Brachman

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Dear Matthew:

I am embarassed that I am so late in responding to the notes of your discussions held in Moscow in September, 1986 that you sent me last February. Additionally, I indicated that I would send you a bibliography of recent reprints dealing with anthrax that I am enclosing with this letter.

I have reviewed your notes concerning the reported outbreak of anthrax in Svredlovsk and I have the same opinion that I have expressed previously, that is, I cannot rule out the occurrence of an outbreak of inhalation anthrax. The data you were given are extremely interesting, and in some respects support consideration of a diagnosis of gastrointestinal anthrax. However, this represents data you were given and I don't know what data is real and what data may not have been provided to you. I would like to ask several questions concerning your report and would be happy to discuss any of this with you further.

As I have previously indicated, there are reports of gastrointestinal anthrax in the Russian literature that summarize cases and small outbreaks of gastrointestinal anthrax in Russia, including the Sverdlovsk area. It would appear that animal anthrax is indiginous to the area and that occasionally human cases of gastrointestinal anthrax result from people ingesting contaminated meat. The fact that they evidently immunize 2 million persons annually in the Soviet Union would suggest an endemic problem. However, is the vaccine used throughout the country or only in geographic areas such as the Sverdlosk area where there is endemic disease? I am surprised that immunity from their vaccine persists for only "about a year". The vaccine used in the United States results in longer immunity, though I am not sure that anyone knows exactly for how many years. Our field studies would suggest that immunity lasts for at least 2 to 4 years and maybe longer. I need to review these data before being more specific.

The occurrence of animal anthrax related to contaminated feed, has also occurred in the United States though I am not certain that "bone-flesh powder" is used in this country. Animal materials from rendering plants are used in preparing bone meal which is used as an animal feed supplement (as well as being used as an ingredient in fertilizer). If the animal

rendered products have come from animals contaminated with Bacillus anthracis and these materials are improperly prepared, spores can persist which subsequently can cause disease in recipients of the rendered by-products. An outbreak among hogs was investigated in Ohio in the 1950's in which the vehicle of infection was contaminated bone meal fed to them. Thus, the chain of transmission as reported by the Russians could occur with resultant human disease.

You indicate in your report that isolates of Bacillus anthracis from the "aramil powder, from infected meat and from human victims" were tested in the laboratory and "were judged to be of the same strain". The tests they did were not very sophisticated and I suspect you would be interested in obtaining subcultures in order to conduct more definitive tests to see whether they were the same or similar strains. However, even if they were judged to be the same strain, we cannot be certain that they came from the individual sources as reported.

The burning of buildings possibly contaminated from slaughtering activities seems rather rigorous but possibly represents their great concern over permanent contamination. I would personally think that this was overreaction but it is hard to judge the emotional atmosphere at the time of the outbreak. I would not expect to find Bacillus anthracis in air samples of hospital wards, etc. since humans, even with inhalation anthrax are not known to create aerosals containing the organism.

The age distribution of cases could provide more meaningful data if we had age specific attack rates. Does the age distribution of cases represent the normal age distribution of their population? If this is not the normal age distribution of the population, then why were there not more cases among those less than 39 years of age?

It is of interest that cases continued to occur through May 19 and yet publicity concerning the outbreak evidently began on April 14. Why did cases continue to occur one month after publicity about the outbreak? I wonder if there is any evidence that cases that occurred towards the end of the epidemic were related to frozen meat or meat stored in some other manner.

I note with interest that Professor Nikoforov was evidently contacted in Moscow after the first two cases occurred and immediately traveled to Sverdlovsk. I wonder why they contacted him after only two cases? What did they suspect? They obviously thought about an infectious disease but did they suspect anthrax that early?

I was interested in your comment on page 5 paragraph 16 that "the initiation of gastrointestinal anthrax is thought to require damaged tissue through which spores can enter." I don't recall hearing of this idea before, especially in human gastrointestinal anthrax and thus wonder why there is a feeling that this is necessary in animal gastrointestinal anthrax? Is there any scientific evidence?

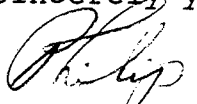
The few reports of gastrointestinal anthrax in humans that have been published in the scientific literature do report the gastrointestinal symptoms that you mention in your report. However, dyspneoa, rapid, shallow breathing and shock are not reported as part of the main symptom complex, but are reported as part of the terminal event. However, the literature does not contain many detailed case reports of human gastrointestinal anthrax.

Another clinical manifestation of gastrointestinal anthrax that has been reported in some outbreaks is known as cervical or oral-pharyageal (or oropharyngeal) disease. There are signs and symptoms of involvement of the lymph nodes and surrounding tissue in the submandibular and cervical regions with the possibility of respiratory distress resulting from compression due to subcutaneous edema. The pathophysiology is that of ingestion of contaminated food with passage of spores through the oral-pharyngeal tissue. They are deposited in the regional lymph nodes, where they germinate, multiply and produce toxin. The toxin is spread locally, and symptoms and signs develop. Thus, in an outbreak of gastrointestinal anthrax, there may be involvement of the gastrointestinal tract, the oral-pharyngeal region, or both. Nowhere in your report do you mention any signs, symptoms, or pathology related to the oral-pharyngeal region. It could be that this form of the disease was not seen but it may be worth exploring this particular point.

