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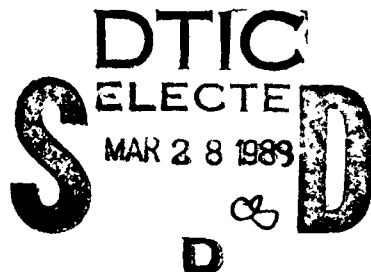
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A data collection research center has been established on Okinawa for the purpose of studying the risk of HTLV-I transmission to active duty personnel stationed there. Research activities include a period prevalence serosurvey for HTLV-I in 5,267 personnel. Thirty-one of this group were positive by ELISA with confirmatory tests and full laboratory epidemiologic analysis pending. In addition, active duty personnel are being accessioned on arrival to Okinawa for prospective follow-up with repeat serologies and questionnaires throughout their tours to determine rates of seroconversion. Greater than 700 participants are currently accessioned. Preliminary results from the seroprevalence survey suggest that transmission rates may be low, however, final conclusions must await completion of the analysis of the seroprevalence draw and prospective study of personnel during their tours.					
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FOREWORD

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X For the protection of human subjects, the investigator(s) have adhered to policies of applicable Federal Law 45CFR46.

In conducting research utilizing recombinant DNA technology, the investigator(s) adhered to current guidelines promulgated by the National Institutes of Health.

SM Bralme 1/18/89
PI Signature Date

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TABLE OF CONTENTS

Introduction

Staff, Equipment, Furniture, Space

Preparatory Briefs

Marine Organization/Study Population

Seroprevalence Survey

Prospective Study

Follow-up of Initial Seropositive Cohort

Year Two Activities

Conclusions

Introduction

The purpose of this protocol is to determine if Human T-Cell Leukemia Virus 1 (HTLV-I) transmission is occurring in active duty forces stationed on Okinawa, Japan. HTLV-I, the first human retrovirus isolated, has been identified as the etiologic agent for Adult T-Cell Leukemia/Lymphoma (ATLL). In addition, HTLV-I has been linked etiologically to a subset of patients with Tropical Spastic Paraparesis (TSP) - a slowly progressive myelopathy. Transmission of the virus occurs parenterally, sexually, and from mother to child (predominantly via breast feeding). Since the original description of the virus in 1979, serologic surveys have been conducted in many parts of the world. Endemic areas for HTLV-I include Southern Japan, the Caribbean Basin, and parts of South America and Africa. The United States, for the most part, is not endemic with the exception of Southeastern Blacks and the Intravenous Drug User population.

Okinawa has one of the highest endemic rates of HTLV-I in the world, with ~15 - 40% of adults being infected. It is unique in the military as it is the only known Hyperendemic region for HTLV-I where we are deploying large numbers of troops and their dependents for extended periods of time. In 1984, a preliminary survey of HTLV-I infection in Marines who had been on-island for greater than one year was done by the P.I. in collaboration with Dr. Blattner (Co-Investigator on Current Protocol) of National Cancer Institute. Fifteen of the 324 individuals (4.4%) were seropositive for the virus.

The objective of the current protocol is to definitively define the risk of acquisition of HTLV-I in active duty troops stationed on Okinawa. It is further planned to identify risk behaviors/exposures and to determine what the clinical and laboratory correlates with HTLV-I infection are. The design of the approved protocol is a three year prospective study in which active duty personnel are accessioned upon arrival to the island and then followed throughout their tour with repeated serologies to document the seroconversion. At the request of the WRAIR senior scientists, an expanded seroprevalence survey was added prior to the initiation of the prospective study. The purpose of the seroprevalence survey was to more rapidly approximate the risk and extent of HTLV-I infection in active duty personnel on Okinawa. This was felt to be particularly important as HTLV-I can be transmitted very efficiently via blood transfusion and there is no on-going screening of blood units for HTLV-I in the Armed Forces Blood Program. (This will be initiated in 1989.) This annual report details the work accomplished with Year 1 funding.

