Operation Whitecoat 1954-73: Ethical Use of Human Subjects in Infectious Disease Research

Arthur O. Anderson MD
Fort Detrick in the 1950’s

The cross shaped building (center bottom) is the station hospital. It is linked to the support laboratories and the USAMU building to the right. The white cube near the middle of the photo is the 8 ball.
The station hospital, originally activated in 1943, provided a “unique opportunity to study the inception, course and therapeutics of many rare diseases in patients whose baseline health data was known” LTC Abram Benenson MC

This was primarily “opportunist” research that depended upon occupational incidents among workers in the various biowarfare facilities.
Occupational Illnesses at Fort Detrick 1943 - 1946

During the 26 months of wartime operations through 6 months after the end of the war there were 190 occupational exposures that resulted in 79 infections and no deaths. There were 25 cases of cutaneous anthrax, 17 cases of brucellosis, 26 cases of clinical of subclinical tularemia, 3 cases of psitticosis (2 meningo-pneumonitis and 1 classical), 2 cases of glanders

* Development of “containment” technology under Dr. Wedum, and development of “new” vaccines reduced occupational infections nearly to zero. Only 4 deaths, 2 of anthrax, 1 of machupo virus and 1 due to trauma between 1943 and 2002.
By the end of the war years it was clear that the facilities, staff and low numbers of occupational cases at the station hospital were not adequate for a systematic program for development of drugs, and vaccines. Human volunteer exposure studies were needed.

* Extrapolation of animal data to man was opposed, data from direct human challenge was needed.
Human Vulnerability to BW Aerosols Not Tested Before 1950’s

• In 1952, national leaders were unsure about human vulnerability to biological warfare and whether existing medical countermeasures would be effective under realistic scenarios using actual BW agents.

• An Ohio State contract for human volunteer studies and CD-22 Research Programs were planned by an ad hoc committee at Fort Detrick.
Nuremberg Code of 1947

1. Voluntary Consent of subject is absolutely essential
2. Valid research for good of society - by no other means
3. Human studies must be preceded by survey of existing knowledge and research with animal models to identify potential risks and benefits
4. Avoid unnecessary physical and mental suffering & injury
5. Prohibits research with *apriori* risk of death or disabling injury
6. Degree of risk never to exceed benefit or humanitarian value
7. Prepare to minimize risk of injury, disability or death
8. Investigator must have credentials appropriate to study
9. Subjects must have freedom to withdraw
10. Scientist may terminate study to reduce serious risk
Wilson Memorandum of 1953

The Nuremberg Code principles were incorporated into the Wilson Memorandum to the Secretaries of the Army, Navy and Air Force dated 26 Feb 1953.

* Use of these principles for non-clinical research related to nuclear, biological and chemical warfare defense was promoted before the research programs were planned and funded.
Army Directive CS-385 (1953) had Nuremberg Code Subject Protections

1. Retained Emphasis on "Voluntary Consent".
2. Added Consent must be in writing.
3. Jurisdiction & responsibility of secretary of military branch of P.I. conducting the study irrespective of source of subjects or personnel.
4. Required use of minimum number of subjects for valid outcome, no POWs as subjects.
5. Defined limiting characteristics of acceptable test agents and required additional safeguards for protection of volunteers.
Objectives of Multifaceted CD-22 were designed to determine:

- Human vulnerability in realistic BW scenarios.
- Effective prevention and treatment of BW casualties.
- Determination of minimal infective doses.
- Effectiveness of vaccines and drugs.
- Serological responses to infections, and.
- Clinical effects of various doses of infectious agents.
The CD-22 program focused on Human responses to prototypes:

Q fever and Tularemia were regarded by CES of AFEB as acceptable prototypical BW agents for testing in Humans that satisfied limiting characteristics* of low lethality, no serious chronicity anticipated, effective therapy available and there was adequate animal experimental data on safety and protective efficacy *[also described in cs-385].
USAMU was created to develop the means to diagnose, treat and prevent diseases caused by biological warfare agents. Approval of the cs-385 directive for ethical operation, plans for organization of the institute, preparation of protocols and initiation of the first human studies took place within 3-6 months of its creation.
October 1954 Colonel Tigertt contacted Dr. Theodore R. Flaiz of Seventh Day Adventist General Conference about seeking 1A-O SDA volunteer subjects. General Conference of the SDA Church approved recruitment of drafted SDA volunteer subjects into Operation Whitecoat program.
Operation Whitecoat Volunteers were Seventh Day Adventist “Conscientious Objectors” recruited from Medic Training school at Fort Sam Houston.

