50 Years of Ethical Human Subjects Research at Fort Detrick

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On 27 January 2005, the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID) celebrated its 35th anniversary since it was given this name. However, this milestone also marks 50 years of research to develop medical countermeasures for protecting military service members, a functionality that has held several names over the years since the early to mid 1950's. In order to carry out research related to determining human vulnerability to biological weapons, and whether prophylaxis or treatment might prevent casualties, the leaders and committees that considered this decided that to do this work it was necessary to create a medical research institute, staff it, equip it and create operational policies, and procedures to ensure that any outcome of this research would clearly be seen as meeting the ethical, legal and moral tenets of the Nuremberg Code.

The resulting plans that emanated from these meetings were written and submitted up the Army chain of command between April 1953 and January 1955 and the first series of human experiments carried out under a program called CD-22 (Camp Detrick – 22) took place on 25 January 1955. This author has extensively researched this history while being the POC for the President's Advisory Commission on Human Radiation Experiments and the President's Advisory Commission on Gulf War Veteran's Illness and has allowed our documents and records to be examined by ethicists and inspectors from outside DoD and it is they who concluded that the human subjects research that took place at CD-22; USAMU, and USAMRIID should be highlighted as "a program of human experimentation that is a moral model for all others, civilian and military."(from front flap of Undue Risk by Jonathan Moreno)

The Institute, which remains the nation's lead biodefense research laboratory, acquired its present name in 1969 as the United States was dismantling its offensive biological warfare (BW) research program at Fort Detrick. However, its roots extend back to 1955, when a research project called "CD-22" began.

CD-22 was the first study to be conducted under a unique program called "Operation Whitecoat." This program was designed to determine the extent to which humans are susceptible to infection with BW agents, in order to develop vaccines and treatments. In some studies, Army volunteers were exposed to actual diseases like Q fever and tularemia in order to understand how these illnesses affected the body. To protect the study participants, the project was carefully managed by the U.S. Army Medical Unit—the agency that later became USAMRIID—under the direction of the Army Surgeon General. Throughout the program's history, from 1954 to 1973, there were no fatalities and no long-term injuries among Whitecoat volunteers.

A Model of "Informed Consent"

Operation Whitecoat served as a model for the ethical use of human subjects in research according to Jonathan Moreno who reviewed the program while serving on the

President's Advisory Committee on Human Radiation Experiments. He has commented on the transparency and rigorous adherence to Nuremberg Code principles in his book, Undue Risk: Secret State Experiments In Humans. In particular, the three stage process of "informed consent"—by which research subjects become familiar with the purpose and scope of a study in order to understand the risks involved before agreeing to participate—was successfully implemented from the program's inception.

Each medical investigator prepared a protocol that was extensively reviewed and modified to comply with each of the 10 ethical principles of the Nuremberg Code. When the committee determined that ethical requirements and scientific validity were assured, it was approved by Army officials. Next, potential volunteers were briefed as a group on the approved protocol and attended a project interview with the scientist where they could ask questions about the study. Informed consent documents would be signed after an obligatory waiting period that ranged from 24 hours to 4 weeks, depending on the presumed risks of the study. The volunteer was encouraged to discuss the study with family members, clergy and his personal physician before making a final decision.

By allowing sufficient time and opportunity for the risks, conduct and potential benefits of the study to be understood, this three-stage informed consent process assured that participation was truly voluntary. Whitecoat soldiers were not required to participate in any of the studies, only to be present for protocol briefings. In fact, about 20 percent of the men did not participate in any studies during their tenure at Fort Detrick. Even 80 percent participation might seem excessive except for the fact that those who came to Fort Detrick as Whitecoat soldiers had been recruited from a much larger pool of potential participants at the AMEDD Center and School because these men found the possibility of participating in military medical research agreeable in principle and analogous to the kinds of sacrifices soldiers make while serving in the armed forces.

Operation Whitecoat volunteers largely consisted of Seventh-Day Adventists, who were trained as medics but whose religious convictions forbade combat. Under an agreement between the Army and church leaders, about 2,300 of these men fulfilled their military obligation by electing to serve with Operation Whitecoat. The program itself was never secret, although some of the volunteers held jobs elsewhere at Fort Detrick where their work was secret.

