

Biodefense: Research Methodology And Animal Models CRC Press (2006) Chapter 3, Pp 25-40. ISBN: 0849328365 James R. Swearngen (Editor). Author's version with Pictures.

3 Scientific and Ethical Importance of Animal Models in Biodefense Research

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Introduction:Contagion and catastrophic illnesses have affected the outcome of wars throughout history. Military officers have duties to protect their soldiers from becoming disease casualties, conserve the fighting strength and assure success of the mission. Discharging those duties requires more than site sanitation and encouraging personal cleanliness. Armies need to have, and should have at their disposal, the best available vaccines and medicines directed against specific disease hazards. The ability to provide procedures, remedies, antidotes, and medical countermeasures has been almost as important as good military training and advanced weaponry in the success of military operations. Decisions to institute a new practice of medicine, use a vaccine or adapt the use of a drug to protect soldiers from disease, often was arbitrary and fraught with risks. Applying new forms of protection from disease was often made compulsory by commanders because military doctrine recognizes the interdependence of soldiers to each other for safety and support and requires that all participate or the mutual support chain might break. This broadly utilitarian ethic of involuntary vaccination or treatment has been critical to protecting soldiers facing battlefield biological hazards during the American war for independence and throughout successive conflicts inside and outside our hemisphere until the recent past [1]. In order to adequately address the topic of the importance of animal models of human disease in biodefense research, we have chosen to trace development of military medical countermeasures from the time of George Washington to the present with an eye on the ethical, moral and legal tensions that led to the recent implementation of an animal efficacy rule by the Federal Food and Drug Administration (FDA).

Smallpox and George Washington's Soldiers: Smallpox was epidemic during the French and Indian War, and outbreaks continued to plague George Washington's army during the revolutionary war. When George Washington ordered his entire army variolated, there was no study carried out in animals to determine if it was safe and effective for him to do so. The use of animals in medical research wasn't a practice until late in the 19th century. However, this anecdote about Washington's

lucky decision is significant for showing that commanders of armies, with limited available information, need to be able to have the discretionary authority to make health and safety decisions on behalf of soldiers in wartime.



Variolation had become accepted among European aristocrats who believed a “mild case” of smallpox would grant immunity. The method used was not vaccination as we know it today. It involved inoculating a person with smallpox scabs obtained from someone who had survived the disease. Many recipients suffered only mild illness, but there was a risk that it might cause serious illness or death in some. George Washington ordered all his soldiers variolated without knowing with certainty that they would be protected. His order rendered the men simultaneously the subjects of “research” and recipients of benefit, if they survived their deliberately induced disease outbreak. Variolation caused several deaths among his soldiers and members of the surrounding community, and Washington’s decision to make it involuntary among his troops became very controversial, especially among the anti-vaccination society in England (see cartoon above). However, his choice protected his troops from smallpox and this was critical to America securing independence from England. In this case the end did justify the means. Indeed, the importance of smallpox and its mitigation to outcome of the revolutionary war figures prominently in Hugh Thursfield’s, “Smallpox in the American War of Independence” and Elizabeth Fenn’s, “Pox Americana” [2, 3]. The negative outcomes of variolation and the need to provide continuous and sustainable progress in providing the means to protect the health and safety of soldiers in any future battlefield in all likelihood led Congress to create the Army Medical Department in the spring of 1818.

Yellow fever and the Spanish American War: The story about the discoverers of mosquito transmission of yellow fever is important to describe because it is a milestone leading up to the need for using animals to prove efficacy of medical countermeasures against serious biological hazards [4 – 6]. The story involves numerous connections with William Welch and William Osler, two of the first four

physician professors of the new Johns Hopkins Hospital, who would become important advocates for medical ethics and use of animals in research.

Yellow fever epidemics frequently broke out in the Caribbean and southern United States, and it especially plagued American soldiers during the Spanish American War. Outbreaks were so prevalent that President Roosevelt asked Army Surgeon General George M. Sternberg to create a commission to study yellow fever in Cuba. He selected Walter Reed and James Carroll as first and second officers in command of the Yellow Fever Commission. Reed and Carroll were highly regarded by Drs. Osler and Welch at Johns Hopkins, who also recommended that Jesse Lazear, the Hopkins clinical laboratory officer, be added to the Commission. Sternberg, Reed and Carroll received research training in William Welch's laboratory at the Johns Hopkins Hospital. Sternberg was the first bacteriologist trained in William Welch's laboratory in the late 1880s before being appointed Army Surgeon General.



