Date: Wed, 17 Mar 2004 07:44:22 -0500
From: "Lindler, Luther E Dr WRAIR-Wash DC"
<Luther.Lindler@NA.AMEDD.ARMY.MIL>
To: "Mathew Meselson (E-mail)" <msm@wjh.harvard.edu>
Subject: FW: Biological Weapons Defense

Dear Dr. Meselson,

I am contacting you to see if you still intend to write the Forward section you committed to some time ago. I know it has been a long time. We had severe difficulty getting the smallpox chapter written. Humana says they can send you some of the chapters in galley form when they are ready. I believe this should be relatively soon. Alternatively, I can send you the final Word documents for ones you are interested in.

Thanks and looking forward to hearing from you soon,
Sincerely,

Luther Lindler, Ph.D.
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-----Original Message-----
From: Zygmunt Dembek, PhD [mailto:makaikauai@msn.com]
Sent: Sunday, March 14, 2004 10:29 PM
To: Luther E Lindler Dr WRAIR-Wash
Subject: Biological Weapons Defense

Hi, Luther,

Congratulations on the listing of Biological Weapons Defense on the Humana Press website:

http://www.humanapress.com/ProductDetail.pasp?txtCatalog=HumanaBooks
<http://www.humanapress.com/ProductDetail.pasp?txtCatalog=HumanaBooks&txtProductID=1-59259-764-5> &txtProductID=1-59259-764-5

It's good to see that your perseverance has paid off! I'll look forward to reading the proofs to see how my chapter came out and also be able to make some minor edits

Best wishes,

Zyg

Zygmunt F. Dembek, PhD
LTC, MS, USAR

[Part 2, Application/MSWORD 302KB.]
[Unable to print this part.]

[Part 3, Image/JPEG 182KB.]
[Unable to print this part.]

[Part 4, Image/JPEG 65KB.]

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OF INTEREST" and a single Table (described above), that follows the rest of Pathogenesis Section's information.

The remainder of the Section(s) cover, to greater and lesser degrees, the body of anthrax pathogenesis research. Again, the important new papers get very short review, while research over 5-10 years old gets most of the text. This is unfortunate.

The details provided in the "GENE REGULATION" section are at a much deeper level than the rest of the chapter. May be an instance ot too much trivia. The only Figure provided is a regulation interaction map. Nothing wrong with the map or the section, but I feel that Gene Regulation Patterns (while of great interest to a very few of us) will be of the LEAST interest to the bulk of your Book's readers.

At least put in some cool Figures for the earlier sections. Pictures/drawings of bacteria, spores, skin lesions, chest X-rays, geographic maps of outbreak zones, etc.

5. 4-HUMAN DISEASE

4.1-Inhalational Anthrax. Here's a spot for updated information to be added from last fall or Sverlovsk. Good spot for Figures (X-rays & other medical imaging published this past year in the medical journals) and some data tables even from either Sverlovsk or the US attacks. The term "...to cause respiratory infections..." probably should be changed to "inhalational" as its not really a respiratory infection but, rather, the lung is the portal of entry for systemic disease. Again the phrase, "when used as a biological warfare agent.....spores are dispersed into respiratory droplets and disseminated within target populations....." needs a reference. What are the effects of humidity, wind conditions, being inside vs. being outside, etc. on becoming exposed and contracting anthrax during this sort of exposure? Why were mortality rates last Fall much less than predicted? Is there acute pnumonia in anthrax attacks that is not seen in natural inhalation anthrax? (I dont know).

4.2-Cutaneous Anthrax. Another good spot for a Figure or two. Especially from cases from last Fall.

4.3-Gastrointestinal Anthrax. Is "50% mortality" with or without active treatment?

6. 5-ANTHRAX PROPHYLAXIS.

"Chemotherapy is rarely effective in cases of inhalational anthrax"??????? Talk about last Fall! "When diagnosed early, inhalational anthrax should be treated with penicillin and streptomycin for at least 30 days." PLEASE, PLEASE, CHECK WITH THE CDC WEBSITE TO GET THE CORRECT TREATMENT RECOMENDATIONS, BOTH WITH DRUGS AND DURATION OF TREATMENT! Be Careful here. Doublecheck Info. Expand this section to be correct, comprehensive and to explain what doctors need to do to best treat their patients. Or at least reference the appropriate materials. Do not give wrong, or outdated, advice in this section. Discuss the pro-con arguments for post-exposure administation of vaccine to those exposed?

