AFEB (13 Nov. 1964) 5th Ind.
SUBJECT: Approval of Research Proposal "Studies on the Use of Live Adenovirus Vaccines in Recruits; request for

Executive Secretary, Armed Forces Epidemiological Board, Office of the Surgeon General, DA, Washington, D. C. 20315 23 December 1964

TO: Chief, Bureau of Medicine and Surgery

1. The Armed Forces Epidemiological Board, meeting in executive session on 8 December 1964, concurred in the recommendation of the Commission on Acute Respiratory Diseases and the concurrent recommendation of the Commission on Influenza:

> THAT THE RESEARCH TASK, "EPIDEMIOLOGY, BIOLOGY, PATHOLOGY, DIAGNOSIS AND PREVENTION OF VIRAL DISEASES, MR 005.09-1203, SUBTASK TITLE," STUDIES ON THE USE OF LIVE ADENOVIRUS VACCINES IN RECRUITS, MR 005.09-1203.17, NAVAL MEDICAL RESEARCH UNIT NO. 4, US NAVAL HOSPITAL, GREAT LAKES DATED 13 NOVEMBER 1964 BE SUPPORTED.

2. The Board was enthusiastic in its endorsement of the proposed research.

3. Although adenoviruses have been described and classified as respiratory viruses, and cause a significant amount of respiratory illness, particularly in military recruits, many adenoviruses have been recovered from the gastro-intestinal tract. Indeed, certain adenovirus serotypes appear to be found only in the gastro-intestinal tract. It was logical to suppose, therefore, that adenoviruses responsible for respiratory disease might also multiply in the gastro-intestinal tract and induce an immune response. Accordingly, attempts to develop a live adenovirus vaccine to be fed in enteric capsules were begun by testing the infectivity and efficacy of enteric coated capsules containing 10^6 TCD50 per capsule of live type 4 adenovirus. The vaccine was fed to Marine recruits at Parris Island before they were exposed to type 4 infections at Camp Lejeune. The vaccine virus produced no disease, but multiplied in the intestinal tract and induced a prompt antibody response. The vaccine virus was not disseminated under the conditions existing at Camp Lejeune. Men given the enteric vaccine were protected against naturally occurring adenovirus type 4 respiratory illness.

AFEB (13 Nov 1964) 5th Ind 23 December 1964
SUBJECT: Approval of Research Proposal "Studies on the Use of Live Adenovirus Vaccines in Recruits; request for

4. The protocol developed by Captain R. O. Peckinpaugh, in consultation with Dr. George Gee Jackson, proposes to confirm and extend these observations. The virus used in the Parris Island-Camp Lejeune study has been extensively safety tested, has none of the characteristics of oncogenic adenoviruses, and has failed to induce tumors in a large number of newborn hamsters. The vaccine virus may be even less harmless than the natural type 4 strains to which recruits are almost universally exposed. Since additional doses of this enteric vaccine are available, it is highly desirable that studies of such a vaccine be continued. Efforts should be made to determine the infectious dose, and to attempt to measure dissemination of vaccine virus under conditions existing at a base such as Great Lakes. At Great Lakes it should be possible to determine whether administration of oral virus will abort a type 4 epidemic already in progress. The knowledge gained should be most helpful when, hopefully, safe strains of adenovirus types 3 and 7 are available for testing in live oral vaccines.

FOR THE ARMED FORCES EPIDEMIOLOGICAL BOARD:

Sidney A. Britten

SIDNEY A. BRITTEN
Captain, MC, USN
Executive Secretary

FOURTH ENDORSEMENT on OINC NAMRU-4 USNH GLAKES ltr NAMRU-4 3930 of 13 Nov 1964

From: Director, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland
To: Chief, Bureau of Medicine and Surgery
Via: President, Armed Forces Epidemiological Board, Office of the Surgeon General, Department of the Army, Washington 25, D.C.

Subject: Approval of Research Proposal "Studies on the Use of Live Adenovirus Vaccines in Recruits"; request for

1. Forwarded, recommending approval.

2. The investigational protocol for the use of the live adenovirus vaccine in naval recruits at Great Lakes, Illinois has been reviewed and its use is approved by the Board for Vaccine Development.

3. The indicated live virus vaccine which this Institute controls will be made available to Naval Medical Research Unit No. 4 upon request, as soon as clarification is obtained from the Division of Biologics Standards, NIH, concerning its policy governing the continued use of adenovirus vaccines.

Dorland J. Davis

Dorland J. Davis, M.D.

