Chapter 24

ETHICAL AND LEGAL DILEMMAS IN BIODEFENSE RESEARCH

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INTRODUCTION

The anthrax attacks of October 2001 made the nation acutely aware of not just the possibility of a large-scale biological weapons attack on US soil, but also has brought to the forefront concerns over the proper measures to be implemented to prepare for such biological warfare scenarios. It is evident that drugs and vaccines may be needed immediately to respond appropriately to emergency or battle situations. Government regulatory agencies, the pharmaceutical industry, and the armed services must work together more effectively so that vaccines and drugs that are not yet approved for marketing but have preclinical evidence of efficacy may be considered and used in the event of bioterrorist attacks or in times of war.

The pharmaceutical industry is not accustomed to responding to such situations; it is in the business of developing drugs to treat natural diseases afflicting patients of the civilian healthcare industry. Profit considerations and sustained business growth are, understandably, the primary objectives of pharmaceutical companies, so drugs are more likely to be developed for common rather than rare diseases. For such naturally occurring, often relatively common diseases, many potential test subjects are ready and willing to participate in drug safety and efficacy trials because of the possibility that the new drug might cure their diseases or help future patients.

This is not the case for products required as countermeasures against biological warfare agents. These infectious disease agents and toxins are usually found in areas of the world where humans have learned it is not safe to settle, or they occur in sporadic, small epidemics that kill everyone affected and fail to spread. In any case, there are rarely enough "naturally" occurring disease outbreaks of this kind to conduct clinical trials yielding substantial evidence of human clinical efficacy.

Over the past 60 years the conditions that must be met in order to use many of these drugs and vaccine products have become more restrictive. Until the approval of an animal efficacy rule and passage of the Project BioShield Act of 2004, Food and Drug Administration (FDA) regulations originating in the 1938 Food, Drug, and Cosmetic Act made emergent medical responses to bioterrorist attacks extremely complex by prohibiting use of investigational products until there was substantial evidence of human clinical efficacy. Gathering evidence in a scientifically valid clinical trial requires the participation of large numbers of subjects who have or are at risk of acquiring the disease, and accumulating these clinical observations takes a long time. Although some disease agents cause sporadic epidemics, others only infect individuals randomly when they happen upon a reservoir of contagion. Biowarfare attacks involving these uncommon agents would likely affect many people suddenly, permitting neither the opportunity to enroll enough subjects in a study nor the time for observation. Although FDA restrictions are meant to protect the public from possible harm, delaying use of potentially beneficial products until outcomes are known can be detrimental in the event of a widespread biowarfare attack. Throughout most of the 20th century and into the 21st century, successful animal studies followed by substantial evidence of efficacy from human clinical trials have been required before a drug could be approved for market. In an emergency, however, it may be beneficial to allow animal study evidence to suffice if the circumstances cannot permit valid human clinical trials.

Current regulations governing research related to biodefense development cover a wide swath of legal and ethical ground. However, the relationship between the military and the FDA is a complex one, partly because of the institutions' different missions. The FDA regulates the manufacture, testing, promotion, and commerce of medical products, and it makes a legal distinction between products that are approved and not approved for marketing. Products not approved for marketing are classified as investigational new drugs (INDs). FDA regulations specify what is necessary to change from the latter status to the former.

Because members of the armed services are at the greatest risk for biowarfare attack, it is prudent for the military to research and develop effective biological defenses that may also be used for treatment in the civilian population in an emergency. But in the military context, FDA regulations pose three significant legal hurdles to the military's ethical responsibility to protect military personnel. First, because diseases that are potential weapons, such as Ebola or Rift Valley fever, are both rare in nature and can be life threatening, it is immoral to conduct clinical trials to determine clinical efficacy because of the inherent risk to participants. Second, outside of clinical trials, the systematic use of INDs (as opposed to single use instances) in emergency life-threatening situations, is illegal. Third, it is illegal to systematically use licensed drugs in large numbers of persons for uses other than those indicated on the label. Ultimately, however, researchers must find ways to circumvent these limitations so that the FDA and Department of Defense (DoD) can fulfill their respective executive branch responsibilities while minimizing conflicts.

Federal regulations serve as practical and praiseworthy legal and ethical safeguards for the conduct of human subjects research. However, as detailed above, regulations governing the conduct of human subjects

research can also have the unintended consequence of slowing the development and advancement of biodefense-related medicine. When the letter of the law is applied, the interests of military personnel may be lost in the shuffle, leaving the following ethical dilemma: on one hand, the military has the duty to adhere to regulations and obey the country's laws; on the other hand, the military has the duty to use all available means to protect its personnel and civilians and accomplish the mission at hand. Some way to bridge the two horns of this dilemma is needed; in particular, there must be a legal way to make protective drugs and vaccines available when the normally required clinical trials cannot be carried out.

This chapter will demonstrate ways to protect military personnel and possibly even the civilian population. The history of the development of biodefense in military medicine and the ethics of biomedical research will be covered. In addition, a summary of the evolution of regulations that influence or inform human subjects research, including research intended and designed in part to meet the needs of the military personnel, will be presented. Then an analysis and discussion of the conflict between regulatory requirements and adherence to ethical principles in the military setting will demonstrate three options the DoD might pursue in relation to the issues outlined. Some of the legislated solutions recently proposed or implemented will also be included.

OVERVIEW OF THE HISTORY OF BIODEFENSE DEVELOPMENT AND MEDICAL ETHICS

Advances in biomedical research have led to considerable breakthroughs in the treatment of diseases that military personnel face. Although the focus of this chapter is on biodefense, the history of research to protect military personnel from disease has frequently targeted naturally occurring diseases unfamiliar to US troops. The need for development of medical treatment in military settings has frequently been the impetus for conceptual breakthroughs in the ethics of human participation in research. Biomedical research involving human subjects in military research facilities must be conducted with oversight from an institutional review board (IRB), per 32 CFR 219.109.[1] Acknowledgment of ethical dimensions in biodefense research requires the cooperation of all military personnel. However, the ethical principles that serve as the foundations of current ethical practices in military medical research did not come about de novo, and neither did the biodefenses and protections. Military medical ethics standards evolved over centuries, often in tandem with or in reaction to biodefense needs, or in response to ethical lapses or controversies. At times the military has assumed the lead in establishing human subjects research ethics precedence.

Biodefense and Ethics in the 18th and 19th Centuries

In 1766, while still a general for England, George Washington and his soldiers were unable to take Quebec in the French and Indian War. In part this failure was due to smallpox outbreaks that affected his troops.[2] Later when Washington led Continental Army troops against the British, a smallpox epidemic reduced his healthy troop strength to half while the British troops, who had been variolated, were already immune to the spreading contagion. Troops were often gathered together from remote parts of the fledgling nation and placed into crowded camps, mingling with local civilian populations, which expanded variola transmission even further into vulnerable populations.[3] Washington proclaimed smallpox to be his "most dangerous enemy," and by 1777 he had all his soldiers variolated before beginning new military operations. In doing so, Washington fulfilled the ethical responsibility of ensuring the health of his military personnel, which in turn served to fulfill his professional responsibility as commander of a military force to preserve the nation. However, his actions were criticized by a public unfamiliar with the stakes or conditions weighing on this choice (Figure 24-1).

Fig. 24-1. George Cruikshank, Vaccination against Small Pox or Mercenary and Merciless spreaders of Death and Devastation driven out of Society! London, England: SW Fores, 1808. General George Washington was strongly criticized in the press because of the risks and his decision to go ahead with forced variolation despite concerns. A political cartoon, published in the 1800s, shows how critically forced variolation was seen by the public despite the Army's intent to benefit its soldiers.

