulinum Toxin Type-A in the Treatment of Tension-type Headache: A Randomized Controlled Trial

KEYWORDS:

PRINCIPAL INVESTIGATOR: Sartori, Roberto MAJ MC
ASSOCIATES: Jabbari, Bahman COL MC, Labutta, Robert LTC MC, Murray, Evan MAJ MC

DEPARTMENT: Neurology STATUS: O
SERVICE: INITIAL APPROVAL DATE: 26 September 2000

STUDY OBJECTIVE:
It is hypothesized that patients who receive injections of Botulinum toxin A (BTX-A) into selected pericranial muscles experience a significant reduction in the frequency of headaches and/or the average severity of attacks. We intend to evaluate the efficacy of BTX-A in the treatment of migraine headache.

TECHNICAL APPROACH:
This study is a prospective, randomized double-blind placebo-controlled trial comparing the efficacy of BTX-A injections versus placebo in migraine headache prevention. Patients record the frequency and intensity of headaches in a daily diary for a 1-month baseline period, and for 6 months after they receive a single treatment or placebo dose to selected pericranial muscles. The primary outcome measure is the average frequency of headache days measure during 30-day blocks for six months. The secondary outcome measure is the severity of attacks using a visual analog scale (VAS) from 0 to 10 (0 = not headache pain; 10 = no headache pain; 10 = most severe headache pain experienced).

Two modifications to the protocol and consent form were approved by the WRAMC HUC/IRB on 6 March 01. (1) The Migraine Specific Quality of Life Questionnaire, Version 2.1 (MSQ v. 2.1) was added as a secondary outcome measure. The MSQ is a 14-item, self-administered instrument originally developed to assess the impact of headache on health related quality of life. A baseline MSQ is administered on the day of injection. Patients then repeat the questionnaire at weeks 12 and 24. (2) We have eliminated the assessment and measurement of pericranial muscle tenderness, either before or after injection. All other aspects of the protocol remain unchanged.

PRIOR AND CURRENT PROGRESS
The total number of 2 subjects have been screened to date. Of these, 1 subject did not meet all study criteria. 1 subject has been enrolled. No subjects have withdrawn from the study. No adverse effects have been reported.

There has been no new published data regarding the effectiveness of Botulinum toxin-A injections in chronic tension headache prevention. However, Relja M recently reported the 1-year follow-up on a prior 3-month open-label prospective study. 24 to 25 patients completed the 15-month treatment period; overall, there was a constant trend in improvement in headache free days. No serious side effects were reported during the study.

CONCLUSIONS
No conclusions have been obtained to date.

Report Date: 01 June 2001 Work Unit # 7144

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: A Controlled Efficacy Study of a Brief Multidisciplinary Brain Injury Rehabilitation Program in Moderately Head-Injured Service Members

KEYWORDS: traumatic brain injury, moderate head injury

PRINCIPAL INVESTIGATOR: Warden, Deborah L. MD
ASSOCIATES:

DEPARTMENT: Neurology STATUS: C
SERVICE: Traumatic Brain Injury Program INITIAL APPROVAL DATE: 31 July 1990

STUDY OBJECTIVES

1) Determine the effectiveness and cost efficiency of a comprehensive TBI rehabilitation program, compared to one providing only counseling and support
2) Determine and quantify the short/long-term neurologic and neuropsychological consequences of moderate head injury in the Army and its impact on some aspects of military performance
3) Develop and test a relatively brief neuropsychological screen that is sensitive to and predictive of effects of minor/moderate head injury.

TECHNICAL APPROACH

Each subject received neurological, neuropsychological, psychiatric, and medical rehabilitation; EEG and evoked potential, and neuro-ophthalmologic testing; physical and occupational therapy; clinical psychiatry interview; and MRI. Following the comprehensive evaluation, patients were randomly assigned to one of two treatment groups. Patients were then returned to duty and followed to determine differences in long term outcome based upon rehabilitation strategy.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

No new patients were enrolled this year. New patient accessions stopped 3 August 1999. Over the past year, we continued to follow enrolled patients for the 24-month evaluation. All follow-up evaluations have now been completed and the protocol is completed.
The number of subjects enrolled to the study since last APR at WRAMC is 0 (zero) and the total enrolled to date at WRAMC is 148 (one hundred forty eight). There has been 1(one) adverse event reported over the last year.

CONCLUSIONS

This study demonstrated that at 1-year follow-up, there was no difference in return to employment between patients who had received the intensive in-hospital cognitive rehabilitation program vs. the limited home rehabilitation program (n=120). There were also no significant differences in cognitive, behavioral or quality of life measures. In a post-hoc subset analysis of patients who were unconscious for more than 1 hour (n=75) following TBI, the in-hospital group had a greater return to employment rate (80% vs 58%, p= 0.05).
A home rehabilitation program may be effective treatment for certain head injured soldiers/ military beneficiaries, specifically those with more mild to moderate TBI. Home follow up has been instituted as the standard of care for these patients referred and evaluated through the DVHIP at WRAMC. Patients with greater than 1 hour loss of consciousness are considered for inpatient rehabilitation at a VA or similar facility. A full-length research article describing the results of the protocol was published in JAMA this year. We are currently finishing quality control and verification of data collected on 24-month outcome from the protocol in preparation for manuscript submission.

Report Date: 12 July 2001 Work Unit # 7154

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: Defense and Veterans Head Injury Program (DVHIP): WRAMC Core Evaluation Protocol

KEYWORDS: traumatic brain injury, head injury

PRINCIPAL INVESTIGATOR: Warden, Deborah MD

DEPARTMENT: Neurology
SERVICE: Brain Injury Program

STATUS: O
INITIAL APPROVAL DATE: 31 August 1993

STUDY OBJECTIVE

To ensure that all military and DVA traumatic brain injured (TBI) patients receive TBI-specific evaluation and follow-up, while at the same time collecting standardized patient outcome data that will allow us to evaluate the relative efficacy and cost of various TBI treatment and rehabilitation strategies, and to define optimal care for victims of TBI

TECHNICAL APPROACH

Each subject receives neurological, neuropsychological, psychiatric examinations; and EEG and MRI testing. We have shortened the evaluation to these key components over the past year due to a 20% increase in new referrals combined with reductions in funding. Additional evaluations, including physical and occupational therapy, audiology, and neuro-ophthalmology are still available and are arranged on an individual basis as clinically indicated. Following the comprehensive evaluation patients are returned to duty and followed.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

The Core Evaluation Protocol remains active as we continue to enroll patients and follow enrolled patients over 24 months. As of June 30th, 2001, 411 patients have been enrolled in the protocol and have received baseline evaluations. This year 79 subjects received baseline evaluations and 91 follow-up evaluations were completed. There have been 12 adverse events reported over the last year, none attributable to the protocol. One patient withdrew from the study.

CONCLUSIONS

In progress.

Report Date: 26 March 2001 Work Unit # 7160

DETAIL SUMMARY SHEET

TITLE: Dityrosine Fluorescence: A Monitor for Oxygen-Free Radical Induced Protein oxidation in Human Cerebrospinal Fluid

KEYWORDS: Free Radical, Dityrosine, CSF

PRINCIPAL INVESTIGATOR: Dr. Ajay Verma. MD, PhD
ASSOCIATES: Dr. Maged Abdelrahim, PhD; Dr. Alain Delgado, MD; Dr. Sabita Lahiri, PhD.

DEPARTMENT: Neurology
SERVICE:

STATUS: C
INITIAL APPROVAL DATE: 17 January 1995

STUDY OBJECTIVE

(1) To measure dityrosine (DY) levels in human CSF samples as a means to follow free radical induced protein oxidation under conditions of oxidant stress in vivo.
(2) To determine if increased CSF DY levels are associated with neurologic diseases thought to be associated with increased oxidative stress.

TECHNICAL APPROACH

(1) Synthesis of pure DY, preparation of a HPLC DY measurement protocol, followed by HPLC determination of DY levels after appropriate preparation of CSF samples. Correlation of CSF DY levels to patient diagnosis.
(2) Determination of DY in CSF samples which have been oxidized in vitro.
(3) Develop dityrosine-haptenized complex for antibody production.

PRIOR AND CURRENT PROGRESS

The work on this project has proceeded with unusual stops and starts. Over the several years that this protocol has been active, we have synthesized our own DY and determined the best way to measure DY in human CSF. We have demonstrated that *in vitro* oxidation of human CSF samples by free radicals generates significant amounts of DY. Analysis of several historical samples of human CSF demonstrates high levels of endogenously generated DY in disease states such as trauma, stroke, and inflammatory states such as meningitis and multiple sclerosis. This looks to be an excellent assay to follow oxidative damage in the CNS and is also applicable to other body fluids. The Walter Reed Neurology residents originally associated with this project have graduated and it has become difficult to readily obtain CSF samples from WRAMC. Indeed, we have not acquired any new samples at Walter Reed for several years. We had wished to run one last set of samples (35 samples) that we were to receive from a NIH study in which Dr. Irene Litvan was the PI. However, the HPLC procedure for monitoring CSF DY levels has changed significantly in the last couple of years and these changes would not allow us to compare any of values obtained previously with the proposed new samples. We therefore would now like to terminate to current protocol and publish the data that has been generated so far. We will write a new protocol for any other measurements

CONCLUSIONS

DY measurements in the CSF appear to be an excellent marker of oxidative injury to the nervous system.

Report Date: 2 March 2001

Work Unit # 7161

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: Proton Magnetic Resonance Spectroscopic Imaging in Patients with Movement Disorders

KEYWORDS: spectroscopy, proton, movement

PRINCIPAL INVESTIGATOR: Jabbari, Bahman COL MC
ASSOCIATES: Rao, Krishna MD

DEPARTMENT: Neurology
SERVICE:

STATUS: O
INITIAL APPROVAL DATE: 25 April 1995

STUDY OBJECTIVE

To determine the yield and utility of Magnetic Resonance Spectroscopy (MRS) in patients with movement disorders.

TECHNICAL APPROACH

Sixty subjects with various movement disorders will undergo MRS, a noninvasive technique which allows focused study of biochemistry within normal and diseased brains. Conventional MRI with additional special equipment and software is utilized to allow spectral analysis.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

The number of subjects enrolled to the study since last APR at WRAMC is 10 and the total enrolled to date at WRAMC is 38. No side effects were noted. The group consists of a variety of movement disorders including patients with Huntington and Parkinson disease. No side effects were noted.

CONCLUSIONS

Patients with Huntington disease (6), demonstrate a prominent glutamate peak consistent with glutamate toxicity. Patients with Parkinson's disease in general demonstrate normal MRS. The number of patients in other groups (PSP, MSA, so forth) is still too small for appropriate statistical analysis.

Report Date: 12 March 2001 Work Unit #7162

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: An Open Label Study of Interferon Beta-la (Recombinant Human Interferon Beta) in Subjects with Multiple Sclerosis (Biogen Protocol Number, C94-801-P, Version 6) updated 20 January 1999

KEYWORDS: multiple sclerosis, interferon, Beta-la

PRINCIPAL INVESTIGATOR: Robert J. Labutta LTC MC
ASSOCIATES: Jason Friedman CPT MC, Judith A. Brooks RN MSN CCRC

DEPARTMENT: Neurology
SERVICE:

STATUS: O
INITIAL APPROVAL DATE: 25 April 1995

STUDY OBJECTIVE

To obtain safety information regarding the use of repeated IFN-B-la dosing in subjects with multiple sclerosis.

TECHNICAL APPROACH

Patients will be administered 30 micrograms of IFN-B-la intramuscularly once a week for 2 years.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

The numbers of subjects enrolled to the study since last APR at WRAMC is none and the total enrolled to date at WRAMC is 30. The total number enrolled study-wide is 382, if multi-site study.
The multicenter retention rate was 78% with a 70% from WRAMC. Within the past year two subjects from WRAMC voluntarily withdrew as they were from out of the state and traveling to WRAMC was too difficult. Serious adverse events have been reported as they occurred. Some of the SAE's have included ischemic colitis, cellulites at injection site, knee abscess, worsened migraine, and several deaths, one due to septic shock, one due to duodenal diverticulitis.

CONCLUSIONS

Biogen has decided not to extend the study beyond the sixth year. Patients will be starting to complete the study in May 2001 and all subjects should be off study by May 2002. WRAMC patients will begin study completion in May 2001 and all patients will have completed the study by 30 November 2001.

Report Date: 2 March 2001 Work Unit # 7165

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: Neurochemical Mechanisms in Patients with Intractable Epilepsy

KEYWORDS: epilepsy, neurochemistry, epileptic focus

PRINCIPAL INVESTIGATOR: Jabbari, Bahman COL MC
ASSOCIATES: James Myerhoff M.D.

DEPARTMENT: Neurology
SERVICE:

STATUS: C
INITIAL APPROVAL DATE: 23 April 1996

STUDY OBJECTIVE

To investigate neurochemical changes at the epileptic region of the cortex in order to gain insight into the cellular and neurochemical mechanisms of human epilepsy. This information will help expand knowledge regarding the basic mechanisms of human epilepsy and may lead to development of more effective antiepileptic drugs.

TECHNICAL APPROACH

Tissue will be obtained during surgery from the temporal lobe of the patients with intractable epilepsy. These patients before surgery have undergone video-EEG monitoring which defined the epileptic focus. Two tissue samples will be examined; one from epileptic and the other from non-epileptic brain regions. Examination includes assessment of changes in calcium homeostasis, in situ hybernization of endoplasmic reticulum, phospholipase C activation, analysis of PI metabolism, and tissue oxidative damage. The data in two patient groups, 20 each, one with and one without hippocampal pathology will be statistically examined and compared Wilcoxon test, two sample t test.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

The number of subjects enrolled to the study since last APR at WRAMC is _0_ and the total enrolled to date at WRAMC is _8_. No side effects were noted.

CONCLUSIONS

A total of eight patients provided satisfactory tissue specimens for biochemical analysis. In five of eight patients application of TRANS-ASPD, an antagonist at glutamate receptor produced tissue hydrolysis at the spiking cortex. The study is closed early due to the departure of the collaborating neurosurgeon (who provided tissue).

Report Date: 12 March 2001 Work Unit #7166

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: An Open Label Uncontrolled Trial of Long-Term Treatment with Poly-ICLC in Patients with Malignant Gliomas and Multiple Sclerosis.

KEYWORDS: poly-ICLC, glioma, multiple sclerosis

PRINCIPAL INVESTIGATOR: Robert J. Labutta LTC MC
ASSOCIATES:

DEPARTMENT: Neurology STATUS: O
SERVICE: INITIAL APPROVAL DATE: 23 April 1996

STUDY OBJECTIVE
To maintain treatment and follow up of patients on intramuscular Poly ICLC for multiple sclerosis and malignant glioma.

TECHNICAL APPROACH
Malignant glioma patients are administered Poly ICLC at 20 mcg/kg three times a week for 36 months and then tapered. The multiple sclerosis patients are receiving between 0.5-10 mg once or twice a week.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 15. The total number enrolled study-wide is N/A, if multi-site study.

CONCLUSIONS
At the present time, this protocol is kept open only until all MS patients have transitioned to one of the FDA-Approved Multiple Sclerosis medications. One glioma patient is still on Poly ICLC on compassionate use.

Report Date: 13 July 2001

Work Unit # 7174-98

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: Markers of Possible Vulnerability to Symptoms Following Traumatic Brain Injury

KEYWORDS: traumatic brain injury, moderate head injury

PRINCIPAL INVESTIGATOR: Warden, Deborah MD
ASSOCIATES:

DEPARTMENTS: Neurology
SERVICE: Brain Injury Program

STATUS: O
INITIAL APPROVAL DATE: 04 August 1998

STUDY OBJECTIVE

To explore possible relationships between biologic factors, i.e., certain allelic frequencies, and response to injury following TBI.

TECHNICAL APPROACH

Genotyping banked blood samples to identify ApoE and serotonin transporter genotypes. Other allelic frequencies may be analyzed subsequently.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Over the past year, collaboration has continued with Drs. Lipsky and Goldman, NIAAA, to explore the effects of genetic markers, specifically those effecting neurotransmitter effects, on patterns of TBI recovery. The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 239. There have been no adverse events or withdrawals from the study this year.

Analysis of the Role of COMT in Cognitive Recovery After Traumatic Brain Injury:

In the central nervous system, Catechol-O-methyltranseferase (COMT) inactivates neurotransmitters such as dopamine, norepinephrine, and epinephrine. Dopamine is linked to many cognitive disabilities including executive functioning. High enzyme activity (COMT Val) and low enzyme activity (COMT Met) are functional polymorphisms resulting from a G to A transition in exon 4 of the COMT gene (codon 108/158) that influence dopamine levels in the brain. To determine the role of TBI on executive functioning, a group of 120 individuals who sustained a TBI were genotyped using a 5' nuclease assay. The effect of genotype on changes in executive function was analyzed using neuropsychological tests including the Wisconsin Card Sort Test (WCST). Individuals homozygous for the COMT Met allele made fewer perseverative responses on the WCST (mean =11.78), whereas those homozygous for COMT Val had the highest number of perseverative responses (mean = 20.47). Heterozygotes made an intermediate number of responses (mean = 13.23). The findings did not change when assessed for potential population stratification. A manuscript reporting these findings is ready for submission to Neurology as a brief report.

The Effect of Serotonin Transporter Genotype on Behavioral Outcome:

Over the past year, Dr. Lipsky has been attempting to genotype the serotonin transporter (5HTT) polymorphisms in order to examine the effect of this variation on behavioral outcome including aggression and irritability. 5HTT has been a difficult assay, but one with potential significance for behavioral outcome and specifically the sertraline study. Although genotypes have been determined for the majority of our sample, details related to failures in certain individuals are still being examined.

CONCLUSIONS

The analysis of the COMT genotype effects on cognitive recovery supports the idea that a functional polymorphism in the COMT gene influences executive functioning following TBI; specifically that the COMT genotype that permits increased dopamine availability is associated with significantly better performance on the Wisconsin Card Sort Test.

Report Date: 28 August 2000

Work Unit # 7176-99

DETAIL SUMMARY SHEET

TITLE: The Neuroprotective Effect of Non-NMDA Receptors in Cultured Rat Cerebellar Granule Cells From Sprague-Dawley Rats Pups

KEYWORDS: AMPA, trans-ACPD, kainic acid, aniracetam, neuroprotection, excitotoxicity

PRINCIPAL INVESTIGATOR: Marini, Ann MD
ASSOCIATES: Krishna Banaudha, Ph.D.

DEPARTMENT: Neurology
SERVICE:

STATUS: O
INITIAL APPROVAL DATE: 17 November 1998

STUDY OBJECTIVE

To determine whether non-N-methyl-D-aspartate receptors protect neurons against the excitotoxic effects of glutamate acting on N-methyl-D-aspartate receptors.

TECHNICAL APPROACH

We are using cultured rat cerebellar granule cells to achieve our objective outlined above. These neurons are relatively homogeneous and express all of the glutamate receptor subtypes including N-methyl-D-aspartate and non-N-methyl-D-aspartate receptors. Cerebellar granule cells are pretreated with variable concentrations of specific non-N-methyl-D-aspartate receptor agonists followed by treatment with an excitotoxic concentration of glutamate (100 μM). Twenty-four hours later the number of viable cells are quantified using fluorescein diacetate.

PRIOR AND CURRENT PROGRESS

We now have convincing evidence that AMPA in the presence of aniracetam protects vulnerable neurons against the excitotoxic effects of glutamate acting on NMDA receptors. We also found that AMPA blocks glutamate-induced apoptosis. We are currently working on the neuroprotective effect of kainic acid on glutamate-induced apoptosis and neuronal cell death.

CONCLUSIONS

AMPA protects neurons against the excitotoxic actions of glutamate and blocks glutamate-mediated apoptosis.

Report Date: 12 January 2001

Work Unit #00-7201

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: Naturalistic Study of Pharmacotherapy in Patients with Schizoaffective Disorder, Bipolar Disorder, and Schizophrenia

KEYWORDS:

PRINCIPAL INVESTIGATOR: Flynn, Julianne CPT, MC
ASSOCIATES: Grieger, Thomas A. CDR, MC

DEPARTMENT: Psychiatry
SERVICE:

STATUS: O
INITIAL APPROVAL DATE: 14 March 2000

STUDY OBJECTIVE

To determine the general demographic characteristics, the trends in pharmacotherapy, the reasons for hospitalization and hospital course of patients hospitalized with the diagnosis of schizoaffective disorder, bipolar disorder, and schizophrenia in a large public sector medical system.

TECHNICAL APPROACH

The methodology has not changed since our protocol submission. Briefly, hospitalization records for all patients with a discharge diagnosis of schizoaffective disorder, bipolar disorder, and schizophrenia during the period from September 1993 - October 1999 are being reviewed, and variables including age at first onset, number of prior hospitalizations, length of stay, reason for hospitalization, medications prior to hospitalization, question of compliance, medications at discharge and reason for medication adjustment are assessed. Patterns of physician medication selection and patient response are then studied to determine both differences and similarities in the treatment of the three disorders over the time period studied.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

This study is a chart review and there have been no adverse events. There have also been no amendments or modifications to the protocol submitted. We are behind in our rate of charts being reviewed; this is the result of a number of the early charts having been archived and the time necessary to retrieve them. I expect we will be asking for an extension on the time allotted to complete the protocol.

The number of subjects enrolled to the study since last APR at WRAMC is 93 and the total enrolled to date at WRAMC is 93.

CONCLUSIONS

Findings to date:

- Divalproex sodium and "atypical" antipsychotics are replacing lithium and "typical" antipsychotics for the treatment of schizoaffective disorder. However, this has not impacted length of stay in the hospital or the time to stabilization (measured by advancement to 'ward' and 'hospital' status)

Report Date: 2 February 2001 Work Unit # 7279-98

DETAIL SUMMARY SHEET

TITLE: The Frequency and Nature of Forensic Issues in an Inpatient Adult General Psychiatric Population

KEYWORDS: Forensic psychiatry, Military psychiatry

PRINCIPAL INVESTIGATOR: Ricky D. Malone, M.D., MPH, LTC, MC, USA
ASSOCIATES

DEPARTMENT: Psychiatry
SERVICE: Inpatient Psychiatry

STATUS: O
INITIAL APPROVAL DATE: 25 March 1998

STUDY OBJECTIVE
This study will tabulate the frequency and nature of forensic issues in adult psychiatric inpatients admitted to this facility and examine for relationships between these issues and demographic and clinical variables.