Copy to:
OINC NAMRU-4

5

J37-00:ja
6700
17 NOV 1964

THIRD ENDORSEMENT on OINC NAMRU-4 USNH GLAKES ltr NAMRU-4 3930 of 13 Nov 1964

From: Commander, U.S. Naval Training Center, Great Lakes, Illinois
To: Chief, Bureau of Medicine and Surgery
Via: (1) Director, Board for Vaccine Development, National Institute of Allergy and Infectious Diseases, National Institute of Health, Bethesda, Maryland
(2) Director, Armed Forces Epidemiological Board, Office of the Surgeon General, Department of the Army, Washington 25, D. C.

Subj: Approval of Research Proposal "Studies on the Use of Live Adenovirus Vaccines in Recruits"; request for

1. Forwarded, recommending approval.

J. O. PHILLIPS

Copy to:
OINC NAMRU-4

4

J23-00:kn
6000
16 November 1964

SECOND ENDORSEMENT on OINC NAMRU-4 USNH GLAKES ltr NAMRU-4 3930 of 13 Nov 1964

From: Commanding Officer, Recruit Training Command, Great Lakes, Illinois
To: Chief, Bureau of Medicine and Surgery
Via: (1) Commander, U.S. Naval Training Center, Great Lakes, Illinois
(2) Director, Board for Vaccine Development, National Institute of Allergy and Infectious Diseases, National Institute of Health, Bethesda, Maryland
(3) Director, Armed Forces Epidemiological Board, Office of the Surgeon General, Department of the Army, Washington 25, D.C.

Subj: Approval of Research Proposal "Studies on the Use of Live Adenovirus Vaccines in Recruits"; request for

1. Forwarded recommending approval on a "not to interfere with training" basis.

IRA M. KING

Copy to:
OINC NAMRU-4

17 NOV 1964

FIRST ENDORSEMENT on OINC NAMRU-4 USNH GLAKES ltr NAMRU-4 3930 of 13 Nov 1964

From: Commanding Officer, Naval Administrative Command, U.S. Naval Training Center, Great Lakes, Illinois
To: Chief, Bureau of Medicine and Surgery
Via: (1) Commanding Officer, Recruit Training Command, U.S. Naval Training Center, Great Lakes, Illinois
(2) Commander, Naval Training Center, Great Lakes, Illinois
(3) Director, Board for Vaccine Development, National Institute of Allergy and Infectious Diseases, National Institute of Health, Bethesda, Maryland
(4) Director, Armed Forces Epidemiological Board, Office of the Surgeon General, Department of the Army, Washington 25, D.C.

Subj: Approval of Research Proposal "Studies on the Use of Live Adenovirus Vaccines in Recruits"; request for

1. Forwarded, recommending approval.

W. H. McCaughey

W. H. McCAUGHEY

Copy to:
OIC NAMRU #4

2

NAVAL MEDICAL RESEARCH UNIT NO. 4
U. S. NAVAL HOSPITAL
GREAT LAKES, ILLINOIS

IN REPLY REFER TO:
NAMRU-4
3930
13 November 1964

From: Officer in Charge, Naval Medical Research Unit No. 4,
U.S. Naval Hospital, Great Lakes, Illinois
To: Chief, Bureau of Medicine and Surgery
Via: (1) Commanding Officer, Naval Administrative Command, U.S. Naval Training Center, Great Lakes, Illinois
(2) Commanding Officer, Recruit Training Command, Great Lakes, Illinois
(3) Commander, Naval Training Center, Great Lakes, Illinois
(4) Director, Board for Vaccine Development, National Institute of Allergy and Infectious Diseases, National Institute of Health, Bethesda, Maryland
(5) President, Armed Forces Epidemiological Board, Office of the Surgeon General, Department of the Army, Washington 25, D. C.

Subj: Approval of Research Proposal "Studies on the Use of Live Adenovirus Vaccines in Recruits"; request for

Ref: (a) Manual of the Medical Department Article 1-10

Encl: (1) NAVMED Form 1436 (Subject Proposal)

1. In accordance with reference (a), approval of enclosure (1) is requested.

R O Peckinpaugh
R. O. PECKINPAUGH

RESEARCH PROPOSAL
NAVMED 1436 (1-63)

DATE 13 November 1964

SECTION I - TO BE COMPLETED BY FACILITY PROPOSING RESEARCH TASK

TASK NUMBER	TASK TITLE (Known or recommended)
MR 005.09-1203	Epidemiology, Biology, Pathology, Diagnosis and Prevention of Viral Diseases
RECOMMENDED SUBTASK NUMBER	SUBTASK TITLE (Never the same as task title)
MR 005.09-1203.17	Studies on the Use of Live Adenovirus Vaccines in Recruits

FACILITY (Name and address of hospital, laboratory, unit, or activity where task is located)

Naval Medical Research Unit No. 4, U.S. Naval Hospital, Great Lakes, Illinois

SECURITY CLASSIFICATION (Recommended)	EXPECTED DURATION	NAVAL RESEARCH REQUIREMENT	ESTIMATED ANNUAL COST	ADDITIONAL FUNDS REQUIRED FROM CURRENT FISCAL YEAR BUMED ALLOCATIONS (If any)
Unclassified	1 year	R005 Biological Sciences	$20,500.00	$5,000.00