Advances in military medicine and hygiene developed through experiences gained in battlefield medicine during the American Civil War were adapted as standards of medical care during the latter part of the 19th century. New medical schools such as Johns Hopkins sought advice about the most advanced patient care facilities, medical practices, and medical treatment lessons learned on the battlefield. The most direct evidence of the influence of military medicine on standard medical care practice is provided by John Shaw Billings.[4] While serving in the office of the Army surgeon general, he designed the Johns Hopkins Hospital building, applying concepts he learned about the importance of hygiene, light, and ventilation while evaluating medical care in Civil War field hospitals. Billings also created an indexing system for medical publications that was used for the Army surgeon general's library and became the nidus of the National Library of Medicine. The Welch Medical Library at the Johns Hopkins University School of Medicine adopted this same system. Additionally, the Army ambulance system was developed during the Civil War because removing injured soldiers to field hospitals had a better outcome than treating soldiers in the field. Furthermore, soldiers suffering war wounds frequently died from infection. This lesson was not lost on military physicians. As the end of the war neared, the fledgling science of bacteriology and epidemiology became hot topics of battlefield military medical research. Surgical techniques and use of anesthesia and antiseptics became commonplace during the Civil War.[5-7]

The Civil War was also a testing ground for medical education. One lesson learned from the war was that many who served as military physicians did not have the skills needed to save lives in the battlefield. So the Army created its own medical school at what later became the old Walter Reed Army Institute of Research building. Those who created this school liked the training being done at Johns Hopkins, where some later became faculty. Later, civilian hospitals adopted the same surgical techniques and treatment methods. Johns Hopkins Medical School created new academic standards not found at "proprietary" medical schools. Thus, with the help and influence of military medical experience, Johns Hopkins set the stage for medical treatment in the modern era.

Surgeon General George Sternberg, who had been trained as a bacteriologist at Johns Hopkins Medical School, appointed Major Walter Reed, another Johns Hopkins medical trainee, to the Yellow Fever Commission in 1900. Reed used "informed consent" statements when he recruited volunteer subjects from among soldiers and civilians during the occupation of Cuba at the end of the Spanish-American War, and those statements could be considered "personal service contracts" (Figure 24-2). These documents clearly communicated the risks and benefits of participation, described the purpose of the study, provided a general timeline for participation, and stated that compensation and medical care would be provided. All of these are standard elements required in informed consent forms provided to research participants today. Even if the yellow fever statements did not directly influence the creation of other military or civilian informed consent documents, it is at least plausible to claim that documentation of informed consent from research participants in the military predates the practice in civilian medicine.

Biodefense, Ethics, and Research in the 20th Century

Ethical issues surrounding informed consent continued into the 20th century. At the same time, the importance of strategic research was emphasized, which influenced the growth of epidemiological and infectious disease research. A 1925 Army regulation (AR) promoting infectious disease research noted that "volunteers" should be used in "experimental" research.[8] In 1932 the secretary of the Navy granted permission for experiments with divers, provided they were "informed volunteers."[9]

The importance of strategic medical research was not unwarranted. In 1939 Japanese scientists attempted to obtain virulent strains of yellow fever virus from Rockefeller University. The attempt was thwarted by vigilant scientists, but it did not take long before the threat of biological weaponry reached the War Department. In 1941 Secretary of War Henry L Stimson wrote to Frank B Jewett, president of the National Academy of Sciences, and asked him to appoint a committee to recommend actions. He wrote, "Because of the dangers that might confront this country from potential enemies employing what may be broadly described as biological warfare, it seems advisable that investigations be initiated to survey the present situation and the future possibilities."[10] In the summer of 1942, the War Research Service was established, under George W Merck, Jr, in the civilian Federal Security Agency to begin development of the US biological warfare program with offensive and defensive objectives. On October 9, 1942, the full committee of the War Research Service endorsed the chairman's statement on the use of humans in research:

> Human experimentation is not only desirable, but necessary in the study of many of the problems of war medicine which confront us. When any risks are involved, volunteers only should be utilized as subjects, and these only after the risks have been fully explained and after signed statements have been

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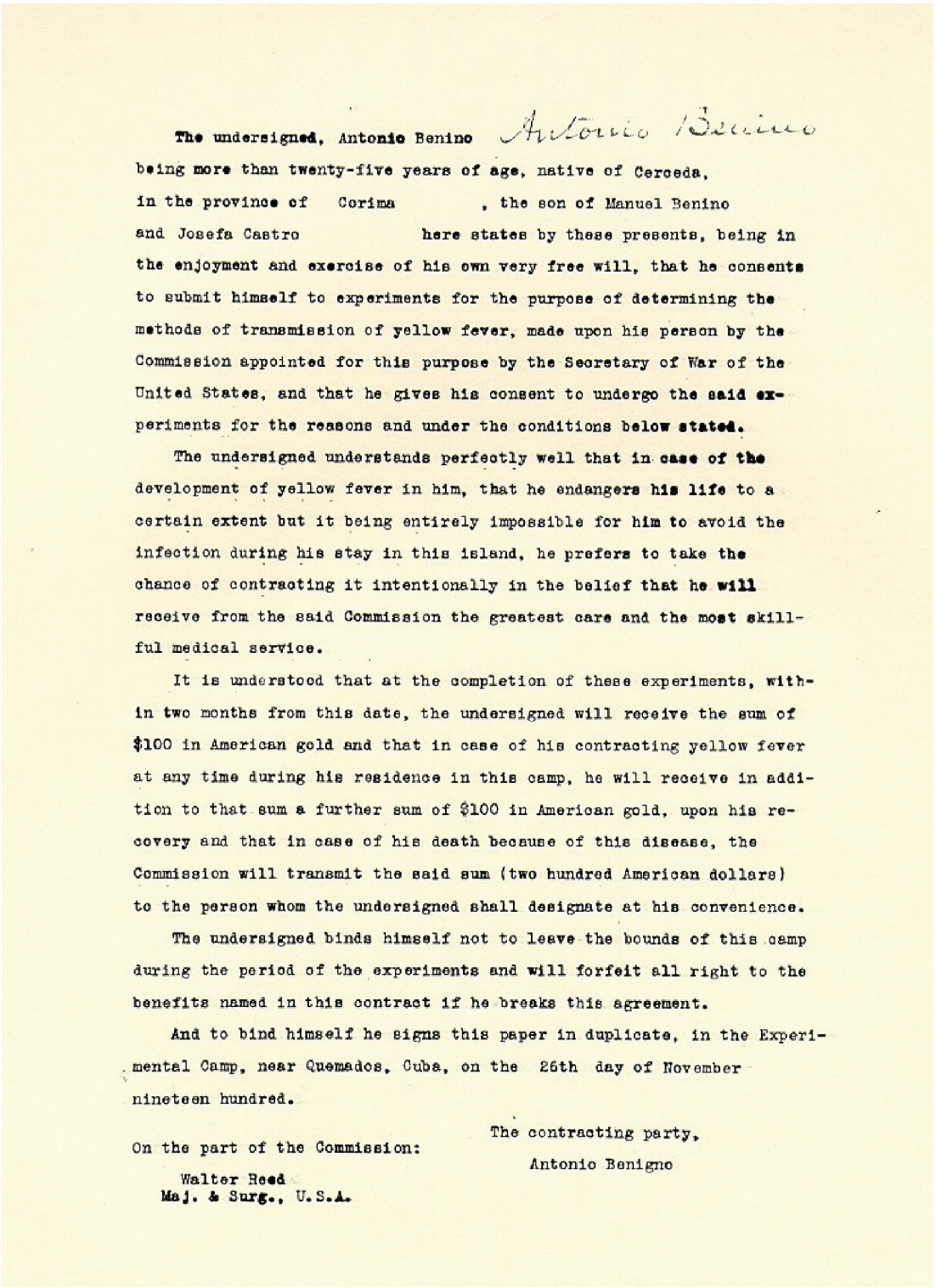


The undersigned, Antonio Benino Antonio Benino
being more than twenty-five years of age, native of Cerceda,
in the province of Corima , the son of Manuel Benino
and Josefa Castro here states by these presents, being in
the enjoyment and exercise of his own very free will, that he consents
to submit himself to experiments for the purpose of determining the
methods of transmission of yellow fever, made upon his person by the
Commission appointed for this purpose by the Secretary of War of the
United States, and that he gives his consent to undergo the said ex-
periments for the reasons and under the conditions below stated.

The undersigned understands perfectly well that in case of the
development of yellow fever in him, that he endangers his life to a
certain extent but it being entirely impossible for him to avoid the
infection during his stay in this island, he prefers to take the
chance of contracting it intentionally in the belief that he will
receive from the said Commission the greatest care and the most skill-
ful medical service.