TECHNICAL APPROACH
Retrospective chart review

PRIOR AND CURRENT PROGRESS
The number of subjects enrolled to the study since last APR at WRAMC is 201 and the total enrolled to date at WRAMC is 301. This study is the total number study-wide, not a multi-site study. If preliminary data analysis on this number shows statistically significant associations, no further data will be collected. If no trends are identified, then up to 500 records will be reviewed. A review of recent literature shows that his is an area that has still not been addressed.

CONCLUSIONS
None to date. Anticipate conclusion by June 2002.

Report Date: 29 January 2001

Work Unit # 7280-98

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: Suicidal Behavior in Active Duty Patients

KEYWORDS:

PRINCIPAL INVESTIGATOR: Ritchie, Cameron MAJ MC
ASSOCIATES: William Keppler, MD, Collaborator: Joe Rothberg, PhD

DEPARTMENT: Psychiatry
SERVICE:

STATUS: O
INITIAL APPROVAL DATE: 10 April 1998

STUDY OBJECTIVE
To examine the relationship between demographics, depressive symptoms, suicidal behavior, motive for self-destructive acts, substance abuse, and effect on a military member's career.

TECHNICAL APPROACH
To review 100 charts for relevant information. An addendum is enclosed, which describes a change in the charts reviewed, to include more recent charts between 1 Aug 1998 and 1 March 1999 (which are on CIS).

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
140 (40 paper and 100 computer) charts have been reviewed, and the data entered and analyzed. The data is being compared to data from other prior studies. A paper is in the process of being written. The number of subjects enrolled to the study since last APR at WRAMC is none, and the total enrolled to date at WRAMC is 140.

CONCLUSIONS
The paper is still in draft form. We had hoped to complete it by this time, but, due to other commitments, it has been delayed.

Report Date: 22 September 2000 Work Unit # 7284-99

DETAIL SUMMARY SHEET

TITLE: Comparison of Parental Therapeutic Alliances Before and After Initial Psychiatric Interviews: Telepsychiatry Versus In-Person Appointments

KEYWORDS: Therapeutic Alliance, Telepsychiatry

PRINCIPAL INVESTIGATOR: CPT Rene Melendez, MD
ASSOCIATES: LTC Stephen Cozza, MD; CPT Kevin Leary, MD; Jessica McMahon, MD; Ms. Anna Crane

DEPARTMENT: Psychiatry
SERVICE: Child and Adolescent Psychiatry

STATUS: O
INITIAL APPROVAL DATE: 17 November 1998

STUDY OBJECTIVE

The objectives of this study are to examine the elements of the developing therapeutic alliance from the first psychiatric interview based upon the parental perspective. The primary distinction will be made in determining whether there is a significant difference between the questionnaires obtained from in-person interviews and those obtained from telepsychiatry interviews. Another objective is to compare the parental opinions both before and after interviews.

TECHNICAL APPROACH

Questionnaires approved by WRAMC human use committee will be distributed to all participants who consent both in-person and telepsychiatry initial intakes done by staff at the Child and Adolescent outpatient clinic at WRAMC. These questionnaires are designed to quantify parents' perceptions of the potential for an alliance to be made between the provider and the patient/family. All participants will also fill out the YOUTH OUTCOME QUESTIONNAIRE (YOQ™2.0 (1) which is already part of the paperwork involved with an initial intake. Symptom Severity Data obtained from the YOUTH OUTCOME QUESTIONNAIRE (YOQ™2.0 (1) will be used to match the in-person and telepsychiatry participants by level of severity. These matched groups then will be examined to determine of any statistically significant trends regarding parental perception of the potential for alliance to form exist. A post interview questionnaire will be given to parents of the telepsychiatry group to monitor the change their perceptions of the ability to form alliance before and after the interview. We anticipate enrolling the next 40 telepsychiatry cases and the next 100 in-person cases that consent to be involved in the study.

PRIOR AND CURRENT PROGRESS

A preliminary review of the study was completed on 19 July 2000 by Dr. Dinauer at the request of the principal investigator (PI). The review found 78 subjects had potentially enrolled in the study. It was determined that 49 subjects had completed all documents for the study (consent form and 2 questionnaires). 20 subjects had not completed any questionnaires, 5 subjects completed the questionnaires but did not fill out the consent form, and 4 subjects completed the questionnaires but had incomplete consent forms. Dr. Dinauer and the PI discussed means to improve data collection and now enrollment is tracked. Dr. Dinauer suggested pre-numbering the consent forms and keeping a logbook at the front desk in the CAPS clinic. A formal audit was scheduled for 16 August 2000 to review all administrative documents, including data collected from remote telepsychiatry sites and pertinent SOP. Results of this review revealed major deviations in compliance with the study protocol and data management. Strong recommendations were made to assign a research assistant to assist in the enrollment process, data collection and in consenting subjects. In addition, the auditors, Dr. Dinauer and Mrs. Bicknell, suggested that the files be reorganized by subjects having completed all documents, subjects who had completed the questionnaires but not the consent forms and subjects with incomplete consent forms. A second meeting/audit with Dr. Dinauer and Mrs. Bicknell took place on 22 September 2000. Dr. Dinauer informed PI of the HUC recommendation to

discard subjects with missing questionnaires and/or those with missing consent forms. Following the guidance of the HUC, the study now has 98 potential enrollees, 63 with all data completed and 35 with incomplete data. The HUC is looking into how to improve the process of handing over the study from one PI to a new PI. Data collection from the remote sites was also discussed. The PI introduced the research assistant, Ms. Anna Crane and inquired whether Ms. Crane could consent and sign the witness signature block for the telepsychiatry subjects. We determined that in light of limited resources at the remote sites, having Ms. Crane consent and sign the witness signature block would allow for simplification and centralization of data management. Dr. Dinauer agreed to ask the HUC at the next scheduled meeting about these changes.

CONCLUSIONS

Data collection is ongoing. Efforts to improve data management at the remote sites are being undertaken. The centralization and simplification of data management as well as the addition of a part-time is vital to the success of the study. A request for an addendum to increase the number of subjects in the study should be considered in the future.

Report Date: 18 December 2000 Work Unit # 7285-99

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: Assessing Pre-Military Psychiatric Illness, Risk Factors Leading to Early Onset of Psychiatric Illness and Inter-Rater Reliability of Psychiatric Diagnosis

KEYWORDS:

PRINCIPAL INVESTIGATOR: Ritchie, E. Cameron LTC MC
ASSOCIATES: Grammer, Geoffrey G. CPT MC

DEPARTMENT: Psychiatry
SERVICE:

STATUS: O
INITIAL APPROVAL DATE: 02 February 1999

STUDY OBJECTIVE

1. To determine if patients had active symptoms or prodromal signs of illness prior to entering the military.
2. To examine precipitating stressful life events for military personnel that were admitted to inpatient psychiatric wards at WRAMC.
3. To document the accuracy of DOD diagnoses.

TECHNICAL APPROACH

No change, retrospective chart review.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

The comparison between the diagnoses made by the WRAMC physicians in the medical record and the diagnoses from the independent blinded reviewers has been completed.
The original protocol asked for permission to review up to 400 charts. These were charts of patients who were hospitalized in the first year of active duty. However, fewer charts than expected had patients who were hospitalized within a year and whose charts contained enough information to analyze. The data from 69 inpatient charts on prodromal signs of illness has been compiled and partially analyzed.
Psychological testing data has not yet been analyzed.
The last step, to review MRI scans for abnormalities, has not been completed.
This is a retrospective chart review. Therefore there have been no adverse actions or patients withdrawn from the protocol.

CONCLUSIONS

There is excellent diagnostic reliability between the WRAMC physicians and blinded reviewers. The kappa for interrater reliability was .84. This kappa is a chance-related reliability measure. The uncorrected percent agreement between the independent psychiatrists and the Medical Board was 88%. The main source of discrepancy came from questions about the length of illness, which occasionally was not well documented in the Medical Board.

Report Date: 17 July 2001 Work Unit # 00-7301

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: Computerized Neuropsychological Assessment of Army Aviators (CNAAA): Development of a Digitized Database and Preliminary Investigator of the Relationship of ANAM, CogScreen and MicroCog to Aviator Trainee Checkflight Performances

PRINCIPAL INVESTIGATOR: Christensen, Daniel K. CPT MS
ASSOCIATES: Kelly, Mark P. DAC, Gahm, Gregory LTC MS, Leso, John CPT MS, Baggett, Mark MAJ MS, Goodlett, Georgie, B.A.

DEPARTMENT: Psychology
SERVICE:

STATUS: O
INITIAL APPROVAL DATE: 1 August 2000

STUDY OBJECTIVES:
1) Develop a digitized database for computerized neuropsychological measures,
2) Develop a system to electronically transmit neuropsychological test data collected at a remote location to a centralized database, and 3) Explore the relationship of select neuropsychological variables (derived from ANAM, CogScreen & MicroCog) to initial checkflight performances during Initial Entry Rotary Wing (IERW) training.

TECHNICAL APPROACH
Subjects are given a detailed overview of the study requirements followed by a 48-hour period in which to give consent. Once consent is obtained, subjects are scheduled for the interview and testing session within 2 weeks. The interview and testing are conducted on the same day and require approximately 4 hours to complete. At these session subjects complete a brief structured, computerized questionnaire designed to gather demographic information and information about past medical history. The questionnaire data will be used to describe the sample and to make statistical comparisons based on demographic variables. Completion of the questionnaire is followed by a brief interview to clarify information on the questionnaire and to query any missing information. Following this, each subject is given individual instructions on how to begin the first computerized neuropsychological test. Once the instructions are fully understood, each subject completes the tests by following additional instructions presented on the computer screen. All subjects will complete the 3 different tests during a 4-hour period on the same day allowing for a 15-minute break between tests. Trained personnel are available for questions throughout the testing period. All tests are computer administrated and each lasts approximately 45-60 minutes. The questionnaire and interview takes approximately 15 minutes to complete. All data are saved on the testing computer and, if feasible, securely transported via electronic medium (computer modem, or internet transmission), to a centralized database at WRAMC for analysis.

Data are stored and transported using security features mandated by the NARMC Telemedicine Directorate. These features include encryption, password security and access controls. Only the investigators and the trained civilian research assistant have access to the data. Study data for individual subjects are not made part of the subject's medical record or made available to the chain of command. All personal identifiers are stripped and a case number is assigned before transmittal of the data. Personal identifying information (i.e., name and Social Security number) is required in order to accurately collect Checkflight Performance scores on only the study participants and no other aviator trainees. Information collected in this study will be maintained indefinitely in the digitized database (Microsoft Access or SQL) for future data analysis. However, at the time of final storage of data, all personal identifiers (i.e., name and Social Security number) will have been stripped, thereby ensuring anonymity of data in the final database.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Thus far we have developed the initial database using Microsoft SQL7 (objective 1), and we have developed the "electronic data transmission" method, which involves uploading data via a secure website and to a secure server (objective 2). There have been no substantive modifications, no adverse events, and no subjects have withdrawn. The number of subjects enrolled to the study since last APR at Fort Rucker, AL is _22__ and the total enrolled to date at Fort Rucker, AL is ___22____. The total number enrolled study-wide is __N/A___, if multi-site study.

CONCLUSIONS

Thus far, the findings indicate that it is feasible to electronically transmit data from a remote location using a secure server database. The implication from this finding is the possibility of greater access to neuropsychological services. Further conclusions about the usefulness of the individual neuropsychological tests (e.g., ANAM, MicroCog, CogScreen) are pending completion of data collection.

Report Date: 7 May 2001

Work Unit # 7302

DETAIL SUMMARY SHEET

TITLE: Analysis of Component Neurocognitive Processes for the Trial-Making Test: An Examination of Age Related Changes

KEYWORDS: Trail Making Test, Aging

PRINCIPAL INVESTIGATOR: Jones, Alvin Ph.D., DAC
ASSOCIATES: Kratz, Kris E. MA; Bluestein, Brendon W. MA

DEPARTMENT: Psychology
SERVICE: Clinical Psychology

STATUS: O
INITIAL APPROVAL DATE: 8 July 1997

STUDY OBJECTIVE

There are three objectives:

(1) To determine if the component neurocognitive process (motor speed, visual scanning etc.) can be determined and reliably measured for the Trial Making Test;
(2) To examine the effects of age on the component neurocognitive processes;
(3) Establish preliminary normative data for clinical interpretation of test results.

TECHNICAL APPROACH

There are three phases of research:

(1) development of standardized test materials;
(2) establishing test-retest reliability for the testing material;
(3) collection of data to examine how performance changes on the component neurocognitive process over the life span. The final stage will also provide preliminary normative data for clinical interpretation of test results.

PRIOR AND CURRENT PROGRESS

Phase I of the research has been completed. There have been no adverse events

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 3. (erroneously reported as 4 in last APR)

CONCLUSIONS

No conclusion can be drawn at this time.

Report Date: 23 May 2001

Work Unit # 7304-98

DETAIL SUMMARY SHEET

TITLE: Efficacy of Using Interactive Video Conferencing During Neuropsychological Assessments

KEYWORDS: Video Conferencing, Neuropsychological

PRINCIPAL INVESTIGATOR: Kelly, Mark MD, DAC
ASSOCIATES:

DEPARTMENT: Psychology
SERVICE: Neuropsychology

STATUS: C
INITIAL APPROVAL DATE: 21 July 98

STUDY OBJECTIVE
To determine whether there is any difference between face-to-face interviewing vs. tele-video conferencing.

TECHNICAL APPROACH
A direct comparison of two experimental conditions is planned; there is no change to the original protocol.

PRIOR AND CURRENT PROGRESS
No subjects have been enrolled into this study, and there are no plans to enroll any subjects in the future. We therefore request that the protocol be closed.
The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 0. The total number enrolled study-wide is 0, if multi-site study.

CONCLUSIONS
The study was not conducted due to the PCS of the original PI. A related study is in the planning stages and a new protocol will be submitted to DCI for review.

Report Date: 4 October 2000 Work Unit # 00-7501

DETAIL SUMMARY SHEET

TITLE: Evaluation of a Virtual Reality Simulator in Sustainment Training

KEYWORDS: Military Training, Virtual Reality, Readiness

PRINCIPAL INVESTIGATOR: Agazio, Janice LTC AN
ASSOCIATES: Connie Pavlides DNSc RN, Caterina Lasome MAJ AN

DEPARTMENT: Nursing
SERVICE: Nursing Research

STATUS: C
INITIAL APPROVAL DATE: 02 November 1999

STUDY OBJECTIVE:
The purpose of this pilot was to assess the usefulness, cost-effectiveness, and user satisfaction of the Cath-Sim Intravenous Training System™ for teaching and achieving competence at IV insertion while in the MOPP level 4 for military medical personnel. This pilot project used a randomized controlled trial to examine the efficacy of the Cath-Sim Intravenous Training System™ virtual reality simulator training upon the success and timely IV insertion under chem.-bio conditions (MOPP 4)

TECHNICAL APPROACH:
Grounded in adult psychomotor learning principles and in the evaluation model developed by Holzemer (1988) from the work of Donabedian (1981) and Chater (1975), participants were tested on both models and then randomly assigned to practice on either the IV arm model or Cath-Sim while at MOPP 4. One week later, participants were again assigned to both models. Outcome measures included 1) a computer-generated score sheet measuring time to success and criterion success/non-success, 2) time and success rating from IV insertion on the IV arm model, and 3) satisfaction evaluations completed by the participants. Demographics were collected to provide descriptive data of the participants. Descriptive statistics were used to describe the characteristics of the sample. Content analysis was used to evaluate the qualitative aspects of the satisfaction evaluations.

PRIOR AND CURRENT PROGRESS:
Data collection was completed in May 2000. There were a total of 60 participants. Fifty-one were in the final data set as 9 data sets were incomplete due to no return for final testing, emergency leave, and claustrophobia in the mask (couldn't complete the baseline). There were 25 participants in the IV arm group and 26 in the Cath-Sim group. There were no adverse events to report.

CONCLUSIONS:
Only 16 in the entire group were successful on both the IV arm and the Cath-Sim. All 16 had longer times on the Cath-Sim in the final test than at baseline in MOPP gear. Fourteen of 16 participants improved IV arm times compared to Cath-Sim times. The IV arm performed better on the Cath Sim final testing but not significantly better. There was no difference between groups on time to success or success rate (slight edge for IV group, but not significant). The groups offered conflicting evaluations for recommending one model over the other. There appeared to be some subjective benefit to each model depending on user, setting, and purpose.

Report Date: 24 April 2001 Work Unit # 00-7502

DETAIL SUMMARY SHEET

TITLE: A Prospective Study of Stress in Army Reservists

KEYWORDS: Army Reservists Occupational Stress; Longitudinal Study

PRINCIPAL INVESTIGATOR: LTC Laura R. Brosch
ASSOCIATES: Jacqueline Agnew, Ph.D.

DEPARTMENT: Nursing
SERVICE: Nursing Research

STATUS: O
INITIAL APPROVAL DATE: 16 May 2000

STUDY OBJECTIVE

The overall goal is to apply the newly developed Reserve-Specific Stress Inventory to a cohort of Selected Reservists in a prospective study design. This will allow the identification of stressors related to reserve, civilian job, and family roles that are associated with adverse health outcomes. The subscales of the Inventory will enable examination of individual and organizational factors that mitigate stress under high stressor conditions.

TECHNICAL APPROACH

This study will be prospective in design, with each subject followed at six-month intervals for one year following an initial data collection session. Participants will be volunteers who have been randomly selected from unit rosters of Army Reserve units belonging to the 99th Regional Support Command in Pittsburgh. After enrolling in the study and providing signed information consent, Reservists will be interviewed by telephone using a survey that will address their roles as reservists, civilian workers, students (if applicable), and family members as well as psychological health factors. The newly developed Reserve-Specific Stress Inventory will be used to assess specific stressors as well as personal and organizational resources that can mitigate stress. Outcomes will emphasize injury and stress-related experiences. The data to be collected by interview will measure components of the model that relate to the conceptual framework of the study, i.e. the demand-control model. Because of the geographic dispersion of units and need to distribute initial contact over time, subjects will be enrolled over a period of six months at the rate of approximately 30 participants per month. Total anticipated enrollment: n = 180.

PRIOR AND CURRENT PROGRESS

No activity has been initiated on this protocol. The funding agency has established the requirement that all activity on a previous grant (Work Unit # 7577-99; MDA 905-98-Z-0019) be completed prior to initiation of the present protocol. This requirement should be fulfilled within two calendar months.
The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 0.

CONCLUSIONS

No conclusions regarding this protocol are available at this time.

Report Date: 7 June 2001 Work Unit # 00-7503

DETAIL SUMMARY SHEET

TITLE: Ethical Issues in Department of Army Nursing Practice

KEYWORDS: ethical issues, nursing practice, instrument development

PRINCIPAL INVESTIGATOR: LTC Laura Brosch, AN
ASSOCIATES: COL Janet Harris, AN; LTC (Ret) Janice Agazio, AN

DEPARTMENT: Nursing
SERVICE: Nursing Research

STATUS: O
INITIAL APPROVAL DATE: 22 September 2000

STUDY OBJECTIVE

The aims of this study are: 1) identify the ethical issues experienced by Army Nurse Corps (ANC) officers and Department of the Army civilian (DAC) registered nurses (RNs) in their practices and the frequency of their occurrence; 2) identify how disturbed ANC and DAC RNs are by these ethical issues; and 3) determine the ethics education needs of ANC and DAC RNs.

TECHNICAL APPROACH

This study involves 2 phases. In phase I, focus groups will be used to identify and incorporate Department of the Army and military environment-specific ethical issues into the Ethical Issues Scale. Participants for the focus groups will include ANC officers in TOE units and both ANC and DAC RNs in Medical Treatment Facilities and TOE units. Approximately 30 minutes will be required to complete the survey. Ordinal level data will be analyzed with frequency and contingency tables. Interval level data will be described with means, ranges, and standard deviations, as appropriate. Nonparametric, Chi-Sqaure, will be used to determine is there is a significant difference in the issues experienced by ANC officers and DAC RNs. This study will provide information about the ethical issues experienced in the workplace by ANC and DAC RNs. There has been no modification to the methodology.

PRIOR AND CURRENT PROGRESS

Three focus groups have been conducted, one at Dewitt Army Community Hospital at Fort Belvoir and two focus groups at Fort Bragg. The 23 participants in the focus groups included ANC officers in TOE units and both ANC and DAC RNs in Medical Treatment Facilities. The tapes of the focus groups have been transcribed and analyzed. Additional items are being added to the Ethical Issues Scale. No adverse events have occurred in this study.

The number of subjects enrolled to the study since last APR at WRAMC (DeWitt) is 8 and the total enrolled to date at WRAMC (DeWitt) is 8. The total number enrolled study-wide is 23, if multi-site study.

CONCLUSIONS

None

Report Date: 29 June 2001 Work Unit # 00-7504

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: Nursing Experience And Critical Care Outcomes

KEYWORDS:

PRINCIPAL INVESTIGATOR: LTC Patricia A. Patrician AN
ASSOCIATES: LTC Debra D. Mark AN

DEPARTMENT: Nursing
SERVICE: Nursing Research

STATUS: C
INITIAL APPROVAL DATE: 11 July 2001

STUDY OBJECTIVE

A triangulated, prospective design was selected to evaluate change in outcomes as a function of system characteristics, critical care nurses' interventions, and client characteristics.