SUBJECTS TO BE USED (Human subjects require SECNAV approval NAVMED 1-11)

Naval personnel at U.S. Naval Training Center, Great Lakes, Illinois

PRINCIPAL INVESTIGATOR

Captain R.O. Peckinpaugh, MC USN

CONSULTANTS

George G. Jackson, M.D., University of Illinois College of Medicine, Chicago, Illinois

COLLABORATORS

LCDR W.E. Frazier, MC USN; M.J. Rosenbaum, Ph.D.; E.A. Edwards; LCDR J.M. Dowd, MC USNR; LCDR J.P. Griffin, MC USN; W.E. Pierce

OBJECTIVES AND EXPERIMENTAL DESIGN (Continue on additional blank sheets if necessary)

INTRODUCTION

Inactivated adenovirus vaccines have been evaluated in naval recruits since 1954. The effectiveness of these vaccines in reducing acute respiratory disease and pneumonia has resulted in their adoption as a routine immunization for incoming recruits of the Recruit Training Command, Great Lakes, Illinois.

No further commercial supply of inactivated polyvalent adenovirus vaccines, produced in monkey kidney tissue cultures, will be available when the present stock is exhausted. At the present rate of usage, approximately one month's supply of the old vaccine remains in this command.

A limited amount of live, adenovirus, type 4, vaccine produced in human embryonic tissue cultures is available in enteric capsule form from the Board for Vaccine Development, National Institutes of Health. Both the host cells and the seed adenovirus, type 4, have passed exhaustive and lengthy safety tests (see addendum) and several thousand doses of vaccines made in similar host cells have been given to human subjects since 1961 without serious reactions.

In January 1964 two hundred eighty doses of adenovirus, type 4, in enteric capsule were administered experimentally to marine recruits at Parris Island, South Carolina where adenovirus disease occurs epidemically. Reports of the study thus far have

SECTION II - TO BE COMPLETED BY RESEARCH DIVISION, BUREAU OF MEDICINE AND SURGERY

PROJECT NUMBER	PROJECT TITLE
DATE APPROVED	BUREAU CODE NUMBER

THIS FORM SUPERSEDES ALL EDITIONS OF FORM NAVMED-98 WHICH IS NO LONGER USEABLE.

indicated that the vaccine produced only minimal reactions, produced better immunological responses than any previous inactivated adenovirus vaccine, and was associated with a remarkable degree of protection against adenovirus disease. No spread of vaccine virus to contacts was observed. These results indicate that a safe, effective alternative to vaccines derived from animal source is available. It is therefore proposed that such studies be initiated at U.S. Naval Training Center, Great Lakes, Illinois where adenovirus disease is endemic, to extend and confirm the results of the earlier study. A proposal to use the live adenovirus vaccine in the naval recruits at Great Lakes was approved, in principle, by the Commissions on Acute Respiratory Disease and Influenza.

OBJECTIVES

Phase 1: to assess the acceptability of the live adenovirus vaccine with respect to (1) the possible spread of the vaccine virus to uninoculated subjects and its potential for causing disease in such subjects, and (2) the potential of the vaccine for causing untoward reactions or side-effects in vaccinated subjects.

Information relevant to the following points may also become available:

1. The homotypic antigenicity of the live monovalent, type 4, adenovirus vaccine.

2. The heterotypic antigenicity of the live monovalent, type 4, adenovirus vaccine.

3. The effect of the live monovalent, type 4, adenovirus vaccine on acute respiratory disease associated with adenovirus.

4. The effect of live monovalent, type 4, adenovirus vaccine on acute respiratory disease of other etiology.

Phase II: to assess the protective efficacy of the live monovalent, type 4, adenovirus vaccine in preventing disease of specific etiology among vaccinated subjects.

Information relevant to the following points may also become available:

1. The comparative protective efficacy of inactivated versus live adenovirus vaccines in the presence of naturally occurring infection.

2. The effect of live monovalent, type 4, adenovirus vaccine on recruit acute respiratory disease of non-adenoviral etiology.

3. The effect of live monovalent, type 4, adenovirus vaccine on other disease conditions.

4. Further experience to assess the potential for spread of the vaccine virus and the acceptability of the live monovalent, type 4, adenovirus vaccine regarding reactions.

METHODS:

Phase I: Two recruit companies of approximately 80 men each will be employed. After the completion of the processing period and prior to commencement of training the first company, Company A, will be randomly divided into 2 approximately equal

groups: Group 1 will receive oral live monovalent, type 4, adenovirus vaccine. Group 2 will receive an enteric placebo. The second company, Company B, will be randomly divided into 2 approximately equal groups. The first group will receive injections of an inactivated, monovalent, type 4, preparation, and group 2 will receive a saline placebo. Live Sabin polio vaccines will be withheld from these companies. Prior to the receipt of treatment, both companies will be bled and a throat and rectal swab for virus isolation will be obtained.