It is understood that at the completion of these experiments, with-
in two months from this date, the undersigned will receive the sum of
$100 in American gold and that in case of his contracting yellow fever
at any time during his residence in this camp, he will receive in addi-
tion to that sum a further sum of $100 in American gold, upon his re-
covery and that in case of his death because of this disease, the
Commission will transmit the said sum (two hundred American dollars)
to the person whom the undersigned shall designate at his convenience.

The undersigned binds himself not to leave the bounds of this camp
during the period of the experiments and will forfeit all right to the
benefits named in this contract if he breaks this agreement.

And to bind himself he signs this paper in duplicate, in the Experi-
mental Camp, near Quemados, Cuba, on the 26th day of November
nineteen hundred.

The contracting party,
Antonio Benigno

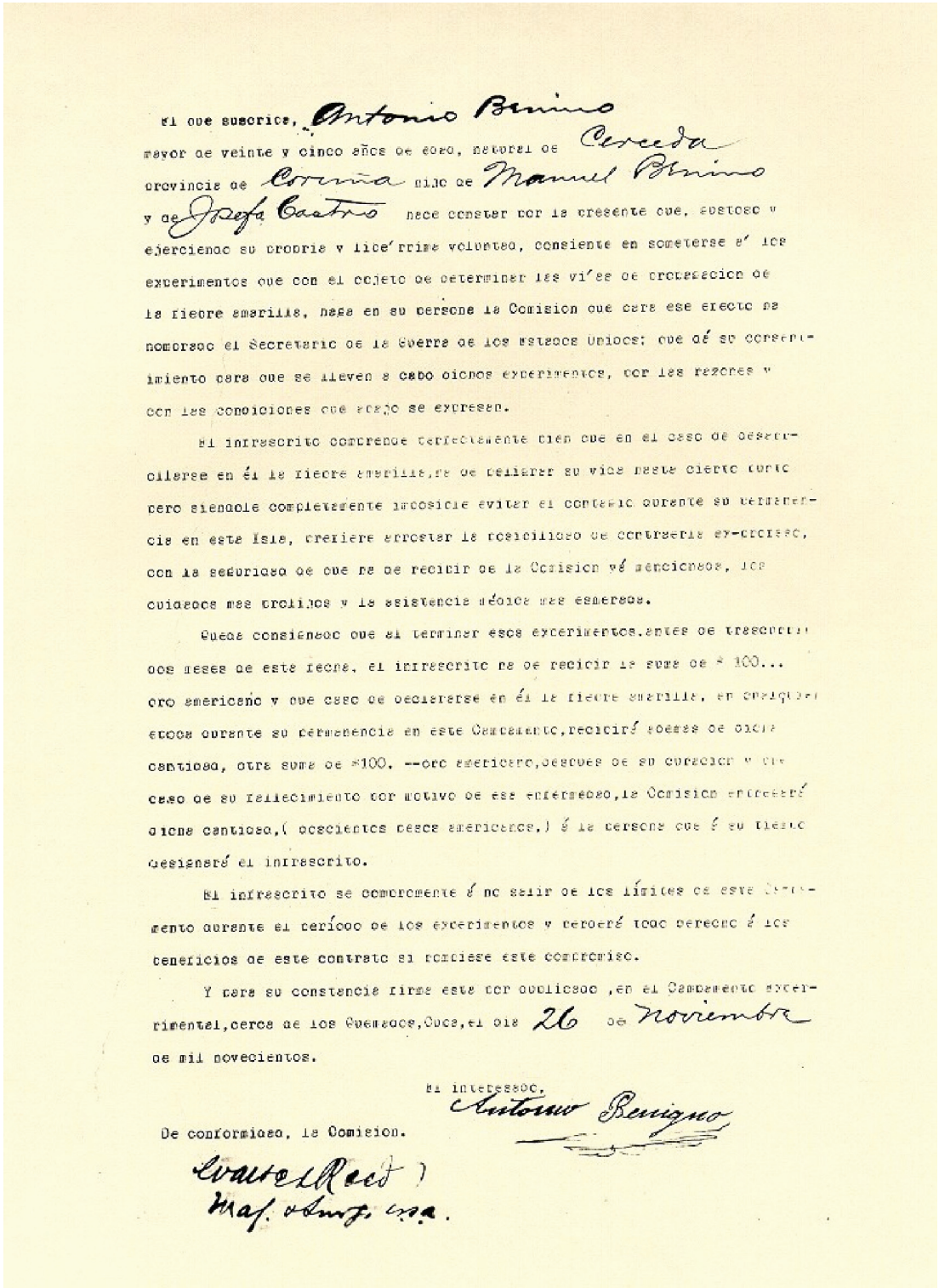
On the part of the Commission:
Walter Reed
Maj. & Surg., U.S.A.

Fig. 24-2. (**a**) English translation of the yellow fever informed consent document. (**b**) Spanish version of the yellow fever informed consent documents. Major Walter Reed, who was appointed to the Yellow Fever Commission in 1900, used "informed consent" statements when he recruited volunteer subjects from among soldiers and civilians during the occupation of Cuba at the end of the Spanish-American War, which could be considered "personal service contracts." However, these

(**Figure 24-2** *continues*)

Figure 24-2 *continued*

b



El que suscribe, Antonio Benigno
mayor de veinte y cinco años de edad, natural de Cerceda
provincia de Coruña hijo de Manuel Benigno
y de Josefa Castro hace constar por la presente que, gustoso y
ejerciendo su propria y libérrima voluntad, consiente en someterse á los
experimentos que con el objeto de determinar las vías de propagación de
la fiebre amarilla, hace en su persona la Comisión que cerca ese efecto ha
nombrado el Secretario de la Guerra de los Estados Unidos; que á su conocimiento cuenta que se lleven á cabo dichos experimentos, con las rezones y
con las condiciones que abajo se expresan.

El infrascrito comprende perfectamente bien que en el caso de desarrollarse en él la fiebre amarilla, se le pellejar su vida hasta cierto punto
pero siéndole completamente imposible evitar el contagio durante su permanencia en este isla, prefiere arrostar la peligrosa de contraerla ex-profeso,
con la seguridad de que se le recibir de la Comisión yá mencionada, los
cuidados mas prolijos y la asistencia médica mas esmerada.

Queda consistendo que al terminar esos experimentos, antes de trascurrir
dos meses de este fecha, el infrascrito se le recibir la suma de $ 100...
oro americano y que caso de declararse en él la fiebre amarilla, en cualquier
época durante su permanencia en este Campamento, recibirá además de dicha
cantidad, otra suma de $100. --oro americano, después de su curación ó en
caso de su fallecimiento por motivo de esa enfermedad, la Comisión entregará
dicha cantidad, (doscientos pesos americanos,) á la persona que á su ruego designará el infrascrito.

El infrascrito se compromete á no salir de los límites de este Campamento durante el período de los experimentos y perderá todo derecho á los
beneficios de este contrato si rompiese este compromiso.

Y para su constancia firma este por duplicado, en el Campamento experimental, cerca de los Cuemados, Cuba, el día 26 de noviembre
de mil novecientos.

El interesado,
Antonio Benigno

De conformidad, la Comisión.
Walter Reed
Maj. Med. U.S.A.

documents clearly communicated the risks and benefits of participation, described the purpose of the study, provided a general timeline for participation, and stated that compensation and medical care would be provided. All of these are standard elements required in informed consent forms provided to research participants today.
Documents: Courtesy of Historical Collections and Services, Claude Moore Health Sciences Library, University of Virginia, Charlottesville, Virginia.

> obtained which shall prove that the volunteer offered his services with full knowledge and that claims for damage will be waived. An accurate record should be kept of the terms in which the risks involved were described.[11]

Despite the War Research Service's ethical commitment to adequately inform subjects of the risks involved in research, the statement includes an assertion of waiver of rights that is now considered unethical to include in military informed consent documents. The War Research Service also supported other experiments performed by civilian scientists that involved subjects whose capacity to give valid consent to participate was doubtful, including institutionalized people with cognitive disabilities.