Reed, standing second from right, Volunteers, and others at Camp Lazear, 1901

Major Reed's research into the cause and transmission of yellow fever in Cuba did not involve experiments in animals primarily because there was confusion about what kind of agent actually was the cause of the disease. Some felt the disease spread through the air in fomites from the bedding of previously ill patients. Others, Sternberg, Reed and Carroll included, thought the disease was caused by a new form of bacterium that needed to be discovered. Several of the members of the commission, especially Aristides Agramonte and Jesse W. Lazear, had other reasons to include still unknown causes for the disease. Agramonte proved that patients suffering from yellow fever were not infected with a bacterium widely believed to be the cause. Lazear, who had been a student of malaria and knew about mosquito transmission, allowed himself to be bitten by a mosquito that had been feeding on a patient suffering from yellow fever. Lazear died from the illness resulting from this mosquito bite, thus fixing mosquito transmission of yellow fever as the leading hypothesis [6]. Human volunteers were

recruited from among Major Reed's military detachment and Cuban civilians also came forward and volunteered. Walter Reed's use of volunteer contracts that spelled out the full extent of risk and possible benefits of participation in this research is regarded as an ethics milestone by introducing to medicine the concept of voluntary consent. The research risks they accepted enabled the discovery that yellow fever was transmitted by mosquitoes. This knowledge contributed immeasurably to public health because the spread of the disease could be prevented by mosquito control [4 – 6].

Experimental use of animals was becoming popular in the laboratories of William Osler, William Welch and other physician scientists of the Johns Hopkins Hospital. Their approach would revolutionize medicine by demonstrating that experimental evidence could be obtained to support the scientific practice of medicine. Rather than being immediately recognized by the public as a good development, Walter Reed's experiments in humans and experimental use of animals for medical research attracted criticism by antivivisectionists who had become very influential in England and the U.S. during the early 1900's [4, 5].



In 1907, William Osler was invited to address the Congress of American Physicians and Surgeons about the evolution of the idea of experiment in medicine. Osler was a strong proponent of academic medicine and a well-respected medical philosopher. He had been busy testifying during the past several years in legislative forums in the U.S. and abroad about the value of research, because this was under attack by antivivisectionists [4]. This is what he said about the need for animal experimentation and also about the voluntary nature of the participation of soldiers in Walter Reed's yellow fever experiments:

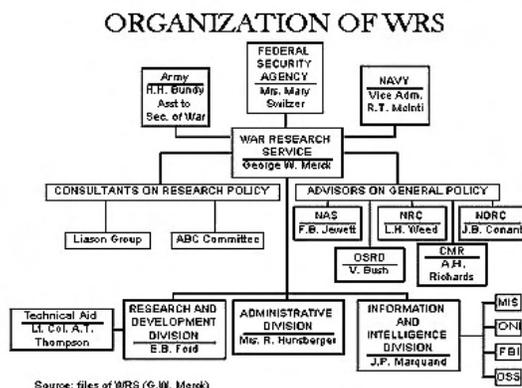
*“The limits of justifiable experimentation upon our fellow creatures are well and clearly defined. The final test of every new procedure, medical or surgical must be made on man, **but never before it has been tried on animals**.....*

*For man **absolute safety and full consent** are the conditions which make such tests allowable. We have no right to use patients entrusted to our care for the purpose of experimentation **unless direct benefit to the individual is likely to follow**. Once this limit is transgressed the sacred cord which binds physician and patient snaps instantly” [4].*

When Osler testified before the U.S. Congress and British Parliament to defend medical research from being blocked by legislation triggered by the activities of antivivisectionists, his presentations often paired the medical fruits of research conducted with human volunteers with the benefits of testing drugs and vaccines in animals [5]. This may have assured that these paired concepts would endure. Thus, at the dawn of the 20th century medicine had arrived at two truths that would help define what was required for research with humans to be regarded as ethical.

The first was the need for experiments in animals to assess the risk or validate the disease causality before involving human subjects in tests. The second was that participation of human subjects in tests of efficacy must be voluntary, and can take place only after human subjects are told the risks and benefits of participation in the research.

World War II and the Threat of Biowarfare: During the first third of the 20th century, research with animals was becoming an important vehicle for scientific biomedical discovery across the globe. Animal experimentation would become even more important as World War II approached and the U.S. was not prepared to deal with a biological warfare threat. Facing the emergency of war in 1941, Secretary of War Henry L. Stimson asked the president of the National Academy of Sciences, Frank B. Jewett, to appoint a committee that would recommend a course of action “*because of the dangers that might confront this country from potential enemies employing what may be broadly described as biological warfare* [7].” This committee, chaired by Edwin B. Fred, reported to Secretary Stimson that, “*There is but one logical course to pursue, namely, to study the possibilities of such warfare from every angle, make every preparation for reducing its effectiveness, and thereby reduce the likelihood of its use* [7].”



To accelerate a development of programs to respond to the biological warfare threat, the War Research Service (WRS) was established, under George W. Merck Jr. inside the civilian Federal Security Agency (FSA) to begin development of the US Biological Warfare program with offensive and defensive objectives. The first major objective of WRS was to develop defensive measures against possible biological weapons attack [8]. Under the guidance of Ira Baldwin the Army Chemical Warfare Service (CWS) commenced operation of large-scale research and development program, and the facility at Camp Detrick was the first of the laboratories and pilot plants to be constructed, starting in April 1943 [8, 9].

Most of the serious infectious diseases regarded as biological warfare threats were natural diseases of agricultural animals that could also cause devastating illness in humans. Indeed, one may make the argument that all serious infectious diseases come about by interaction of humans with animals, even those diseases with limited host-range specificity [10]. The risk that humans might die due to infection or intoxication by biological threat agents was so great that a major commitment to testing in animals was incorporated into program objectives and the design of the Camp Detrick laboratories. Animal models of disease figured prominently in validating what could be learned about human disease diagnostics and medical countermeasures. These serious risks also prompted a major commitment to developing safe working environments, occupational health practices and on-site medical care in a station hospital to reduce the risk of injury or death to workers [9].

