

Scientific and Ethical Importance of Animal Models in Biodefense Research

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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 their fighting strength, and ensure the 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.

Historically, decisions to institute a new medical practice, 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 on 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 Revolutionary War and throughout successive conflicts both 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 the 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 U.S. Food and Drug Administration (FDA).

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 had been no study carried out in animals to determine whether it was safe and effective for him to do so. The use of animals in medical research was not a practice until late in the 19th century. However, this anecdote about Washington's lucky decision is significant in showing that commanders of armies who have 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 that a “mild case” of smallpox would grant immunity. The method of variolation was not vaccination as we know it today. Variolation 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 variolation might cause serious illness, or even death in some. George Washington ordered all his soldiers to undergo variolation without knowing with certainty that his men would be protected. His men became simultaneously the subjects of “research” and recipients of benefit — if they survived their deliberately induced disease outbreak. Variolation did cause some deaths among his soldiers and among members of the communities where his soldiers were encamped. Although both the idea of variolation and Washington’s decision to make it involuntary among his troops became very controversial, his choice protected his troops from smallpox, which was critical to America securing independence from England. Indeed, the importance of smallpox and its mitigation of the 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.

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 the use of animals in research.

Yellow fever epidemics frequently broke out in the Caribbean and the 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. Sternberg selected Walter Reed and James Carroll as the 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.

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 the 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. He subsequently 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, introducing to medicine the concept of voluntary consent. The research risks the patients accepted enabled the discovery that yellow fever was transmitted by mosquitoes, which contributed immeasurably to public health because now 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 United States during the early 1900s [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 last several years in legislative forums in the United States and abroad about the value of research, because it 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. . . . Risk to the individual may be taken with his consent and full knowledge of the circumstances, as has been done in scores of cases, and we cannot honor too highly the bravery of such men as the soldiers who voluntarily submitted to the experiments on yellow fever in Cuba under the direction of Reed and Carroll. [4]

When Osler testified before the U.S. Congress and British Parliament to protect 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], which may have ensured 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.

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 United States 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 the development of programs to respond to the biological warfare threat, the War Research Service was established, under George W. Merck Jr., inside the civilian Federal Security Agency to begin development of the U.S. Biological Warfare program, with both offensive and defensive objectives. The first major objective of War Research Service 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 a 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 because of 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 Federal Security Agency grants after review by the War Research Service 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 nonpathogenic simulant in humans instead of the more hazardous pathogen that would be used for animal exposures [14]. Nonpathogenic simulants were used in model human aerosol exposures so that risks of harming human volunteers would be held to 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 World War II.

In December 1946, Dr. Andrew Ivy released to the American Medical Association a draft of his list of conditions required for research in healthy subjects to be regarded as ethical shortly before he left for Germany to participate in the tribunal. Ivy 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 a 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 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 Armed Forces Medical Policy Council 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; however, 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 February 26, 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].

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 the design of several prototype research protocols and the 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 June 30, 1953 a directive (cs-385) derived from the Wilson Memorandum. Cs-385 contained additional safeguards not mentioned in the Wilson Memorandum that were proposed by the scientists who had attended the ad hoc meetings [21].

Under cs-385, the only studies of human infections and of the efficacy of vaccines in protection, or the efficacy of drugs in treatment of a biological warfare agent, that scientists felt were ethical were the diseases Q fever (*Coxiella burnetii*) and tularemia (*Francisella tularensis*). These disease agents were able to be made 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 an 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 go as high as the secretary of the military service

sponsoring the study, depending on the level of risk or the military organization structure at the time the study was conducted.

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 noncombatants, 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 that 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 birth abnormalities in the limbs. U.S. Senate hearings followed, and in 1962, the so-called “Kefauver-Harris Amendments” to the Food, Drug, and Cosmetic Act were passed into law to ensure drug efficacy and greater drug safety. For the first time, drug manufacturers were required to prove to the 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 March 26, 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.]

Having recognized that the 1962 Food, Drug, and Cosmetic amendments now required that there be substantial evidence of human clinical efficacy, a requirement that would perilously put humans in harm’s 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 the protection from or treatment of biowarfare hazards, irrespective of their FDA approval status [25]. This MOU was important because the DoD had no intention of conducting hazardous challenge studies in humans to prove human clinical efficacy. The MOU allowed the 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 the DoD to use investigational products in classified clinical investigations and nonclassified research programs. The term “nonclassified 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 Vietnam, an investigational plague vaccine that 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. Also in 1972, 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 [23].