Meanwhile, military involvement in the development of infectious diseases research was advancing. One of the military's clear successes was the progress it made against acute respiratory disease. Because of crowded living conditions and other physical stresses, acute respiratory disease had consistently been a cause of morbidity among soldiers and an increasing economic liability for the military. In the early 1950s military researchers under Maurice Hilleman at the Walter Reed Army Institute of Research identified seven distinct types of adenoviruses and created vaccines against them—the quick, successful development of medical countermeasures.

As the medical research community began preparing for biological threat and committing resources and time to attendant research, the undercurrent of doubts among human subjects research continued. It was not until Nazi war crimes became public that human subjects research issues came to the forefront of the dialogue on the role and value of science in society. Dr Andrew Ivy compiled 10 conditions that must be met for research involving human subjects for the Nuremberg Tribunal in December 1946. This document, now famously referred to as the "Nuremberg Code," was part of the Tribunal outcomes. In 1947 the Nuremberg Code was published in response to widespread knowledge of Nazi atrocities, including the unethical and traumatizing practices of Nazi doctors. The Nuremberg Code provided a clear statement of the ethical conditions to be met for humans as medical research subjects (Exhibit 24-1).

The DoD adopted all of the elements of the Nuremberg Code verbatim and added a prisoner-of-war provision.[12] The Army included the code in directive Cs-385, which required that informed consent must be in writing, excluded prisoners of war from participation, and included a method for DoD compensation for research-related injuries sustained by participants. In 1962 Cs-385 became AR 70-25, *Use of Volunteers as Subjects of Research*,[13] which regulated Army research until 1983.

In 1952 the Armed Forces Medical Policy Council noted that nonpathogenic biological warfare simulations conducted at Fort Detrick and at various locations across the United States showed that the population was vulnerable to biological attack. Additionally, experiments with virulent disease agents in animal models attested to the incapacitating and lethal effects of these agents when delivered as weapons. However, there was doubt among the council members that extrapolation of animal data to humans was valid, and human studies appeared necessary. Ad hoc meetings of scientists, Armed Forces Epidemiology Board advisors, and military leaders occurred at Fort Detrick during the spring of 1953.[14,15] Thorough consideration of the ethical and legal basis for human subjects research resulted in the design of several prototype research protocols and creation of the US Army Medical Unit (Figures 24-3 and 24-4). This unit heavily invested in animal experimentation but aimed at modeling human infectious diseases to study pathogenesis and response to vaccines and therapeutics. Later, the US Army Medical Unit became the US Army Medical Research Institute of Infectious Diseases (USAMRIID).

In 1955 military research studies using human participants began in a program called CD-22 (Camp Detrick–22) that included soldier participants in a project called Operation Whitecoat. The participants were mainly conscientious objectors who were Seventh-day Adventists trained as Army medics. The program was designed to determine the extent to which humans are susceptible to infection with biological warfare agents. The soldier participants were exposed to actual diseases such as Q fever and tularemia to understand how these illnesses affected the body and to determine indices of human vulnerability that might be used to design clinical efficacy studies. In keeping with the charge in the Nuremberg Code to protect study participants, the US Army Medical Unit, under the direction of the Army surgeon general, carefully managed the project. Throughout the program's history from 1954 to 1973, no fatalities or long-term injuries occurred among Operation Whitecoat volunteers.

Operation Whitecoat serves as a morally praiseworthy model for the conduct of biodefense research involving human subjects. The process of informed consent was successfully implemented from the inception of Operation Whitecoat. Each medical investigator prepared a protocol that was extensively reviewed and modified to comply with each of the elements of the Nuremberg Code. After a committee determined whether ethical requirements and scientific validity

The Nuremberg Code (1947)

1. The voluntary consent of the human subjects 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, overreaching, 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 enlightened 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 duty and responsibility for ascertaining the quality of the consent rests upon each individual who initiates, directs or engages in the experiment. It is a personal duty and responsibility which may not be delegated to another with impunity.

2. The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature.

3. 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.

4. The experiment should be so conducted as to avoid all unnecessary physical and mental suffering and injury.

5. No experiments should be conducted where there is an a priori reason to believe that death or disabling injury will occur; except, perhaps, in those experiments where the experimental physicians also serve as subjects.*

6. 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.

7. Proper preparations should be made and adequate facilities provided to protect the experimental subject against even remote possibilities of injury, disability, or death.

8. The experiments 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.

9. 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.

10. 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 self-experimentation clause of item 5 was omitted from the Wilson Memorandum and subsequent directives and regulations such as Cs-385 and AR 70-25 because it would be irresponsible for the person whose knowledge was essential for the safety and welfare of subjects to render himself incapacitated by taking the test agent along with his subjects.

Exhibit 24-1. The Nuremberg military tribunal's decision in the case of the *United States v Karl Brandt et al* includes what is now called the Nuremberg Code, a 10-point statement delimiting permissible medical experimentation on human subjects. According to this statement, human experimentation is justified only if the results benefit society, and only if carried out in accord with basic principles that "satisfy moral, ethical and legal concepts."
Data source: Permissible medical experiments. In: *Trials of War Criminals before the Nuremberg Military Tribunals under Control Council Law No. 10*. Vol 2. Washington, DC: US Government Printing Office; 1946–1949.

were met, Army officials approved the protocol. Then potential volunteers were briefed as a group regarding the approved protocol, and they attended a project interview with the medical investigator in which the potential volunteers could ask questions about the study. Informed consent documents (Figure 24-5) were signed after an obligatory waiting period that ranged from 24 hours to 4 weeks, depending on the risk involved in the study. Volunteers were encouraged to discuss the study with family members, clergy, and personal physicians before making a final decision. By allowing volunteers sufficient time and opportunity to

Fig. 24-3. Aerial photograph of Fort Detrick, 1958. The US Army Medical Unit was assembled from existing Fort Detrick components concerned with occupational health and safety, the dispensary, and a small hospital referred to as Ward 200 of Walter Reed Army Medical Center. These components originated under separate Army commands, yet they formed an integrated, functional unit.
Photograph: Courtesy of the Department of the Army.

ask questions about risks, potential benefits, and the conduct of the study, this multistage informed consent process ensured that participation was voluntary. Soldiers were told that their participation in the research was not compulsory. Approximately 20% of those soldiers approached for participation in Operation Whitecoat declined. Review of Operation Whitecoat records of interviews with many of the volunteers and investigators revealed that the researchers informed participants that the research was scientifically valid and potentially dangerous, and that any harm to the participants would be minimized.