Animals stood in for humans in most of the offensive and defensive biological warfare research conducted at Camp Detrick during the war. In addition, research in animals was directed by prominent civilian medical researchers at universities, companies, and research institutes who received FSA grants after review by the WRS Committee on Medical Research. A list of persons directing specific contract protocols included eminent scientists, future Nobel Prize winners, and corporate leaders who shaped modern biology, pharmaceuticals, and medicine [8–14].

Any involvement of humans at Camp Detrick was limited to epidemiological studies of workers with occupational exposures seen in the dispensary or treated at the station hospital. One study involving human subjects was carried out so that data from animal models of aerosol exposure could accurately be extrapolated to humans. *Serratia marcescens* was used as a putatively non-pathogenic simulant in humans instead of the more hazardous pathogen that would be used for animal exposures [14]. Non-pathogenic simulants were used in model human aerosol exposures so that risks of harming human volunteers would be held at a minimum [11]. In contrast, the Nazi doctors who used holocaust victims and prisoners of war in research at concentration camps made no attempt to minimize risk because genocide was a major objective. The details of the immoral Nazi experiments became known to the world via the media and were further revealed at the War Crimes Tribunal held in Nuremberg at the end of WWII.

Dr. Andrew Ivy released to the American Medical Association (AMA) a draft of his list conditions required for research in healthy subjects to be regarded as ethical in December 1946, shortly before he left for Germany to participate in the Tribunal. He and Dr. Leo Alexander, the court's medical consultant, testified as to the ethical standards of medical practice and compiled for the Tribunal 10 conditions that must be met for research involving human subjects to be permissible [15]. This list of conditions, now referred to as The Nuremberg Code [16], included one describing the requirement for prior animal experimentation validating the possible risks and benefits of the research to be completed before humans would be involved.

In 1952, the Armed Forces Medical Policy Council (AFMPC) noted that tests at Fort Detrick with biological warfare simulants showed U.S. vulnerability to biological attack. Similar experiments with virulent disease agents in animal models attested to incapacitating and lethal effects of these agents when delivered as weapons [8, 15]. However, a long time had passed without any human testing and there was doubt among AFMPC members that extrapolation of animal data to humans was valid.

Human vulnerability to actual biological agents delivered under realistic scenarios was not known and human studies were strongly encouraged to prove that continuation of the biological warfare program was justified, but military medical scientists assigned to Fort Detrick were reluctant to pursue human testing without thorough discussion of the ethical, moral and legal basis for such studies [17 – 19]. A memorandum dealing with human experimentation was issued to the military branches by Secretary of Defense Charles Wilson on 26 February 1953. Referred to as the Wilson memorandum, this memorandum adopted the 10 principles of the Nuremberg Code including the need for prior animal experimentation as official guidance promulgating ethical research involving human subjects [20].

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DEPARTMENT OF THE ARMY
Office of the Chief of Staff
Washington 25, D. C.

CS: 385 (30 Jun 53) 30 June 1953

MEMORANDUM FROM: ASSISTANT CHIEF OF STAFF, G-4
TO: ASSISTANT CHIEF OF STAFF, G-4
THE SURGEON GENERAL

SUBJECT: Use of Volunteers in Research
Agreement ABC

1. This directive prescribes policies and procedures governing the use of volunteers in research in defense against atomic, biological and chemical warfare. The purpose of this research is to permit a realistic evaluation and/or development of effective preventive measures of defense against atomic, biological or chemical agents.

2. Certain basic principles must be observed in order to satisfy moral, ethical and legal concepts. These basic principles are:

- The voluntary consent of the human subject is absolutely essential.
 - This means that the person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, over-reaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and unlightened decision. This latter element requires that before the acceptance of an affirmative decision by the experimental subject there should be made known to him the nature, duration, and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonably to be expected; and the effects upon his health or person which may possibly come from his participation in the experiment.
 - The consent of the human subject shall be in writing, his signature shall be affixed to a written instrument setting forth substantially the aforementioned requirements and shall be signed in the presence of at least one witness who shall attest to such signature in writing.
 - In experiments where personnel from more than one Service are involved, the Secretary of the Service which is exercising primary responsibility for conducting the experiment is designated to prepare such an instrument and coordinate it for use by all the Services having human volunteers involved in the experiment.
- The duty and responsibility for ascertaining the quality of the consent rests upon each individual who initiates, directs or manages the experiment. It is a personal duty and responsibility which may not be delegated to another with impunity.
 - The experiment should be such as to yield fruitful results for the good of society, unreplicable by other methods or means of study, and not random and unnecessary in nature.
 - The number of volunteers used shall be kept at a minimum consistent with item b. above.
 - The experiment should be so designed and based on the results of animal experimentation and a knowledge of the natural history of the disease or other problem under study that the anticipated results will justify the performance of the experiment.
 - The experiment should be so conducted as to avoid all unnecessary physical and mental suffering and injury.
 - No experiment should be conducted where there is a prior reason to believe that death or disabling injury will occur.
 - The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.
 - Proper preparations should be made and adequate facilities provided to protect the experimental subject against even remote possibilities of injury, disability, or death.
 - The experiment should be conducted only by scientifically qualified persons. The highest degree of skill and care should be required through all stages of the experiment of those who conduct or engage in the experiment.
 - During the course of the experiment the human subject should be at liberty to bring the experiment to an end if he has reached the physical or mental state where continuation of the experiment seems to him to be impossible.
 - During the course of the experiment the scientist in charge must be prepared to terminate the experiment at any stage, if he has probable cause to believe, in the exercise of the good faith, superior skill and careful judgment required of him that a continuation of the experiment is likely to result in injury, disability, or death to the experimental subject.