TECHNICAL APPROACH

This study used quantitative and qualitative methodologies to determine the effect of nursing care on the health outcomes of critical care patients. The non-experimental correlational quantitative portion of this study examined the effect of nursing experience, ratings of the level of nursing care provided, and nurse staffing on the patient's discharge health status. The qualitative exploratory portion of this study described the influence of nurse-patient interactions on patient outcomes from the perspectives of both patients and nurses.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Quantitative Findings

A total of 121 patients were available for recruitment; 109 (90%) volunteered for the study. The final sample of 86 patients consisted of people ranging in age from 25 to 85 years old. One patient changed his mind about participating and withdrew after providing consent to participate, but before completing the initial survey. The age of the patients correlated negatively with three measurements of pre-operative health status and with three measurements of discharge health status. Also, the older the patient, the higher the severity of illness, the greater need for more ICU nursing care, the longer the hospital length of stay.

The patient's pre-operative health status ranged from 35% to 73% of excellent health (or 100%); the average physical component score was 11% lower than the general U.S. population, but the average mental component score was just 3% lower. Pre-operative physical health status measurements positively correlated primarily with each other and, occasionally, with mental health status measurements.

The same is true for the mental health status measurements; they correlated positively primarily with each other and occasionally with physical health status measurements. However, pre-operative mental health failed to correlate with some pre- and post-operative mental health constructs, the APACHE III score, ICU measurements of length of stay and nursing care, and hospital length of stay. On occasion, pre-operative mental health correlated positively with the APACHE III score.

The average APACHE III score was 27 points, 23 points lower than the national average of 50 points. The APACHE III score correlated negatively with discharge health status measurements, both physical and mental constructs. It also correlated positively with ICU length of stay measurements, requirements for ICU nursing care, and hospital length of stay.

The average weighted years of nursing experience and years of critical care nursing experience correlated positively with nurse staff mix and patient perceptions at discharge about their health change over the previous year. However, the average weighted level of care hours failed to correlate with any health status measurement. Average weighted years of experience regressed positively and average weighted level of care regressed negatively on the single item querying the patient about health change

over the last year measured at discharge.

The length of the intensive care unit stay measurements correlated positively with each other and with the hospital length of stay. Four of the five measurements varied with nurse-sensitive outcomes. However, ICU measurements of length of stay failed to correlate with any of the discharge health status measurements.

Compared to the pre-operative measurements, this typical patient would leave the hospital with a reduction on six of the nine sub-scales; his health status scores would decrease by between 4% and 24%. However, at discharge, this patient would also report a 2% increase in general health, a 2% increase in emotional wellbeing, and a 23% increase in their health over the last year. The physical component score would diminish by 10%, but the mental component score would increase by 3%.

Discharge physical health status measurements positively correlated primarily with each other and with pre-operative physical health status measurements. They occasionally correlated positively with both pre-operative and discharge mental health status measurements. Discharge mental health status measurements also positively correlated primarily with each other and occasionally with physical health status measurements.

The multiple regression model predicted discharge general health with pre-operative physical component scores (in combination with other predictors). The relationship was positive, as one would expect. However, the only discharge health status measurements predicted by multiple regression were those that were general, and physical, in nature. The specific subscales and even the two component scores (consisting of four subscales each) were not predicted by any of the pre-operative measurements of health.

The nine change scores were predicted by primarily their pre-operative controls. The one exception was the change score for perceived health change over the past year that was predicted by the average weighted years of critical care experience.

The average length of post-op stay was 11 days and correlated positively with the patient's age, generally all of the pre-operative physical measurements of health status, severity of illness, all five measurements of the ICU length of stay, and four of the health status change scores, but it failed to correlate with any measurements of discharge health status.

The sample of 77 nurses was relatively young and consisted of more male nurses, when compared to the national average. The major independent variables, years of experience, years of critical care experience, and self-ratings of the level of care revealed that this sample's experience levels clustered at the low end with an average of six years of experience and three years of critical care experience. The average self-rating of the level of care provided was 3.08, indicating a proficient level of nursing care.

Years of nursing experience was positively related to years of critical care experience and level of care ratings. Of interest is the finding that nursing experience and critical care nursing experience varied with employer. Civil service nurses were more experienced than contract nurses and active duty nurses. Years of critical care nursing experience was also positively related to level of care ratings; contract nurses rated themselves higher on the level of care provided than active duty members.

Qualitative Findings

The sample for the qualitative portion of this study included surgical intensive care unit patients and nurses. An attempt was made to interview all of the patients. However, the majority of the patients (43 patients) were unavailable for interviews. There was also a group of patients (14 patients), that when asked about what nurses did that made a difference in their recovery, could not think of any specific situation or globally made reference to the fact that everyone was good to them. Therefore, interviews were conducted with 34 patients. Interviews were also conducted with a purposive sample of five critical care nurses.

Most of the patients chose to begin their interview with a positive experience. However, when patients discussed several situations, the majority of the subsequent stories were negative.

Nurses and patients generally agreed about what nurses did or didn't do that made a difference in a patient's recovery. They thought that getting to know the patient, providing competent care, and establishing a presence were important. The three themes identified in the data were: (1) knowing the patient, (2) professional competence, and (3) being there. These findings are supported in the literature (Benner, Hooper-Kyriakidis, & Stannard, 1999; Green, 1994; Guterman & Bargal, 1996; Hawley, 2000;

Oermann & Templin, 2000; Radwin, 1993; Radwin, 1998; Redmond & Sorrell, 1999; Wilde et al., 1993; Williams, 1998).

However, there were categories that were emphasized differently by patients and nurses. This is not surprising given the literature supporting this finding (Gerbert et al., 1996; Laitinen, 1994; Middleton & Lumby, 1999; Minnick, Young, & Roberts, 1995; Proctor, 1998; Singleton-Bowie, 1995; Slauenwhite & Simpson, 1998). Patients gave a higher priority to timeliness and presencing more so than nurses. And nurses emphasized a strong professional knowledge base more so than patients.

A pattern emerged across the themes: evolution of intimacy. Patients and nurses alike suggested in their stories that a higher level of intimacy was expected if patient outcomes were to be enhanced.
The number of subjects enrolled to the study since last APR at WRAMC is 109 patients and 77 nurses and the total enrolled to date at WRAMC is 109 patients and 77 nurses.

CONCLUSIONS

This study used quantitative and qualitative methodologies to determine the effect of nursing experience on the health outcomes of critical care patients. A triangulated, prospective design was selected in order to evaluate change in patient outcomes as a function of system characteristics, critical care nurses' interventions, and client characteristics using the Quality Health Outcomes Model (Mitchell, Ferketich, & Jennings, 1998). This model was specifically designed to assist in determining nursing's contribution to outcomes of care. For this study, outcomes of care included nurse-sensitive outcomes, as well as several measurements of health status.

System characteristics are said to mediate the effect of interventions on outcomes. These included the experience and staff mix of the nurses in the intensive care unit. The findings of this study demonstrate that these particular system characteristics did not impact patient outcomes. The relationship between nursing experience levels and patient outcomes needs further investigation. Perhaps different instruments, the inclusion of other health care providers, and the timing of measuring health status may lend more insight into how nursing experience influences the recovery trajectory of patients. Nurse staff mix also failed to relate to patient outcomes. Since much of the literature refutes this finding, further research in this area is also suggested.

Client characteristics mediate the effect of interventions on outcomes and included the patient's age, pre-operative health status, APACHE III score, and their perceptions of nurse contributions to their recovery. Study findings revealed that client characteristics were related to and predicted several measurements of health status at discharge; they did not relate to or predict nurse-sensitive outcomes.

The positive relationship between length of ICU stay and nurse-sensitive outcomes was of interest. Future research would be better suited to include the measurement of nurse-sensitive outcomes and nursing care over the entire hospital stay and the impact of these outcomes not only on length of hospital stay but on health status, as well. The somewhat spurious relationship between mental health and physical health is of interest. Further study is required to determine if, indeed, there is a relationship, and how it impacts the delivery of nursing care. The lack of a relationship between hospital length of stay and discharge health status indicates that the patient's perception of their health status is apparently not considered in discharge decisions. Further research is necessary to corroborate these findings. Patients also indicated several areas where nurses made a difference in their recovery, inclusive of knowing them as a person, demonstrating professional competence, and being there.

Interventions typically include clinical processes. For this study, the nurses' self-rating of the level of care and their perceptions of their contribution to patient outcomes were examined. The level of care failed to correlate or predict any of the outcomes measured, but nurses generally agreed with patients about what nurses did or didn't do that made a difference in their recovery. Interestingly, not all interventions were considered clinical in nature. The evolution of intimacy was evidently important to both nurses and patients in order to enhance recovery. Future qualitative research is needed to further explore the pattern revealed in this study.

Questions continue to persist about nursings contribution to patient outcomes and further research is warranted.

Report Date: 08 January 2001 Work Unit # 7559

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: Active and Passive Smoking in Military Women

KEYWORDS: smoking, passive smoke, environmental tobacco smoke

PRINCIPAL INVESTIGATOR: LTC Janice Agazio
ASSOCIATES: Martinelli, Angela DNSc

DEPARTMENT: Nursing
SERVICE: Nursing Research

STATUS: C
INITIAL APPROVAL DATE: 18 May 1999

STUDY OBJECTIVE

The purpose of this study was to determine the status of active and passive smoking in military women and dependents and to determine whether current educational and preventive measures are effective or whether a fundamentally different approach, which combines both active and passive smoking prevention and treatment is needed.

TECHNICAL APPROACH

This study used a cross-sectional, predictive design in a sample of 157 female smokers with children and 81 female non-smokers with children. The subjects, military women or female military dependents with children, were recruited at WRAMC and Womack AMC. A series of questions and measures that explore active and passive smoking behavior were used. Data were analyzed using descriptive statistics, X squared test of association, Pearson correlations and multiple regressions. Results provide a model of active and passive smoking behaviors and beliefs and data relevant to the development of tailored stage-specific education strategies in interventions related to both active and passive smoking.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Data collection was completed in May 2000. Approximately 700 forms were distributed until 300 were returned for a return rate of 43%. Some questionnaires were deemed unusable to missing data. The final sample consisted of 157 smokers and 81 non-smokers. There were no adverse events.

CONCLUSIONS

Results showed that for non-smokers, exposure was related to stage of ETS avoidance, pros and cons of exposure, self-efficacy to resist exposure, and ETS avoidance. Non-smokers children's exposure was related to mother's self-efficacy for herself and her child. For smokers, exposure was related to the pros of smoking; for their children exposure was related to mother's exposure and inversely related to mother's efficacy to resist ETS exposure for her child. Both non-smokers and their children had lower exposure scores than smokers and their children. For women, exposure was predicted living with smoke for children exposure was predicted by mother's education.

Report Date: 12 March 2001 Work Unit #7568-98

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: Health Promotion in Military Women: Active Duty and Reservists

KEYWORDS: Health promotion, Women, Working Women

PRINCIPAL INVESTIGATOR: Agazio, Janice LTCAN
ASSOCIATES: Paula Ephraim MSN RN; Norma Flaherty BSN RN

DEPARTMENT: Nursing
SERVICE: Nursing Research

STATUS: C
INITIAL APPROVAL DATE: 21 April 1998

STUDY OBJECTIVE

The purpose of this study was to determine the extent to which selected demographic characteristics, definition of health, perceived health status, perceived self-efficacy and resources are related to the health promoting behaviors of military women. These results will be compared with other published reports to determine how military women compare to other American women in their health promoting behaviors. A second purpose of this study was to describe quantitatively the experience of being military women to further identify the barriers and strategies that military women use to pursue health promotion.

TECHNICAL APPROACH

A sample of active duty women without children and reservists with and without children were recruited during clinic visits for a one-time completion of study measures. A subset of women participated in short focused interview. The research instruments included: (a) a demographic data sheet; (b) Laffrey Health Conception Scale; (c) Family Inventory of Resources for Management (FIRM); (d) Perceived Competence Measure; (e) Perceived Health Status Scale; and (f) Health-Promoting Lifestyle Profile II (HPLP-11). Descriptive statistics will be used for demographics and to describe the other major variables. Relationships between the variables and to health promoting lifestyle scores will be analyzed using multiple regression to test casual models as hypothesized in the proposed models of relationships. Differences between the groups will be explored using MANOVA. Qualitative data analysis as described by Miles and Huberman (1984) will be used to simultaneously analyze and direct data collection to describe the health promotion barriers and strategies identified by military women.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Subject recruitment ended in May 2000. The total sample included 345 subjects completed surveys. The active duty with children group filled under protocol #7555. Fifteen interviews have been conducted under this protocol; five interviews from each group (AD without children, Reservists with and without children). Upon the PI's employment at USUHS, she was awarded a small project grant to fund data transcription. Final data analysis results should be completed over summer, 2001 and will be submitted in a final report at WRAMC and USUHS.

CONCLUSIONS

There have not been any serious or unexpected adverse reactions in this minimal risk study. No analysis has yet been performed on any data at present.

Report Date: 18 October 2000

Work Unit # 7574-99

DETAIL SUMMARY SHEET

TITLE: A Comparison of Two Lubricants When Used with the Laryngeal Mask Airway on the Incidence and Severity of Sore Throat

KEYWORDS:

PRINCIPAL INVESTIGATOR: Timothy A. Newcomer LTC AN
ASSOCIATES:

DEPARTMENT: Nursing
SERVICE: Anesthesia Nursing

STATUS: C
INITIAL APPROVAL DATE: 20 October 1998

STUDY OBJECTIVE

Detection of a difference if the incidence and severity of sore throat between plain water soluble lubricant and 25 lidocaine jelly when used to lubricate the Laryngeal Mask Airway (LMA).

TECHNICAL APPROACH

This study was a prospective double blind randomized clinical trial examining the difference in the incidence and severity of sore throat post LMA when either plain water-soluble lubricant or 2% lidocaine is used for LAM insertion.

PRIOR AND CURRENT

Data collection was terminated 1 August 1999 with 103 subjects enrolled. Data was collected at WRAMC (n=12 and Kimbrough Ambulatory Care Center, n=91). No adverse reactions have been reported, and one subject was withdrawn from the study because the researcher was unable to place the LAM after three attempts, which was consistent with the protocol. This subject did not experience any adverse reactions. No benefits to patients have been identified at this time. The results and findings have been analyzed and discussed.

CONCLUSIONS

Our incidence of sore throat (20%), while high, remains within the reported range for postoperative sore throat with the LMA. We found no statistical or clinical difference between lubricants regarding insertion difficulty or presence of co-morbidites. We found that the incidence of sore throat with 2% lidocaine jelly (24%, 13/53) was slightly higher than plain water-soluble lubricant (15%, 7/46). This small effect size is statistically and clinically irrelevant. As with previous studies, no improvement in patient outcome was demonstrated when the LAM was lubricated with 2% lidocaine jelly. Thus, it would seem prudent to follow the manufacturer's recommendation not to use lidocaine jelly as a lubricant for the LMA.

Report Date: 02 February 2001 Work Unit # 7576-99

DETAIL SUMMARY SHEET (Human Use Protocol)

TTTLE: E-mail as a Communication Tool in Army Nursing Management

KEYWORDS: email, communication, nursing, management

PRINCIPAL INVESTIGATOR: Brosch, Laura LTC AN
ASSOCIATES: Lasome, Caterina MAJ AN

DEPARTMENT: Nursing
SERVICE: Nursing Research

STATUS: O
INITIAL APPROVAL DATE: 09 February 1999

STUDY OBJECTIVE

The purpose of this grounded theory study is: 1) to determine the impact of email on the management relationship between Head Nurses (HN) and Clinical Staff Nurses (CSN) in a military health care setting, and 2) to determine the consistency between perceptions versus actual messages sent by email. The aim of this study is to qualitatively describe the experiences of HNs and CSNs who use email technology.

TECHNICAL APPROACH

A focused interview guide, organized around the topic of email, will be administered during individual interviews. Participants complete a demographic data sheet. Prior to the conclusion of data collection, a HN and CSN group will be invited to participate in a discussion to clarify and validate themes that emerged from the data. Descriptive statistics will be used to describe the sample (age, gender, frequency of email use, etc.). The constant comparative method of analysis will be used to simultaneously analyze and direct data collection. NUDIST computer software program will be used for all coding and clustering of data and then to map relationships between the codes, categories and themes in building the grounded theory.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

23 participants have been recruited to date; 9 HNs and 13 CSNs. Access to participants in the three Army medical facilities has occurred without complication. Interviews have proceeded according to protocol using tape recorders and note taking techniques. No participants have refused to complete their interviews nor offered complaints about the interview process.

Interviews have been continuously coded and analyzed using the constant comparative method for grounded theory research. Findings from previous interviews guide discussion and probes in subsequent interviews. Interviews have also been reviewed independently by two consultants. At this time, there is evidence of theoretical saturation and no additional interviews will be conducted until more formalized analysis of the data is complete.

Preliminary findings support two core variables: trust and security. Themes surrounding these two core variables cluster into four major categories: 1) intrapersonal trust, 2) interpersonal trust, 3) organizational trust, 4) technological security. The study investigators plan to develop a preliminary theory of trust and security in Army Nursing communication which will then be presented to focus groups for validation and refinement. Additional interviews may be necessary to clarify new or existing themes.

Textual analysis of group email for 14 participants has provided few additional findings. These data will be subsumed in the grounded theory.

CONCLUSIONS

Analysis of data is ongoing. There are preliminary indications that nursing personnel from this study are slow to accept email technology. A TSNRP grant proposal has been submitted by the study co-investigator, LTC (Ret.) Janice Agazio to study this phenomenon further.

Report Date: 12 December 2000

Work Unit # 7577-99

DETAIL SUMMARY SHEET (Human Use Protocol)

TTTLE: Development of a Reserve-Specific Stress Inventory

KEYWORDS: Army Reserve, Stress, Psychosocial Factors

PRINCIPAL INVESTIGATOR: Brosch, Laura LTC AN
ASSOCIATES: Jacqueline Agnew, PhD COL AN USAR

DEPARTMENT: Nursing
SERVICE: Nursing Research

STATUS: O
INITIAL APPROVAL DATE: 09 February 1999

STUDY OBJECTIVE

The overall goal is to develop a tool to be used in research programs and eventually interventions that address the health, and therefore readiness status, of reservists. This reserve-specific occupational stress inventory will be based on a review of the literature and qualitative results from previous research funded by the TriService Nursing Research Program (TSNRP). Common occupational stress models form the framework for elements of the instrument.

TECHNICAL APPROACH

Volunteer participants are members of the selected reserves, a group whose health status has received very little study. They were randomly selected from unit rosters of Army Reserve medical units subordinate to the 99th RSC in Maryland, Pennsylvania, Virginia, West Virginia and the District of Columbia. Methods included development of potential stress inventory items from previously administered interviews and focus group study results. The development of the proposed instrument included a series of eight cognitive interviews. An initial administration of this preliminary instrument to 100 volunteers yielded a database for item analysis and reduction. A second administration of the revised instrument was planned to obtain a target population of 300 randomly selected individuals to allow further refinement and validation of the stress inventory. Finally, a subgroup of 75, are being asked to repeat the second instrument for assessment of reliability.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

As of 31 December 1999, 109 subjects were enrolled. As of 31 December 2000, 497 subjects were enrolled. A no cost extension through 28 February 2001 was granted by the TSNRP, due to delays encountered with human subject use protocol approvals and delays in subject recruitment. The following steps of the protocol have been completed: cognitive interviews (n=8); administration and analyses of the preliminary instrument (n=101); and administration of the revised instrument (n=388). Data analysis of the revised instrument is scheduled to begin in January 2001. The repeat administration of surveys to subgroup (estimated at 75) is underway. All potential study subjects have now been contacted. The recruitment total for administration of the revised instrument (n=388) exceeds the initial goal of 300 because the response rate unexpectedly increased during the second half of data collection. No recent research reports address the topic of this research or impact the conduct of this study.

CONCLUSIONS

The reserve specific occupational stress inventory under development in this study shows promise as a measure of reserve-related stressors and resources that may impact the health and readiness status of military reservists. The inventory is comprised of six distinct scales: demands, control, social support, reserve-family interface and fatigue. The Chronbach's Alpha coefficients for the scales range from 0.84 to 0.92. Other psychometric properties measured during the development of the inventory suggest the scales will perform successfully in subsequent administration. The result of the final survey implementation will help to substantiate the strength of the scales observed in the small sample (n=100) utilized during scale development and item reduction.

Report Date: 10 May 2001

Work Unit # 7578-99

DETAIL SUMMARY SHEET

TITLE: Development and Evaluation of the Military Nursing Moral Distress Scale

KEYWORDS: Military Nursing, Moral Distress; Crisis Deployment

PRINCIPAL INVESTIGATOR: LTC Laura Ruse Brosch, AN
ASSOCIATES: COL Ann Hurley, DNSc, Sara T. Fry, PhD, Barbara Jo Foley, PhD

DEPARTMENT: Nursing
SERVICE: Research Service

STATUS: O
INITIAL APPROVAL DATE: 27 July 1999

STUDY OBJECTIVE

The purpose of this project is to develop and test the Military Moral Distress Scale (MMDS), a tool to measure moral distress in the military nurse. Specific Aims of the project are 1. Identify the phenomenon of moral distress in nurses' stories of patient care; 2. Develop the content of items for constructing the Military Distress Scale (MMDS); 3. Develop a tool to measure military moral distress in U.S. Army Nurses; 4. Conduct the psychometric evaluation of the military Moral Distress Scale.

