

Were the rights of human subjects violated at the Arms Mill in Manchester, New Hampshire in 1957 during the human anthrax vaccine trials?

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Abstract

Ethical limitations of the clinical trial of anthrax vaccine as exemplified at the Arms Mill in Manchester, New Hampshire in 1957 are described and discussed. Researchers and physicians have codes to “do no harm.” Once the epidemic began and one worker had died, far better coordination should have occurred between the Arms Mill, local hospitals, local physicians, and the government specialists in anthrax infections. It would be interesting to have today’s institutional review boards evaluate the design of the 1955–1959 trials. It is doubted that the design would be considered ethically acceptable today, as well as lacking sufficient protocols for protecting workers should they become infected. Thus, not only were the design and statistical issues in the trials problematic, but the procedures and protocols of the study can be challenged from an ethical standpoint. As it reviews the efficacy and safety of the anthrax vaccine, the Food and Drug Administration should consider the root of the tree, the uncertain ethical validity of this key study of the anthrax vaccine.

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1. Background

The only published (U.S.) attempt to conduct a human clinical trial of anthrax vaccine occurred as part of a study at four textile mills that processed goat and wool fibers from 1955 to 1959 [1, 2, 3]. The study was a test of an anthrax vaccine developed by Army researchers at Fort Detrick, Maryland. Dr. Brachman worked for the Centers for Disease Control in Atlanta while Dr. Plotkin worked for the University of Pennsylvania Wistar Institute, which obtained much of its funding from the CDC and Army biological warfare contracts [3: 6]. Given the study’s sponsors, its goal was probably to establish effectiveness of the vaccine against inhalation anthrax because that would be the primary military application (hence, the need for a defense against it). Tests had begun at other mills, but in May 1957 tests began at the Arms Mill in Manchester, New Hampshire. The first three series of vaccinations, as well as placebo injections, had occurred by August 1957 for those mill workers who volunteered for the study. Then in late August, workers began to fall ill. Four died of inhalation anthrax (one survived), while four others developed cutaneous infections that were cured.

1.1 Issue

Many of the limitations of the Brachman et al. [1] design and its statistical errors and limitation have been detailed elsewhere [4, 5, 6]. Here the concern is not scientific validity but ethical validity. In a written letter to the Food and Drug Administration concerning the safety and efficacy of the anthrax vaccine, Dr. Brachman indicated that “When possible cases of cutaneous or inhalation anthrax infections were reported among the employees, I was immediately notified and I flew to the

mill in order to confirm the diagnosis [7].” At first, that statement might seem of minimal importance. However, research not only has an empirical validity side but also an ethical side. Today, numerous institutional review boards function to protect clinical subjects and defend their human rights. Even if there were few such review agencies in 1957 to watch out for the rights of human subjects, such rights have always been self-evident to conscientious researchers, as well as physicians.

2. Purpose

The main question to resolve is whether the events after the first case of inhalation anthrax at the Arms Mill in Manchester conformed to ethical practice with respect to the professions of health research and of medicine.

3. Methods

Plotkin, Brachman, Utell, Bumford, & Atchison [2] described what occurred with each of the nine patients who became infected with anthrax after their textile mill was hit by a large amount of anthrax spores, presumably from a specific bale of goat hair that was delivered to the mill from a shipment from Asia. From that information and independent research into the obituaries of the victims, a timeline will be constructed with respect to each patient and their course of diagnosis, treatment, and clinical outcome.

The ultimate question is whether enough was done to treat the victims of the epidemic. Was it reasonable at the time for more to have been done? Dr. Brachman [7] can be presumed to have flown immediately to the Arms Mill after the first victim’s autopsy. At that point was he not in a position to put into effect the best protocols for minimizing the outcome of the epidemic?

4. Results

Table 1 shows the results of the timeline derived from Plotkin et al. [2].

The first inhalation anthrax patient (TT) became ill on August 27th and died on August 30th. The last patient became ill on October 30th and died on November 3rd.