The consequences of the Nazi war crimes and availability of the code principles motivated military medical researchers to find the moral high ground while developing medical countermeasures against nuclear, biological and chemical agents during the Cold War [9, 15]. Military physicians assigned to develop medical countermeasures against biological weapons were reluctant to put humans at risk in experiments without first obtaining sufficient information from other sources that could be used to mitigate the danger. Responding to the need to conduct human studies, ad hoc meetings of scientists, Armed Forces Epidemiology Board advisors and military leaders took place at Fort Detrick during the spring of 1953 [18, 19]. The depth and breadth of these discussions resulted in design of several prototype research protocols and creation of an institute heavily invested in animal experimentation aimed at modeling human infectious diseases so that pathogenesis and response to vaccines and therapeutics could be studied. The Army Chief of Staff issued on 30 June 1953 a directive (cs-385) that was derived from the Wilson memorandum, which contained additional safeguards proposed by the scientists who had attended the ad hoc meetings [21].

Under cs-385, the only studies of human infections and efficacy of vaccines in

protection or efficacy of drugs in treatment of a biological warfare agent that scientists felt were ethical were the diseases Q-fever (*Coxiella burnettii*) and tularemia (*Francisella tularensis*). These disease agents were less likely to result in mortality by limiting infectious dose, substantial information on disease pathogenesis and vaccine efficacy in animals was already known and there were drugs available that could be used to quickly end the infections for the safety of the volunteers. This left all of the other agents on the biological warfare threat list ineligible for testing in humans on the grounds that to do so would be immoral.

Vaccines or drugs against most of the agents on the threat list were tested for efficacy in animal challenge models whose responses could be compared to the responses of humans tested in the safety trials that included assessment of markers of immunity or drug metabolism and kinetics. Except for tularemia and Q-fever which were regarded as ethically acceptable, no threat agent challenges to prove efficacy of medical countermeasures were performed in humans.

The idea that medical countermeasures against hazardous viruses, bacteria and toxins would be tested for prophylactic or therapeutic efficacy in valid animal models was intrinsic to all military research programs for developing products that would be used in humans. The investigational products that showed efficacy in animals were tested in humans for safety and if determined to be safe were used to protect or treat workers after approval by the appropriate members of the chain of command up to the most senior level as defined in regulations. This could be the Army Surgeon General or, as was required in the 1940s, the secretary of the military service sponsoring the study depending on the level of risk and/or the military organization structure at the time the study was conducted.



Operation Whitecoat involved Human Testing: Human research volunteers were recruited from among Seventh Day Adventist conscientious objectors who were being trained as medics at Fort Sam Houston Texas. These men who were willing to serve at Fort Detrick as non-combatants, participated as volunteers in reviewed and approved studies testing human vulnerability to biological warfare agents in realistic scenarios. Multiple new products for defense against biological warfare and hazardous infectious diseases were developed and tested for human safety and for

surrogate markers of efficacy with their participation.

Using animals as surrogates for humans in efficacy trials came under regulatory pressures in the late 1950s. The FDA strengthened their drug regulations because of new drugs that were being introduced that either were not effective or had serious but undiscovered side effects. Thalidomide, a new sedative drug that was already introduced in Europe, was blocked by an FDA reviewer because there was evidence that its use was associated with fetal limb abnormalities. U.S. Senate hearings followed and in 1962, the so-called "Kefauver-Harris Amendments" to the Food, Drug and Cosmetic (F, D & C) Act were passed into law to ensure drug efficacy and greater drug safety. For the first time, drug manufacturers were required to prove to FDA the human clinical efficacy of their products before marketing approval would be granted [22, 23].