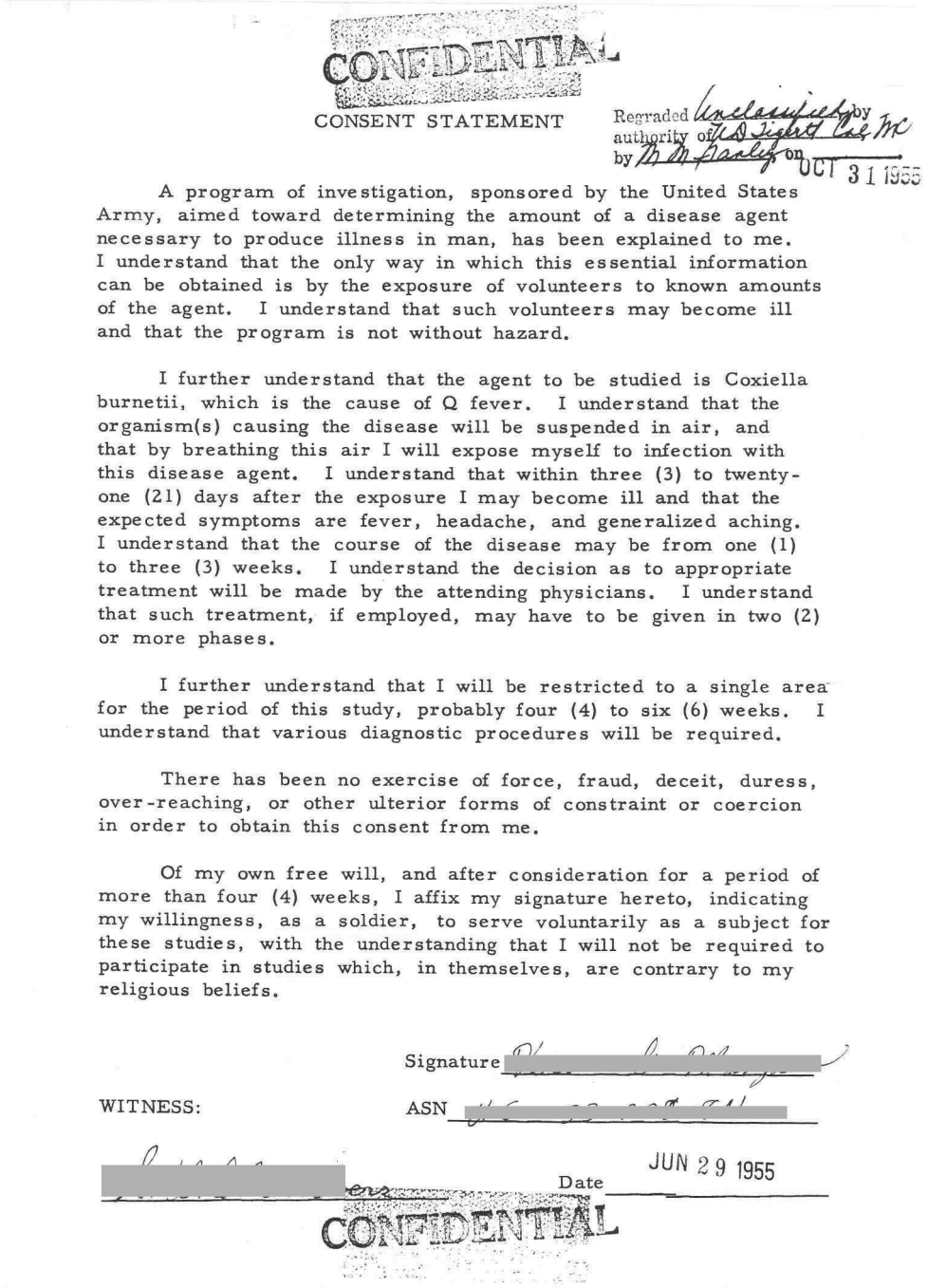
Approximately 150 studies related to the diagnosis, prevention, and treatment of various diseases were completed during Operation Whitecoat, including research on Q fever and tularemia infections and staphylococcal enterotoxins. Vaccines to be used against Venezuelan equine encephalitis, plague, tularemia, Rocky Mountain spotted fever, and Rift Valley fever were tested for evidence of safety in humans. However, scientists conducted animal studies before human subjects research. For instance, researchers exposed Operation Whitecoat volunteers to aerosolized Q fever organisms only after completion of animal safety and efficacy studies. The first exposure occurred on January 25, 1955, with the use of a 1-million-liter stainless steel sphere at Fort Detrick known as the "Eight Ball." This research device was designed to allow exposure of animals and humans to carefully controlled numbers of organisms by an aerosol route.

Research conducted during Operation Whitecoat also contributed to the development of equipment and procedures that established the standard for laboratory biosafety throughout the world. The ethical commitment to the safety of laboratory workers engaged with dangerous toxins, viruses, and diseases was manifested by the development of biological safety cabinets with laminar flow hoods, "hot suites" with differential air pressure to contain pathogens, decontamination procedures, prototype fermentors, incubators, refrigerated centrifuges, particle sizers, and various other types of specially fabricated laboratory equipment. Many of the techniques and systems developed at Fort Detrick to ensure worker safety while handling hazardous materials are now used in hospitals, pharmacies, and various manufacturing industries.

Operation Whitecoat was not the only example of US military involvement in human subjects research, and not all involvement in human subjects research reflects favorably on the US military. For example, the US military conducted unethical research involving LSD on uninformed human subjects from 1958 to 1964.[16]

Congress enacted the National Research Act of 1974 because federally funded researchers violated human subjects' rights, most famously in the Tuskegee syphilis experiments. This act immediately imposed rules for the protection of human subjects involved in research, requiring informed consent from subjects and review of research by institutional review boards. The act created the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, which

Fig. 24-4. The US Army Medical Unit at Fort Detrick, under Colonel William Tigertt (center) was staffed with personnel drawn from the US Army, Navy, Air Force, and Public Health Service, whose assignment was given the highest national priority because of their unique expertise in infectious disease medical care, research, and epidemiology, and because of their determination to provide the Operation Whitecoat volunteers the best care and support for their safety during the trials. Photograph taken in 1957.
Photograph: Courtesy of the Department of the Army.



CONFIDENTIAL

CONSENT STATEMENT

Regraded Unclassified by authority of U.S. Light Col. MC by M. M. Bailey on OCT 31 1955

A program of investigation, sponsored by the United States Army, aimed toward determining the amount of a disease agent necessary to produce illness in man, has been explained to me. I understand that the only way in which this essential information can be obtained is by the exposure of volunteers to known amounts of the agent. I understand that such volunteers may become ill and that the program is not without hazard.

I further understand that the agent to be studied is Coxiella burnetii, which is the cause of Q fever. I understand that the organism(s) causing the disease will be suspended in air, and that by breathing this air I will expose myself to infection with this disease agent. I understand that within three (3) to twenty-one (21) days after the exposure I may become ill and that the expected symptoms are fever, headache, and generalized aching. I understand that the course of the disease may be from one (1) to three (3) weeks. I understand the decision as to appropriate treatment will be made by the attending physicians. I understand that such treatment, if employed, may have to be given in two (2) or more phases.

I further understand that I will be restricted to a single area for the period of this study, probably four (4) to six (6) weeks. I understand that various diagnostic procedures will be required.

There has been no exercise of force, fraud, deceit, duress, over-reaching, or other ulterior forms of constraint or coercion in order to obtain this consent from me.

Of my own free will, and after consideration for a period of more than four (4) weeks, I affix my signature hereto, indicating my willingness, as a soldier, to serve voluntarily as a subject for these studies, with the understanding that I will not be required to participate in studies which, in themselves, are contrary to my religious beliefs.

Signature [redacted]

WITNESS: ASN [redacted]

[redacted] Date JUN 29 1955

CONFIDENTIAL

Fig. 24-5. Early (1955) informed consent used for one of the Camp Detrick-22 Operation Whitecoat experiments. Document: Courtesy of Medical Records Archives, US Army Medical Research Institute of Infectious Diseases, Fort Detrick, Maryland.

published the Belmont Report, a compilation of the principles implicit in ethical medical practices, in 1979. The commission also provided a schema for the formal review of research by standing committees. Belmont Report findings were incorporated into AR 70-25 in 1983.[13]

The ethical principles identified in the report, including the principles of respect for persons, beneficence, and justice, were compiled from a review of codes of conduct and standard medical and research ethics practices. Respect for persons refers to those

practices whereby the right of individuals to make fully informed decisions is respected, and the need for protection of persons who are less able to exercise autonomy is recognized. Beneficence refers to the deliberate intention to do good and the assurance that participation in the research is more likely to result in good than in harm. Justice demands that the potential benefit and harm of the research be distributed fairly in society, which has typically been understood to mean that the research cannot solely assist or exploit any certain demographic.

In practice, these three principles yield the research requirements respectively for informed consent, risk/benefit analysis, and fair inclusion/exclusion criteria for participants. Much has been written about these principles, their flexibility and adequacy as guides, and their connection to philosophical foundations,[17-19] and they remain appreciated as a practical approach to considering actions in biomedical contexts. The principles are secular but not incompatible with religious views, and they recognize the value of human individuals and the importance of collective benefits. The principles were incorporated into all federal institutions that fund research, including the DoD, as part of this common rule. Hence "common rule" became the catch phrase used to refer to the institution-wide incorporation of explicit ethical requirements as identified in the Belmont Report.