Annual Report 1987 - 1988

Staff

The Principal Investigator is CDR Stephanie Brodine with Co-Investigators Dr. William Blattner, CDR Edward Oldfield, LT Andrew Corwin, and LCDR Richard Thomas. CDR Brodine is completing an Infectious Diseases fellowship at Naval Hospital, San Diego (NHSD) and will remain at NHSD as staff in the Infectious Diseases Division. Dr. Blattner is Chief, Viral Epidemiology, Retroviral Section at National Cancer Institute. CDR Oldfield is Head, Infectious Disease Division, NHSD. LT Corwin is an Epidemiologist with 3rd Marine Division, Okinawa and LCDR Thomas is an Epidemiologist at Naval Environmental Preventive Medicine Unit-6, Pearl Harbor, Hawaii.

The Okinawa staff includes LCDR A. Ryan as the On-Island Study Manager, two Research Nurses, and two Medical Technicians. LCDR Ryan is the Medical Administrative Officer for the 3rd Marine Division Surgeon's Office, 3rd MEF, and coordinates medical activities for the Marine Forces on Okinawa. As Study Manager, he supervises the civilian staff, facilitates interaction with key military line and medical personnel, and has assisted with the on-site study design and implementation of the project. LT Corwin, a co-investigator, also attached to Division Surgeons Office, has played a critical role in protocol design, initiation of the project, and completion of the seroprevalence survey. He has been reassigned to the Naval Medical Research Unit, Cairo, Egypt (8/88).

The hired civilian staff on Okinawa includes two part-time Research Nurses and two part-time Medical Technicians. During the Seroprevalence survey, the staff was augmented to three Research Nurses and two Medical Technicians. The two permanent Research Nurses, Cindy Spinelli and Cheryl Baker, both are RN's, and Cindy has a Masters degree in Nursing. Their primary responsibilities (see Appendix for job descriptions) include accessioning and follow-up of study enrollees, maintenance of the on-island data files, and shipping of questionnaires for data entry. They further assist in the counseling process for confirmed HTLV-I seropositives. The two Medical Technicians, Sondra Budny, who has a medical laboratory technician degree and Rosemarie Gresham, are primarily responsible for the processing, storing, and shipping of sera, and ordering of supplies. Both of the Medical Technicians are also cross-trained in the accessioning process. Rosemarie has a one year degree in Computer Science Service and will be assisting with the data base management done on-island during Years 2 and 3.

Computer data base management and statistical support is provided by the San Diego Epidemiology Project, headed by Dr. Craig Molgaard. Dr. Molgaard, an Associate Professor in the Division of Epidemiology and Biostatistics, Graduate School of Public Health, San Diego State University, has provided expertise in questionnaire development, study design, and field procedures. Dr. Amanda Golbeck, an Associate Professor and Division Head in Statistics, Department of Mathematical Sciences, San Diego State University, has assisted with study design and will direct the analytic procedures. Alicia Ryden, who has an M.P.H. in

Epidemiology, serves as the data base manager and supervises data entry, quality control procedures, and assists with statistical analysis. Dr. Abram Benenson, Distinguished Visiting Lecturer, Division of Epidemiology and Biostatistics, Graduate School of Public Health, San Diego State University, is a senior consultant for the project.

Laboratory support is provided by Biotech Laboratory, Washington, D.C., and the National Cancer Institute, Human Retrovirus Laboratory, Fort Detrick, Maryland. Biotech Laboratory inventories the incoming sera from Okinawa. Each specimen is sent in a robot rack (with a total of 96 specimens per rack) and a single nunc cryo tube. The robot rack is sent to Fort Detrick for the initial HTLV-I ELISA and RIA p24 serologic screening. The duplicate nunc tube is stored at Biotech. Confirmatory Western Blots are performed at Biotech on all samples identified as seropositive on preliminary screening. Additional serologic testing available includes a Recombinant EISA to Envelope Protein and a Radioimmune Precipitation Assay (RIPA). Viral detection assays (Viral Isolation, Polymerization Chain Reaction (PCR)) will be done on all confirmed seropositives.