TECHNICAL APPROACH

Phase one of the study included the analysis of interviews and focus group discussions to identify and validate the construct of moral distress in military nurses. Using interview data, researchers wrote the items for the Moral Distress in Military Nurses Scale. Focus group discussions with respondents and experts in moral distress were used to assure that we saturated the universe of the content domain of moral distress and items were congruent with theoretical definitions, clearly stated and described experiences common to nurses. In phase two, researchers further developed the content validity through use of judges who were U.S. Army Nurse c Corps Officers with crisis military deployment experience and doctoral prepared nurses with expertise in ethics. The last step was to pilot test the wording by administering the tool in person to 10 Army nurses did no participate in any of the e preceding steps. After final revisions we mailed packets including the Military Nursing Moral Distress Scale, a letter providing informed consent information, instructions and a return envelope with postage to be paid by Northeastern University. This mail system avoided the use of a postmark and was another step in preserving the anonymity of respondents. We do not know the number of participants under the aegis of the WRAMC IRB, but obtained a total of 1500 returned scales. Addendum: On February 10, 2000 we requested approval to examine the test-related stability of the scale in a subset that agreed to participate. Approval to incorporate the changes requested was granted on April 20, 20000, by the WRAMC Human Use Committee.

PRIOR AND CURRENT PROGRESS

Phase I (analysis of interviews and focus group discussions) and phases I and II of the study. We have completed data collection for the final phase and no longer seek enrollment in the study. Total enrollment to date study wide is 1500. No adverse reactions have been noted. No subjects have been withdrawn from the study. There are no direct benefits to Nurse Officer subjects in the study, however several subjects have reported that they valued the study and its goals.

CONCLUSIONS

We have received 1500 completed responses to the Military Nursing Moral Distress Scale. All from their sites. Data were entered using an SPSS computer program. We are completing the analysis of data and will continue to study results and prepare document for publication.

Report Date: 01 June 2001 Work Unit # 7579-99

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: Nurses Influence on Patient Outcomes in US Army Hospitals

KEYWORDS: Nurses, Patients, Outcomes

PRINCIPAL INVESTIGATOR: Patrician, Patricia LTC AN
ASSOCIATES:

DEPARTMENT: Nursing STATUS: O
SERVICE: INITIAL APPROVAL DATE: 27 July 1999

STUDY OBJECTIVES
The research questions are:
1. What is the patient outcome performance of US Army hospitals as measured by occurrence of adverse events, length of stay, and severity-adjusted mortality while in the hospital; and how do patients rate their satisfaction with nursing care, symptom management, and functional health status following discharge?
2. How can US Army hospitals be characterized in terms of mursing organizational structures such as nursing practice model, nursing skill mix, and the educational and experiential backgrounds of RNs?
3. How do nurses in US Army hospitals rate nursing organizational processes including job satisfaction, the degree autonomy in nursing practice or the discretionary judgment accorded nurses in the work environment, the level of RN and physician collaboration, the degree of clinical expertise, and the extent to which and ethical working environment is present in the US Army hospitals?

TECHNICAL APPROACH
The proposal is being followed in the original and as the procedures were amended by WRAMC Institutional Review Board during the initial approval process. The amended WRAMC procedures are that lists of recently discharged patients are obtained; surveys and consent forms are mailed to them with two follow-up reminders (a reminder postcard and then a second survey); and information from the medical record is obtained only from discharged patients who return their surveys with a signed consent form or who are deceased.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE
Data collection and analysis for the nurses' survey is complete and a manuscript is being prepared for review by a nursing journal. Data collection and data entry for patient medical records and the returned mailed patient is nearing completion. Our goal is to complete both and to have preliminary analyses done by August of this year.

The number of subjects enrolled to the study since last APR at WRAMC is (PLEASE SEE BELOW) and the total enrolled to date at WRAMC is (PLEASE SEE BELOW). The total number enrolled study-wide is (PLEASE SEE BELOW), if multi-site study.

Number of new subjects since last APR
No new nurse respondents since last APR
Medical records reviewed since last APR: 165
New completed mailed patient surveys since last APR: 74

Total subjects enrolled at WRAMC to date:
Total usable nurse surveys to date: 72 (1 survey from last APR discarded because of too many missing data)
Total medical records reviewed to date: 165
Total completed mailed patient surveys: 182 (includes 16 without consents that will not have associated medical record data as a result)

Total subjects enrolled at both study sites to date
Total usable nurse surveys for both study sites: 125
Total medical records from both study sites to date: 330
Total completed patient surveys from both study sites to date: 237

CONCLUSIONS
Data entry is not complete for any of the patient data so that no conclusion can be made.

The nurse data is complete. Response rate including both sites was 47%. Fifty-five percent were active-duty military and 41% were civilian. Diversity was present for age, nursing education and experience, gender and race. A total of 38% had nursing certification of some type. Certification is associated with nursing expertise so this finding is important. The nurse's scores on study scales were all at midpoint or above. Autonomy scale scores were slightly higher for nurses working in mixed bed units; reports in the literature show that autonomy is higher for nurses working in specialty units. Scale scores on nurse and physician collaboration were higher than those reported in the literature. There were significant bivariate correlations between study scales, and a very few significant differences were found between nurses working on mixed bed versus specialty units and between military nurses and the civilian nurses working in the military hospitals. These data are in the process of being assessed and interpreted.

Report Date: 4 May 2001 Work Unit # 00-8101

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: A Prospective Study to Evaluate the Testing of Individual Donor Units from Voluntary Blood Donation for the Presence of HIV-1/HCV RNA

KEYWORDS:

PRINCIPAL INVESTIGATOR: MAJ Sheryl L. Dunn, MS
ASSOCIATES: Sherri S. Hall, DAC

DEPARTMENT: Fort Knox, KY 40121 STATUS: O
SERVICE: Camp Memorial Blood Center INITIAL APPROVAL DATE: 20 June 2000

STUDY OBJECTIVE

The overall study objective is to collect scientific data from individual donor samples with documented serological assay results for anti-HIV and anti-HCV in support of the intended use of the TMA HIV-1/HCV Assay. TMA results will be compared to results from licensed antibody (HIV-1 and HCV) and p24 Ag (HIV) tests. The primary objective is to determine specificity, sensitivity, and reproducibility of the TMA HIV-1/HCV Assay. Specifically, it is to determine whether the TMA HIV-1/HCV Assay allows earlier detection of HIV-1/HCV infection than serological screening tests.
This clinical study is a collaboration between Camp Memorial Blood Center (CMBC) and Gen-Probe Incorporated, San Diego CA.

TECHNICAL APPROACH

Blood donations from volunteer allogenic donors accepted for routine donation at approved military blood collection centers were included in this study. Blood was screened for anti-HIV, HIV p24 Ag, and anti-HCV using FDA licensed tests. The TMA HIV-1/HCV Assay was used to test plasma samples and results were compared to the screening results. Donors who tested TMA HIV-1/HCV positive were added to the follow-up study. Follow-up for HCV reactive donors is monthly for one year; for HIV reactive donors it is weekly for 3 months, or when seroconversion occurs. Follow-up also will take place for any seropositive samples resulting in a non-reactive or equivocal final TMA Assay result. This plasma is shipped frozen to Gen-Probe for an alternate NAT test. All NAT data was released to Gen-Probe Inc. for incorporation into demographic studies. Gen-Probe analyzed the data and forwarded their findings to the FDA to support licensing of this test.

There have been no modifications to the procedure.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

The number of subjects enrolled to the study since last APR at WRAMC is 12,812 and the total enrolled to date is the same. There have been zero adverse reactions for this study.

CMBC has not identified any cases where a donor tests TMA positive, EIA negative. These donors would be placed in the follow-up study to determine seroconversion status. The advantage would be in the earlier detection of an HIV/HCV positive donor. This increases the safety of the military blood supply.

Prior to CMBC getting approval to perform NAT testing, donor samples were tested by Fort Hoods NAT lab under their IND (MEDCOM directed). In June, one CMBC donor tested NAT positive for HCV, but was EIA negative. Fort Hood performed the follow-up study and later the donor seroconverted for HCV (both EIA and RIBA). Due to the early detection by NAT, the original unit of blood was destroyed by CMBC.

TMA Reactive Results	Number	TMA Interpretation At Index	Seroconversion Upon Follow-Up		
TMA HIV-1/HCV Reactive Donors	**24**				
TMA Initial Reactive Only	10	True Neg			
TMA Multiplex (RR) - Non-Discriminated	0	Equivocal			
TMA Reactive - Discriminated	14				
TMA(Reactive)/Sero Pending	0	Not interpretable			
TMA(R)/Sero(Pos)	14	True Pos			
TMA(R)/Sero(Indeterm)	0	True Pos			
TMA Reactive/Sero Negative	0				
TMA(R)/Alternative NAT(R)	0	True Pos	Yes	0	True Pos
			No	0	True Pos
TMA(R)/Alternative NAT(NR)	0	False Pos	Yes	0	True Pos
			No	0	False Pos
TMA(R)/No Alternative NAT	0	False Pos	Yes	0	True Pos
			No	0	False Pos

Serology Reactive Results with Procleix Nonreactive	Number	TMA Interpretation At Index
EIA Repeat Reactive	**63**	
Supplemental Pending	0	Not Interpretable
Supplemental Negative	49	True Neg
Supplemental Indeterminate	13	
Alternative NAT (R)	0	False Neg
Alternative NAT (NR)	2	True Neg
Alt NAT Pending	11	Not Interpretable
Supplemental Positive	1	
Alternative NAT (R)	0	False Neg
Alternative NAT (NR)	0	True Neg
Alt NAT Pending	1	Not Interpretable

CONCLUSIONS

Of the 24 TMA HIV-1/HCV Reactive Donors, 14 were seropositive by Enzyme Immunoassay (EIA) Testing. These 14 donors confirmed positive by supplemental testing. There were 10 samples that initially tested TMA reactive, but were negative upon repeat TMA testing (false positive).

There were 63 cases where the EIA test was reactive with a non-reactive TMA result (39 anti-HCV, 23 anti-HIV, and 1 HIV p24 Ag). Supplemental RIBA 3.0 testing indicated that 1 confirmed positive, 5 were indeterminate, and 33 confirmed negative for HCV. Supplemental Western Blot testing for the 24 HIV cases indicated 8 were indeterminate and 16 confirmed negative. There were zero HIV confirmed positive cases that were TMA negative. For all HCV and HIV indeterminate cases, a frozen sample was sent to a reference lab for alternate NAT testing. Two results have returned one for HCV and one for HIV. Both were negative by alternate NAT, indicating the specimen is a true negative and the EIA reaction was a false positive test.

There were no donors who confirmed positive for HIV or HCV through TMA testing alone.

Report Date: 07 November 2000

Work Unit #8102-98

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: Factors Related to Medical Readiness in U.S. Military Reservists

KEYWORDS: Health Promotion, reservists, readiness, eating behavior, exercise behavior

PRINCIPAL INVESTIGATOR: Sisk, Rebecca
ASSOCIATES: M. Jane Shane-Cox, MAJ Marte Glass, MAJ Patricia Hanaard

DEPARTMENT: 7024th Installation Medical Support Unit
SERVICE:

STATUS: C
INITIAL APPROVAL DATE: 10 March 1998

STUDY OBJECTIVE

The goal of this study was to investigate factors related to medical readiness in US Military reservists. We specifically examined factors related to eating and exercise behavior.

TECHNICAL APPROACH

Data were gathered through questionnaires distributed to reservists who are receiving their military physical examinations. Data analysis consisted of descriptive statistics and multiple regression.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

We recruited 216 subjects, finishing data collection on April 15, 2000. We experienced no problems with data collection. The mean age of participants was 32.8 years, SD=9.7 years, range=18-64 years. There were 176 males and 35 females (missing=5), 32 officers and 165 enlisted (missing=19), 45 minority and 157 non-minority (missing=14), and 53 students and 161 non-students (missing=2)

CONCLUSIONS

The predictors of eating behavior were eating self-efficacy, prior related behavior (measured with four items related to previous eating, exercise, and weight control), command emphasis on physical fitness (measured with four items related to command encouragement and role modeling), and being enlisted predicted eating behavior, $F(df=13, 202)=9.4$, $p<.001$, adjusted $R^2 = 33.8\%$. The predictors of exercise behavior were exercise self-efficacy, prior related behavior, perceiving benefits of exercise, perceiving fewer barriers to exercise, being a student, and command emphasis on physical fitness predicted physical activity behavior. $F(df=15, 200)=13.9$, $p<.001$, adjusted $R^2=47.4\%$.

The study generally supports the Pender Health Promotion model. Suggestions resulting from the research are that:

- The military should assess prior eating and exercise behavior before bringing people into the reserves.
- Family support programs should emphasize the importance of family and friend support for exercising and healthy eating prior to activation.
- The study needs to be replicated with a larger, random sample from all branches of the service to improve the ability to generalize results and further explore Pender's model.
- Interventions to improve self-efficacy, increase command emphasis, increase family/friend support, provide a fitness buddy, and eliminate barriers to exercise need to be tested.

Report Date: 03 November 2000 Work Unit # 8500-99

DETAIL SUMMARY SHEET

TITLE: An Analysis and Comparison of Pharmacy Service Provider Selection Among Military Beneficiaries for Maintenance Medication

KEYWORDS: customer satisfaction, pharmacy services

PRINCIPAL INVESTIGATOR: Spain, John MAJ MS
ASSOCIATES: Julia Gannon; Dr. Dong-Churl Suh

DEPARTMENT: Pharmacy
SERVICE:

STATUS: O
INITIAL APPROVAL DATE: 05 January 1998

STUDY OBJECTIVE:
To analyze and compare costs, satisfaction with pharmacy services, beneficiary quality of life, and beneficiary selection criteria associated with three pharmacy benefit options: Military pharmacy, TRICARE retail network pharmacy, and mail order pharmacy. The following identifies specific objectives.

TECHNICAL APPROACH:
A questionnaire will measure differences in quality of life and customer satisfaction between the prescription plan options available. The impact of pharmaceutical care initiatives on provider selection and willingness to accept a co-payment for non-stocked medications at MTF pharmacies will be assessed.

PRIOR AND CURRENT PROGRESS
Approval received by DOD-HA. Memorandum forwarded for approval of required modifications.

CONCLUSIONS
None at this time.

Report Date: 14 November 2000

Work Unit # 00-8501

DETAIL SUMMARY SHEET

TITLE: Prevalence of Helicobacter pylori Seropositivity in Allergic Rhinitis and Asthma

KEYWORDS: Helicobacter pylori, asthma, allergic rhinitis

PRINCIPAL INVESTIGATOR: COL Francis Morris
ASSOCIATE INVESTIGOR:

DEPARTMENT: Medicine
SERVICE: Allergy-Immunology

STATUS: O
INITIAL APPROVAL DATE: 11 January 2000

STUDY OBJECTIVES:
Determine if there is a difference in the prevalence of Helibacter pylori colonization among the following three groups: asthma patients; allergic rhinitis patients; controls. A positive result may suggest a causative or protective role for Helibacter pylori in these two disease processes.

TECHNICAL APPROACH:
The three groups of patients will be recruited from the usual patient flow through the Allergy/Immunology Clinic at Landstuhl Regional Medical Center (the controls will be patients presenting for routine immunizations). Each research subject will have a blood specimen drawn for the measurement of antibodies against Helicobacter pylori.

PRIOR AND CURRENT PROGRESS:
Only one patient (with allergic rhinitis) has been recruited so far, and the serum specimen obtained is now frozen at -20°C. The final approval for this protocol was received after the main allergy season (Apr-Jun) when I would expect to have allergic rhinitis patients referred in. Therefore, I expect very slow progress in recruiting subjects until next spring when there should be a large number of patients referred in. The other two study groups (asthma patients, normal controls) will be easy to recruit and will be delayed until after most allergic rhinitis are recruited so that matching by age and gender can be accomplished. There are no adverse results to report.

CONCLUSIONS:
None, so far. However, I have noticed a great increase in research concerning Helibacter pylori and I suspect that other researchers will soon start looking at the role of Helibacter in asthma.

Report Date: 29 May 2001 Work Unit # 00-8502

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: Tele-Psychiatry in the Division: A Study of Diagnostic Reliability and Cost Benefits Using Desktop VTC

KEYWORDS: Tele-Psychiatry, Tele-Mental Health, VTC, Diagnostic Reliability

PRINCIPAL INVESTIGATOR: Schneider, Brett CPT MC
ASSOCIATES:

DEPARTMENT: Office of Division Surgeon, 1st Infantry Division STATUS: O
SERVICE: Division Mental Health INITIAL APPROVAL DATE: 18 July 2000

STUDY OBJECTIVE

-Determine the diagnostic agreement of clinical psychiatric examinations using in-person, face-to-face evaluations vs. VTC evaluations at a 384kb connection.
-Explore patient satisfaction with examinations using VTC
-Estimate the cost (direct, lost productivity, and lost time) savings of using VTC vs. traditional face-to-face consultations.

TECHNICAL APPROACH

Each patient enrollment will involve initial brief and consent. The division mental health staff at the Schweinfurt clinic will recruit patients. Only patients that are being evaluated in the clinic will be recruited. No advertisements, announcements or posters, etc will be used. Upon completing initial intake evaluation in the Schweinfurt clinic for both command and self referred patients, if, in the view of the provider seeing the patient, a medication evaluation is warranted for the patient, the provider will at that time inform the patient regarding the study being conducted in the clinic. They will inform them that we are attempting to use a new form of technology- two-way interactive tele-video to do the same kind of evaluations we do in person and ultimately try to save people trips to be seen. They will be asked if they are interested in hearing more about the study. If they say yes, they will be scheduled for an f/u appointment with another provider in the clinic on the same day that they will perform the SCID examination. That provider will perform the informed consent prior to the patient beginning the study.

Patients who have been identified as warranting a medication evaluation will have an appointment set up for them with one of the mental health technicians at the Schweinfurt clinic who has not been involved with their treatment to date. This appointment will occur on the same day that the provider who is performing the SCID's is available. Because there are only 4 providers in the clinic and the recruitment of patients will be coming from each of the provider's patient load, we will be unable to have only one person perform all informed consent, as it would disqualify all of his or her patients from the opportunity to enroll in the study. The NCOIC of the clinic will be responsible for scheduling all of the patients identified as potential candidates for the study for both the informed consent meeting and the subsequent SCID evaluation.

The patient will then be administered the SCID. The patient will also be asked to fill out an O-Q (outcome questionnaire) at the time of SCID. Neither psychiatrist will know the results of the SCID until after the patients participation in the study has ended. After the initial evaluation, one of the two psychiatrists will be assigned as the primary provider for the patients requiring follow up. The results of the SCID and the O-Q can be made known to them. Patients will then be assessed by Psychiatrist #1 using either face-to-face or VTC as outlined above. Psychiatrist #2, who will be blinded to the results of the previous exams, will then see the patients. Psychiatrist #2 will use the opposite interviewing technique of psychiatrist #1 (VTC or face-to-face). After each assessment, the clinician will document a maximum of two diagnoses and a GAF (global assessment of function) score. The psychiatrist seeing the patient in

person will be responsible for the clinical note and chart maintenance and will render the actual clinical diagnosis for the patient's active chart. The GAF is part of the routine psychiatric Axis I-V diagnostic framework. At the end of the interviews, the patient will be given an evaluation sheet to collect demographic information to help evaluate costs and to document patient satisfaction with the VTC experience. The patients will be asked to complete a satisfaction survey using a 10cm visual analog scale following each interview. Patients will then be released from the clinic unless clinical intervention is warranted. The psychiatrist who saw them in person will follow patients evaluated for medications who actually need medication treatment. The results of the SCID and tele-psychiatry evaluation will be made known to the provider prior to the first follow up appointment in order to help the provider confirm his diagnosis, which could be beneficial to the patient.

The SCID has been shown to have excellent interater agreement for broad diagnostic categories such as Psychotic disorders (kappa, 1.00), mood disorders (kappa, .93), anxiety disorders (kappa, .82) and substance use disorders (kappa, .93). Reliability was as follows for specific diagnoses; schizophrenia (kappa, .94), major depression (kappa, .93), dysthymia (kappa, .88), generalized anxiety disorder (kappa, .95), panic disorder (kappa, .88), alcohol use disorder (kappa, .96), cyclothymia (kappa, .80), PTSD (kappa, .77), bipolar disorder (kappa, .79), adjustment disorder (kappa, .74), and obsessive-compulsive disorder (kappa, .40). [10] Few studies exist comparing diagnostic reliability between the SCID and a routine psychiatric evaluation. One study by Fennig et al (1994) showed agreement as follows for an initial evaluation; major depression (kappa .75), schizophrenia (kappa .86), and bipolar disorder (kappa .89).

The OQ^{tm}-45.2 has been shown to have a test-retest reliability correlation coefficient of 0.84. In an outpatient psychiatric clinic population it was found to have validity ranging from 0.71 to 0.84.[12]

The GAF scale has been shown to have a validity of –0.73 when compared to other Zung Depression Scale. The original GAF has an interater reliability of .62. A modified version of the GAF has a higher interater reliability of 0.81. The authors of this scale and the study comparing the original GAF to the modified GAF suggested that the modified GAF may be a better scale to use in research protocols. The correlation between the original GAF and the modified GAF was shown to be high (0.80)

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 0. The total number enrolled study-wide is 0, if multi-site study. No amendments or modifications since study received approval. No AE's to report. A Medline literature review was performed to ascertain if any new literature pertaining to the subject matter had been published. The review was done using keywords "tele medicine, tele psychiatry and diagnostic accuracy" looking for articles published since April 2000. The following articles were found;

Elford R, White H, Bowering R, et al. A randomized, controlled trial of child psychiatric assessments conducted using videoconferencing. *J Telemed Telecare* 2000; 6(2):73-82.
Freuh, BC, Deitsch SE, Santos AB, et al. Procedural and methodological issues in telepsychiatry research and program development. *Psychiatric Serv* 2000 Dec; 51(12):1522-1527.
Ramirez Basco M, Bostic JQ, Davies D, et al. Methods to improve diagnostic accuracy in a community mental health setting. Am J Psychiatry 2000 Oct; 157(10):1599-1605.

CONCLUSIONS

None to date.