Between 1954 and 1973 2,300 Seventh Day Adventist participants of Operation Whitecoat served at Fort Detrick and associated locations.
Protocol Review during Operation Whitecoat

- Medical investigator prepares protocol.
- Reviewed for approval at a “Protocol Meeting” attended by Commander, Scientific Advisor, and the Research Division Chiefs.
- Approved protocols forwarded to HQDA (SGRD-DR) for further approval. This could entail review by CES of AFEB (before 1962) or HSRRB (after 1962 *).
- When final approval is given, Whitecoat volunteers are briefed, attend a project interview, and informed consent documents are signed after at least 24 hours have passed.

*AR 70-25 published in 1962 was identical to cs-385.
Review and Approval Process

USAMU 1955-73 vs USAMRIID

- **1955 – 73** USAMU Protocol Meeting Minutes were one page long with only one sentence for the committee decision. Issues were not documented.

- **1976** – USAMRIID IRB Minutes 5 pages long, 4 of which were Q&A that documented issues.

- **Presently** – USAMRIID IRB Minutes are > 14 pages long with 2 pages of narrative summary, 2.5 pages of Q&A per protocol with decision plus 9 pages of expedite approval ratifications, continuing review and SAE discussion.
Protocol Briefing
Operation Whitecoat served as a model of the ethical use of human subjects in research. The three step process of informed consent - by which research subjects become familiar with the purpose of a study in order to understand the risks and potential benefits involved before agreeing to participate - was successfully implemented from the program’s inception. The soldiers were not required to participate in any of the studies, only to be present for briefings by principal investigators seeking volunteers. Two more steps occurred before subjects were asked to consent. About 20 percent of the men did not participate in any studies during their tenure at Fort Detrick.
Vaccines that were tested under approved clinical protocols included those for Q fever, Tularemia, Yellow Fever, Eastern Western and Venezuelan equine encephalitis (EEE, WEE & VEE), Hepatitis, Plague and Rift Valley fever.
Aerosol Efficacy Studies in 8 Ball

Q-fever and Tularemia were approved for these studies because safety criteria were met and cure was assured.
In addition to the advances made in vaccine and drug development, Whitecoat volunteers contributed to a better understanding of the signs, symptoms, and clinical diagnostic parameters in human disease associated with Q-fever, Tularemia, Sandfly fever, and staphylococcal enterotoxins.
Volunteer from the Aerosol Q-fever Study at Dugway Proving Grounds

Many of the subjects fell violently ill, but none died.

Another Q fever study took place in the Utah desert, to simulate germs being released under battlefield conditions.

"They put two of us at each station along with several monkeys and guinea pigs and mice and air sampling apparatus," said Merlin Neff, a volunteer.

He said he did not worry about the possibility of death. "You don't die when you're 20," said Neff.
"They knew that they were going to inhale a certain number of organisms, and that as soon as they became ill, they would be treated with appropriate antibiotics," said Dr. Peter Bartelloni, who was involved in the research.
Ethical Accomplishments: Operation Whitecoat

• Effectively Used Nuremberg Code Principles
• Created Effective Informed Consent Process
• Involved “Community” of the SDA Volunteers
• Local and Extramural Oversight / Monitoring
Biosafety invented at Camp Detrick before bioweapons developed
Medical Accomplishments: Operation Whitecoat

• Several vaccines used today by industry and laboratory workers were developed as a result of Operation Whitecoat.

• Licensed vaccines (approved by the Food and Drug Administration) include those for yellow fever, hepatitis, and plague.

• Investigational New Drug (IND) vaccines, used under approved clinical protocols for research immunization of laboratory personnel, include those for Venezuelan equine encephalitis (VEE), Rift Valley fever, Q fever, and tularemia.
Medical Accomplishments: Operation Whitecoat

- First Real Tests of Human Vulnerability and Protection Involved Whitecoat Volunteers
- Effective systems for biological hazard containment were developed and tested with participation of Whitecoat volunteers.
- in 1968 and 1969 many Whitecoat volunteers participated in the development of Rift Valley Fever Virus vaccine, NDBR 103 RVFV, was used routinely to immunize at risk workers in research laboratories at USAMRIID, CDC and Plum Island Animal Disease Laboratory.
Medical Accomplishments: Operation Whitecoat

• In 1977 a major outbreak of Rift Valley fever in Egypt involved up to 200,000 humans and virtually all the sheep caused 2,000 human deaths and enormous loss of sheep.

• Egypt and Israel found that our RVF vaccine was the only one that had been tested for safety in humans under an IND from the FDA.

• This was the same vaccine that had been tested in Operation Whitecoat Volunteers in 1968.
RVF Vaccine caused Peace to break out in the middle east

- Therefore, a little known benefit that Operation Whitecoat Volunteers provided was to enable peace between Egypt and Israel to “break out” because obtaining RVF Vaccine was an important bargaining chip to both parties.

- Emissaries from Egypt and Israel requested RVFV as Sadat & Begin met at Camp David.
Chief, Human Use and Ethics
US Army Medical Research Institute of Infectious Diseases
arthur.anderson@det.amedd.army.mil