The Army replaced cs-385, which had guided the ethical use of humans in drug and vaccine research, with a more widely distributed Army Regulation 70-25 (AR 70-25) on 26 March 1962 [24]. The new FDA requirements to prove human clinical efficacy caused the Army to introduce the following exemptions in paragraph 3 of the new AR 70-25:

3. The following categories of activities and investigative programs are exempt from the provisions of these regulations:
 - a. Research and non-research programs, tasks, and tests which may involve inherent occupational hazards to health or exposure of personnel to potentially hazardous situations encountered as part of training or other normal duties, e.g., flight training, jump training, marksmanship training, ranger training, fire drills, gas drills, and handling of explosives.
 - b. That portion of human factors research which involves normal training or other military duties as part of an experiment, wherein disclosure of experimental conditions to participating personnel would reveal the artificial nature of such conditions and defeat the purpose of the investigation.
 - c. Ethical medical and clinical investigations involving the basic disease process or new treatment procedures conducted by the Army Medical Service for the benefit of patients. *(This exemption permitted use of FDA – unapproved products in clinical studies, force health protection, experimental infections and vaccine challenge studies).*

Ethical Dilemma of Better FDA Regulation: The terms “safety and efficacy” may be deceiving with reference to the requirements for approval of drugs, biologics and medical devices by the FDA. It is hard to imagine circumstances where insisting on proving “safety and efficacy” while developing medical countermeasures might cause serious harm or death to participants in research so focused. Most drugs and devices being tested in healthcare facilities are aimed at finding a treatment for a disease that presently afflicts the subject. While it is possible that a new drug or device might worsen the patient’s condition, the chance that it may result in clinical improvement is usually considered a reasonable justification to proceed with the study. Pivotal efficacy trials usually involve large numbers of subjects, some of whom receive active drug or vaccine, while others receive placebo as controls. Then, all are exposed to the disease-causing agent. In the case of testing medical countermeasures against biological warfare agents, it would be expected that a high proportion of those receiving only placebo would likely die if the test was for a drug or vaccine against anthrax or chemical nerve agents, a circumstance that clearly is immoral.

Having recognized that the 1962 F, D & C amendments now required that there be substantial evidence of human clinical efficacy, a requirement that would perilously put humans in harms way, the Department of Defense (DoD) negotiated a memorandum of understanding (MOU) with the FDA in 1964 so that it could continue to provide its troops with the best available products for protection or treatment of biowarfare hazards irrespective of their FDA approval status [25]. This MOU was important because DoD had no intention to conduct hazardous challenge studies in humans to prove human clinical efficacy. The MOU allowed DoD to continue to approve its own use of these products without having to comply with FDA requirements for providing investigational products to soldiers under a clinical trial format when this would confuse the intent to benefit in emergency operations with an unintended objective,, that of conducting an experiment for marketing approval [24].

This MOU permitted DoD to use investigational products in classified clinical investigations or non-classified research programs. The term “non-classified research programs” included “ethical medical and clinical investigations involving the basic disease process or new treatment procedures conducted by the Army Medical Service for the benefit of patients [24].” Clinical research with drugs and biologics required submission of an Investigational New Drug (IND) application to the FDA or Public Health Service. Because of “intent to benefit,” the Special Immunizations Program, which provided laboratory workers with investigational vaccines intended to provide additional protections above environmental safety considerations, were also permitted by this MOU [25].

During the war in Viet Nam, an investigational plague vaccine which had been tested for safety in human volunteers and for efficacy in experimental animals was given to troops without investigational labels or data collection requirements [8, 19]. Plague was a serious battlefield hazard, and epidemiological data subsequently showed that the plague vaccine provided a benefit and reduced the incidence of plague in vaccine recipients. Under the MOU these data were submitted to the Public Health Service which subsequently approved the vaccine.

In 1972 congress added Title 10 US Code 980 to the defense appropriation bill [26]. This public law mandates that informed consent must be obtained from subjects or their guardians, irrespective of levels of risk, for all research including that intended to benefit the patient. The authority for regulating biologics including serums, vaccines, and blood products was transferred from the Public Health Service/National Institutes of Health to the FDA in 1972 [23].

And, also in 1972, the U.S. Public Health Service syphilis study created a major public controversy. This was a study of indigent black men from Tuskegee, Alabama who were prevented from receiving treatment so the natural course of syphilis could be studied. It ran from 1932 until it was exposed in 1972. Irrespective of the ability to cure syphilis with penicillin, the subjects were never told about it nor were they treated after penicillin became available. These revelations led to passage of the National Research Act of 1974 [27] which added additional restrictions and oversight to research involving human subjects.

Among the new requirements of the National Research Act were (a) the requirement for informed consent and (b) the need for a review committee, knowledgeable in the basic ethical principles of beneficence, respect for persons and justice, to assess the risk-benefit criteria, and the appropriateness of research involving human subjects.

This committee, referred to as an institutional review board (IRB) was expected to be independent of the chain of command so that no conflict of interest would exist between the need to develop a product and the need to protect the rights and welfare of the human volunteer subjects. The act provided no guidance on IRB structure or operation of the IRB, however. The Army Regulation 70-25 already specified these conditions so no specific changes were needed at this time other than consideration of moving the IRB function out of the commander's office and into a more independent forum.

The Army revised AR70-25 in 1974 to account for a reorganization within DoD that resulted in transfer of final approval authority from the Chief of Research, Development, Testing and Evaluation (RDTE) to the Surgeon General of the Army Medical Department (AMEDD) for all research using volunteers [28]. It distinguished between research conducted in Army Medical Services and that conducted by Army Medical Research and Development Command, and it identified the requirements for use of active duty military personnel as volunteers.