Success in incorporating ethical principles into human subjects research in the military in the early and mid 20th century was complemented by military researchers' numerous achievements in vaccine development with a variety of infections, including yellow fever (1900), typhoid fever (1911), pneumonia (1945), hepatitis A (1945), influenza (1957), rubella (1961), adenovirus (1952–1969), and meningitis (1966).[3]

IMPACT OF REGULATING AGENCIES ON STRATEGIC RESEARCH

The evolution of regulatory bodies overseeing human subjects research paralleled the evolution of military medical research ethics. These regulatory bodies influenced military research in positive and negative ways.

In 1901 in Missouri, 13 children died of tetanus after receiving horse serum contaminated by *Clostridium tetani* for treatment of diphtheria. In 1902 Congress enacted the Biologics Control Act (the Virus-Toxin Law), which gave the federal government authority to require standards for the production of biological products, including vaccines. The act contained provisions for establishing a board (including the surgeons general of the Navy, Army, and Marine Hospital Service) with the power to create regulations for licensing vaccines and antitoxins. Thereafter, only annually licensed, inspected facilities were permitted to produce biologics. This act marked the commencement of America's federal public health policy for biologics.

The 1938 Food, Drug, and Cosmetics Act regulated biologics through mid-century. For the first time, drug production had to meet standards for safety before receiving approval for marketing. The 1944 Public Health Service Act reinforced or expanded public health policy standards in two ways: (1) it became the mechanism containing explicit regulation of biologics, and (2) it created the FDA. Under its new authority, the FDA approved the influenza vaccine, chiefly on the strength of data provided by the Army.[20]

In 1962 Congress passed the FDA Kefauver-Harris Drug Amendments, which effectively launched the modern US drug regulatory system. These amendments stipulated an intense premarketing approval system, giving the FDA the power to deny approval for products with safety concerns. The amendments also required proof of human efficacy for all drugs and biologics, including vaccines.

The requirement for proof of efficacy of all medical countermeasures, premised on the principle of protecting the lives and other interests of human subjects, is a responsible action. But the Kefauver-Harris Drug Amendments also categorized the only available medical countermeasures against biological weapons as INDs, which created an ethical dilemma for the DoD. Compliance with the FDA regulations meant that the DoD either had to risk the deaths of human subjects in a valid clinical trial, or withhold potentially life-saving drugs or vaccines because they lacked substantial evidence of human clinical efficacy. (Of course, the drugs and vaccines in question would all require evidence of animal efficacy, unless no animal model of human disease could be found. Additionally, AR 70-25 [1962 and 1974][14] contained clauses [3c] that exempted biodefense research and testing if there was intent to benefit the research subject.) To resolve this issue, the DoD sought exceptions to these new regulations by negotiating memoranda of understanding (MOU) with the FDA in 1964, 1974, and 1987. The most recent MOU provided the FDA an assurance that the DoD would conduct clinical testing of biologics, categorized as INDs, under FDA regulations, including requirements for human subject informed consent, IRB review, and controlled clinical trials in medical research (see 21 CFR 50 and 56).[21] The MOU states that the DoD will meet these requirements without jeopardizing responsibilities related to its mission of protecting national interests and safety.

CONFLICT BETWEEN REGULATIONS AND ETHICAL RESPONSIBILITIES

The military situation is unique. In the tension between the good of the individual and the good for the social organization, the latter justifiably holds greater weight in decision-making procedures in the military context. Members of the military have unique responsibilities, which include being fit for duty. The military organization also has responsibilities to its service members, including providing healthcare specific to the dangers encountered in battle zones.

Department of Defense/Food and Drug Administration Memorandum of Understanding (1987)

The 1991 Persian Gulf War brought into focus the inadequacy of the 1987 MOU and the conflicts between the duties of the two agencies. The DoD's mission is to protect the interests of the United States through use of military force. The DoD also recognizes its ethical responsibility to protect the health of military personnel. Thus, the DoD is doubly obligated to the mission and to service members. It is the responsibility of service members to keep themselves fit throughout the current mission and for future missions. When troops are threatened by biowarfare, in the absence of an approved biodefense product, one supported by preclinical data may be the only available option for troop protection. With a credible threat, the situation is similar to that of patients with an incurable disease who wish to try a potential remedy in advance of large clinical trials if it offers plausible expectation of some benefit. Such a product administered but proven ineffective would be analogous to sending troops to battle with faulty equipment. Such a product later proven unsafe would be analogous to friendly fire—perhaps an even more damaging situation for morale. Thus, the military requires a fine balance between necessity and caution. Proper biodefensive posture requires vaccination against credible threats. Vaccinations include licensed anthrax and smallpox vaccines and unlicensed vaccines for botulism toxin poisoning and a variety of encephalitides, including Venezuelan equine encephalitis, western equine encephalitis, and eastern equine encephalitis. Data for these unlicensed vaccines support human safety and efficacy,[22] even though efficacy has been demonstrated only in animals. Medical experts favor the use of these vaccines in protecting human beings when threat dictates. Because the vaccines are not licensed and will not, for ethical reasons, undergo the clinical efficacy trials required by FDA, they can only be used in an IND status.

Investigational New Drug Status of Vaccines

FDA considers any administration of an IND to a human to constitute research and authorizes the administration of an investigational product only in the context of a clinical research trial. Because the therapeutic benefit of the IND is unknown, FDA also requires informed consent. Administration of an IND requires specific and detailed recordkeeping measures. However, the recordkeeping requirements relate specifically to research, not to emergency or preventive measures connected to imminent risk of biological attacks on the battlefield. Collecting data from and recordkeeping for 100,000 soldiers would take exponentially longer than merely administering an unlicensed vaccine for treatment or prevention purposes. The consenting process alone for 100,000 individuals receiving an IND would take so long that strategic combat moves, such as immediate mobilization and deployment of a unit, would be impossible. Storing informed consent documents for 100,000 soldiers, and the accompanying logistical challenge of reconsenting soldiers if new risk information emerged during deployment, would also be daunting tasks. Furthermore, continuous data collection, as required by the FDA's good clinical practices (GCPs), is unfeasible and would effectively result in noncompliance problems, such as occurred during the Persian Gulf War. FDA regulations governing storage and distribution of INDs (21 CFR 312.57 and 59)[21] are rigid and restrictive, which would render any immunization schedule impossible in the field.

The FDA's commitment to protecting the citizenry from the unknown effects of medical treatments has thus resulted in two legal quandaries. First, the FDA permits the use of INDs, including the vaccines in question, for research purposes. However, the situation in war is not a research situation. Giving these products to military personnel before engagement in war for purposes of thwarting the onset of some horrific disease constitutes a treatment application of the product, not research. No benefit is believed to accrue to an individual receiving an IND. Thus, administration of IND vaccinations to military personnel in wartime does not constitute research, even though it is the only classification FDA permits for these unlicensed and untried vaccines. Continuing to categorize such vaccines and drugs as "investigational" also fails to inspire confidence in soldiers asked to receive the vaccine, even if there is limited evidence that the vaccine is not only safe but likely efficacious based on extrapolation from animal data. The label "investigational" does not communicate the strength of the data from animal studies that supports the safety and

efficacy of the product. It creates the perception that soldiers at risk of losing their lives in combat are also being used as subjects of research, or "guinea pigs," despite the intent to use these products solely for the soldiers' protection.

The FDA requires informed consent from subjects receiving INDs. Consequently, subjects have the right to decide whether they will receive the IND, and soldiers understand that they cannot be required to take IND products. The requirement for informed consent is based on the Nuremberg Trial findings related to research in which benefits did not directly accrue to research participants. In the context of preventive treatment in a military conflict, the requirement for informed consent is a misapplication of a principle of research ethics. Enlisted and commissioned soldiers surrender much of their autonomy in matters of choice and accept the relinquishment of autonomy as a standard of military discipline. Specifically, one of the rights that military personnel forsake is the discretionary authority over their medical treatment. The requirement for informed consent threatens to put a divisive wedge between commander and subordinates, and such discord is counterproductive to military recruitment, retention, and mission accomplishment. One solution to this problem may be to move IND products to licensure either by animal efficacy rule or by BioShield emergency use authorization, with all of the attendant medical subject matter expert board review and input afforded to products going before the FDA.