Equipment and Furniture

- Okinawa:
- 1) - 70 ° freezer
 - 2) 128 Tube centrifuge (on loan)
 - 3) Xerox machine (leased)
 - 4) Zenith lap top micro-computer (model 183-92)

San
Diego: San Diego Epidemiology Project: Compaq Deskpro
Microcomputer with full accessories and extensive
software inventory. San Diego State University:
Campus computers include a CYBER 750, a CYBER 760,
a VAX 780, a RUAC VAX, a VAX 750, a PRIME, and a
HARRIS VAX.

Space

- Okinawa: 1) Office space (15' x 12') for Research Nurse,
Camp Courtney Battalion Aid Station (BAS).
2) Office space (12' x 12') for Research Nurse,
Camp Kinser, BAS.
3) Laboratory space (50' x 20') Pacific Blood
Program Office (PACOM), Camp Lester.

San
Diego: San Diego Epidemiology Project: 700 square feet
suite with 5 offices plus a conference room.

Research Activities

The research activities of the first year of the HTLV-I
study are as follows:

- (I) Required Preparatory Briefings;
- (II) Seroprevalence Survey;
- (III) Prospective Study; and
- (IV) Follow-Up on Original Seropositive Cohort.

I. Preparatory Briefs

Due to the sensitive nature of the project, extensive
briefing of key military medical and line personnel was required
prior to implementation of the project. Briefings were

predominately conducted by the Principal Investigator and Co-Investigators. (See trip reports in Appendix for full details.) The personnel briefed can be grouped by geographical location.

Washington, D.C.

RADM R. Summitt, MC, USN, Medical Officer of the Marine Corps;
RADM R. Higgins, MC, USN, Medical Officer of the Marine Corps;
CAPT. R. Haynes, MC, USN, Assistant to Medical Officer of the
Marine Corps;

Pearl Harbor, Hawaii

ADM. R. M. Marlbor, MC, USN, Surgeon, U.S. Pacific Fleet
CAPT. Payton, MSC, USN, Admin. Officer, CINCPACFLT
CAPT. B. Shima, MC, USN, Surgeon, Fleet Marine Force, Pacific
CAPT. N. Dean, Officer in Charge, Naval Environmental Preventive
Medicine Unit - 6 (NEPMU - 6)
CAPT. S. Steele, MC, USN, Head Operations and Plans Dept.,
NAVMEDCOM, Pacific Region
COL. Livermore, MSC, USA Medical Logistics, CINCPAC
MAJ. Wittgam, MSC, USAF, Medical Logistics, CINCPAC
CDR L. Roach, MSC, USN, Headquarters, Medical Administration
Officer, Fleet Marine Force Pacific
LT Sandy Stairs, Public Affairs Officer NAVMEDCOM, Pacific
Region

Okinawa

CAPT. Bloys, MC, USN, 3rd MARDIV/III Marine Expeditionary Force
(MEF) Surgeon

CAPT. C.D. Saul, MC, USN, 3rd Force Services and Support Group
(FSSG) Surgeon

CAPT. Wendall Lovan, MC, USN, 1st Marine Air Wing (MAW) Surgeon

CAPT. Anne Langley, NC, USN, Commanding Officer, Naval Hospital

LCDR Jerry Holmberg, MSC, USN, Director, Pacific Blood Program
Office (PACOM), Naval Hospital