Throat and rectal swabs for virus isolation studies will be obtained from each man in Companies A and B three times a week. Serum samples will be obtained from each man in Companies A and B once a week. Samples will be collected throughout the 9 weeks of training.

Constant medical evaluation by weekly interviews of Companies A and B will be maintained with particular emphasis on detection of symptomatology possible referrable to the vaccine. Oral temperatures will be taken and subjective symptoms regarding state of health will be ascertained.

All admissions to the infirmary from either company for inpatient care will be seen by the above team of medical examiners and throat and rectal swabs and acute and 21-day convalescent blood specimens obtained. A medical history regarding signs and symptoms shall be obtained also at the time of admission.

Phase II: This phase of the study will be conducted when proper epidemiological conditions prevail (i.e., when routine surveillance reveals that natural infection with type 4 adenovirus and/or illness reach appreciable proportions).

The Phase II portion of the study will contain approximately 24 companies. Twelve companies will receive a single dose of the live preparation and placebo, while 12 companies will receive an injection of the inactivated preparation and placebo.

Treatment and placebo groups within companies will be randomized as in Phase I. All men in each company shall be bled prior to the receipt of the vaccine or placebo and again at mid-training and at the completion of training. Live polio vaccine will be omitted in these recruits. All men admitted to the infirmary and hospital for inpatient care shall be seen by the above team of medical examiners and symptoms solicited. Throat and rectal swabs will be obtained, as well as acute and 21-day convalescent blood specimens. Each cohort of companies shall be seen by a team of medical examiners during the first, second, third, fifth, seventh, and ninth weeks of training. Oral temperatures and subjective symptoms will be obtained. Data on admission to the sick list as well as visits to the infirmary for outpatient care shall be abstracted on each man prior to his departure from the recruit camp.

DISCUSSION

The basic study design which consists of cohorts of two companies on two different treatments, the number 1 company of each cohort will receive the live treatment and placebo. Number 2 company will receive the inactivated preparation and placebo. This type of design will allow the following comparison incohorts of companies on different treatment regimes: the live versus placebo, the inactivated versus placebo, the live versus the inactivated, and the placebo that has been associated with live vaccines versus the placebo from the inactivated preparation. Total study population will be approximately 2,000 men, 500 men in each treatment regime or placebo.

The vaccine materials needed for this study and to be available or reserved on or before 1 January 1965 are:

Live, type 4, adenovirus vaccine - 550 doses

Enteric coated inert placebo - 550 doses

Enteric coated Biological placebo - 550 doses (if available)

Inactivated, type 4, adenovirus vaccine - 500 doses

Injectible saline placebo - 500 doses

Additional related studies which may be incorporated into the above programs or performed in the future depending on the availability of materials are:

1. Effect of secondary (enteric capsule) and tertiary (oral fluid) feeding on the immunological and virological status of the host.

2. Effect of prior immunization with inactivated adenovirus vaccine on the establishment of enteric infection with subsequent feeding of live adenovirus vaccine.

3. Effect of adenovirus hyperimmune gamma globulin treatment on immunization with live adenovirus vaccines.

4. Determination of effective dosage (ED_{50}) of live adenovirus vaccine in recruits (serological and virological).

5. Antigenicity of adenovirus sub unit purified fractions in naval recruits.

ADDENDUM

A. Safety of vaccine of human embryonic cell cultures (diploid)

1. Lack of tumor formation in parentally inoculated:

   a. Animals: Hayflick, L. et al. Am. J. Hyg. 75:240, 1962.

   b. Humans: ibid

2. Previous use in various vaccine programs for human subjects (7,000):

   Hayflick, L. Post Graduate Medicine 35:503, 1964.

B. Safety of adenovirus seed and diploid host cell used in this vaccine:

Chanock, R. Personal communication.

Virus: Type 4 adenovirus enteric capsule vaccine.

Strain: Recovered from a marine with febrile ARD, Camp Lejeune, N.C.

Passage history: Recovered in WI 26 (human diploid fibroblasts) and subsequently propagated in WI 26 or WI 38 for 11 passages.

Safety tests: 11th passage pool free of adventitious microbial agents (viruses, bacterial and mycoplasmas) by standard safety tests. Not oncogenic in hamsters after 11 months of observation.

Preparation: Virus lyophilized and packaged in enteric coated capsules 10^6 TCD_{50} per capsule, stored -70°C.

C. Use of this live adenovirus vaccine in marine recruits: Edmundson, et al, ARD Commission 1963-1964.