In the first Persian Gulf War, the DoD was acutely concerned with protecting military personnel from harm related to biological weapons. Intelligence indicated that Iraq had not only used chemical weapons against humans in the past, but had also manufactured and stockpiled biological weapons that were believed to be ready for use. In documents sent to the FDA regarding implementing proper biodefense in military personnel against botulism, the DoD argued that waiver of informed consent was justified because a botulism vaccine (also referred to as the "pentavalent botulinum toxoid vaccine") was to be administered as protection of and not as research on military personnel. The FDA accepted this DoD argument and exempted the DoD from the data gathering and recordkeeping requirements typically required during the administration of INDs.

This decision had historic consequences. Some commentators characterized the FDA's accommodation of the DoD's wishes as unethical. This accusation resulted in changes in the relationship between the FDA and DoD after veterans claimed "Gulf War syndrome" injuries. Gulf War syndrome is a phrase used to capture the constellation of injury claims stemming from symptoms experienced by Gulf War veterans after the conflict, some of which have been attributed to anthrax and/or botulism vaccination. Despite repeated high visibility studies conducted by the Institute of Medicine of the National Academies of Science, no evidence of causal relation has been shown between these symptoms and receipt of vaccine. Most soldiers who received inoculations from the same lots of vaccine as those who claim illness did not experience any of the associated symptoms. Furthermore, the majority of claims of illness were associated with receipt of a vaccine involved the anthrax vaccination, which was an FDA-licensed product at the time of deployment for the first Persian Gulf War, rather than the botulism vaccination, which few soldiers received. Articles that summarize long-term outcomes after receipt of multiple vaccines, including those used during the Persian Gulf War, address the safety of these vaccines.[23-25] But even if the existence of a causal relationship between receipt of the vaccine and the manifestations of the Gulf War syndrome is accepted, the DoD's use of the vaccines to protect the force was an ethically supportable decision. It was an ethically supportable decision first and foremost because military intelligence indicated botulism was Iraq's biological weapon of choice, which meant there was a likelihood of its use during military operations. Any use of botulism by the Iraqi forces would place American soldiers directly in harm's way, but to an extent greater than would be faced during most traditional 20th century warfare. The DoD had an obligation to meet this extra threat, for the health of its soldiers, and for the benefit of the military mission. To meet this threat in as ethical a manner as possible, subject matter experts weighed in on risks and benefits of the use of the vaccine, and discussions between the DoD and FDA were held. That there may have been ill effects from the vaccine is an unintended consequence of the situation, the facts of which could not have been known beforehand, and which do not alter the ethically supportable dimensions of the decision-making process, the intentions, or even the execution of the plan to vaccinate soldiers.

Summary Points

Human Subjects Protections Regulations are Incompatible with Department of Defense Deployments

The immediacy of war preparations works against requirements of human subjects protection, including the requirement to solicit and obtain informed consent from subjects. Receipt of an IND drug must be voluntary. However, by definition, true force health protection (FHP) measures cannot be "voluntary." The voluntary nature of FDA-regulated research could

undercut the effectiveness of FHP measures, which rely on universal compliance for their efficacy. FHP measures, which are necessary for success in war, are imposed to safeguard the soldiers' health. If left to the choice of individual soldiers, the health benefit to the soldier may be compromised. Military personnel, who have ceded part of their autonomy to the government as a condition of service, are obligated to accept command-directed protective measures in the United States (immunizations are voluntary in the United Kingdom and in most European militaries).

However, waiving the requirement for informed consent for receipt of INDs can undermine public trust and military morale. FDA requirement for informed consent for receipt of an IND is premised on the idea that administration of an IND is for research purposes, and the safety and efficacy of the drug are unknown. If countermeasures without medically significant contraindications were licensed for therapeutic purposes, this would lower the threshold for requiring informed consent. Licensure "for military use" would remove the stigma attached to use of an agent categorized as "investigational" for research purposes.

Realities of Deployment Conflict with Food and Drug Administration Regulations and Guidance

GCP data requirements support new product license applications, but GCP data collection does not serve the purposes of DoD military use of selected (unlicensed) medical products. The FDA enforces clinical data collection on IND products as a function of stringent protection of research integrity. Shortfalls in data management, such as missing data, missing vials, or missing forms, are inevitable during expediencies of real-time deployment and the exigencies of warfare, making it difficult for the DoD to meet FDA requirements. Protocol violations inevitably occur, even under ideal investigational circumstances, and even when researchers fully intend to strictly follow GCP requirements. Unforeseen circumstances encountered in war are unavoidable. Scientific misconduct, then, may be suspected when the realities of deployment work against traditional scripted research strategies. Ultimately force protection, not research, is the primary purpose of the military use of these countermeasures.

OPTIONS FOR FULFILLING MISSION AND ETHICAL RESPONSIBILITIES TO MILITARY PERSONNEL

Option 1: Continue to Use Investigational New Drug Products Without Full Compliance

The DoD can continue to use IND products, even though full compliance will not be achieved. GCP conflicts with the requirements of countermeasure use during wartime, as seen during the first Persian Gulf War. The ethical responsibility of the DoD to protect soldier health and welfare does not commit the DoD to creating marketable products. However, if the data gathered on these INDs during wartime are to be used for increasing product knowledge, then GCP restrictions should be relaxed for wartime military use. These changes would permit the DoD to contribute to research by adding to the data gathered before bringing INDs to market. DoD can choose to move forward with a particular IND product while doing its best to use the product according to FDA requirements, including adhering to GCP when practical.

Problems

Any relaxation of FDA standards could facilitate an impression of abuse of power by the DoD. Accusations of product approvals without sufficient consideration of safety issues could result in legal and economic fallout for the federal government. Most importantly, relaxing these standards, which the FDA has put in place to protect citizens, could result in a patient's injury or death.

Option 2: Negotiate for Accelerated Licensure

The DoD can negotiate with the FDA for assistance in hastening licensure of products required in contingencies or for FHP. If the DoD negotiates directly with the FDA, then drugs and vaccines could be given without the burden of research format and documentation. Epidemiological follow-up, not case report forms, would determine benefit, and decisions to retain or withdraw approval could be based on epidemiological analyses. The DoD could ask the FDA to waive IND requirements that cannot be practicably met in specific cases. Finally, the DoD and FDA could negotiate and agree to an updated MOU that permits the exemption of certain products for contingency use in protecting or treating soldiers.

Problems

The potential for DoD abuse of such power, or even the perception of abuse of such powers, will always be present.

Option 3: Institute Waiver of Informed Consent

Although considered a necessary condition for research to be ethical, the requirements for obtaining informed consent (21 CFR 50.20-.27, 32 CFR 219.116-.117, 45 CFR 46.116-.117)[21,26,27] are not absolute. If informed consent is unfeasible or contrary to the best interests of recipients (21 CFR 50),[21] such as in emergency situations or where the subject cannot give informed consent because of a medical condition and no representative for the subject can be found, the requirement can be waived. Executive Order 13139 and the Strom Thurmond National Defense Authorization Act of 1999 give the president of the United States the power to waive the requirement for informed consent for the administration of an unlicensed product to military personnel in connection with their participation in a particular operation.[28] The requirements are a formal request from the secretary of defense for such a waiver, based on evidence of safety and efficacy weighed against medical risks, and the requirement that a duly constituted institutional review board must approve the waiver, recordkeeping capabilities, and the information to be distributed to soldiers before receipt of the drug or vaccine.

One might argue that there is no need for a waiver of informed consent. If a soldier refuses receipt of a particular unlicensed product, he or she can be replaced by another soldier who is willing. But one does not have to search far for a scenario where waiver of informed consent might be warranted. The present day worries over recruitment and retention reflect this situation.

Problems

Some existing regulations conflict with the president's recent power to waive informed consent requirements for military personnel, including conflicts and limitations posed by Title 10 USC Section 980 (10 USC 980),[29] AR 70-25.[13] Title 10 USC 980 reads as follows:

> Funds appropriated to the Department of Defense may not be used for research involving a human being as an experimental subject unless – (1) the informed consent of the subject is obtained in advance; or (2) in the case of research intended to be beneficial to the subject, the informed consent of the subject or a legal representative of the subjects is obtained in advance.[30]

10 USC 980 contains no provision for waiver of the requirement for informed consent, not even for the president, and neither of its two conditions for waiving the requirement would be met by a presidential waiver.