Report Date: 30 May 2001 Work Unit # 00-8503

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: Genetic Investigations of Psueofolliculitits Barbae, PFB, in United States Armed Forces

PRINCIPAL INVESTIGATOR: MAJ Daniel J. Schissel MC
ASSOCIATES:

DEPARTMENT: Surgery STATUS: O
SERVICE: Dermatology INITIAL APPROVAL DATE: 15 August 2000

STUDY OBJECTIVE : This study will investigate the association of PFB with the cytokeratin K6hf mutation found in the hair follicle.

TECHNICAL APPROACH Research blood sample collection from selected male and female individuals will be obtained after written informed consent and processed as outlined below:

a. Isolation of blood DNA
b. PCR amplification of distinct segments of the human K6hf gene.
c. Agarose gel separation of PCR products
d. Extraction of PCR products from agarose gels
e. Automated sequencing of the PCR products
f. Mutation analysis of the keratin sequences
g. Statistical evaluation of the results

Diagnostic confirmatory histological punch biopsies (standard of care) will be done on the initial 10 PFB patients to ensure clinical diagnosis is consistent with histopathological diagnosis. If 70% or more of the clinical PFB patient do not have histological evidence of PFB the study will be halted.

Control Subjects – These subjects will be recruited from orthopedic clinic and will have no clinical history or physical evidence of PFB. Control subjects will be asked to have one red top tube of blood drawn in the hospital lab, which will be sent to the German Cancer Research Center. Control subjects will be part of this study only for the one-day their blood is drawn.

Digital clinical photos of representative diseased areas (usually the lower face) of the PFB research subjects will be obtained as is the standard operating procedure for the dermatology clinic and is considered a standardized means of tracking improvement. The photos are stored on a computer system (Canfield Clinical Systems) for teaching purposes in the clinic, for clinical purposes, and will be used for research/publication. Photos will be taken at each follow-up visit. Once the study is complete, the photos will be stored indefinitely, filed by disease process and without any patient identifiers. The digital photos will only be accessible by the PI.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE: There has been no recent literature published on this topic. There have been no amendments or modifications to the study. Number of subjects enrolled since last APR review and the total enrollment to date.

African-American males, with clinical signs of PFB	44/56
African-American males, without clinical signs or family history of PFB	4/56
African-American females with clinical signs of PFB	7/56
African-American females, without clinical signs or family history of PFB	3/56
Non-African-American males with or without clinical signs of PFB	19/56
Non-African-American females with or without clinical signs of PFB	8/56
Total	85/336

There have been no adverse events (AE) expected and/or serious for HDB site – none LRMC - No patients have withdrawn from the study.

CONCLUSIONS: Study ongoing with out difficulty.

Report Date: 17 July 2001

Work Unit # 00-8504

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: Racial Differences in Central Corneal Thickness Between Caucasian and African-American Subjects

KEYWORDS:

PRINCIPAL INVESTIGATOR: Hess, Todd LTC MC
ASSOCIATES:

DEPARTMENT: Surgery (LRMC)
SERVICE: Ophthalmology

STATUS: O
INITIAL APPROVAL DATE: 19 September 2000

STUDY OBJECTIVE

To determine whether there is a clinically significant difference in central corneal thickness as measured by ultrasound between a group of African-American and a group of Caucasian subjects.

TECHNICAL APPROACH

Corneal applanative pachymetry is performed on subjects after consent and with topical corneal anaesthesia. Three measurements are taken per eye and the lowest is recorded.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

No recent literature has provided any insight into this study. The study is still in the data collection phase, with a total of 250 subjects (499 eyes) enrolled. No adverse advents have occurred. No patients have withdrawn from the study. No findings have been established as the study is still in the data collection phase.

CONCLUSIONS

We will continue with data collection. The examination technique is well tolerated and accurate.

Report Date: 10 October 2000 Work Unit #8502-99

DETAIL SUMMARY SHEET

TITLE: Highly Toxic Clone of *Actinobacillus actinomycetemcomltans* and Polymorphism in Interleukin I and Tumor Necrosis Fact -a gene

KEYWORDS:

PRINCIPAL INVESTIGATOR: Etzenbach, John LTC DE
ASSOCIATES:

DEPARTMENT: Landstuhl Regional Medical Center STATUS: O
SERVICE: Dental INITIAL APPROVAL DATE: 15 December 1997

STUDY OBJECTIVE:
To detect risk factors for early onset periodontitis and compare genetic differences between European Caucasian and African-American populations.

TECHNICAL APPROACH:
No changes have been made to the original protocol. Patients receive a comprehensive periodontal examination, to include measurement of probing depths, attachment levels, plaque levels, and bleeding points on probing. Additionally, plaque samples are obtained from the saliva, left and right buccal mucosa, and dorsal surface of the tongue. Finally, a finger stick is done to obtain 2 drops of blood on a piece of absorbent paper for further research in the lab.

PRIOR AND CURRENT PROGRESS :
As of the report date, 67 individuals have been examined for the status of periodontal disease and presence or absence of *A. actinomycetemcomitans*. There have been no adverse reactions and no individuals have withdrawn from the program

CONCLUSIONS:
No conclusions have been reached at this stage of the investigation.

Report Date: 26 July 2001

Work Unit # 00-8601

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: Tele-Ergonomic Assessment Methodologies Study

KEYWORDS: Telemedicine, ergonomics, military

PRINCIPAL INVESTIGATOR: LTC Mary Lopez MS
ASSOCIATES: D. Todd Nay

DEPARTMENT: Ergonomics Program
SERVICE: DOHS, USACHPPM

STATUS: C
INITIAL APPROVAL DATE: 13 June 2000

STUDY OBJECTIVE:

The overall goal of this study was to examine the feasibility and accuracy of a tele-ergonomics protocol using available unit health and safety personnel to collect data, which would be used by distant ergonomist in a task assessment. The results of the distant ergonomist were compared to those of an on-site ergonomist to validate the accuracy of data collected by the unit health and safety personnel. The objective was to identify a viable alternative to an on-site ergonomist and the most accurate methodology for distance ergonomic assessments. The study resulted in a tele-ergonomics methodology which can be applied in garrison, field and deployed environments.

The study had three specific goals:

Specific goal 1: To assess the amount of agreement in ergonomic measurements taken by unit health and safety POCs and on-site ergonomists.

Specific goal 2: To assess the amount of agreement in the evaluation and assessment of the ergonomic measurements between distant ergonomists and on-site ergonomists.

Specific goal 3: To identify the preferred standardized assessment methodology out of a battery of assessment tools based on the amount of agreement for both ergonomic measurements and expert evaluations and the end user evaluation of the assessment tools in terms of ease of administration, time requirements and feasibility in a variety of military environments.

TECHNICAL APPROACH

Study Design. The study was designed to:

1. compare on-site measurements taken by unit health and safety POCs and on-site ergonomists
2. compare assessment conclusions between distant and on-site ergonomists.

The study consisted of two basic phases: on-site data collection and the assessment of the results. The study involved assessments of high risk tasks for each of five high risk Army military occupational specialties at five Army installations (Fort Drum, Fort Knox, Fort Bragg, Fort Lee, Fort Eustis) for a total of 125 task assessments. Both the unit health and safety POC and the on-site ergonomist collected data on the 125 tasks and both the off- and on-site ergonomists assessed results for these tasks.

Phase 1: On-site data collection.

Unit health and safety points of contact from each of the targeted installations collected data for a battery of standardized ergonomic assessment tools for each of the five high risk MOSs and the five tasks within the MOS (25 total assessments per installation). These non-invasive assessment tools involved observation of soldiers performing routine, high-risk tasks. Unit health or safety personnel were provided with written information containing data collection and videotaping instructions and an administration script (as required) for each of the assessment tools.

Ergonomic data was collected by both the unit health and safety POC and the on-site expert ergonomist; however, neither was allowed to view the other's activities. Both collected data on the *same* soldier performing the *same* task to avoid any confounding due to subject, task, environment or temporal factors.

After completing data collection for the 25 high risk tasks, the unit health and safety POC completed a five point Likert scale rating of each of the assessment tools on the ease of administration, adequacy of written instructions, preparation time, administration time, and the feasibility of use in garrison, field, deployed environments.

Phase 2: Analysis and interpretation of data.

The measurement data was transported to the off-site ergonomist. Videotapes of the task were hand-carried for purposes of this study.

The off-site and on-site ergonomists scored and analyzed the collected data. Neither was aware of the results of the other's evaluation.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

The data collection portion of the study was completed in February 2001 and the data analysis / reporting was completed in May 2001.

The total number of subjects enrolled in this study were:

11 on-site technicians (collecting the data) (4 males; 7 females)

91 soldiers observed performing physically demanding task (76 males; 15 females)

2 off site ergonomists

There were no adverse events during the study.

No soldiers decided to withdraw from the study.

The number of subjects enrolled to the study since last APR at Fort Knox, Fort Drum, Fort Bragg, Fort Lee, Fort Eustis is 102 and the total enrolled study-wide in this multi-site study is 102.

CONCLUSIONS

The attached final report provides study findings and conclusions.

Report Date: 01 September 2000 Work Unit # 8700

DETAIL SUMMARY SHEET

TITLE: Evaluation of Telesurgical/Robotic Presence

KEYWORDS: Telesurgical mentoring, urology, telestration, robotics

PRINCIPAL INVESTIGATOR: Bauer, John MAJ MC
ASSOCIATES: Poropatich, Ronald K. COL MC

DEPARTMENT: Telemedicine
SERVICE: Urology

STATUS: O
INITIAL APPROVAL DATE: 25 November 1997

STUDY OBJECTIVE

The purpose of this study is to establish a telesurgical presence program between Walter Reed Army Medical Center, Johns Hopkins University and Ft Detrick, MD and evaluate the feasibility of telementoring less experienced surgeons, fellows, residents and medical students during open surgical cases and endoscopic surgery. Additionally, the use of a remotely controlled robotic arm to hold a laparoscope, as the laparoscopist's assistant, will be evaluated at these longer distances to determine the effect if any on remote telementoring. This system will in turn serve as the test bed for future telesurgical applications as they are developed and as a remote site for future deployed telesurgical systems.

TECHNICAL APPROACH

This proposal will evaluate the feasibility of telementoring both laparoscopic and open surgical procedures using telecommunications links between Johns Hopkins University, Ft. Detrick and Walter Reed Army Medical Center. We will use a T-1 PRI telecommunications link for Video Tele-Conferencing (VTC) and remote control of the AF-SOP robotic arm that holds the laparoscope. We will also employ a white-boarding function to telestrate the procedures. Our goal is to establish that this sort of remote mentoring of surgical procedures is feasible and can be potentially applied to far-forward military medical facilities in times of combat and also for medical education procedures.

PRIOR AND CURRENT PROGRESS

The actual accrual of patients has not started yet secondary to continued delays in installing the MEDNET communications network to building one at WRAMC and most currently the renovation of the OR rooms. The other portion of the link is installed and has been tested (Ft. Detrick to Johns Hopkins). Until the correct high-bandwidth communications network is installed at WRAMC this project cannot move forward.

CONCLUSIONS

Project is on hold until the MEDNET communications network at WRAMC is functional.

Report Date: 8 May 2001 Work Unit # 8701-98

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: Clinical Evaluation of a High-Resolution Digitized Stereo Video Slit Lamp for Use in Teleophthalmology

KEYWORDS: telemedicine, ophthalmology, diagnosis, digital images, slit lamp biomicroscopy, anterior segment

PRINCIPAL INVESTIGATOR: Bower, Kraig LTC MC
ASSOCIATES: CPT Erik Niemi, MC; COL (Ret) Kenyon Kramer; LTC Edward Trudo, MC

DEPARTMENT: SURGERY
SERVICE: OPHTHALMOLOGY

STATUS: O
INITIAL APPROVAL DATE: 7 July 1998

STUDY OBJECTIVE: The purpose of this study is to compare the clinical diagnostic performance of the high resolution digitized stereo video slit lamp with in-person slit lamp examination in patients presenting to a general ophthalmology clinic.

TECHNICAL APPROACH: This is a prospective observational study. Investigators at Walter Reed Army Medical Center Ophthalmology Service and the John Moran Eye Center at the University of Utah will select consecutive patients from their clinics according to the previously published inclusion/exclusion criteria. A total of 50 patients will be recruited from each site. Each patient will be identified with a distinct ID number. The investigator will perform a standard clinical slit lamp exam on both eyes and note all findings in the patient chart and on the study exam report form. The patient will then be examined with the video digital slit lamp according to a standard protocol. The patients will resume the intended course of treatment for the remainder of their appointment. The video, digitized exams will be evaluated by masked reviewers at both institutions at a time subsequent to the actual patient exams. Using the live exams as the gold standard, the proportion of correct diagnosis made using the video exam will be described using proportions with 95% confidence intervals (CI).

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE: Enrollment is completed for this phase of the study. WRAMC enrolled a total of 58 eyes of 29 patients for the study. John Moran Eye Center of the University of Utah enrolled 84 eyes of 42 patients. There were no complications or adverse events. We are no longer enrolling subjects in the parent study. However, we are submitting a modification request to evaluate in more depth a particular subset of patients with corneal transplants to determine the potential utility of this imaging system in the remote management of patients postoperatively. We have also submitted a related protocol for the evaluation of lid lesions and are working on an additional protocol to evaluate lens opacities with this system.
The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 29. The total number enrolled study-wide is 71, if multi-site study.

CONCLUSIONS: The ability of this system to make accurate diagnoses was particularly evident in evaluating corneal pathology. With a sensitivity of 87.8% and specificity of 73.75% on average, reviewers noted that the stereo dynamic imagery gave a realistic sense of the depth of corneal lesions rather than inferring their location from two-dimensional clues. We were surprised that the sensitivity and specificity of lid lesions was not higher. This technology seems to lend itself particularly well to surface lesions. A closer look at this digital stereo imaging system in evaluating eyelid lesions may be warranted in the future. This digital slit lamp system is unique in its ability to give the reviewer a dynamic, three-dimensional image. It provides some of the best imagery available in teleophthalmology to date and is the first that we know of, to provide dynamic stereo imagery. Although this system does not replace the in-person examination by a trained ophthalmologist, it could be effective as a screening tool for remote areas without easy access to quality ophthalmologist.

Report Date: 2 October 2000

Work Unit # 8832

DETAIL SUMMARY SHEET

TITLE: Immunoregulation and Pathogenesis of Symptomatic, Primary HIV-1

KEYWORDS: HIV-1 infection, immunology, virology

PRINCIPAL INVESTIGATOR: Robb, Merlin LTC MC
ASSOCIATES: Michael, N. LTC MC

DEPARTMENT: Medicine
SERVICE: Infectious Disease

STATUS: C
INTIAL APPROVAL DATE: 26 October 1993

STUDY OBJECTIVE

To: 1) characterize immunologic and virologic parameters in patients experiencing symptomatic, primary HIV-1 infection as a means of deciphering the molecular and cellular events involved in immune regulation of the virus early after infection; 2) establish a "bank" of properly stored peripheral blood mononuclear cells, plasma, sera, and other body fluids from this group of patients for potential use in future studies.

TECHNICAL APPROACH

There have, as yet, been no modifications from the original protocol. Essentially, patients meeting the inclusion criteria will undergo sequential bleeds, and their specimens will be processed at the Division of Retrovirology, WRAIR. Viral burden will be quantitated using DNA and RT-PCR; genotypic analysis will be assessed by sequencing a portion of gp120; HIV-1-specific humoral immune responses will be assessed using immunoblot technology and multiple gp160 epitopes; and T cell responses will be assessed by lymphocyte proliferation assays with epitope mapping done using expanded CD4+ clones from a subgroup of the patients.

PRIOR AND CURRENT PROGRESS

No patients with acute retroviral syndrome were recognized in the last year and consequently, no active enrollment has occurred. Previously collected samples have not been utilized in the last year and remain in the repository.

CONCLUSIONS

Early findings from this study revealed an impaired cell mediated immune response to recall antigens during the first several months after infection with HIV. Samples were evaluated for maturation of envelope antibody responses over time. This analysis reveals that HIV infected patients respond preferentially to their own HIV strain, envelop and only slowly develop recognition to a broad array of HIV strains. The advent and widespread use of antiviral therapy during acute seroconversion to HIV would prevent the study from accomplishing its objectives and it will therefore be closed.

Report Date: 28 July 2001

Work Unit # 8836

DETAIL SUMMARY SHEET

TITLE: A Phase I Dose Escalation Study of Polyclonal CD4 T Cell EX Vivo Expansion for Immune System Restoration of HIV Infection

KEYWORDS: immune reconstitution, HIV, CD4 infusions

PRINCIPAL INVESTIGATOR: Aronson, Naomi COL MC
ASSOCIATES: Thompson, Jennifer MAJ MC

DEPARTMENT: Medicine
SERVICE: Infectious Disease

STATUS: O
INITIAL APPROVAL DATE: 30 September 1997

STUDY OBJECTIVE

Determine the safety and feasibility of CD4 cell ex vivo expansion and rein fusion in HIV infected patients. Study endpoints are plasma HIV RNA measures and circulating CD4 lymphocyte mass. As a secondary objective, the safety of escalating doses of CD4 lymphocyte infusions will be evaluated.

TECHNICAL APPROACH

Antilogous CD4 lymphocytes are acquired by leukapheresis from HIV infected persons and expanded ex vivo using anti CD3/anti CD28 antibodies in the presence of antiretroviral therapy. Rein fusion of 10 to 10 range CD4 cells is performed. Six addenda have been approved.

PRIOR AND CURRENT PROGRESS

Four patients were enrolled at WRAMC, six at NNMC. One patient at NNMC. One patient at NNMC was excluded when he was found to have a T cell tropic (CXCR4 dependent) HIV strain and another when he was found to have elevated liver associated enzymes with a new diagnosis of Hepatitis C. Both did not receive any infusions. In addition, one patient was terminated before the last infusion because the HMJF/NMRI laboratory at NMRI closed and grownup of lymphocytes was not longer available. The patient was informed of this development.

Overall, 50 infusions were given, median 5 per patient (range 3-10). All patients had increases in %CD4, CD4/CD8 ratio, seven had increases in the absolute CD4 count. 32 of 50 infusions had grade 1 or 2 toxicities associated with infusions. There were no SAEs reported from WRAMC and I am not aware of any at NNMC (the protocol has been closed at NNMC for some time).

At this time, we request that this protocol remain open for completion of laboratory analysis of collected samples and data analysis. Enrollment and intervention is finished.

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 4. The total number enrolled study-wide is 10, if multi-site study.

CONCLUSIONS

The administration of antilogous CD3CD28 costimulated CD4 cells in the setting of antiretroviral therapy is safety and feasible. The concurrent use of antiretroviral therapy must be considered when interpreting the increases in absolute CD4, %CD4 and CD4/CD8. Further study suggests that these increases are due to expansion of the peripheral T cell pool.

Report Date: 14 July 2001

Work Unit # 8837

DETAIL SUMMARY SHEET

TITLE: Molecular Epidemiology of HIV-1 in Military Populations.

KEYWORDS: HIV, military, seroconvertors

PRINCIPAL INVESTIGATOR: Aronson, Naomi COL MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Infectious Disease

STATUS: O
INITIAL APPROVAL DATE: 30 September 1997

STUDY OBJECTIVE

To describe the subtype and viral resistance patterns of HIV seroconverting military personnel correlating this with information regarding deployment, risk behaviors, potential contributing factors, in order to target military populations for intensive prevention training programs.

TECHNICAL APPROACH

All military seroconvertors (in past 4 years) are eligible. Serum is obtained for genetic HIV subtype testing. Genotypic HIV viral resistance determinations are performed on all samples with detectable viral loads. The participant fills out a confidential survey instrument. Addendum to assess phenotypic resistance in a subpopulation. Addendum to allow banking of samples by patient identification number in the HIV repository. Addendum submitted currently to assess Kaposi Sarcoma Virus (KSV) and Herpes Simplex Virus Type II antibodies correlated with reported risk exposures. Subject enrollment will stop 31 July 2001 at all study sites.

PRIOR AND CURRENT PROGRESS

The number of subjects enrolled to the study since last APR at WRAMC is 14 and the total enrolled to date at WRAMC is 86. The total number enrolled study-wide is 603.
There are no adverse events reported, one withdrawal from the protocol at WRAMC, information unknown at other sites.
Study findings at WRAMC include that 4% of HIV seroconvertors are non B HIV subtype, 14% of those enrolled prior to any antiretroviral treatment showed resistance to at least one drug. The "subtype/clade L" reported last APR has been reclassified as a recombinant virus. HIV seroconversion was associated with high use of alcohol, poor condom compliance, and frequent casual sex partner exposure in the seroconvertor window. Most did not feel personally susceptible to HIV. 48% had overseas travel during the seroconvertor window period.
Interesting, evaluation of the clinical progress of HIV seroconvertors found to have genotypic resistance pre antiretroviral therapy, showed that on treatment 6 months they had greater CD4 increases and HIV viral load decreases compared to those who showed no initial resistance.

CONCLUSIONS

Preliminary data suggest that the acquisition of non B HIV subtypes is associated with overseas deployment in the overall military study population. In the U.S. drug resistant virus is being transmitted and the initial clinical course of those with resistant virus is better than those with no resistance, suggesting that resistance may decrease viral fitness or cause hypersensitivity to other retroviral drugs. Numerous areas for further intervention for prevention of HIV in active duty military have been identified including alcohol use, condom use, choice of sexual partners, increase risk awareness, risk during overseas deployment.

Report Date: 01 February 2001

Work Unit #8838-98

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: A Triservice Study of Human Immunodeficiency Virus Disease in United States Military Beneficiaries

KEYWORDS:

PRINCIPAL INVESTIGATOR: Hawkes, Clifton LTC MC
ASSOCIATES:

DEPARTMENT: Medicine
SERVICE: Infectious Disease

STATUS: O
INITIAL APPROVAL DATE: 31 March 1998

STUDY OBJECTIVE

To systemically document the natural disease progression of HIV infection and the effect of therapeutic intervention on the course of the disease. To study factors related to HIV transmission in sexual partners not yet infected with HIV. To develop and evaluate new and/or improved laboratory methods for diagnosing and staging HIV disease.