CDR John Greenan, MSC, USN, 3rd MED Bn Commander, 3rd FSSG

LT Updegrove, 1st MAW Medical Administrative Officer

HMCM Sprague, 3rd MARDIV HMCM

BRIG GEN Johnston, Assistant Division Commander, 3rd Marine
Division

COL Stephenson, USMC, 3rd FSSG, Chief of Staff

COL D.E. Damon, USMC, Chief of Staff, Marine Corps Base

COL P.J. Jones, USMC, Chief of Staff, III MEF

COL Pappas, Chief of Staff, 1st Marine Air Wing (MAW)

COL Russom, Base Commander, 3rd MARDIV, Camp Courtney

COL Metzger, Head, III MEF, G-4

MAJ James Vance, MC, Public Affairs Officer

3rd FSSG S1 (Logistics) staff

Mr. R. Gibson, Political Military Officer and Deputy,
American Consulate General, Okinawa

Yokosouka, Japan

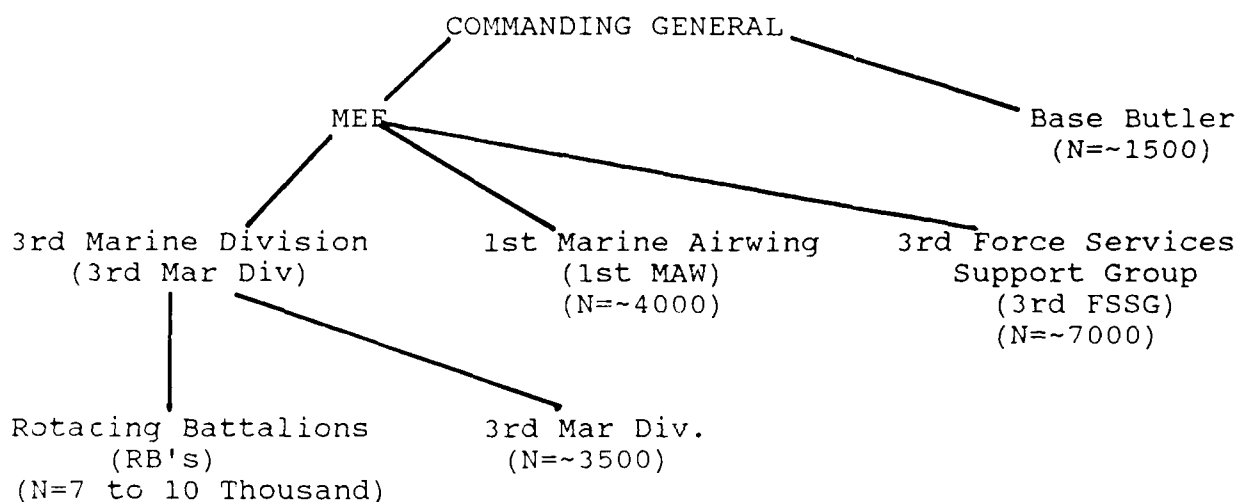
RADM J. Cossey, Commander US Naval Forces, Japan

II. Marine Organization/Study Population

Background

The Marine organization on Okinawa comes under the umbrella of the Marine Expeditionary Forces (MEF). Within the MEF there

are 3 primary components: Infantry (3rd Marine Division - 3rd MARDIV), Support (3rd Forces Service Support Group - 3rd FSSG), and Wing (1st Marine Airwing - 1st MAW). These 3 components are located on 6 bases on Okinawa (see map in Appendix). Base Butler is made up of nondeployable forces whose mission is to maintain the base support on Okinawa in the event of mass MEF deployment.



3rd MARDIV and 1st MAW have both permanent personnel and 'rotators' - personnel who deploy to Okinawa for 6 months only. Actual time spent on Okinawa for these rotators may be as brief as 1 month or as long as 6 months, depending on the Pacific arena military exercises they participate in. The approximate strength of the 3rd MARDIV permanent personnel is 3500 (vs 7 to 10 thousand in rotating battalions). The approximate strength of 1st MAW is 4,000 with the majority of these personnel being in rotating squadrons. 3rd FSSG (N=~7,000) is made up primarily of 'permanent' personnel serving either 1 year unaccompanied tours or 3 year accompanied tours.