Although it does not appear that these changes in the regulation were associated with either of the previous regulatory developments, it did necessitate negotiating a new MOU with the FDA because of the transfer of authority [29]. The FDA had also undergone changes during the period between the 1964 MOU and the MOU signed with DoD on 24 October 1974 so it included additional FDA review requirements [23]. Again, the additional restrictions provided improved protections for human volunteer subjects who participated in research, but the restrictions would also prevent use by the military of well-studied, potentially beneficial products that had not completed all the tests needed for FDA approval unless agreed to in the MOU.

The 1974 MOU [29] restricted DOD authority to use investigational products for force health protection. Classified clinical investigations could be exempted from the F, D and C Act. However, both DOD and FDA would need to review and approve use of products in military personnel that were not approved by the FDA but were "tested under IND regulations sufficiently to establish with reasonable certainty their safety and efficacy [29]." All other clinical testing of investigational drugs sponsored or conducted by the DoD required submission of an IND application to the FDA.

The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, created by the National Research Act of 1974, published its report entitled Ethical Principles and Guidelines for the Protection of Human Subjects of Research (popularly referred to as the Belmont Report) on 18 April 1979 [30]. And, in 1981 The Department of Health and Human Services (DHHS) and FDA published convergent regulations based on the Belmont principles, adding additional restrictions to what may be regarded as research versus treatment and use of unapproved drugs and biologics [31, 32].

Furthermore, The FDA was undergoing a reorganization during the late 1980's that would vastly increase its position in a department whose director, the Secretary of Health and Human Services, held a cabinet office [22]. This change necessitated that DoD negotiate a new MOU with FDA if it wished to continue to provide unapproved drugs or vaccines for force health protection or medical use under an intent to benefit. The new MOU between DoD and FDA that was signed 21 May 1987 removed the discretionary privileges that enabled DoD to use FDA unapproved products in wartime or to protect at-risk personnel who worked in hazardous environments [33]. DoD no

longer had FDA permitted authority to approve use of drugs, vaccines and devices that remained in IND/IDE status.

The 1987 MOU is still in effect. This MOU requires FDA review for the use of any IND by the DoD (i.e., no exemptions from the F, D and C Act, including the requirement to provide substantial evidence of human clinical efficacy). In the case of classified research, DoD must submit a “classified IND application or investigational device exemption (IDE) application” [33] for review and approval by FDA. FDA is responsible for having reviewers with the security clearance needed to assess these activities. It also ended exempt status for use of IND vaccines in the Special Immunization Program for vaccinating workers at-risk to occupational exposure to hazardous disease agents. The new MOU with the FDA required complete compliance with FDA regulations on products labeled investigational, i.e. investigational products may only be used in conjunction with IRB approved clinical trials. DoD could no longer exclude from FDA requirements products they wished to use in contingency situations or for force health protection.

These new changes occurred as the situation in the Persian Gulf heated up and it became clear that U.S. forces would be deployed against an enemy who had a large program for developing chemical and biological weapons and who had used such weapons on opposing factions within his own country. The U.S. preparations to enter Iraq during Desert Shield/Desert Storm produced a moral dichotomy because some of the medical countermeasures that might be used to protect or treat soldiers for chemical or biological hazards were still not approved by the FDA because of the lack of substantial evidence of human clinical efficacy. It was once possible for DoD to use intent as a means of determining how a product would be used and under what kind of restrictions. Was the intended use “research” or was it “intent to benefit?” The new MOU made the ability to use products labeled IND to benefit war fighters and laboratory personnel less clear.



A National Biodefense Program Produces an Ethical Dichotomy:

- Overarching **circumstances** may effect what kinds of actions ethical analyses may determine are preferred.
- Respect the rights and welfare of subjects who participate in **research** designed to discover, validate and gain FDA marketing approval for products to be used in prevention and treatment of possible bioterrorism casualties.
 - **Versus**
- Urgent **need to use** unapproved products reasonably thought to be beneficial for **protection** from - or immediate **treatment** of bioterrorism when there is an emergency and no approved alternatives are available.

It was expected that exploratory research with IND products to discover new treatment uses and to generate data requirements to apply for new drug marketing approval would continue to rigorously follow DoD and FDA requirements. But what if investigational status prevented life saving use of the only available product to protect against anticipated mass casualties produced by biological weapons? If drugs or vaccines still under IND status were needed for protecting or treating persons during a national emergency, they would have to be given according to research protocols. Creating the

pretense of experiment to get around the moratorium on use of unlicensed products seems disingenuous when the basis of the intent is really based on knowledge of human safety and animal efficacy of the product. Furthermore, the need to quickly provide prophylaxis or treatment of whole populations who could be suffering from nuclear, chemical, and biological injuries might require drastic emergency actions not anticipated by clinical trial protocols. The alternative choice of not providing soldiers prophylaxis or treatment because a product is not FDA approved was also an unsatisfactory solution.