Chapter 3, section 1, paragraph (f) of AR 70-25 states that "voluntary consent of the human subject is essential. Military personnel are not subject to punishment under the Uniform Code of Military Justice for choosing not to take part as human subjects. No administrative sanctions will be taken against military or civilian personnel for choosing not to participate as human subjects."[13] Thus, the Army's own regulations can be interpreted to conflict with a presidential waiver of consent, and if soldiers cannot be compelled to receive vaccines or drugs intended to fight diseases, the presidential waiver fails to accomplish its intent.

An additional problem with presidential waiver of informed consent is the requirement that such a waiver be posted for public review in the *Federal Register*. This requirement makes operational secrecy impossible, especially given the length of time some vaccines require to elicit adequate titers in recipients.

Also, public perception is a looming issue. If the requirement for informed consent is waived, even by the president, public backlash is not likely to be quiet or short lived. Public awareness of research subject abuse has grown, and the public is aware that informed consent is essential for the ethical use of products for which the FDA cannot claim knowledge of safety and efficacy. Public outrage directed at the military, and the subsequent erosion of trust between the government and the governed, is a risk that also must be considered.

CURRENT MOVEMENTS IN THE REGULATORY ENVIRONMENT

Further restricting the ability of the DoD to properly protect military personnel with vaccines with preclinical evidence of efficacy would not be the best solution to this legal and ethical dilemma. If the DoD were to eschew unlicensed products and the IND issue entirely, an argument could be made that military personnel would be at greater risk from infectious agents. However, several options are available to address this issue, some of which have seen dialogue or attention in the form of legislation.

The Public Health Security and Bioterrorism Preparedness and Response Act of 2002

The Public Health Security and Bioterrorism Preparedness and Response Act of 2002, also called the Bioterrorism Act, contains a provision to "fast track" certain products under the Federal Drug Act, including vaccines and other "priority countermeasures" eligible for accelerated approval, clearance, or licensing. Title

II of the act also contains the kernel of what is known as "biosurety," which is a combination of biosafety, security, and personal reliability needed to safeguard select biological agents and toxins that could potentially be used in bioterrorism. Finally, this act approved the "animal efficacy rule."[30]

The Animal Efficacy Rule

Another regulatory response that reflects a positive move toward reducing conflicts in responsibilities between the FDA and DoD was the creation of an animal efficacy rule. A draft animal efficacy rule was prepared by the FDA commissioner's office and had been published for public comment 2 years before the terrorist attacks in 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. These products, such as current IND vaccines, cannot be safely or ethically tested for effectiveness in humans because of the nature of the illnesses they are designed to treat.

The FDA amended its new drug and biological product regulations so that certain human drugs and biologics intended to relieve 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 FDA 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 the 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 the 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 on October 5, 1999, and the rule took effect on June 30, 2002. The advent of the animal efficacy rule shows the importance of animals in finding safe and effective countermeasures to the myriad of toxic biological, chemical, radiological, and nuclear threats.

Using animal surrogates to prove clinical efficacy is not a perfect solution, even though 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. Furthermore, because drugs approved by the animal efficacy rule may still not be "proven" efficacious in humans, postmarketing epidemiological studies are necessary to monitor outcomes. Finally, some diseases, such as dengue and smallpox, only affect human beings and do not affect animals. If animal efficacy data cannot be produced for a disease, the implication is that no vaccine could be created or used in human beings, which hardly seems a fitting solution.

BioShield Act of 2004

Perhaps the most promising solution to the current impasse is the BioShield Act of 2004, which President George W Bush outlined in his 2003 State of the Union address as a key legislative priority for his administration. Project BioShield is designed to speed the development and availability of medical countermeasures in response to bioweapons threats by accelerating and streamlining government research on countermeasures, creating incentives for private companies to develop countermeasures for inclusion in a national stockpile, and giving the government the ability to make these products quickly and widely available in a public health emergency to protect citizens from an attack using an unmodified select agent.

The BioShield Act of 2004 creates permanent funding for the procurement of medical countermeasures and gives the federal government the power to purchase available vaccines. The FDA and Department of Health and Human Services are tasked not only with determining that new vaccines and treatment measures are safe and efficacious, but also with the responsibility of making promising vaccines and treatment measures expeditiously available for emergency situations. The newly created FDA Emergency Use Authorization for Promising Medical Countermeasures provides one of the best ways of getting such products to those who might need them most, including military personnel. The legislation also requires the secretary of the Department of Health and Human Services to approve such emergency use

measures, with the added requirement of FDA expert opinion that the benefits of the vaccine or treatment outweigh the risks involved in its application. Just such an emergency use of anthrax vaccine adsorbed (Biothrax, BioPort Corporation, Lansing, Mich) was approved by Health and Human Services Secretary Tommy G Thompson on January 14, 2005, authorizing its emergency use.

However, Project BioShield contains a provision that still conflicts with DoD discretionary authority over medical treatment for military personnel, continuing to require voluntary willingness to receive a vaccine or other treatment approved under the category of "emergency use." Although the language in the legislation refers specifically to "civilians," how this requirement will play out in the military setting, especially in wartime, is unclear. For maximum military effectiveness, a further stipulation in the legislation is required that the voluntary acceptance of treatment be waived in emergency situations, presumably on authority of the president of the United States with expert opinion from ethicists, legal scholars, and scientists. Additionally, there is no profit motive for private companies to engage in the research that this legislation aims to foster, and indemnification concerns also exist. There is no guarantee of efficacy of the theoretical drug or vaccine, and accountability measures should be created if the legislation is going to achieve its intended results.

The Turner Bill

Another bill (HR 4258 "Rapid Pathogen Identification to Delivery of Cures Act"), introduced by Congressman Jim Turner et alia on May 4, 2004, allows research and development of medical countermeasures and diagnostics to move at a quicker pace so that new products can rapidly be made available for emergencies. In addition, the Turner Bill provides for research and development of drugs and vaccines against genetically modified pathogens not accounted for in the Project BioShield legislation, which covered only countermeasures related to existing unmodified threat agents.

Project BioShield and the Turner Bill together establish an FDA emergency use authorization for critical biomedical countermeasures. The FDA may approve solely for emergency use a product not approved for full commercial marketing. For products that are near final approval but may not have met all the criteria, the FDA has created a streamlined IND process, with the animal efficacy rule playing a central role, for products designed to protect against or treat conditions caused by nuclear, chemical, or biological terrorism. Such a process was used to obtain FDA approval for pyridostigmine, which is licensed for use in treating myasthenia gravis but had not been approved for use against chemical warfare agents.

Biodefense and Pandemic Vaccine and Drug Development Act of 2005

In October 2005 Senator Richard Burr of North Carolina introduced the Biodefense and Pandemic Vaccine and Drug Development Act of 2005 (S 1873). This bill establishes the Biomedical Advanced Research and Development Agency as the lead federal agency for the development of countermeasures against bioterrorism. The new agency would report directly to the secretary of Health and Human Services. The bill provides incentives for domestic manufacturing of vaccines and countermeasures, and it gives broad liability protections to companies that develop vaccines for biological weapons. This bill may appear to settle the residual concerns left unresolved by Project BioShield, but it has raised additional controversy because of public perceptions that it is too favorable to the pharmaceutical industry and issues related to secrecy provisions.

SUMMARY

This chapter has provided a view of the history of ethically conducted human subjects research in the military and has presented some of the problems that still exist among the distinct regulatory bodies that impact this research. The DoD has an ethical responsibility to protect military personnel, yet there is disagreement over how to best protect them against biochemical weapons attacks, in light of equal commitments to respecting agency autonomy and limiting government power over individual decisions regarding what constitutes one's own best interests. These issues and problems are not a mystery to those who confront them on a daily basis, and many thoughtful individuals are focusing their attention on resolving these dilemmas. Some progress is being made, at least in terms of productive dialogue and substantive attention to legislation that might impact research.

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