



DEPARTMENT OF THE ARMY
US ARMY MEDICAL RESEARCH INSTITUTE OF INFECTIOUS DISEASES
1425 PORTER STREET
FORT DETRICK, MARYLAND 21702-5011

REPLY TO
ATTENTION OF:

March 21, 2005

MCMR-UIM-R

Food & Drug Administration
Division of Dockets Management
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Reference: Docket Number 1980N-0208, Final Rule & Final Order Involving Bacterial Vaccines and Toxoids.

Ladies & Gentlemen:

Our understanding of the disease anthrax has grown in recent decades, yet it is remarkable how well this disease was understood in the middle of the 20th century. The central experience of that era related to protection against anthrax by vaccination comes from the experience of investigators from the Center for Disease Control (sic) at four textile mills in the northeastern United States. That experience is reflected in multiple published articles of that era. The best known of these articles is the report of a well-controlled human field trial, known as the Brachman study (Brachman et al, 1962). Brachman's test of anthrax vaccine efficacy tested the vaccine against exposure to anthrax spores, regardless of route of entry. The Brachman study calculated 92.5% vaccine efficacy against all forms of anthrax disease observed, both cutaneous and inhalation anthrax. This is evident in Table 8 of the Brachman publication. Their calculations took into account the amount of time individual workers were employed in the mills under study.

Combining both forms of disease for this analysis is consistent with our knowledge of how this disease affects the human body, insofar as both forms share a common pathophysiology. The common pathophysiology results from the same pathogenic toxins that are secreted by the bacteria, regardless of the route by which anthrax spores entered the body. Regardless of route of entry, the bacteria secrete the same toxins, which lead to similar kinds of cellular damage.

In 1970, Lincoln and Fish published a textbook chapter on bacterial toxins, in which they wrote: "The generalized or septicemic form of anthrax (Lincoln et al., 1964a; Stamatina, 1964a; Nungester, 1967) may either arise from the cutaneous form or result from infection via the respiratory route, infection *per os* [orally], gastrointestinal leakage, or infection of a wound. Regardless of how the infection is established, it develops in an orderly and predictable fashion. The spores germinate and then invade the lymph system. From here, they spill into the bloodstream and are picked up by the reticuloendothelial system, but they soon overgrow this defense system and establish secondary foci of infection." (pages 382-383)

Lincoln and his colleagues based this statement, in part, on their experimental work in rabbits published in 1965. In this work, they compared manifestations of anthrax disease through

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several routes of exposure: "After challenge by all routes (intraperitoneal, intradermal, and aerosol) other than intravenous, bacilli were detected in the thoracic lymph approximately 12 hours before detection in the blood." (page 493)

Advances in science since the 1960s have not changed the ways anthrax spores and bacteria cause harm. Studies in the 1990s by Zaucha and colleagues resulted in findings similar to those of the 1960s: "The pathology of anthrax in rabbits exposed by either route [subcutaneous or aerosol] was similar, with principal findings occurring in the spleen, lymph nodes, lungs, gastrointestinal tract, and adrenal glands." (page 982)

Regrettably, the 22 cases of human anthrax during the anthrax spore bioattacks of fall 2001 allowed modern tools of histopathology to be applied to human cases of cutaneous and inhalation anthrax. In 1993, data about long-hidden pathology specimens from the 1979 Sverdlovsk anthrax outbreak was published. A thoughtful reading of three published reviews of pathologic data from patients infected with anthrax shows common aspects at the cellular level (Guarner et al, 2003; Shieh et al, 2003; Abramova et al, 1993). While all the 2001 cutaneous cases survived, their involved cells exhibited edema, necrosis, hemorrhage, infiltrates, and other manifestations also found in the fatal and surviving cases of inhalation anthrax.