TECHNICAL APPROACH

Medical information related to HIV disease is routinely being collected as part of the standard care for HIV patients. This information will be collected and organized into a computerized database, which will facilitate scientific review and assist in the generation of hypotheses, which can be tested utilizing various statistical analyses. Blood that is collected will be used to identify new methods of detecting replicating HIV virus, as well as patterns and mechanisms of resistance. Safeguards to patient confidentiality are met. This database forms the core around which other specific protocols can be built.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

The number of subjects enrolled to the study since last APR at WRAMC is 22 and the total enrollment to date at WRAMC is 417. The total number enrolled study-wide is 1395, if multi-site study. The have been seven (7) serious adverse events involving the deaths of study participants. Those in which an immediate cause of death could be identified included one with tracheal stenosis, one with brain lymphoma, one with pneumonia, one with disseminated mycobacterium avium complex infection and three who died with late stage HIV disease, but no immediate cause of death identified. These deaths were not expected and were felt to be part of the natural progression of this disease. Four (4) study participants withdrew informed consent. Three (3) patients transferred to another study site.

CONCLUSIONS

No conclusions reached during this reporting period; data collection continues.

Report Date: 22 November 2000

Work Unit # 8839-99

DETAIL SUMMARY SHEET

TITLE: A Phase I/II Study of the Safety, Survival, and Trafficking of Autologous CD4-zeta Gene-Modified T Cells With and Without Exogenous IL-2 in HIV Infected Patients

KEYWORDS:

PRINCIPAL INVESTIGATOR: Aronson, Naomi COL MC
ASSOCIATES: Wortmann, Glenn LTC; Bernstein, Wendy COL MC; Cash, Brooks LT MC; Gibbs, Barnett CPT

DEPARTMENT: Medicine
SERVICE: Infectious Disease

STATUS: O
INITIAL APPROVAL DATE: 19 January 1999

STUDY OBJECTIVE:
To assess the safety, tolerability and feasibility of administering an infusion of autologous CD4 zeta gene modified CD4+ T cells in an outpatient setting of highly active antiretroviral therapy (HAART) with and without Il-2 at a maximum non-toxic daily dose of 1.2M IIU/m2 subcutaneously daily for 56 days. Assess the effect of daily subcutaneous IL2 on the persistence and trafficking of CD4 zeta gene-modified T cells in the circulation and lymphoid (rectal) tissue. Determine the effect of CD4 zeta infusions with and without IL-2 on viral load (plasma HIV-1 RNA, tissue HIV-1 RNA, and frequency latent replication-competent HIV-1 in PBMC).

TECHNICAL APPROACH:
This 3 arm, randomized study of gene modified costimulated CD4 cells (about 10^{10} infused) with or without daily subcutaneous IL-2 in HIV patients with undetectable viral load has an active interventional duration of 20 weeks. Replication competent retrovirus will be intermittently checked for as long as the individual agrees to participate. Rectal biopsy and peripheral blood mononuclear cells will be assessed for viral load and latent replication, as well as CD4 zeta. Assays to include cytotoxic lymphocytes, neutralizing antibody and lymphocyte proliferation assays are planned to assess the helper effect of CD4 zeta infusion.

PRIOR AND CURRENT PROGRESS
No patients have been enrolled to date, still awaiting final arrangements by the University of Pennsylvania. All WRAMC regulatory pre-trial responsibilities have been completed. Site initiation visits from Cell Genesys and University of Pennsylvania have occurred. We anticipate initiating enrollment in the next month.

CONCLUSIONS
We are ready to enroll study participants as soon as we receive notification from Dr. June (University of Pennsylvania) that we may start.

Report Date: 14 April 2001

Work Unit # 8839-99

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: A Phase I/II Study of the Safety, Survival, and Trafficking of Autologous CD4-zeta Gene-Modified T Cells and without Exogenous IL-2 in HIV Infected Patients

KEYWORDS:

PRINCIPAL INVESTIGATOR: Aronson, Naomi COL MC
ASSOCIATES: Wortmann, Glenn LTC MC; Bernstein, Wendy COL MC; Cash, Brooks LT MC

DEPARTMENT: Medicine
SERVICE: Infectious Disease

STATUS: O
INITIAL APPROVAL DATE: 19 January 1999

STUDY OBJECTIVE

To assess the safety, tolerability, and feasibility of administering an infusion of autologous CD4 zeta gene modified CD4+ T cells in an outpatient setting of highly active antiretroviral therapy (HAART) with and without IL-2 at a maximum non-toxic daily dose of 1.2 M IU/m^2 subcutaneously daily for 56 days. Assess the effect of daily subcutaneous IL2 on the persistence and trafficking of CD4 zeta gene-modified T cells in the circulation and lymphoid (rectal) tissue. Determine the effect of CD4 zeta infusion with and without IL-2 on viral load (plasma HIV-1 RNA, tissue HIV-1 RNA, and frequency of latent replication-competent HIV-1 in PMBC).

TECHNICAL APPROACH

This 3 arm, randomized study of gene modified costimulated CD4 cells (about 10^{10} infused) with or without daily subcutaneous IL-2 in HIV patients with undetectable viral load has an active interventional duration of 20 weeks. Replication competent retrovirus will be intermittently checked for as long as the individual aggress to participate. Rectal biopsy and peripheral blood mononuclear cells will be assessed for viral load and latent replication, as well as CD4 zeta. Assays to include cytoxic lymphocytes, neutralizing antibody and lymphocyte proliferation assays are planned to assess the helper effect of CD4 zeta infusion.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

This project is still awaiting IRB approval at the University of Pennsylvania where our product will be made. We understand this approval to be forthcoming shortly.
The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 0. The total number enrolled study-wide is N/A, if multi-site study.

CONCLUSIONS

Rigorous review approval is needed for gene therapy trials. We anticipate trial initiation shortly.

Report Date: 1 September 2000 Work Unit # 00-8901

DETAIL SUMMARY SHEET

TITLE: Surveys of Stressors and Their Impacts on Women in the Army and Army Reserves

KEYWORDS: Stressors, Women, Army, Army Reserve

PRINCIPAL INVESTIGATOR: Engel, Charles LTC MC
ASSOCIATES:

DEPARTMENT: Deployment health Clinical Center STATUS: C
SERVICE: INITIAL APPROVAL DATE: 12 October 1999

STUDY OBJECTIVE

A) Identify the most important stressors and their outcomes among women in the Army and Army Reserves.
B) Describe the relationship between stressors and risk factors, including mediating factors such as socio-demographic and buffering agents.
C) Make recommendations about prevention strategies that may be employed to reduce stressors and their impact.

TECHNICAL APPROACH

To administer questionnaires to volunteer WRAMC active duty women recruited at the bi-monthly Birth Month Activity Registration (BMAR).

PRIOR AND CURRENT PROGRESS

This study recruitment ended at WRAMC 30 April 2000. RTI has completed data collection and is currently analyzing data.

CONCLUSIONS

N/A. DHCC's role was limited to recruitment and providing a site for the 4 surveys (at BMARs of 24 Feb 00, 8 Mar 00, 22 Mar 00, 19 Apr 00)

Report Date: 26 January 2001

Work Unit #8900-99

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: Antibiotic Treatment of Gulf War Veterans' Illnesses

KEYWORDS: Gulf War Veterans' Illnesses, antibiotic, doxycycline, Mycoplasma, chronic fatigue, neurocognitive dysfunction, joint pain

PRINCIPAL INVESTIGATOR: Engel, Charles LTC MC
ASSOCIATES: Chung, Raymond COL MC

DEPARTMENT: Deployment Health Clinical Center
SERVICE:

STATUS: O
INITIAL APPROVAL DATE: 23 March 1999

STUDY OBJECTIVE

The primary objective is to determine whether a 12-month course of doxycycline treatment in deployed Gulf War veterans presenting with Gulf War Veterans Illnesses and testing as mycoplasma positive improved patients' functional status. The secondary objectives are to determine whether doxycycline treatment reduces symptoms of Gulf War Veterans Illnesses, including pain, fatigue and neurocognitive concerns, whether doxycycline treatment converts mycoplasma (+) patients to mycoplasma (-) status. If so, it will be determined whether these subjects revert to mycoplasma (+) status when doxycycline treatment terminates. Also, the relationship of changes in mycoplasma status will be associated with changes in functioning and symptoms. Finally, we will determine if the benefits of 12 months doxycycline treatment persist after termination of treatment.

TECHNICAL APPROACH

The study employs a randomized, double blind design that compares two groups of patients. All veterans who were on active duty, or in the National Guard, or the Reserves between August 1990 and August 1991 and were deployed to Gulf region during that time are considered for participation. To be eligible, a veteran must:
1) Have at least two of the following three symptoms that began after August 1990, have lasted for more than six months and are occurring up to the present:

a) Fatigue that limits usual activities (work, recreation, or social)
b) Musculoskeletal pain involving two or more regions of the body, and
c) Neurocognitive dysfunction (self-reported difficulties in memory, concentration or attention) and
d) Must test as mycoplasma positive on PCR testing by central laboratory.

Patients meeting all enrollment criteria and who give informed consent to participate in the study are randomized to one of the following two groups. In the first group, the patients will be treated with doxycycline for 12 months and the second group will be treated with placebo for 12 months. Patients who are assigned doxycycline receive 200mg/day. They are instructed to take their pill the same time each day, preferably in the morning. Patients assigned to the placebo group receive identical appearing medication preparations. Because doxycycline can cause photosensitivity to sunlight, all patients are provided with a potent sunblock preparation. All patients receive the study drugs for one year. Patients are followed for an additional six months after cessation of study drugs to determine relapse rates. Major patient assessments are completed at baseline and at 3,6,9,12 and 18 months. Major assessment consists of the SF-36V, the McGill Pain Questionnaires, the Multidimensional Fatigue Inventory, the Cognitive Failures Questionnaire and the Gulf War Illness Questionnaire. Monthly follow-up visits are done to dispense medication, check compliance, and obtain data on hospitalizations and clinic visits. The use of PCR for detection and identification of *Mycoplasma* species is done at 0, 6, 12 and 18 months.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

The number of subjects enrolled to the study since last APR at WRAMC is 3 and the total enrolled to data at WRAMC is 13. The total number enrolled study-wide is 491, if multi-site study. A presentation of the basic study objectives, design and initial recruitment data was held on 24 January 2001 at the Conference on Illnesses among Gulf War Veterans: A Decade of Scientific Research in Alexandria, VA. It was announced that 39.3% of eligible patients were positive for Mycoplasma.

CONCLUSIONS

This study is still in progress, and as such, no conclusions have yet been made.

Report Date: 26 January 2001

Work Unit #8901-99

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: A Randomized, Multicenter, Controlled Trial of Multi-Modal Therapy in Veterans with Gulf War Illnesses

KEYWORDS: aerobic exercise, Gulf War Veterans Illness, cognitive behavioral therapy, fatigue, memory loss, joint pain

PRINCIPAL INVESTIGATOR: Engel, Charles LTC MC
ASSOCIATES: Smith, Samantha Ph.D.

DEPARTMENT: Deployment Health Clinical Center
SERVICE:

STATUS: O
INITIAL APPROVAL DATE: 23 March 1999

STUDY OBJECTIVE

Primary Hypothesis

The primary hypothesis of this study is that both aerobic exercise and cognitive behavioral therapy will significantly improve physical function (as measured by the Physical Component Scale of the SF-36V) in veterans with Gulf War Illness (GWI), and the combination of cognitive behavioral therapy and aerobic exercise will be more beneficial than either therapy alone.

Central to this hypothesis is the belief that GWI is an unexplained illness within the same spectrum as fibromyalgia and CSF, and modalities effective in these other conditions can successfully treat GWI. Although some data support the independent efficacy of these two modalities in fibromyalgia and CFS, no randomized, controlled trial has examined the combined effects of these two treatments. Multi-modal programs may be more efficacious than individual therapies and there may be an added benefit to combining these two modalities, but this hypothesis has not been tested with GWI.

Secondary Hypothesis

1. Both aerobic exercise and CBT will lead to improvements in the cardinal symptoms of GWI (e.g., pain as measured by the short form of the McGill Pain Questionnaire, fatigue as measured by the Multidimensional Fatigue Inventory and cognitive difficulties as measured by the Cognitive Failures Questionnaire.)
2. Both aerobic exercise and CBT will lead to decreased levels of distress in persons with GWI, as measured by the MM-5 of the SF-36V.
3. Both aerobic exercise and CBT will lead to improvements in emotional functioning in persons with GWI, as measured by the Mental Compound Scale of the SF-36V.

Tertiary Objectives

1. To determine which "process measures" play a role in achieving the desired outcomes. There are several reasons that patients may improve in response to the two interventions. These include changes in: 1) a physiological effect mediated by increased aerobic fitness, 2) the person's overall pain threshold (measured by dolorimetry), 3) attitudes regarding illness and symptoms, and 4) satisfaction with previous and current treatment. We will assess which of these mechanisms correlate with changes in each of the primary and secondary outcome variables, i.e., which process measures are mediators of outcome.
2. To develop a focus group consent document and compare its utility with the original study consent document with respect to patient-centered outcomes (recall, expectation of participation, availability of study personnel) and adherence to assigned therapy.
3. To develop a minimally clinically important difference for the Physical Component Scale of the SF-36V.

TECHNICAL APPROACH

This clinical trial will study Gulf War era veterans who have unexplained chronic physical symptoms such as pain, fatigue and/or cognitive difficulties. Patients will be randomized to one of four groups: 1) CBT plus aerobic exercise, 2) aerobic exercise alone, 3) CBT alone and 4) usual and customary care. The primary outcome will be a clinically meaningful improvement in the Physical Component Summary scale of the SF-36V at one year relative to baseline. All patients will be followed over for one year and outcome will be measured at 3 months (immediately following the end of treatment), 6 months and 12 months post randomization.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

The number of subjects enrolled in the study since the last APR at WRAMC is 43 and the total enrolled to date at WRAMC is 63. The total number enrolled study-wide is 1356. There have been no serious adverse events at the Walter Reed site. Detailed records of all types of adverse events and injuries are kept by the CSPCC in West Haven; details, dates and subject numbers can be obtained from that office. The Chairman of the Data Monitoring Board received and reviews Adverse Events and Serious Adverse Events on an ongoing basis, and no action has been taken in regard to any Adverse or Serious Adverse Event to date.

CONCLUSIONS

There are no conclusions at present. The study is ongoing.

Report Date: 29 August 2000 Work Unit # 00-9201

DETAIL SUMMARY SHEET

TITLE: Role of Focal Adhesion Kinase and E-Cadherin in Differentiated Thyroid Cancer

KEYWORDS: cadherin, focal adhesion kinase, thyroid, cancer

PRINCIPAL INVESTIGATOR: Gary L. Francis COL MC
ASSOCIATES:

DEPARTMENT: Clinical Investigation
SERVICE: Pediatric Endocrine

STATUS: O
INITIAL APPROVAL DATE: 5 October 1999

STUDY OBJECTIVE

This study was designed to examine the expression of one adhesion molecule (E-cadherin) and one adhesion kinase (Focal adhesion kinase, FAK) in benign and malignant thyroid lesions and to correlate the expression of each with the risk of mestastasis and recurrence.

TECHNICAL APPROACH

Archived thyroid tumors are sectioned and stained by immunoperoxidase specific for FAK and E-cadherin expression. The intensity of staining is then correlated with the risk of mestasis and recurrence.

PRIOR AND CURRENT PROGRESS

A total of 27 papillary thyroid cancers, 9 follicular thyroid cancers, and 11 benign lesions have been stained for expression of FAK and E-cadherin. Data is currently being analyzed.

CONCLUSIONS

The technique for immunohistochemistry has been optimized for both of these molecules, and the slides have been adapted and stained. Data is currently being analyzed. Progress has been excellent on this project and the preliminary results should be available soon.

Report Date: 05 April 2001 Work Unit #9206

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: Are Heat Shock Proteins Target Antigens of the Immune System in Renal Allograft Recipients?

KEYWORDS: heat shock protein, kidney transplantation, immunology

PRINCIPAL INVESTIGATOR: Yuan, Christina LTC MC
ASSOCIATES: John Swanson, Shirley Polly, Erin Bohen, Joyce Hershey

DEPARTMENT: Medicine
SERVICE: Nephrology

STATUS: O
INITIAL APPROVAL DATE: 09 April 1996

STUDY OBJECTIVE

1. To determine retrospectively and prospectively whether heat shock proteins (hsps) are target antigens of the immune system in renal allograft recipients. More specifically to determine if renal allograft recipients develop antibodies and/or cellular immune response specific for hsps.
2. To correlate development of humoral and/or cell-mediated immune responses specific for hsps with renal allograft outcome.

TECHNICAL APPROACH

Phase I: This phase of the study is a retrospective cohort study. Fifty patients who have previously received a renal transplant and fifty age, sex and race matched controls will be selected for testing for anti-hsps antibodies (by ELISA), and for circulating T cells reactive to hsps (by flow cytometry).
Phase II: This phase of the study is a prospective cohort study. Forty consecutive subjects undergoing first cadaveric renal transplantation will be tested for anti-hsps antibodies and for T cells reactive to hsps immediately pre-transplantation and at serial time points post transplantation.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Phase I: All patients and controls have entered into this phase of the study – 50 of each, for a total of 100 subjects. ELISA assays are completed. Preliminary results show that Hsp70 antibody levels are relatively less in patients vs. controls, as are Hsp27 antibody levels. Anti Hsp60 antibody levels were not statistically different between the two groups. Chart review is completed, as in data entry regarding donor-recipient matching. Data analysis is ongoing analysis. Phase II will not be undertaken. Closed to accrual, and open only for data analysis at this time.

CONCLUSIONS

See progress above.
The number of subjects enrolled to the study since the last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 100. The total number enrolled study-wide is N/A, if multi-site study.

Report Date: 03 October 2000 Work Unit # 9208

DETAIL SUMMARY SHEET

TITLE: Intron A + Rabavirin for Treatment of Patients with Interferon-Refractory or Interferon-Relapsed Chronic Hepatitis C

KEYWORDS:

PRINCIPAL INVESTIGATOR: Sjogren, Maria COL MC
ASSOCIATES: Holtzmuller, Kent COL MC

DEPARTMENT: Clinical Investigation
SERVICE:

STATUS: C
INITIAL APPROVAL DATE: 26 November 1996

STUDY OBJECTIVE

To determine the eradication rate of hepatitis C utilizing the combined therapy of interferon and ribavirin for six or 12 months, in patients who were nonresponders to prior treatment with interferon. Nonresponders are defined as patients who, after treatment with interferon, either remained infected with the hepatitis C virus (HCV) or experienced relapse. A successful outcome in this study is defined as absence of HCV RNA in serum six months after cessation of therapy.

TECHNICAL APPROACH

The study is being conducted using a FDA approved drug for the treatment of hepatitis C (interferon alpha 2b) and ribavirin, which was a non approved drug under IND status and subsequently approved in June 1998. The patients are randomized into two treatment groups: Group A: Interferon 3 million units 3 times/week and 1,000 mg ribavirin/day for 6 months. Group B: Interferon 3 million units 3 times/week and 1,000 mg ribavirin/day for 12 months. Interferon lcc is administered subcutaneously and ribavirin orally (200 mg capsules). An addendum was submitted to RRS to withdraw language concerning IND status of ribavirin. This drug has been approved by the FDA for treatment of hepatitis C infection.

PRIOR AND CURRENT PROGRESS

The study was closed to enrollment. No volunteers were enrolled during the last 12 months. No deaths occurred. The monitoring phase of the study has been completed.

	WRAMC	BAMC	Wright-Patterson	Tripler	Kaiser	Total
Enrolled	32	30	4	5	21	92
AE's	66	5	0	2	2	75
Serious AE's	0	1	0	0	0	1
Hosp	0	1	0	0	0	1
Withdrawn	2*	2	0	1	3**	8

* One withdrawn due to alcohol induced altercation with police, the other elected to withdraw due to increased irritability which caused arguments with spouse and kids.

** One withdrawn due to low hemoglobin, one withdrawn due to low white blood count, one withdrawn due to non-compliance with protocol requirements.

CONCLUSIONS

The following table shows the viral response to treatment. End of treatment response is measured during the last week of therapy while end of follow-up is determined 24 weeks after cessation of therapy. The latter is the value used to show sustained response.

		HCV RNA Negative	
Group	N	End of Treatment (Week 24 or 48)	End of Follow-Up (Week 48 or 72)
Relapsers - 24 Weeks of Tx	16	10/16 (62.5%)	5/16 (31.3%)
Relapsers - 48 Weeks of Tx	15	10/15 (66.7%)	10/15 (66.7%)
Non-responders 24 Weeks of Tx	32	10/32 (31.3%)	2/32 (6.3%)
Non-responders 48 Weeks of Tx	28	8/28 (28.6%)	7/28 (25%)

The following table shows the biochemical response to treatment. End of treatment response if measured during the last week of therapy while end of follow-up is determined 24 weeks after cessation of therapy. The latter is the value used to show sustained response.

		Normal ALT	
Group	N	End of Treatment (Week 24 or 28)	End of Follow-Up (Week 48 or 72)
Relapsers – 24 weeks of Tx	16	12/16 (75%)	6/14 (42.9%) *
Relapsers – 48 weeks of Tx	15	13/15 (86.7%)	13/15 (86.7%)
Non-responders 24 weeks of Tx	32	20/32 (62.5%)	6/31 (19.4%)**
Non-responders 48 weeks of Tx	28	19/28 (67.9%)	1/27 (40.7%)***

* Two subjects were lost to follow-up.
** One subject was lost to follow-up.
*** One subject was lost to follow-up.

In conclusion, 48 weeks of therapy was superior to 24 weeks of therapy for both relapsers and non-responders. This data is being written up for publication.