Because of this situation, the Department of Defense decided to apply for a waiver from the FDA. The FDA grants waivers of certain requirements of its regulations usually because it is unfeasible or impracticable to comply. A waiver of the requirement for “informed consent” was requested and IND products that were the only drugs or vaccines developed to a degree that might enable DoD to conclude that it would be protective or beneficial could be used. However, this waiver removed an essential ethical principle. The principle of “respect for persons” respects a person’s self-determination and autonomy and is a component of his dignity. It is understood that an unconscious person in need of lifesaving treatment may be unable to give consent, in which case providing an IND drug or antidote to prevent death would be acceptable. The FDA regulations already had such an allowance but it limited its use to a small number of subjects or a single incident. In a military emergency, hundreds or thousands of subjects would need to receive the IND product, and that is not allowed by regulation. Through ethical analysis one could conclude that it should be allowed. But the FDA regulations are law, which is immutable. Given the decision to use Waiver of Informed Consent or not is a difficult choice [34 – 38].

There are other waivers that could have resolved this conflict without having to abandon an ethical principle for utility. At a symposium convened on 30 September 1988 at Fort Detrick by the Post Chaplain, the rhetorical question was asked, “Would it would ever be legal, moral or ethical to do a real test of the safety and effectiveness of an antidote developed to protect humans from a lethal nerve gas exposure [34, 35]?” Carol Levine, speaking as Executive Director of the Citizens Commission on AIDS for New York City and Managing Editor of *IRB: A Review of Human Subjects Research* gave a “yes or no” answer to the question of whether there are ethical exceptions for military medical research. Levels of risk and the voluntariness of participation affected which answer she would give. Further, she allowed that it would be easier to say “yes” if the difficult affirmative choice were made by “regulators” [34]. Richard Cooper, who had been the chief counsel for the FDA between 1977 and 1979, also struggled with these choices. However, he recommended choosing to request a waiver of the requirement to provide substantial evidence of human clinical efficacy over a waiver of informed consent, for reasons similar to what has been expressed earlier in this chapter [35]. In 1990, the DoD sent the U.S. military into the Persian Gulf having chosen a waiver of informed consent and over the first half of the 1990’s codified this in regulation [39-42].

DoD was one of the 17 federal departments & agencies that agreed to adopt the basic human subject protections of 45 CFR 46 referred to as the “Common Rule.” Thus, all federally sponsored research involving human subjects was now covered by a common set of policies, assurances and protections (DoD uses 32 CFR 219) The current version of AR 70-25, published 25 January 1990, already complied with the common rule [43].

Additional FDA enforcement laws enacted in 1993–2002 made compliance with FDA

IND and Good Clinical Practices (GCP) Act requirements during diagnosis, treatment or prophylaxis for emergencies related to domestic or biological warfare virtually impossible unless relief from these rules was obtained. Clearly, it was not possible to efficiently and effectively obtain FDA approval for important military medical countermeasures without relief from the additional requirements. It would be immoral to conduct valid challenge trials to prove human clinical efficacy needed for FDA approval, and it was also not feasible to fully comply with all the GCP requirements [34 -36]. There was no other choice but to resolve to comply with all of them to the best of their ability and use the IND products needed to protect soldiers in the battlefield [39 – 42].

Most of the IND products DoD may want to use in contingency situations were supported by a great deal of animal efficacy and human safety data, but could not be licensed until they also had substantial evidence of human clinical efficacy. These biological agents were hazardous and performing clinical challenge studies was certain to cause deaths. Thus, the F, D and C law required immoral efficacy studies in order to achieve licensure and relief from this requirement [37, 38, 44-46]. Fortunately, the argument was made that FDA approval on the basis of human safety and substantial evidence of efficacy in animal models might suffice in circumstances where it would be unfeasible or immoral to attempt to obtain substantial evidence of human clinical efficacy.

Mary Pendergast was the Deputy Commissioner of the FDA at the time the reconsideration of the DoD waiver of informed consent was coming up for review. At the time, she was also considering a new rule for allowing emergency medical device research for development of new lifesaving devices that would have to be tested in civilian emergency rooms. Memoranda submitted to the docket on reconsideration of the DoD waiver of informed consent included several that proposed an ethical construction that threaded its way between the need to prove safety and efficacy, and the need to provide lifesaving products for extremely hazardous conditions where it would be unfeasible or immoral to conduct human clinical efficacy trials [36-38, 44-46]. A draft animal efficacy rule was prepared by the FDA Commissioners office and had been published for public comment 2 years before the terrorist attacks of fall 2001. The FDA recognized the acute need for an “animal efficacy rule” that would help make certain essential new pharmaceutical products available much sooner. Those are products that, because of the very nature of what they are designed to treat, cannot be safely or ethically tested for effectiveness in humans [47].

Animal Efficacy Rule Remedy for Ethical – Legal Dilemma: The FDA amended its new drug and biological product regulations so that certain human drugs and biologics that are intended to reduce or prevent serious or life-threatening conditions may be approved for marketing based on evidence of effectiveness from appropriate animal studies when human efficacy studies are not ethical or feasible. The agency took this action because it recognized the need for adequate medical responses to protect or treat individuals exposed to lethal or permanently disabling toxic substances or organisms. This new rule, part of FDA's effort to help improve the nation's ability to respond to emergencies, including terrorist events, will apply when adequate and well-controlled clinical studies in humans cannot be ethically conducted because the studies would involve administering a potentially lethal or permanently disabling toxic substance or organism to healthy human volunteers.