Study Population

The study population is the permanent personnel in the 3rd MARDIV and 3rd FSSG (Total N=~10,000). The 1st MAW has been excluded at this time as the majority of personnel are rotators, the permanent personnel can be transferred between Okinawa and Iwakuni, and the mission of the Airwing is more easily disrupted by individual or unit research activities.

III. Seroprevalence Survey

Background

Sera was collected over a three month period (April to July) from active duty Marine Corps personnel of the 3rd Marine Division (3rd MARDIV) and 3rd Force Services and Support Group (3rd FSSG). All Marine Corps personnel on Okinawa were required to have serologic testing for Human Immunodeficiency Virus (HIV) by October, 1988. Permission was obtained by Navy medical personnel on-island to have the HTLV-I serologic survey done in conjunction with the mass HIV draws. Unit draws - organized primarily by company or battalion - were scheduled after completion of the Team Spirit Exercises in April and were continued until mid July. Viral Epidemiology Project (VEP) staff were present for these draws to deliver a brief, administer a questionnaire and consent form, and draw blood. All personnel present were required to fill out a questionnaire; for those consenting, two consent forms (one copy for the individual to keep) and 15 cc of blood was drawn. Each sera was split into four nunc storage tubes and a robot rack test well. Sera was frozen to -70 and shipped in batches to Biotech Laboratories for

inventory, with transfer to the NCI Human Retrovirus Laboratory for analysis. One nunc cryotube per specimen was stored at Biotech Laboratories. Questionnaires were xeroxed and copies were sent to the San Diego Epidemiology Project for coding and data base entry. (See Appendix for full explanations of procedures.)

Interim Results

Participants accessioned: 5,267

Total N of targeted population: 10,500

Number of HIV draws done (by Marine Medical Assets): ~7,400

Questionnaires shipped: 5,267

Questionnaires coded and entered: 5,208

Sera shipped: 5,267

Sera received, inventoried: 5,267

ELISA Serologies Completed: 5,267

Positive ELISA'S: 30

Western Blots: 11

Positive Western Blots: 2
(p24 and p19 bands present)

Indeterminate Western Blots: 4
(p19 or p24 bands present)

Sera has been drawn and questionnaires obtained from 5,267 Marine Corps active duty personnel from 3rd MARDIV and 3rd FSSG, Okinawa. All battalions of 3rd FSSG and 3rd MARDIV are represented in the survey except for 1 which was deployed during the sampling period. VEP study staff accessioned ~71% of the personnel who had a mandatory HIV draw done during the 3 month survey period. The sera has all been shipped, inventoried, and

screened serologically for HTLV-I by ELISA and p24 RIA. The Questionnaires have all been duplicated and shipped to the San Diego Epidemiology Project. Coding and entering of the data base is nearly completed.

IV. Prospective Study

Approximately 3,000 Marines assigned to 3rd MARDIV or 3rd FSSG in 1988, 1989 will be followed prospectively throughout their tour on Okinawa. As all incoming active duty personnel must check-in their medical records at the Battalion Aid Station (BAS) within one week of arrival, the BAS has been chosen as the accessioning site. One Research Nurse is "stationed" at the Camp Kinser BAS (3rd FSSG) and the other Research Nurse is at Camp Courtney's BAS (3rd MARDIV). Commencing August 1988, all active duty personnel checking in to either of these BAS's have been directed to the VEP study staff by the BAS medical staff. The accessioning process is the same as described previously with each individual filling out a questionnaire and consent form and donating 15 cc of blood. All individuals confirmed to be seronegative on the initial screen are being followed prospectively during their tour on Okinawa with repeat serologies at annual intervals. Individuals who seroconvert are confirmed with a second specimen. Seroconvertors will have a full physical exam, review of medical record, and laboratory screening tests. Counselling will be done by the investigators and the VEP Research Nurse (see appendix for counseling document). Nested case control analysis comparing a minimum of two seronegatives

per seroconverter will be done to determine potential risk behaviors for seroconversion.