Report Date: 16 May 2001 Work Unit # 9210

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: Hepatitis C Virus Protection: Quasispecies and Mechanisms of Disease Progression

KEYWORDS:

PRINCIPAL INVESTIGATOR: Sjogren, Maria COL MC
ASSOCIATES:

DEPARTMENT: Clinical Investigation STATUS: C
SERVICE: INITIAL APPROVAL DATE: 29 July 1997

STUDY OBJECTIVE

1. To compare rate of progression of liver disease in patients infected with HCV genotype 1 to patients infected with other HCV genotypes.
2. To identify predictors of progression of liver disease.
3. To determine risk factors for HCV infection (genotype 1 vs. other).
4. To describe the natural history of HCV infection in military and veteran populations.
5. To determine the effect of risk factors in the acquisition of HCV in military and veteran population.

TECHNICAL APPROACH

Enroll retrospective cohort of patients at the Veterans Administration Medical Center and Walter Reed Army Hospital. Two-hundred active duty or veterans infected with HCV will be enrolled. A control of 200 non-HCV infected service members (age, sex and race matched) will also be enrolled. A questionnaire will be administered every 6 months. Patients will have periodic serological testing and liver biopsies at enrollment and 4 years later.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

No new subjects were enrolled in this study during this APR period because a grant was approved from MRMC. However there were multiple revisions required and it took most of the year to get them approved at MRMC and WRAMC. This protocol was approaching the 5-year limit. The questionnaire changed substantially and only active duty subjects will be allowed in the new protocol, which has been assigned a new number. Eligible subjects will be re-consented for new protocol and prior data will be usable. To date 86 subjects were enrolled in 9210 at WRAMC. No AE or deaths occurred.
The number of subjects enrolled to the study since last APR at WRAMC is _0_ and the total enrolled to date at WRAMC is __86. The total number enrolled study-wide is the same.

CONCLUSIONS

The bulk of the subjects were enrolled in year 2000, not enough follow-up to allow meaningful conclusions. The new study where eligible subjects will be offered to enter will allow use of the data

Report Date: 25 August 2000

Work Unit # 9211

DETAIL SUMMARY SHEET

TITLE: Intron A+Rlbavirin for Treatment of Patients with Chronic Hepatitis C Not Previously Treated with Interferon

KEYWORDS: Hepatitis C, Interferon alfa 2b, Ribavirin

PRINCIPAL INVESTIGATOR: Sjogren, Maria COL MC
ASSOCIATES: Holtzmuller, Kent LTC MC

DEPARTMENT: Clinical Investigation
SERVICE:

STATUS: C
INITIAL APPROVAL DATE: 14 October 1997

STUDY OBJECTIVE

To provide ribavirin for use in combination with Intron® A for the treatment of hepatitis C patients who have not previously received interferon therapy. To obtain safety and treatment regimen information on interferon/ribavirin patients not previously treated with Intron® A.

TECHNICAL APPROACH

Multicenter study with Wright Patterson AFB (Ohio), Brooke AMC (Texas), and Kaiser Permanente, Falls Church, (VA). All patients have chronic hepatitis C and have never received treatment for this condition. All patients will receive an induction dose of interferon (5 million units/daily for four weeks). Following the 4 weeks, patients will be randomized to two groups:
Group A: Will receive maintenance dose of interferon Q MIJ, three times a week) and 1,000 mg/day of oral ribavirin for up to 48 weeks. Group B: Will receive maintenance dose of interferon (3 MU, three times a week) and placebo tablets (identical in appearance to the ribavirin tablets) for up to 48 weeks.
At week 12 of treatment, patients will be evaluated for virological response:
- Patients in group A who are non-responders (fail to reduce their viral load by at least half) will be discontinued from receiving further therapy.
- Patients in group B who are non-responders will be crossed-over to interferon and ribavirin.
- At Week 24 of treatment, patients will be evaluated for virological response:
- Patients in group A who are non- responders (detectable HCV RNA) will be discontinued from receiving further therapy.
- Patients in group B who are non-responders will be crossed-over to interferon and ribavirin.
At week 48 (conclusion of treatment), patients will be evaluated for virological response.
Patients will be followed for 24 weeks after treatment and be evaluated for viral load at weeks 12 and 24 of follow-up.

PRIOR AND CURRENT PROGRESS

The study is closed to enrollment. No volunteers were enrolled during the last 12 months. One new dropout was observed during the monitoring phase. No deaths occurred. The monitoring phase of the study has been completed.

	WRAMC	BAMC	Wright-Patterson	Kaiser	Total
Enrolled	25	9	4	4***	42
AE's	67	0	1	1	69
Serious AE's	1 (ANC 352)*	0	0	0	1
Hosp	0	0	0	0	0
Withdrawn	5**	0	1 (transferred to WRAMC)	1	7

* Reported to HUC
** one patient withdrawn due to side effects, one withdrawn due to low TSH, one withdrawn due to depression, one withdrawn due to low neutrophil count, one withdrawn due to alcohol use.
*** one subject from Kaiser never started treatment.

CONCLUSIONS

		HCV RNA Negative	
Group	N	End of Treatment (Week 48)	End of Follow-Up (Week 72)
A	20	11/20 (55%)	8/20 (40%)
B	21*	6/20 (30%)	4/20 (20%)

*One subject was lost to follow-up. Did not come in for Week 48 or scheduled appointments thereafter. The data suggest that interferon alfa 2b induction doses do not appear to have a major clinical impact on long-term remission rates in patients with chronic hepatitis C. In addition, combination therapy (interferon and ribavirin) when started sooner (immediately after induction time) had superior remission rate (40%) as compared to 20% when combination therapy was started later (8 or 20 weeks after induction dose).

This study is now completed and is being prepared for publication.

Report Date: 20 November 2000

Work Unit # 9212

DETAIL SUMMARY SHEET

TITLE: Hormonal Regulation of the Vitamin D Receptor

KEYWORDS:

PRINCIPAL INVESTIGATOR: Lukes, Yvonne DAC
ASSOCIATES:

DEPARTMENT: Clinical Investigation
SERVICE: Research Operations

STATUS: O
INITIAL APPROVAL DATE: 09 December 1997

STUDY OBJECTIVE

To determine the effects if different steroids on and number of Vitamin D receptors in four different cell lines; MDA-MB-23 1, T4-7D, Hep G2 and HL-60

TECHNICAL APPROACH

Each cell line is exposed to stripped fetal calf serum for 24 hours followed by the addition of either tretinoic acid, prednisone, 17-B estradiol or T3 for 72 hours, 48, 24 and baseline 0.

PRIOR AND CURRENT PROGRESS

Two cell lines have currently been studied. T47-D and MDA-MB-231.
Human kidney serves as an internal control for amplification efficiency

CONCLUSIONS

MDA-MB-231 a low expressor of vitamin D with values too low for detection.
The calculated copy number for vitamin D expression for mRNA appears to occur between 0-24 hours and compares favorably to the literature. Approximately 20000 copies of vitamin D receptors per ng of GAPDH can be detected following the addition of 1x10 6M vitamin D.

Report Date: 08 January 2001

Work Unit # 9213

DETAIL SUMMARY SHEET

TITLE: Quantitative Measurement of Thyroglobulin mRNA Detected in Peripheral Blood Using Reverse Transcriptase Polymerase Chain Reaction

KEYWORDS: RT-PCR, thyroglobulin, thyroid cancer

PRINCIPAL INVESTIGATOR: Anderson, Jeff DAC
ASSOCIATES: R Michael Tuttle, YY Djuh, Matthew Ringle

DEPARTMENT: Clinical Investigation
SERVICE:

STATUS: C
INITIAL APPROVAL DATE: 13 January 1998

STUDY OBJECTIVE:

To optimize the technique required to perform quantitative reverse transcriptase polymerase chain reaction on thyroglobulin mRNA recovered from peripheral blood. To determine if patients with metastatic thyroid cancer have higher concentrations of circulating thyroglobulin mRNA in the peripheral blood than (1) patients "cured" of thyroid cancer, or (2) "normal" patients.

TECHNICAL APPROACH:

Total RNA was recovered from whole blood samples, quantified, and amplified with RT-PCR using the TaqMan ABI 7700 Detection System. An addendum was submitted and accepted 30 November 1999 to expand by up to 500 the number of sample assays performed.

PRIOR AND CURRENT PROGRESS

In the first APR dated 07 January 1999, we reported successful results in detecting residual or recurrent thyroid cancer vs normals in a small groups (N=45) of subjects with no adverse events. We also reported the publication and presentation of two abstracts. This work was awarded the Knoll Clinical Research at the Annual Meeting of the Endocrine Society in 1998. On 30 November 1998 an addendum was submitted and approved to expand this study to include 500 new samples being collected at Johns Hopkins and the Washington Hospital Center.

To date, 498 samples have been analyzed with no adverse results. The thyroglobulin mRNA results were compared to results obtained from the same subjects by the generally accepted diagnostic methodologies (I-131 Whole Body Scan, Thyroglobulin protein immunoassay). Results were comparable for all groups in identifying the patient status (cured vs. local/regional invasion vs. distant metastases) with some notable exceptions.

The thyroglobulin mRNA assay was shown to be significantly more sensitive than the widely used thyroglobulin immunoassay. In patients known to have metastatic disease, 96% were detected by our assay versus 86% by immunoassay. In patients with known local invasion, the difference was 89% versus 60%. The standard immunoassay technique is known to suffer from interference from circulating antibodies to thyroglobulin, which are present in 25% of patients. No interference was detected with the thyroglobulin mRNA assay in patients known to be antibody positive.

CONCLUSIONS

The thyroglobulin mRNA assay developed and optimized under this protocol, displays considerable potential as an alternative diagnostic tool for follow-up monitoring of patients after surgical resection of the thyroid for treatment of metastatic thyroid disease. Significant interest in this methodology has been expressed by the medical community and further development is presently underway at collaborating institutions.

Report Date: 16 February 2001 Work Unit #9217-98

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: Does Abnormal Alanine Aminotransferase Mean Hepatitis C Infection?

KEYWORDS:

PRINCIPAL INVESTIGATOR: Sjogren, Maria COL MC
ASSOCIATES:

DEPARTMENT: Clinical Investigation
SERVICE:

STATUS: C
INITIAL APPROVAL DATE: 28 April 1998

STUDY OBJECTIVE

To observe the prevalence of hepatitis C infection among subjects with abnormal alanine aminotransferase (ALT).
To observe the rate of hepatitis B infection among hepatitis C infected subjects.
To observe physician-order patterns in patients with hepatitis C.
To observe if asking for informed consent form impedes obtaining an accurate rate of HCV infection in this population.

TECHNICAL APPROACH

Collect 1000 sera from DPALS from subjects who are tested for ALT for clinical purposes and are shown to have an abnormal test. Additional 1000 sera from controls (normal ALT) who are age and sex-matched will also be collected. Consent forms will be mailed to all 1000 subjects with abnormal ALT.
Testing for HCV antibody, HCV RNA, HCV genotype will be done without identifiers in all samples. In volunteers who mail back a signed consent form, an aliquot of serum with identifiers will be tested and the results will be made available to the subjects. Subjects with detectable HCV markers will be tested for HBV (HBsAg) marker. Through CHCS or chart review we will gather physician-order patterns for at least one year prior to collection of serum. An approved addendum increased number of abnormal ALT samples.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

There is no new information in the literature about this subject matter. No more subjects were enrolled since the last APR. The total enrollment remains at 2000 serum samples. No adverse events were expected or occurred. No sample was withdrawn from the study. The testing was completed. The study showed that subjects with abnormal ALT have an increased likelihood to be infected with hepatitis C as compared to controls (8% vs 1.8%, $p<0.0001$). Physician order patterns in HCV-infected subjects showed abnormal ALT for one to seven years prior to testing for HCV serological markers. Hepatitis B played no role in this population.
The number of samples enrolled to the study since last APR at WRAMC is _0_ and the total enrolled to date at WRAMC is 2000. The total number enrolled study-wide is _NA_, if multi-site study.

CONCLUSIONS

The study is completed. HCV infection is more prevalent in subjects with abnormal ALT than in subjects (age and sex-matched) with normal ALT. Clinician delay of tests for HCV infection in subjects with abnormal ALT is problematic and may result in costly delays of diagnosis and therapy.

Report Date: 07 August 2001

Work Unit # 9218-98

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: ICP-MS Analysis of Depleted Uranium: A Study to Assess Uranium Levels and Isotopic Ratios in Biological Fluids

KEYWORDS: uranium, isotopes, depleted, urine, ICP-MS

PRINCIPAL INVESTIGATOR: Morris, Elena MT
ASSOCIATES: LT Shelly J. Hodge, Ph.D.; Dr. Melissa McDiarmid

DEPARTMENT: Clinical Investigation
SERVICE:

STATUS: C
INITIAL APPROVAL DATE: 15 September 1998

STUDY OBJECTIVE

During the Persian Gulf War soldiers were injured and/or exposed to depleted uranium (DU). Depleting uranium of ^{235}U and ^{234}U during the uranium enrichment process for nuclear fuel makes DU. Because of the DU density, availability, and relative low costs, it has been incorporated into both projectiles and armor by the military of the United States. Soldiers may have inhaled airborne DU particles, ingested DU particles, and/or experienced wound contamination by DU. The use of DU by the military has resulted in the need for an assay in which military personnel can be screened for DU exposure to monitor health effects. The goal is to establish and validate a method for measuring uranium in biological fluids at pg/ml (PPT) concentrations and determine percent isotopic ratios of ^{235}U and ^{238}U by Inductively Coupled Plasma Spectroscopy (ICP-MS).

TECHNICAL APPROACH

The isotopic composition of uranium in urine samples from individuals enrolled in the depleted uranium follows up program at the Baltimore Veterans Administration Hospital was determined by an inductively coupled plasma mass spectrometer (ICPMS). The isotopic composition of uranium was determined by measuring the plasma mass isotopic ratio. Each sample was measured six times and the results averaged. The percent ^{235}U and ^{238}U was calculated from $^{235}U/^{238}U$ isotopic ratio. The percent DU present in the urine was calculated using the following formula:
B=((((A-D)-(0.0072*A))/-0.0052)/A)*100 where, A is the intensity of ^{235}U measured by ICPMS, B is the percent DU present in the sample, D is the fraction of ^{235}U determined from the ICPMS. DU is defined as $\leq$0.2% ^{235}U.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

There will be follow-up studies to monitor the levels of depleted uranium in people who have significant amounts. These measurements will be done at the AFRRI. The number of subjects enrolled to the study since last APR at WRAMC is __0__ and the total enrolled to date at WRAMC is __61_____. The total number enrolled study-wide is _____, if multi-site study.

CONCLUSIONS

This protocol has been completed. The archival samples have all been assayed for depleted uranium and no new patients were recruited for this protocol.

Report Date: 12 September 2000 Work Unit # 9219-99

DETAIL SUMMARY SHEET

TITLE: Molecular Marker of Radiation Induced Thyroid Disease Developing In Subjects Who Lived Downwind of the Hanford Nuclear Power Plant During Childhood

KEYWORDS: radiation, thyroid, cancer

PRINCIPAL INVESTIGATOR: Gary L. Francis, COL MC
ASSOCIATES: Yvonne Lukes, DAC

DEPARTMENT: Pediatrics
SERVICE: Endocrinology

STATUS: O
INITIAL APPROVAL DATE: 17 November 1998

STUDY OBJECTIVE

To determine the pattern of oncogene activation in paraffin embedded tissue samples from subjects exposed to Hanford Nuclear Power Plant radiation in the 1950's.

TECHNICAL APPROACH

Paraffin embedded thyroid samples (benign and malignant) that were collected for clinically indicated reasons and exist on the shelf at the time of approval of this project will be collected by collaborators at Fred Hutchinson Cancer Center. This protocol has also been approved by the Fred Hutchinson Cancer Center IRB. Samples will be provided to the WRAMC DCI laboratory for oncogene analysis. Corresponding clinical data and radiation dose reconstruction data will be maintained by collaborators at Fred Hutchinson Cancer Center.

PRIOR AND CURRENT PROGRESS

No samples have yet been analyzed for oncogene activation. The protocol is still of great interest and we are still making arrangements to have the samples forwarded for analysis.

CONCLUSIONS

This protocol is still of major interest and as soon as samples can be released, work will continue.

Report Date: 12 September 2000

Work Unit # 9220-99

DETAIL SUMMARY SHEET

TITLE: Molecular Markers of Radiation Induced Thyroid Disease Developing in Subject Treated with External Beam Irradiation for Tinea Capitus as Children

KEYWORDS: radiation, thyroid, cancer

PRINCIPAL INVESTIGATOR: Gary Francis COL MC
ASSOCIATES: Yvonne Lukes, DAC

DEPARTMENT: Pediatrics
SERVICE: Endocrinology

STATUS: O
INITIAL APPROVAL DATE: 17 November 1998

STUDY OBJECTIVE

To determine the pattern of oncogene activation in paraffin embedded tissue samples from subjects exposed to external beam irradiation for Tinea Capitus as children in the 1950's.

TECHNICAL APPROACH

Paraffin embedded thyroid samples (benign and malignant) that were collected for clinically indicated reason and exist on the shelf at the time of approval of this project will be collected by collaborators at in Israel. This protocol has also been approved by appropriate IRB in Israel. Samples will be provided to the WRAMC DCI laboratory for oncogene analysis. Collaborators in Israel will maintain corresponding clinical data and radiation dose reconstruction data.

PRIOR AND CURRENT PROGRESS

There have not been any samples provided from the laboratory in Israel at this time. However, negotiation between R. Michael Tuttle, MD and collaborators in Israel is on going.

CONCLUSIONS

This protocol is of major interest to the laboratory and of great importance to the DoD. Negotiations are continuing to complete delivery of the required samples. Work will progress as soon as they are available.

Report Date: 3 November 2000

Work Unit #9221-99

DETAIL SUMMARY SHEET

TITLE: Combination of Ribavirin with Interferon Alfacon-1 or with Interferon Alfa 2b as Initial Treatment for Chronic Hepatitis C

KEYWORDS: hepatitis C, interferon, ribavirin, human trial

PRINCIPAL INVESTIGATOR: Sjogrën, Maria COL MC
ASSOCIATES: Kent Holtzmuller COL MC

DEPARTMENT: Clinical Investigation
SERVICE: Gastroenterology

STATUS: O
INITIAL APPROVAL DATE: 15 December 1998

STUDY OBJECTIVE

To observe the response to a new interferon (alfacon-1) in combination with ribavirin as compared to standard therapy (interferon alfa-2b and ribavirin) in volunteers with chronic hepatitis C infection.

TECHNICAL APPROACH

Subjects with established diagnosis of chronic hepatitis C (serology and liver biopsy) are randomized to one of two groups of therapy: interferon alfacon-1 and ribavirin or interferon alfa-2b and ribavirin. Volunteers receive treatment for 24 weeks, at this point a HCV RNA is tested in serum. If detectable, the volunteer does not continue therapy (both groups) - If HCVRNA is undetectable, treatment continues on for up to 48 weeks. Therapy is stopped at 48 weeks and volunteers are monitored for an additional 24 weeks. A final test of HCVRNA is done at 72 weeks. If negative, the volunteer is a responder; if positive, the volunteer is a non-responder. A second liver biopsy will be done in patients who are responders.
In March 2000 an addendum was approved to increase WRAMC enrollment to 100 subjects.

PRIOR AND CURRENT PROGRESS

The study is still open to enrollment. To date 96 subjects have been enrolled (all sites), 74 new subjects were enrolled during the last year. At WRAMC: 59 subjects participated in the study, 34 new subjects were enrolled during the last year. The following table shows the viral response to treatment. End of treatment response is measured during the last week of therapy (week 48). Week 72 data are not available yet.

		HCV RNA Negative	
Group	N	Week 24*	Week 48**
Interferon alfa-2b 3 MU/TIW + Ribavirin 1000 mg/day	47	18/32 (56.3%)	6/8 (75%)
Alfacon-1 15 mcg/TIW + Ribavirin 1000 mg/day	49	21/33 (63.6%)	6/8 (75%)

- Not all subjects have reached week 24. ** Only 16 subjects have reached week 48.

Discontinuations

Interferon alfa-2b + Ribavirin - 13 subjects discontinued
9 - Positive HCV RNA at Week 24 (study design discontinuations)
3 - Patient withdrew consent
1 - Adverse Event (reported to HUC)

Alfacon-1 + Ribavirin - 14 subjects discontinued
11 - Positive HCV RNA at Week 24 (study design discontinuations)
2 - Patient withdrew consent
1 - Adverse Event (reported to HUC)
No deaths occurred.

CONCLUSIONS

Too early to make final conclusions. The study is progressing well.

Report Date: 26 January 2001

Work Unit #9222-99

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: Significance of Tyrosine Kinases in Differentiated Thyroid Cancer

KEYWORDS: Tyrosine kinase, thyroid cancer

PRINCIPAL INVESTIGATOR: Ramirez, Raul LTC MC
ASSOCIATES: Francis, Gary COL MC, Anderson, Jeff DAC; Lukes, Yvonne DAC

DEPARTMENT: Clinical Investigation
SERVICE: Research Operations

STATUS: O
INITIAL APPROVAL DATE: 02 March 1999

STUDY OBJECTIVE

This protocol was designed to quantitatively determine the mRNA levels encoding 21 different tyrosine kinase enzymes in a limited number of fresh-frozen thyroid cancers.

TECHNICAL APPROACH –

RNA was successfully isolated from 5 tumors, reverse transcribed, and amplified using primers specific for each of the tyrosine kinases. Levels of the mRNA were determined using the ABI 7700 sequence detection system. The levels of two of these tyrosine kinases, cMET and VEGF appear to be increased in several samples. Current activity is focused on repeat determination of these levels to confirm this observation, as well as improved definition of the VEGF mRNA amplified.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE –

We have also purchased 10 thyroid cancer tissue blocks from Georgetown University tissue bank. We are currently determining the expression of cMET and each of the VGF isoforms by RT PCR on these tumors. The results will be correlated with the histologic type of each tumor. The number of subjects enrolled to the study since the last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 5. The total number enrolled study-wide is 15, if multi-site study (10 additional samples were purchased under authorization of protocol (00-6503, 00-65040 and 00-9201).