In total, about 150 studies of the diagnosis, prevention, and treatment of various diseases were completed during the Whitecoat years. The protocols under which volunteers were exposed to disease-causing agents primarily included Q fever and tularemia infection, immunity and drug therapy studies. Later studies of staphylococcal enterotoxins were included among the high risk exposures. Whitecoat volunteers also participated in safety and immunogenicity studies of inactivated or attenuated vaccines designed for protection against Venezuelan equine encephalitis (VEE), plague, tularemia, Q fever, Rocky Mountain spotted fever and Rift Valley fever.

Q Fever and the "Eight Ball"

The first Whitecoat study, CD-22, was conducted using Coxiella burnetti, the pathogen that causes Q fever. It was regarded as acceptable to use in human studies for two reasons: its severity could be controlled with careful metering of the dose, and it responded rapidly to treatment with antibiotics. But before human volunteers could be exposed, phase I animal studies were conducted to gather data on safety and protective efficacy of the Q fever vaccine.

During the President's advisory committee on human radiation experiments and the President's committee on gulf war veteran's illness, I had the opportunity to extensively review the Operation Whitecoat records, and I have conducted interviews with many of the volunteers and investigators involved in the program. These people were dedicated to making sure that no one would be harmed. They clearly understood both the danger and the significance of embarking on this kind of experiment.

On January 25, 1955, the first Whitecoat volunteers were exposed with the use of the one-million-liter sphere commonly known as the "Eight Ball." This research device, which is still standing at Fort Detrick, was designed to allow simultaneous exposure of humans and laboratory animals to carefully controlled numbers of organisms by the aerosol, or inhalation, route.

Over the next two months, the minimal infectious dosage to be employed in human field trials was determined, as was the effectiveness of the Q fever vaccine in protecting volunteers exposed under carefully controlled laboratory conditions using a cloud chamber. After completion of this second phase of the study, preparation for phases III and IV was initiated. Phase III was a field study using animals, while phase IV would expose humans to a Q fever aerosol under field conditions that mimicked a biological warfare event. These studies were conducted at Dugway Proving Ground, Utah.

Benefits of Whitecoat Research

Several vaccines were developed as a result of Operation Whitecoat, according to project records. Many of these vaccines are used today by industry and laboratory workers, including USAMRIID personnel who receive special immunizations to work in Biosafety Level 3 containment laboratories. Licensed vaccines (approved by the Food and Drug Administration) include those for yellow fever and hepatitis. Investigational New Drug (IND) vaccines, used under approved clinical protocols for research or immunization of laboratory personnel, include those for Q fever, Venezuelan equine encephalitis (VEE), Rift Valley fever, and tularemia. In addition to the advances made in vaccine development, Operation Whitecoat contributed to a better understanding of the signs, symptoms, and clinical parameters of biological warfare pathogens in human disease.

Research conducted during the Whitecoat years at Fort Detrick also contributed to the development of equipment and procedures that established the standard for laboratory biosafety throughout the world. Biological safety cabinets with laminar flow hoods,

"hot suites" with differential air pressure to contain pathogens, decontamination procedures, prototype fermentors, incubators, refrigerated centrifuges, particle sizers, and various other types of specially fabricated laboratory equipment provided enormous value to the scientific community and to the pharmaceutical industry.

Many of the same techniques and systems developed to ensure worker safety while handling hazardous materials are in use today to sustain life in patients with immune deficiencies or immunosuppression. This includes burn patients, AIDS patients, transplant recipients and people with primary immunodeficiency, such as the famous case of the "boy in a bubble."

Operation Whitecoat ended in 1973, when the draft was eliminated, but the need to progress in development of medical countermeasures resulted in establishment of the Medical Research Volunteer Subject (MRVS) program during the period of the "All Volunteer Army." Essentially, this program was identical to Operation Whitecoat in that the MRVS were soldier trainees in 91B Combat Medic training school at Fort Sam Houston, Texas, when they were recruited to serve. Unlike the Whitecoats, the MRVS were not Seventh-Day Adventists, nor were they conscientious objectors subject to the draft. The MRVS program continued under Institutional Review Board oversight in 1975 after the USAMRIID Human Use Committee was created according to new federal and DoD requirements that were implemented in 1974.

Beginning with the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research that was appointed on 12 July 1974 by the National Research Act (Public Law 93-348) the USAMRIID Human Use Committee continued to stay abreast of progressive changes and improvement in human subject protections through to the present. The National Commission identified the known basic ethical principles for human subjects research and published their consensus guidelines as a document now known as the Belmont Report but which bore the title, "Ethical Principles and Guidelines for the Protection of Human Subjects of Research, Report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research." The Belmont report subsequently led to Health and Human Services regulation 45 CFR 46 in 1983 which is now referred to as the Common Rule. In 1997 DoD was one of 17 Federal Agencies who agreed to follow the common rule in any research involving human subjects. Prior to passage of the Common Rule, The Army followed AR 70-25 (first published as a directive, cs-385 on 30 June 1953) which incorporated the Nuremberg Code principles as guidance for ethical research involving human subjects. AR 70-25 was published 26 March 1962.