Interim Results

Prospective Participants Accessioned: ~700

Questionnaires Shipped: ~550

Questionnaires Coded and Entered: 0

Sera Screened: 0

700 participants have been accessioned since mid August. As the BAS medical staff are becoming aware of the project, there has been increasing compliance with the directing of active duty personnel to project staff. Additional methods to augment the accessioning process are being explored presently.

V. Follow-Up of Initial Seropositive Cohort

In the initial 1984 pilot study of HTLV-I seroprevalence in active duty Marines stationed on Okinawa for greater than one year, there were 15 confirmed seropositives (by ELISA and RIPA). Follow-up study of these individuals includes: 1) A repeat specimen for HTLV-I serologies; 2) HTLV-I viral detection assays; 3) Physical exam and a retrospective medical chart review; 4) Administration of the supplemental questionnaire; and 5) Counseling for those with repeat positive serologies.

A counseling document has been prepared. Assistance was provided from the Transfusion Safety Project (Principal Investigator Dr. J. Mosely, USC Medical Center). Ten of the initial 15 seropositive individuals who remain on active duty have been located. Five individuals have been released from the

service. Three of the active duty members have been interviewed with repeat serologies and questionnaire analysis pending.

VI. Year Two Activities

Seroprevalence Survey

During the 2nd year it is planned to complete the laboratory evaluation of preliminary seropositives (i.e., perform additional serologic confirmatory and viral detection assays), complete the data entry process of questionnaires and lab data, and apply statistical analysis. All individuals with a second confirmed seropositive result will have a physical exam, medical chart review, screening laboratory tests, and receive counseling. A nested case control analysis comparing seronegatives will be done to identify potential risk factors.

Prospective Study

During year 2 there will be continued accessioning of the study population to obtain a minimum N of 3,000 (see original protocol in Appendix). Confirmed seroconvertors will have a full physical, laboratory screening tests and will be counseled. Analysis will be done to identify potential risk exposures for seroconversions. Family members of seropositive active duty personnel will be offered testing.

Consideration is being given to retesting a cohort of individuals from the seroprevalence survey who were seronegative on baseline screening. In addition, the accessioning of

potentially high risk subsets such as personnel with Sexually Transmitted Diseases (STDs) is being explored.

Follow-up of Original Seropositive Cohort

During the 2nd year, it is planned to contact and process the individuals who remain on active duty. Individuals who confirm positive - by serologies or viral detection-will be counseled and testing will be offered to family members.

Conclusions

In summary, a data collection research center has been established on Okinawa for the purpose of studying the risk of HTLV-I transmission to active duty personnel stationed there. Year 1 activities have succeeded in: 1) securing approval from Marine Line Personnel to conduct the study; 2) procurement of military and civilian on-island staff as well as the necessary space and equipment; 3) enrolling collaborative assistance from NEPMU-6 staff; 4) obtaining the expertise and support necessary for data entry, questionnaire design, and statistical analysis; 5) implementation of a successful mechanism for the accessioning and serologic testing of participants.

A serosurvey representing a period prevalence of HTLV-I seropositivity in Marines stationed on Okinawa has been done in 5,267 personnel. Analysis of this survey, both laboratory and epidemiologic, will be completed during Year 2. Preliminary results (31 ELISA positive) - suggest that transmission rates may be quite low. In addition, greater than 700 participants have been accessioned for prospective follow-up. The accessioning process will continue into Year 2. Finally, follow-up of the 1984 cohort has been initiated and will continue into Year 2. Assessment of the risk of HTLV-I transmission to active duty personnel in Okinawa must await full analysis of the seroprevalence draw, prospective study of personnel during their tours, as well as follow-up of the 1984 cohort.