CONCLUSIONS

The study has allowed direct quantitative determination of cMET and VGF expression as well as the determination of each VGF isoform produced. We are currently correlating the expression of thyrosine kinases with histologic features of aggressive tumor behavior. This study should be completed in the near future.

Report Date: 06 February 2001

Work Unit #9223-99

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: An Investigation of Oxidative Damage to Proteins in Thyroid Autoimmunity

KEYWORDS:

PRINCIPAL INVESTIGATOR: Lahiri, Sabita DAC
ASSOCIATES:

DEPARTMENT: Clinical Investigation
SERVICE:

STATUS: O
INITIAL APPROVAL DATE: 06 April 1999

STUDY OBJECTIVE

The objective of this protocol is to study the oxidative damage to proteins in thyroid autoimmunity. It has been established previously that compound Dityrosine is formed as a result of oxidation of proteins by free radicals. The free radicals are formed more in the disease condition than normal. Therefore, monitoring the level of Dityrosine is a useful tool to determine the oxidative stress in Autoimmune Thyroid disease. The protocol involves in the determination of the Dityrosine in the serum of Normal, Graves' and Hashimotos thyroidities patients. The protocol proposes to assess the actual modification of the thyroid patients i.e. Thyroglobulin in the serum of patients with autoimmune thyroid disease by isolating and characterizing Tg in the serum.

TECHNICAL APPROACH

Extraction and purification of Dityrosine from the serum was done by the following procedures: a. Digestion with Proteinase K to cleave Dityrosine from the proteins b. Separation and purification of the cleaved Dityrosine were done by centrifugation using Micron Centrifugal Filter devices. c. Eluate containing Dityrosine an other components of Mol..Wt. below 3,000 was treated with chloroform and 0.1% trifluoroacetic acid, centrifuged and aqueous layer collected and dried. The dried sample was dissolved in 0.1% TFA and injected to HPLC column. The chromatographic separation of the Dityrosine was achieved using Weaters HPLC system, detected in Fluorescence detector. The mobile phase used for the separation of Dityrosine from the other components in the serum as following A) HPLC water with Pic B (1- Heptane Sulfonic Acid), B) 100% methanol with Pic B, C) 100% methanol, D) HPLC water. We used Waters Nova pack C 18 column and proper gradient profile. Identification and quantitation was done by comparing the retention time of pure Dityrosine previously synthesized and characterized by Mass Spect. A standard curve was also developed with pure Dityrosine. We plan to determine the actual modification of the thyroid protein i.e. Thyroglobulin (one of the thyroid antigens) by the following procedures: 1. isolation of using antibody to Tg. 3. HPLC separation of the Tg and comparison of the peaks in pure and modified Tg. 3. further characterization of the Tg from the serum of the group of patients studied using Sepharose CL 6B column. 2. Identification of Tg in the collected fraction using Mass Spect (TOF).

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

We reported our progress in the last APR. We changed the gradient profile in the HPLC since our last report and we were able to achieve a better separation of Dityrosine from the serum using the gradient of 81 minutes. We estimated the Dityrosine levels in the serum of 12 Normals, 25 Graves, 12 Hashimoto's Thyroidities, 12 Nodular Thyroid and 8 Thyroid cancer (including PTC). An abstract of this study was published in the International Thyroid Congress and was presented as poster at the ATA meeting on October 2000. An addendum to the protocol was introduced on August 2000, to increase the number of patients in each group to be studied. We are preparing a manuscript on the method of assay of Dityrosine in the serum. We need to repeat a few experiments for this purpose. Our present plan is to continue working on the alteration of the thyroid protein in autoimmune thyroid disease. We asked for a fund of

$5,000 for supplies in fiscal 2001 to complete this study. The number of subject enrolled since last APR at WRAMC is 46 and the total enrolled to date at WRAMC is 69.

CONCLUSIONS

As we mentioned in our current progress report that we obtained interesting data in the year 2000, and were able to publish as an abstract in the International Meeting of American Thyroid Association in October 2000. We are in the process of publishing another paper on the method of assay of Dityrosine in the serum. Our present plan is to focus on the study of the alteration of the thyroid patients and therefore to establish the hypothesis that the free radicals could be responsible for the autoimmune thyroid disease.

Report Date: 02 March 2001 Work Unit #9224-99

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: Quantitative Examination of the Expression of Thyroid Hormone Responsive mRNA Species in Hyperthyroidism, Hypothyroidism, and the Polar T3 Syndrome.

KEYWORDS: RT-PCR, hyperthyroidsm, hypothyroidism, polar T3 syndrome

PRINCIPAL INVESTIGATOR: Anderson, Jeff DAC.
ASSOCIATES:

DEPARTMENT: Clinical Investigation
SERVICE: Research Operations

STATUS: C
INITIAL APPROVAL DATE: 06 April 1999

STUDY OBJECTIVE

To determine relative quantitative changes of key thyroid responsive mRNA species in human skeletal muscle in normal subjects after prolonged cold exposure (Polar T3 Syndrome) compared to hyperthyroid and hypothyroid patient subjects.

TECHNICAL APPROACH

Total RNA was recovered from skeletal muscle biopsy samples, quantified, and amplified with RT-PCR using the TaqMan ABI 7700 Detection System. An addendum was submitted on 24 June 1999 to allow inclusion of four additional mRNA assays.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

The number of subjects enrolled to the study since last APR at WRAMC is 0 and the total enrolled to date at WRAMC is 0. The total number enrolled study-wide is 25, if multi-site study.

Needle Aspiration skeletal muscle biopsy samples were obtained from Dr Lester Reed (Polar T3 samples, n=10 paired samples) and from Dr James Hennessey (hypothyroid, hyperthyroid samples, n=15 paired samples) as described in protocol. Total RNA was extracted from each sample using standard organic extraction techniques. Approximately 10-20 ug of total RNA was obtained from each sample. Quality and quantity was determined by agarose gel electrophoresis and spectrophotometric analysis.

Quantitative reverse transcriptase polymerase chain reaction assays were developed and validated for thyroid hormone receptor alpha, thyroid hormone receptor beta, malic enzyme, type I and II deiodinase, phospholamban, and Uncoupling Protein 3 (UCP3). Amplification of known quantities of commercially purchased cardiac total RNA was used as the standard curve against which all unknowns were measured with one notable exception. Both the skeletal muscle RNA and cardiac standard RNA failed to show expression of Type I deiodinase. The skeletal muscle and cardiac RNA samples were repeated using standards prepared from a commercially purchased thyroid total RNA, known to express Type I deiodinase, to rule out failure of the assay chemistry. A highly sensitive standard curve was obtained from the serially diluted thyroid RNA standard but again failed to be detectable in human skeletal muscle or human cardiac muscle. This was a particularly surprising result because both Type I and Type II deiodinase have been shown to be expressed in a wide array of tissue types. Absence of expression of Type I deiodinase in muscle tissue has not, to our knowledge, been previously reported.

All assays were validated by agarose gel electrophoresis of the amplification products and direct sequencing of several products. The coefficient of variation of each of the assays was less than 2% with correlation of standard curve points consistently greater than 0.96 for each run.

Samples from test subjects and hyper-/hypothyroid patients were then quantitated using the validated assays. Results obtained from the malic enzyme, thyroid receptor alpha and thyroid receptor beta mRNA assays and their statistical analyses were presented in detail in our Request for Change in Protocol Addendum dated 24 June 1999. In brief, malic enzyme and thyroid receptor alpha showed significant changes in skeletal muscle mRNA expression between euthyroid and hyperthyroid patient subjects. Cold

exposed subjects demonstrated a 'mild' muscle thyrotoxic state despite high levels of thyroid hormone within the muscle cells.

Assays for Type I deiodinase, Type II deiodinase, phospholamban, and UCP3 have been successfully completed and statistical analyses are in progress

CONCLUSIONS

It has long been recognized that adaptation to changes in environmental temperature is an important function of thyroid activity. Patients with altered thyroid function frequently present with limited ability to tolerate changes in environmental temperature. It has also been established that prolonged exposure to cold in normal subjects causes significant changes in thyroid status resulting in alterations of muscular heat production, energy metabolism, and mental function (Polar T3 Syndrome). In conjunction with a larger Antarctic residence study funded by the National Science Foundation, our data has expanded and extended the findings of this larger effort.

Report Date: 28 June 2001

Work Unit # 00-9401

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: Laryngeal Mask Airway Use in General Anesthesia for Outpatient Third Molar Surgery: Intraoperative Management and Postoperative Outcomes

KEYWORDS:

PRINCIPAL INVESTIGATOR: Taylor, Steven LTC DE
ASSOCIATES: Bagby, Shan MAJ DE

DEPARTMENT: DENTAC
SERVICE: OMFS

STATUS: C
INITIAL APPROVAL DATE: 15 August 2000

STUDY OBJECTIVE

As stated in item #6 P.1 of protocol

TECHNICAL APPROACH

The subjects were queried prior to and following surgery to determine their level of sore throat utilizing the Likert scale. Surgical and anesthesia times were subdivided into induction and device insertion, procedure, and emergence phases and recorded by an independent observer. The same surgeon and anesthesia provider performed each case to limit operator and technique variability.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

No amendments or modifications to report. Re-review of literature is not complete. There were no adverse events. The number of subjects enrolled to the study since last APR at WRAMC is 17 and the total enrolled to date at WRAMC is 17. The total number enrolled study-wide is NA, if multi-site study. The study had to be closed due to PCS of the associate investigator. Dr. Bagby who was my staff on this study departed the area before we could effectively enroll the appropriate number of subjects. We discovered that more patients were smokers than expected. As this was one of the exclusion criterias the study was affected.

CONCLUSIONS

We have analysis for the data that had been collected up to that point which were the 17 subjects. The results and opinions of the authors are pending.

Report Date: 22 March 2001 Work Unit # 9400-99

DETAIL SUMMARY SHEET (Human Use Protocol)

TTTLE: Absorption Rate of a New Bioabsorbable Membrane- A Pilot Study

KEYWORDS:

PRINCIPAL INVESTIGATOR: Theberge, Daniel COL DE
ASSOCIATES: Tempel, Carl G. MAJ DE

DEPARTMENT: DENTAC STATUS: O
SERVICE: Oral/Maxillofacial Surgery INITIAL APPROVAL DATE: 02 February 1999

STUDY OBJECTIVE

(1) To determine the absorption rate of a new bioabsorbable membrane in a human patient
(2) To study the histologic process of membrane absorption

TECHNICAL APPROACH

Place 10 dental implants, each covered with an identical bioabsorbable membrane (Resolut XT), into an edentulous maxillary or mandibular arch. Serially uncover the implants and place healing abutments, using a tissue punch and local anesthetic at 1,2,3,4,6,8,12,16,20,24 and 28 weeks. Examine the tissue punch specimens histologically.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

Suitable patient for the study has not been found – still pursuing patient for the study.

CONCLUSIONS

Not applicable at this point.

Report Date: 19 October 2000 Work Unit # 9400

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: An Outcome-Based Assessment of the Straumann ITI Dental Implant System by General Dentists

KEYWORDS: implants

PRINCIPAL INVESTIGATOR: Chesla, Robert LTC DE
ASSOCIATES:

DEPARTMENT: DENTAC STATUS: C
SERVICE: INITIAL APPROVAL DATE: 27 August 1996

STUDY OBJECTIVE

To document clinical success of the Straumann ITI Dental Implant System in dental patients and record the subjective clinical restorative experience of general dentists with limited experience in oral implant restoration.

TECHNICAL APPROACH

Single or multiple missing teeth will be restored with ITI implants in 20 patients. All patients will be treated at WRAMC as the implant board at Ft. Bragg declined to participate in the study. General dentists will restore the cases and objective and subjective data will be collected on data sheets. The data will be analyzed with regard to implant success and restorative complexity.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

28 ITI dental implants were placed in 20 patients. 21 implants were successful, 2 were marginally successful, and five failed. Dental restoration of all implants has been completed and no adverse reactions were noted. Patient treatment was completed in January 1999 and six and 12 month follow-up was completed in March 2000. Data analysis is complete and the report is in progress.

CONCLUSIONS

Data confirms that the ITI solid abutment implant system is successful and simple to restore but might not be generally applicable to all restorative situations, especially esthetically demanding ones.

Report Date: 31 January 2001

Work Unit # 00-9601

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: Skin-Contact Monochromatic Infrared Irradiation on Lateral Epicondylitis

KEYWORDS:

PRINCIPAL INVESTIGATOR: Paul E. Pasquina, MD
ASSOCIATES: Mary Ellen Earwood, MD

DEPARTMENT: Orthopedics and Rehabilitation
SERVICE: PM & R

STATUS: O
INITIAL APPROVAL DATE: 22 February 2000

STUDY OBJECTIVE

Determine whether the pain response after application of Skin-Contact Monochromatic Infrared Irradiation differs from that of placebo in the treatment of lateral epicondylitis.

TECHNICAL APPROACH

Randomized, double-blinded, placebo controlled prospective study of active vs. placebo unit.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE

We did not receive the units from the Androdyne Company until two months ago. Instructions have been provided on their proper use and we are currently trying to recruit patients.

CONCLUSIONS

No conclusions to date.

Report Date: 2 March 2001 Work Unit #00-9602

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: Comprehensive Prospective Gait Evaluation of Patients with Spinal Cord Pathology

KEYWORDS: Gait Analysis, Spinal Cord Injury, Spinal Cord Pathology

PRINCIPAL INVESTIGATOR: LTC Steven Shannon, MC
ASSOCIATES: LCDR Sean Kelly, MC; COL Bahman Jabbari, MC

DEPARTMENT: Orthopedics and Rehabilitation
SERVICE: Physical Medicine and Rehabilitation

STATUS: O
INITIAL APPROVAL DATE: 18 April 2000

STUDY OBJECTIVE:
To describe the gait characteristics of subjects with spinal cord pathology (SCP) during the first year after diagnosis.

TECHNICAL APPROACH:
SCP subjects and controls will be tested with a computerized 3-D gait laboratory including a dynamic EMG machine, and descriptive statistics will be presented and analyzed.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE:
No progress to date – still waiting for grant approval/release of funds. The number of subjects enrolled to the study since last APR at WRAMC is __0__ and the total enrolled to date at WRAMC is ____0___.

CONCLUSIONS:
None.

Report Date: 10 April 2001

Work Unit # 00-9603

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: Comparison of Biochemical Markers Between Active Duty U.S. Service Members with Chronic Myofascial Pain Syndrome and Matched Controls

KEYWORDS:

PRINCIPAL INVESTIGATOR: J. Gambel
ASSOCIATES: S. Shannon, M. Rubertone, R. Howard, R. Gerwin

DEPARTMENT: Orthopedics and Rehabilitation
SERVICE: Physical Medicine and Rehabilitation

STATUS: O
INITIAL APPROVAL DATE: 6 Jun 2000

STUDY OBJECTIVE:
To evaluate the association of four common metabolic markers (uric acid, TSH, FT4, and serum ferritin) with chronic myofascial pain syndrome in active duty military population and matched controls.

TECHNICAL APPROACH:
A case group was composed of U.S.military active duty patients with chronic MPS from a Physical Medicine and Rehabilitation outpatient clinic. Each patient had a history of myofascial pain of at least six months duration with active trigger points. Cases were assigned a case date of approximately one year after the onset of their symptoms. Closest available sera prior to case date was obtained for cases and for matched controls from the U.S. Department of Defense Serum Repository. All sera were batch tested for uric acid, thyroid stimulating hormone (TSH), free T4 (FT4), and ferritin.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE:
The case and control groups each included 32 participants and was 56% female. On average, sera was drawn approximately ten months prior to case date. No significant differences were found between the laboratory test results of case and controls with regards to uric acid, TSH, FT4, and ferritin.
The number of subjects enrolled to the study since last APR at WRAMC is 64 and the total enrolled to date at WRAMC is 64.

CONCLUSIONS:
In the study population, no association was identified between the four metabolic markers and chronic MPS. The relatively equal proportion of study participants by gender may have obscured potential differences in the case and control groups that were used to track the three clinical conditions: hypometabolism, iron deficiency, and hyperuricemia. Laboratory testing may be more revealing if these markers, alone or in combination with other factors of interest, were assessed prospectively over the clinical course of those diagnosed with MPS.

Report Date: 12 July 2001 Work Unit # 00-9604

DETAIL SUMMARY SHEET (Human Use Protocol)

TITLE: Determination of Low Back Muscle Usage by MRI Before and After Stepper Machine Exercise

KEYWORDS: MRI, exercise, back musculature

PRINCIPAL INVESTIGATOR: LTC Raul Marin MC
ASSOCIATES: MAJ Phil Dinauer MC; MAJ Roberto Perez-Millan MC; LTC Jeffrey Gambel MC; CPT Deydre S. Teyhen MS

DEPARTMENT: Orthopedics and Rehabilitation
SERVICE: Physical Medicine and Rehabilitation

STATUS: O
INITIAL APPROVAL DATE: 19 September 2000

STUDY OBJECTIVE

Compare the effect of 2 methods of using the stepper machine on the recruitment ("usage") of back muscles in normal subjects using MRI.

TECHNICAL APPROACH

a. Subjects:

Male and female subjects between the ages of 18 and 39 years. Volunteers were recruited by word of mouth. Although equal numbers of male and female subjects were to be recruited, we were unable to accomplish this (6 males and 2 females were recruited of which 5 males and 1 female actually engaged in the experiment).

b. Study Design:

This was intended to be a prospective, randomized complete block, crossover single blinded trial. Because of our inability to recruit equal numbers of males and females, we were unable to stratify the subjects into to gender specific blocks. The order of the stepping method was randomized via a computer generated randomization table.

d. Methodology:

A baseline MRI (baseline scan # 1) of the lumbar spine with the subject at rest was performed initially. The radiologist performing the MRI readings was blinded as to the condition (rest, regimen 1, regimen 2) associated with the films being read. Subsequently, each subject began exercising in the stepper machine doing either 6 inch short stepping technique with subject's hands free from the bars so as to maintain the upper body weight supported exclusively by the back musculature, or full length stepping technique with subject's hands holding the support bars. A 5-minute warm-up preceded the exercise session. Intensity of exercise was determined by the rate of perceived exertion as stated in the original protocol. MRI scanning occurred immediately after this first exercise session (post-exercise scan # 1), followed by a ten-minute rest period. The rest period was followed by a baseline re-test in the MRI scanner (baseline scan # 2) and subsequently, the subject began the second exercise regimen. Re-scanning followed immediately after this second exercise regimen (post-exercise scan # 2). Thus, each subject was scanned four times (baseline # 1, post-exercise # 1, baseline # 2, post-exercise # 2). Each scan lasted approximately 8 minutes. The placement of each subject in the MRI table was clearly marked, utilizing bony landmarks (greater trochanter of the femur, acromion process of the shoulder, and knee) to ensure that the subsequent scanning sequences occurred with the subject laying in the exact position as he/she was during the first scanning.

PRIOR AND CURRENT PROGRESS and REVIEW OF RECENT LITERATURE :

The number of subjects enrolled to the study since last APR at WRAMC is 6 and the total enrolled to date at WRAMC is 6. No adverse events occurred.

The "dosage" of exercise intensity was determined by stepping method with the 6-inch hands off method being the most strenuous (this is one points that we wanted to assess in this protocol). Water content changes in exercising muscle are dependent on the intensity of the exercise, and these changes determine the MRI's ability to identify muscle usage [1, 2]. At sub maximal workloads, extra cellular water volume

increases more than the intracellular water volume and with maximal workloads, the opposite is true. The higher the intracellular water content, the higher the MRI signal intensity post-exercise, thus allowing for better definition of actual muscles used and the determination of which exercise regimen provided the highest challenge to the lumbar musculature. Furthermore, we were expecting that the back musculature would behave in the same fashion as the leg muscles as described by Zimmermann [3], who found that faster cadences (as in the 6 inch hands off method) result in increased muscle use of the gluteus maximus, quadriceps, and gastrocnemius while performing stepper machine exercise.

Unexpectedly, a preliminary evaluation of the 6 subjects tested showed no differences between the exercise methods. Since the majority of subjects reached their target exercise intensity halfway through the exercise session (and one did not reach it at all), it was felt that the lack of differences was due to inadequate challenge due to short duration of exercise. Thus, the PI (who in April 2001 was cleared by internal medicine to participate in cardiovascular training via an "over 40" physical) underwent a separate testing session in which the exercise period was extended from 10 to 15 minutes for each stepping method. Unfortunately, there were also no differences in back muscle usage by MRI.

A review of the literature was done [4 - 8] and it was found that the function of back extension is a coupled action involving the back extensor muscles *and* the hip extensors (Gluteus Maximus and Hamstrings). Thus, the lack of differences noted could be explained by the inability of the stepper exercise to train the back muscles in isolation and by a larger than expected contribution of the gluteal musculature. The PI intends to undergo another separate testing session as before, this time, focusing the MRI scans procedure on the Gluteus Maximus muscle. If the evaluation of the MRI in this test shows differences between the stepping methods with regards to Gluteus Maximus use, then an addendum will be submitted to the IRB requesting a change in protocol that will allow us to recruit additional subjects so as to perform the experiment focusing on the Gluteus Maximus muscle.

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CONCLUSIONS

Although MRI has been found to reliably identify muscle usage, its use for the documentation of selective activation of the lumbar extensor musculature during stepper-machine exercise appears to be in question. Issues relating to the degree of exertion, the aerobic nature of the exercise (as opposed to strength training), and perhaps, the potential large contribution of the Gluteus Maximus to back extension may be contributing factors to our negative preliminary findings. An exploratory testing on the PI focusing on the Gluteus Maximus may shed light into this issue and allow us to possibly request an addendum to our protocol that will allow us to recruit additional patients to test the hypothesis that the Gluteus Maximus is the main contributor to erect posture and back extension during stepper machine exercise.