At the direction of the U.S. Congress, the National Academy of Sciences and its Institute of Medicine (IOM) conducted a comprehensive review of the scientific evidence for the safety and effectiveness of anthrax vaccine adsorbed. As the IOM noted in its 2002 report: "When anthrax spores are introduced into the body by any route, they are taken up by macrophages and germinate into vegetative bacteria ... The vegetative bacteria multiply and secrete toxins that produce local edema and necrosis." (pages 46-47)

The pathology of cutaneous anthrax and inhalation anthrax at the cellular level is fundamentally the same. We understand that a protein produced by anthrax bacteria called protective antigen (PA) is essential for anthrax disease to develop in humans. Without PA, anthrax bacteria cannot cause human disease, neither cutaneous nor inhalation. As the National Academy of Sciences noted in its 2002 report: "PA is necessary for the anthrax toxins to enter cells and cause damage. ... Therefore, for the anthrax toxins to create injury in the body, PA must be competent to carry out multiple complicated tasks: it must bind to its receptor, form a heptamer, and bring EF and LF into the cell." (page 71)

Administration of anthrax vaccine adsorbed causes the body to make antibodies that bind specifically to PA (Johnson-Winegar, 1984; Pittman et al, 2000; Pittman et al, 2002). It is a fundamental fact of biology that antibodies bind to proteins in a very specific way, similar to the way that a key fits one lock and not others. This specificity allows antibodies to neutralize toxin activity and otherwise interfere with bacterial actions, preventing infection or disease and conferring immunity.

As the IOM noted in its 2002 report: "The efficacy of AVA against a broad spectrum of *B. anthracis* strains is consistent with the critical role of PA in the pathogenesis of anthrax (Bhatnagar and Batra, 2001; Cataldi et al, 1990; Smith and Keppie, 1954)." (page 71) "The available data indicate that immunity to anthrax is associated with the presence of antibody to PA, such as those stimulated by anthrax vaccine." (page 77)

The facts cited above were known in 1970, published in leading journals and textbooks of that era, when the U.S. government granted the license for anthrax vaccine adsorbed. Scientists have added increasing detail to this fact base since 1970. Each additional finding has reinforced the previous conclusions (Brachman et al, 2003). In 1999, scientists from Harvard Medical School published a schematic diagram depicting the biological mechanism by which anthrax toxins enter cells at the molecular level (Miller et al. 1999; reprinted on page 47 of the National Academy of Sciences report). This diagram shows the pivotal role of PA as the "common denominator" to any pathologic manifestation of anthrax disease, either cutaneous or inhalation. Antibodies that bind to PA ("anti-PA antibodies") interfere with the effects of PA before step 5, as depicted in the diagram on page 47. This interference prevents cellular damage (step 5) regardless of how the spores entered the body.

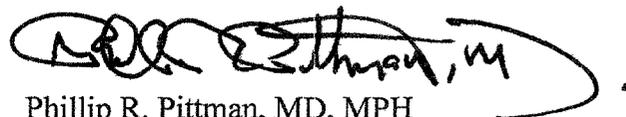
The statistical analysis in the Brachman study was conservative, considering only people who received complete courses of anthrax vaccination or placebo, and ignoring all other data available. When the other workers are considered, including those in the unvaccinated observational group, the conclusions remain the same: vaccinated people have a greatly diminished risk of contracting any form of anthrax when compared to unvaccinated workers. Of the five cases of inhalation anthrax during the Brachman study, all occurred among unvaccinated people and none occurred in vaccinated people.

If one hypothesizes that anthrax vaccine protects only against cutaneous anthrax and not against inhalation anthrax, are there data to support the hypothesis? No. On the contrary, all the data leads to the opposite conclusion. Human inhalation anthrax cases have not occurred in vaccinated people. During Brachman's study, all five inhalation cases occurred among unvaccinated people and none occurred among vaccinated people. Under various experimental conditions in our laboratories, unvaccinated monkeys uniformly developed inhalation anthrax, but 95% of vaccinated monkeys were protected.

Based on the evidence-based reasoning above, the indication section of the labeling for AVA does not specify the route of exposure. Nor should it. Validly, the vaccine is indicated for active immunization against *Bacillus anthracis*, independent of the route of exposure.

If I can offer you any further information or assistance in finding peer-reviewed literature on the topic of anthrax, please do not hesitate to contact me.

Sincerely,



Phillip R. Pittman, MD, MPH
Colonel, United States Army
Senior Military Scientist
Chief, Division of Medicine

Enclosures

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