Under this new rule, certain new drug and biological products used to reduce or prevent the toxicity of chemical, biological, radiological, or nuclear substances may be approved for use in humans based on evidence of effectiveness derived only from appropriate animal studies and any additional supporting data. Products evaluated for effectiveness under this rule will be evaluated for safety under preexisting requirements for establishing the safety of new drug and biological products. FDA proposed this new regulation October 5, 1999. The final rule was published in the *Federal Register* Friday, May 31, 2002 [43], and the rule took effect June 30, 2002. The advent of the animal efficacy rule brings to bear the importance of animals in finding safe and effective countermeasures to the myriad of toxic biological, chemical, radiological, or nuclear threats.

Using animal surrogates to prove clinical efficacy is not a perfect solution. At present it is the only ethical and moral solution in the case of drugs and vaccines aimed at mitigating biowarfare or bioterrorism threats. To improve the validity of animal efficacy studies as models of human clinical efficacy, it is important to be rigorous in searches for the most optimal model that accurately mimics human disease. It is also necessary to draw precise comparisons between immune responses and drug kinetics in the animal surrogate and analogous responses in patients who participate in product safety but not clinical efficacy studies. And finally, as drugs approved by the animal efficacy rule may still not be “proven” to be efficacious in humans, post-marketing epidemiological studies will be necessary (without full clinical trial interventions) to monitor outcomes.

With this new opportunity to advance human and animal health and protect our nation, we also have to recognize that a great responsibility comes with it. That responsibility includes thoroughly researching potential refinements to animal use and incorporating applicable findings into the research. Refinements, such as developing early endpoints and administration of analgesics, must be discussed ahead of time with the FDA to ensure the animal model will meet the necessary criteria to clearly show a product’s effectiveness.

The FDA will consider approval of a new drug product under the auspices of the animal efficacy rule only if four requirements are met. The first requirement necessitates a well understood pathophysiological mechanism of how the threat of concern causes damage to the body and how damage is prevented or substantially reduced. This requirement goes far beyond a proof of concept study that may be designed to strictly look at whether a product shows an obvious benefit to make a determination on future development of that product. The effect of the agent of concern and the response of the animal to treatment should be thoroughly understood for an animal model to be used to submit data for drug approval under the animal efficacy rule. Albeit, a full understanding of the pathophysiological processes of a disease and treatment are not required when human studies are used to support approval of a new product, the requirement for animal studies represents the need for additional assurance that information obtained from animal studies can be applied with confidence to humans.

The second requirement is one that has led to a frequent misperception by scientists and lay persons alike, and is why the animal efficacy rule is many times referred to as the “two animal rule.” The animal efficacy rule states that the effect of a product should be demonstrated in more than one animal species whose responses have been shown to be predictive for those of humans. However, the rule goes on to state that a single animal model may be used if it is sufficiently well characterized for predicting the response in humans. Because using animal efficacy data to approve drugs that have

no evidence of efficacy in humans is a significant deviation from previously standard practices, there will likely be extremely close scrutiny of the animal models by the FDA and an expectation of testing to be performed in two species, unless a very strong case can be made for use of a single model. As an example, many infectious diseases have been studied in great detail for decades, with very well characterized animal models. In cases where a well defined model is used in conjunction with a product that already has significant human data, using a single animal model may be appropriate. Also, in situations where there is only one animal model that represents a response predictive of humans, a single animal model may be considered sufficient.

Animal study endpoints come into play as the third requirement of the animal efficacy rule. It is important in developing animal models to use under this rule that endpoints reflect the desired benefit in humans. Survival is one consideration, but the prevention of morbidity may be equally important. Some infectious disease may have very low mortality, but very high morbidity in humans. Establishing an animal model for this type of disease in a highly susceptible species with death as an endpoint may be completely inappropriate.

The final condition for approval of a product utilizing the animal efficacy rule requires that the animal model being used allows for the collection of data on the kinetics and pharmacodynamics of the product that will allow for an effective dose in humans to be determined. Using an animal model that does not allow the necessary pharmacodynamic and kinetics studies to be performed with the product being tested should be excluded during early phases of model development.

Once a product receives approval under the animal efficacy rule by the FDA, there remain additional requirements that include: postmarketing studies to gather data on the safety and efficacy of the product when used for its approved purpose; labeling requirements that describe how efficacy was determined through the use of animals alone, as well as other relevant product information; and the potential for approval with defined restrictions on the product's use.

Comments on the animal efficacy rule when it was in the proposal stage and more detailed discussions and responses by the FDA can be found in the Federal Register (2002, Vol. 67, No. 105, 21 CFR Parts 314 and 601). These discussions can provide useful insight into the applicability and limitations of the animal efficacy rule.

In conclusion, the animal efficacy rule should be used for product approval only when it is clear that conducting research trials to find substantial evidence of human clinical efficacy would be unethical or immoral. No other justification seems appropriate, because the justification for this rule is not lessening the standards of product approval. Rather, the justification is to allow approval of medical countermeasures needed in emergencies where it would be extremely dangerous to test for efficacy in humans.

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