In discussing the pathology, you indicate they reported widespread lymph node involvement as evidenced by "black and necrotic" nodes. This is, indeed, unusual for gastrointestinal anthrax that has been reported in the literature. There is no question of the involvement of regional lymph nodes such as those in the mesenteric area but there have not been reports of involved nodes in other parts of the body. At the same time, in reports of inhalation anthrax in humans, the hilar lymph nodes have been involved but the mesenteric lymph nodes have not been involved. Thus, I do not know what to make of these particular findings. I would be very much interested in seeing the slides that were evidently given to you. I wonder whether the pathological material that you were given, is adequate for review by a pathologist experienced in the pathology of human anthrax.

We obviously can only interpret the data and material that they provide to us and our final conclusions have to take this into account. I would be very happy to discuss any of this with you. I remain interested in this problem and would be happy to participate in further related activities whether in the United States or in Russia.
I look forward to hearing from you.

Sincerely yours,



Philip S. Brachman, M.D.

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Enclosure: Bibliography

BIBLIOGRAPHY

Cloning and Expression of the Bacillus anthracis Protective Antigen Gene in Bacillus subtilis. Ivins, B. E., Welkos, S.L. Infection and Immunity. 54: No. 2, Nov., 1986

Photoreactivation of Ultraviolet-Irradiated, Plasmid-Bearing, and Plasmid-Free Strains of Bacillus anthracis. Knudson, G.B. Applied and Environmental Microbiology. 52: 444-449, 1986

Immunization Studies with Attenuated Strains of Bacillus anthracis. Ivins, B.E., Ezzell, Jr., J. W. Jemski, J. Hedlund, Hedlund, K. W., Ristroph, J. D., Leppla, S. H. Infection and Immunity. 52: 454-458, 1986

Comparative Efficacy of Bacillus anthracis Live Spore Vaccine and Protective Antigen Vaccine against Anthrax in the Guinea Pig. Infection and Immunity. Little, S. F., Knudson, G. B. Infection and Immunity. 52: 509-512, 1986

Differences in Susceptibility of Inbred Mice to Bacillus anthracis. Welkos, S. L., Keener, T. J., Gibbs, P. H. Infection and Immunity. 51: 795-800, 1986

Induced release of Bacillus Spores from Sporangia by Sodium Sulphate. Burnett, A. M., Ezzell, Jr., J. W., Singh, J., Zipperle, Jr. G. F., Doyle, R. J. Journal of Applied Bacteriology, 60: 337-339, 1986

Abstracts on Hygiene and Tropical Diseases. Turnbull, P.C. B. Thoroughly Modern Anthrax. 61: R1-13, 1986

Transposon Tn916. Mutagenisis of Bacillus Anthracis. (Abs.) Ivins, B., Knudson, G., Leblanc, D. ASM Annual Meeting, March, 1986

Demonstration of a Capsule Plasmid in Bacillus anthracis. Green, B. D., Battisti, L., Koehler, T. M., Thorne, C. B., Ivins, B. E. Infections and Immunity. 49: 291-297, 1985

Anthrax Toxin, Leppla, S. H., Ivins, B. E., Ezzell, Jr. J.W. Microbiology: 63-66, 1985

The Genetic Basis of Pasteur's Attenuation of Bacillus Anthracis Cultures. Ezzell, J. W., Ivins, B. E. World's Debt to Pasteur, pgs. 107-116, 1985. Alan R. Liss, Inc.

Effects of Anthrax Toxin Components on Human Neutrophils. O'Brien, J., Friedlander, A., Dreier, T., Ezzell, J., Leppla, S. Infections and Immunity. 47: 306-310, 1985

Enzyme-Linked Lectinosorbent Assay (ELLA) for Detecting Bacillus antracis. Graham, K., Keller, K., Ezzell, J., Doyle, R. Eur. J. Clin. Microbiol. 3:210-217, 1984

Immunoelectrophoretic Analysis, Toxicity, and Kinetics of In Vitro Protective Antigen and Lethal Factor Components of Bacillus anthracis Toxin. Ezzell, J. W., Ivins, B. E., Leppla, S. H. Infection and Immunity. 45: 761-767, 1984

Glucosamine Substitution and Muramidase Susceptibility in Bacillus anthracis. Zipperle, Jr., G. F., Ezzell, J. W., Jr., Doyle, R. J., Canad. J. Mincro. 30: 553-559, 1984.

Bacillus Anthracis Calmodulin-Dependent Adenylate Cyclase: Chemical and Enzymatic Properties and Interactions with Eucaryotic Cells. Leppla, S. H. Advances in Cyclic Nucleotide and Protein Phosphorylation Research. 17: 189-198, 1984

Cloning of the Protective Antigen Gene of Bacillus anthracis. Vodkin, M. H., Leppla, S. H. Cell. 34: 693-697, 1983

Evidence for Plasmid-Mediated Toxin Production in Bacillus anthracis. Mikesell, P., Ivins, B. E., Ristroph, D. Dreier, T. M. Infections and Immunity. 39: 371-376, 1983

Elaboration of Bacillus anthracis Antigens in a New, Defined Culture Medium. Ristroph, J. D., Ivins, B. E., Infection and Immunity. 39: 483-486, 1983

Plasmids, Pasteur, and Anthrax. Mikesell, P., Ivins, B. E., Ristroph, J. D., Vodkin, M. H., Dreier, T. M., Leppla, S. H. ASM News 49: 320-322, 1983

Anthrax Toxin Edema Factor: A Bacterial Adenylate Cyclase that Increases Cyclis AMP Concentrations in Eukaryotic Cells. Leppla, S. H. Proc. Natl. Acad. Sci. USA 79: 3162-3166, 1982