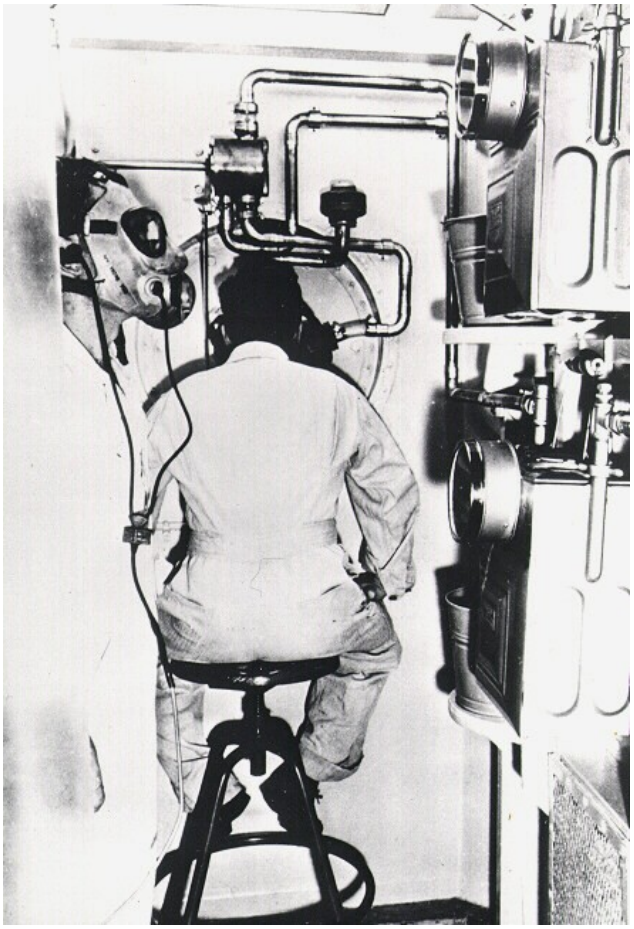
USAMRIID physicians and IRB regulators continue to look after the welfare of present and former research participants. For example, periodic long-term follow-up studies have been conducted to assure that former volunteers have remained healthy as the years passed since their participation. One major study, conducted by White et al, was published in 1974. Most recently, COL Phillip R. Pittman, M.D., chief of USAMRIID's Division of Medicine, completed a long-term follow-up study of Fort Detrick workers who received multiple immunizations to protect them from the risk of

laboratory acquired infections. That study also was extended to Operation Whitecoat volunteers, whose immunization histories usually were more limited to the two- or three-year period of their assignment to Fort Detrick between 20 and 40 years ago.

“As the National Interagency Biodefense Campus gets underway,” Anderson commented, “USAMRIID is well positioned to continue to be a leader in the capability to perform ethical and scientifically valid research involving human subjects. In this age of bioterrorism, our research will benefit warfighters and civilians alike.”

The National Interagency Biodefense Campus is an area at Fort Detrick where federal agencies will co-locate laboratories that support the nation’s Biodefense research program. As currently planned, the campus will include USAMRIID as well as the National Institute of Allergy and Infectious Diseases, The U.S. Department of Agriculture and the Department of Homeland Security.

Figures:



The one-million-liter test sphere, nicknamed the “Eight Ball,” was a cloud chamber used to study static microbial aerosols. During Operation Whitecoat, the volunteers breathed metered aerosols of Q fever or tularemia organisms through ports along the perimeter of the sphere.

This photo shows a volunteer seated with his face in a rubber mask at one of the ports. The individual in the biohazard suit to his left is a medic who was there to assist the subject and to respond to any emergency if it occurred during the exposure.

These kinds of studies were used first to determine safe dosages for initiation of infection and for subsequent studies of efficacy of vaccines or therapeutic drugs.

The U.S. Army Medical Unit later became USAMRIID

Since the Operation Whitecoat volunteers had all been trained as medics prior to assignment to Fort Detrick, many of them participated as clinical clerks and phlebotomists (wearing white coats) during one study and then as subjects (wearing bathrobes) during another.