5. Discussion

Lack of Immediate Response. The first autopsy that might have revealed the true nature of a mill worker's illness was performed at the end of August. Thereafter, the company doctor should have been aware of the situation and have informed the officials monitoring the clinical trial. No later than September 2nd, the site monitors should have been on site; when I was a child my parents drove by car from Alexandria, Virginia to Newbury, Vermont within 12 hours, suggesting that a road trip to Manchester from Atlanta, Georgia would have taken no more than 2 days. Even if the site monitors started work on the morning of September 3rd, they should have been briefed within only a few days on the situations of three of the mill workers. Logic should have dictated that the most vulnerable workers would have been in the first departments to receive the bales of goat hair – the picking, carding, and combing departments. In addition, the first victim, already deceased, had been from the combing department, an indication that later victims might have been from that same or adjacent departments. Workers AJ and EC were already, as of 3 September, experiencing preliminary symptoms. There would have been six more days before LL would experience symptoms and nearly two months before AL did. It was still two or three more days before AJ and EC would be calling on their physician and nine days for LL. If nothing else, with one worker already dead and diagnosed with inhalation anthrax, one male worker from an adjacent (carding) department having been seen by his own physician and another having visited the company's doctor, it was past time for action to have been taken for the next two workers who died. If no one else in the world understood how serious inhalation anthrax was and how essential it was to begin antibiotic treatment as soon as possible, the government team should have been. Yet the first indication that a physician was aware of the issues was when Dr. Utell sensed the urgency of the situation with LL, admitting him to a hospital immediately and beginning antibiotics immediately. It is of note that his diagnosis of LL's condition was not reported [2]; one has to assume Dr. Utell suspected inhalational anthrax infection on the basis of his actions subsequent to meeting LL.

Failure of Later Response. Mill worker AL was at work for two days with "chills, fever, cough, malaise, and generalized muscle aches" [2: 993] and this passed unnoticed by the company's doctor. AL was from the combing department where one worker had already died and two workers from adjacent departments had been infected. Obviously, his own physician had not been informed of the crisis at the mill (which I believe is negligence enough on the part of the government team) because his physician diagnosed the flu, nothing more. By November 2nd, AL had improved, a characteristic of most of the

other dead mill workers and yet nothing was recognized. Even after AL was admitted to a government hospital, Manchester Veterans' Administration Hospital, the symptoms were not recognized because not even the slightest bit of antibiotics were administered

Lack of Coordination with local Medical Agencies.

How difficult would it have been to notify local physicians and hospitals to be on the watch for certain mill workers with a certain sequence of fairly specific symptoms and to immediately begin treatment with appropriate antibiotics? Were a few phone calls too much to save lives? Or was the secrecy of this government trial so important that it was worth killing several mill workers and not even letting perhaps only local physicians and hospitals know about the epidemic that was in progress?

The government team should have been aware of the difficulty of clearing anthrax spores from a building once the building is infected. Yet even after the deaths of three people and survival of a fourth (four total cases of inhalational anthrax and three more of cutaneous anthrax before 30 October) the last case still caught everyone by surprise. Were not the workers in the high risk departments yet informed of the risks? Were not the company nurse and physician(s) informed yet? Were not the local hospitals and independent physicians informed yet? If the protocols of the clinical trial forbade such notification were not those protocols in violation of human rights, with or without having to have an IRB coaxed investigators into consideration of subjects' rights, or at least their welfare?

One Hero Recognized. The one patient (LL) who survived was fortunate enough to meet with Dr. Utell who appeared to be aware of the nature of the symptoms, what they meant, and the urgency of getting specific medical attention under hospital conditions. Frankly the other players in this drama seemed unaware of what Dr. Utell seemed to know. Why Dr. Utell appears to have been the only one so informed and thus responsive may remain an interesting question for future investigators.

6. Counter arguments

One "explanation" of these ethical problems might be that the rights of human subjects were less protected in 1957 than in 2005. In the details, yes – but regarding survival itself? Human life, if anything, may have been more valued in 1957 than it is today (to our shame). Hopefully, a human subjects committee should not have been required to make investigators aware of the need to not allow clinical subjects to die from delayed treatment or other neglect.

A second concern might have been the expense of either vaccinating the remaining workers, both in actual cost and in terms of disrupting the design of the study. The latter might have involved the effective loss of enough data to threaten the entire validity of the study. However, the only mill (S) at which the results were ever significant would have still supported the effectiveness of the vaccine against cutaneous anthrax [5], even without new data from the Arms Mill. It is plausible that there was pressure to let the epidemic run its course before vaccinating all workers in order to obtain as much data as possible from

such a rare event and to assess the effectiveness of the vaccine *against inhalation anthrax*.

As far as actual costs in giving vaccine or antibiotics to those workers not yet vaccinated, it may have been too late to use vaccine for most of the workers but antibiotics could have been administered to them, as suggested [2: 1000] even before inhalation anthrax was formally diagnosed. Even limiting antibiotic treatment to the workers at highest risk who had not been vaccinated would have involved only 141 workers [1: 634]. If the maintenance of the experimental design was critical, at least antibiotics could have been administered to the 354 workers who had refused to participate in the experimental part of the design [1: 634], which might have saved the lives of workers CS and AL since they belonged to that group. Narrowing the antibiotic program to only the high risk combing and carding departments might have lowered the amount of treatment to as few as 26 workers in the carding department and 18 in the combing department [5].