The U.S. Public Health Service syphilis study also created a major public controversy in 1972. This was a study of indigent black men from Tuskegee, Alabama, who were prevented from receiving treatment so that the natural course of syphilis could be studied. The program ran from 1932 until it was exposed in 1972. Irrespective of the physicians’ ability to cure syphilis with penicillin, the subjects were never told about it, nor were they treated after penicillin became widely 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 the requirement for informed consent and 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 the structure or operation of the IRB, however. Army Regulation 70-25 already specified these conditions, so no specific changes were needed at this time, other than the 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 the DoD that resulted in transfer of final approval authority from the Chief of Research, Development, Testing, and Evaluation to the Surgeon General of the Army Medical Department 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 October 24, 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 armed forces health protection. Classified clinical investigations could be exempted from the Food, Drug, and Cosmetic 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 April 18, 1979 [30]. In 1981, the Department of Health and Human Services and the FDA published convergent regulations based on the Belmont principles, adding additional restrictions to what may be regarded as research versus treatment and to the use of unapproved drugs and biologics [31,32].

Furthermore, the FDA underwent a reorganization during the late 1980s that vastly increased 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 armed forces health protection or for medical use under an intent to benefit. The new MOU between the DoD and FDA that was signed May

21, 1987, removed the discretionary privileges that enabled the 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 self-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 Food, Drug, and Cosmetic Act). In the case of classified research, the DoD must submit a “classified IND application or investigational device exemption (IDE) application” [33] for review and approval by FDA. The FDA is responsible for having reviewers with the security clearance needed to assess these activities. The new MOU also ended exempt status for the use of IND vaccines in the Special Immunization Program for vaccinating workers at risk of occupational exposure to hazardous disease agents. The new MOU with the FDA required complete compliance with FDA regulations on products labeled investigational. The 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 the 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.

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 lifesaving 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. The DoD 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 the DoD to conclude that it would be protective or beneficial could be used. However, this waiver was removing an essential ethical principle. The principle of “respect for persons” respects a person’s self-determination and autonomy and is a component of his or her 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. The decision of whether 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 September 30, 1988, at Fort Detrick by the Post Chaplain, the rhetorical question was asked if 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, Levine 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 1990s, we codified this in regulation [39–42].

The DoD was one of the 17 federal departments and 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 (the DoD uses 32 CFR 219). The current version of AR 70-25, published January 25, 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 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 Good Clinical Practices requirements [34–36]. There was no other choice but to resolve to comply with all of them as best as possible and to use the IND products needed to protect soldiers in the battlefield [39–42].

Most of the IND products the 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 Food, Drug, and Cosmetic law required immoral efficacy studies to achieve licensure without 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. This concept was utilized to great extent in August 2000, before the animal efficacy rule was made final, when the FDA approved the first antimicrobial drug for treatment of infection due to a biological agent used intentionally as a weapon [47]. Ciprofloxacin hydrochloride (Bayer) was approved by the FDA under the accelerated approval process for use in the medical management of inhalational anthrax. This approval was based on existing knowledge of the drug's safety profile and efficacy data for other bacterial agents, having a surrogate marker of serum concentrations of ciprofloxacin in humans and extensive animal efficacy data. The animal model for inhalational anthrax and subsequent efficacy and pharmacological data obtained from the model played a key role in the approval by the FDA.

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 under which 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 — those products that because of the very nature of what they are designed to treat cannot be safely or ethically tested for effectiveness in humans — available much sooner [48].

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 on the basis of 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 the 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. It is important to remember that the animal efficacy rule cannot be used when clinical studies in humans can still be performed, such as when the accelerated approval process can be used when surrogate markers or clinical endpoints other than survival or morbidity are available [49].

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. The 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. 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 being rigorous in searching for the most optimal model that accurately mimics human disease and 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. Although 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-animal model. As an example, many infectious diseases have been studied in great detail for decades, with very well characterized animal models. In cases in which 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 in which 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 diseases may have very low mortality — but very high morbidity — in humans, and establishing an animal model for this type of disease in a highly susceptible species with death as an endpoint may be completely inappropriate. Also, since the model should reflect the human clinical condition as much as possible, consideration for supportive care to reflect what would reasonably be expected for people should be incorporated into the animal model and associated control groups [49].

The final condition for approval of a product using 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 an attempt to provide additional clarification, the FDA published a notice in January 2009 announcing the availability of draft guidance designed to identify the critical characteristics of animal models intended for use under the animal efficacy rule [50]. While this guidance is not binding to sponsors using the animal efficacy rule for product approval, it does give some insight to FDA's current interpretation of developing animal models for use under the rule [49].

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. This is the only appropriate justification because the justification for this rule is not lessening the standards of product approval. Many would argue the standards are much greater, and justifiably so in order to provide additional confidence that products will be efficacious in humans. Rather, the justification is to allow approval of medical countermeasures where it would be extremely dangerous to test for efficacy in humans. Future successes will require the scientific and regulatory communities to work closely together to develop and refine effective animal models that lead to safe and efficacious countermeasures to biological, chemical and radiological threats.

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