It could be noted that even after one local hospital had treated an inhalation patient, they still did not succeed at treating a second admitted patient, with one week between patients (See Table 1).

Another argument that could be made here is that these comments are “Monday-morning quarterbacking.” Any study of historic events can be so accused. What is a plausible argument is that the government team wanted to enact some of these preventive measures but perhaps the mill management or the mill’s own physician vetoed them in order to avoid panic or damage to the mill’s reputation; which is something that, as far as this author knows, has never been addressed. The praise for the company’s nurse by name but not any physician identified as the mill’s company physician might reflect such a situation [2: 1000].

8. Conclusions and Implications

My opinion is that when one experiments with human beings who could be killed by the agent to which they are being exposed (even in a naturalistic environment), one should take special care for their welfare should they become exposed. One should not wait to go into action but be proactive at preventing the subjects from dying. There should have been a plan that if even one mill worker died with symptoms (much less an autopsy) of inhalational anthrax, the mill should have changed gears from their routine medical priorities and begun to investigate proactively all illnesses that might have been a preliminary stage of anthrax infection. If the mill didn’t have such a plan already, the government’s team should have made sure that such a plan was implemented, with a focus on the combing and carding department’s workers at the very least.

The key thing to keep in mind is that the clinical trial didn’t require that the workers die to prove its point. They only needed to be diagnosed with inhalational anthrax to be useful for the evaluation of the vaccine. Yet other factors appear historically to have been more important than saving worker’s lives. Perhaps the government was concerned that if they saved

most of the workers who contracted inhalational anthrax that would have vitiated the need for the vaccine. Perhaps they were concerned that the public would have resented such a project being underway without the potential victims being unaware of it. If the mill workers’ participation was truly and fully informed, what would have prevented the mill from informing all workers that the early symptoms of inhalation anthrax needed immediate and serious medical attention? They might have made such an announcement even without mentioning the clinical trial underway; it might have seemed to be merely an educational program sponsored by the mill in the interest of informing its workers. Both researchers and medical personnel have a moral obligation to do all that they can to protect human subjects, both in their rights and with respect to their personal survival.

In conclusion, the first major clinical trial of a human anthrax vaccine [1] not only was characterized by statistical lapses [4, 5, 6] but appears to have suffered from ethical lapses as well. Continual attention to ethical issues is needed for similar projects that are being planned or conducted today. One would hope that is happening. However, in 1998 this author warned the military of the grave national humiliation that might occur if those responsible for enemy prisoners of war took the ethical foundations of the Geneva Conventions lightly, whether because of inadequate training or other reasons [8]. Even though that seemed mere common sense (not to mention unlikely since another Persian Gulf war seemed remote at the time), fully in accord with U.S. law and Army regulations, that advice was ignored with the well-known consequences of prisoner abuse in Guantanamo, Afghanistan, and Iraq [9, 10].

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Table 1. Timeline of events in Manchester, New Hampshire, 1957, for victims of inhalation anthrax

Patients ►	TT	AJ	EC	LL	AL
Events ▼	Male Age 60	Male Age 49	Female Age 65	Male Age 46	Male Age 33
First Became Ill	8-27 Tuesday	9-1	9-2	9-9	10-30
Visited Company Nurse or Doctor	???		9-5		???
Quit Working	8-27	9-5	9-5		10-31
Visited By Own Physician	8-27	9-5	9-6	9-12*	10-31
Diagnosis	Flu	Bronchitis	Cholecystitis	Not Stated	Flu
First Treated with Antibiotic	Never	9-5		9-12	10-31 Given Pills
Felt Better	8-28				11-2
Got Worse	8-29	9-5	9-7		11-3
Entered Hospital	8-30	9-5	9-6	9-12	11-3
Name of Hospital	Elliott, Manchester	St. Joseph's Nashua	Elliott, Manchester	Sacred Heart, Manchester	Veterans' Administration Manchester
Died	8-30	9-6	9-8	Lived	11-3
Autopsy	8-30 or 8-31	9-6 or 9-7	Refused an Autopsy	N/A	11-3 or 11-4
Buried	8-31	9-9	9-11	N/A	11-6
Obituary Published	9-2	9-7	9-9	N/A	11-4

* Visiting Physician was Dr. Milton Utell, one of the authors in Plotkin et al. [2].

Four other mill workers who were infected with cutaneous anthrax, first showed symptoms as follows: VK on 8 October, HT on 10 October, RP on 15 October, and CS on 5 November.