7. 6-PATHOGENESIS

There is WAY too much text on anthrax genes (from the TIGR sequencing effort) that have homology to other pathogens' virulence factors..... BUT HAVE NOT SHOWN TO PLAY ANY ROLE IN ANY ASPECT OF ANTHRAX PATHOGENESIS...YET. Just a single, simple TABLE listing the potential anthrax virulence gene ORF#, the name of the ortholog's from other species, proposed function of the gene, % AA identity, ref# would suffice. It is not justified, at this time, to extrapolate in such great length, and with so much text, just because a gene happens to exist. There are few indications, data, publications, that these genes are important. (Additionally, most of the genes disscussed in detail are ALL found, as a complete set, and with super-high homology in other non-anthrax-causing Bacillus sp. What does this mean for these genes? And what if the gene's regulators are missing/flawed, as in the case of anthrax plcR? What does that mean?.). And be inclusive! Don't just, pick and chose and name a dozen virulence-factor-like genes found by the sequencing project. Cover the entire chromosome and name them all. And, BY ALL MEANS reference the project, the folks that did it, how you used that information, the %-identities you found. Overall, best to cut this part of "new genes" way down....Just one short paragraph entitled "POTENTIAL NEW GENES

structure looks like, how readers might get access the genome sequence to do their own sequence "mining", what constituted (to the authors) sound criteria for defining those few genes discussed in detail later as "novel targets for antiinfective therapies". My guess is that the authors BLAST'ed TIGRs unfinished genome sequence for their "favorite" genes (likely including orthologs of genes they work on in their own labs, those from other species) and simply now "claim" that this represents the ones that "are of interest". Care, explanations (and disclosures) are needed when these types of claim are made.
d. "Respiratory" anthrax should be changed to "inhalation" anthrax for consistency with the rest of the chapter and for consistency with the efforts of most anthrax researchers to be uniform with this particular phrasing. It is NOT a big deal, I admit.
e. The last part of the Introduction talks about the toxins. So a couple of points here. First terminology. LF and EF are not actually "the toxins", but are components of lethal toxin and edema toxin. Being accurate helps build credibility. Second, the sound notion that "....Toxin delivery and activity represent late or final steps of anthrax pathogenesis, and it is not clear whether this strategy (i.e., anti-toxin therapeutics) can provide compounds for the successful treatment of infected hosts.", is an important topic that needs slightly more complex discussion. It needs its own Section. ALSO: Recent work (see Michael Karen's recent Science paper) now suggests that (though lethal toxin is still critical during the late and the final stages of the disease) it may ALSO be involved in earlier stages of the disease. Edema toxin's role makes much more sense at EARLY stages than at it looks bad a anthrax chapter simply ignores its implications (especially if "hard claims" are made in the chapter that are muted by the findings of this research).
f. As mentioned above, a new Section discussing advances (and problems) of toxin-based therapies and their recent papers, would be welcomed by your readers.

3. 2-BACTERIOLOGY
Mostly all fine. All info covered by many other previous reviews (but its still a great story!). You might consider re-naming this section "HISTORY & BACTERIOLOGY"
Page 4: Are B.subtilis and B.cereus really considered "saprobic"? Great section for addition of figures!

4. 3-ANTHRAX OUTBREAKS
3 short paragraphs (Intro, Zimbabwe & Sverdlovsk paragraphs) are not quite enough here for what I preceive as the thrust of your book. The Sverdlovsk paragraph especially should be expanded as to what this event really implied for our knowledge of the state Biowarfare capabilities in our world! And for what we learned about how weaponized anthrax is so different from natural anthrax. Can we now tell the difference from natural outbreak and an attack? How? What did we learn from Sverdlovsk in terms of anthrax biology, anthrax medicine/pathology and anthrax as a weapon! AND HOW COULD ANY CHAPTER ON ANTHRAX IN YOUR BOOK NOT INCLUDE THE DETAILS AND IMPLICATIONS OF LAST FALL'S MAIL ATTACKS!!!!!!!!! We learned so much from that. So much is published. See the CDC websites, the Hopkins Civilian Biodefense websites, the NIH's websites, the DOD sites, the NEJM & JAMA sites for primary references! It looks pretty silly to not give this some print space. Good section to add a Figure.

1. First, and probably most importantly, Drs. Missiakas and Schneewind have a complete mastery of the English language. Your readers, both expert and lay, should not have any problems understanding the phrases, sentences and paragraphs offered in this chapter. As this is often NOT the case with book chapters, you should feel fortunate.

2. Although most of the "old anthrax information" provided is adequate, I am quite disappointed that the most of the entirety of the published anthrax advances of the last 12-18 months were not addressed in detail, most not even mentioned or cited (some of these are VERY high-profile papers in big journals) AND that the immediate questions ("Important stuff we don't know"), that last year's attacks made obvious, were not mentioned.
Good sections missing might include: One highlighting all the new ways folks use molecular forensics (including the genome sequence) for ID'ing anthrax; One highlighting the status of the current vaccine (Institute of Medicine's approval of ?but its not perfect- report on the AVA, the CDC's support of the vaccine website, the DOD's new initiatives, all the new vaccine methods proposed in various publications, etc.) and new vaccine strategies in the very research stage that have been reported on, and who, exactly, should be immunized and who should not; One section on all the MANY high profile articles (in Science and Nature etc) on a variety of very interesting anti-toxin based therapeutics and phage-lytic enzyme therapeutics (these were BIG papers and hard to just ignore altogether; Are drugs and passive Abs etc aimed at the lethal toxin components a feasible idea for an exposed person? Why or why not?); And one section on our areas of important lack of knowledge that became evident with last year's attacks (even if there are no answers yet, they could state the questions "as important"), like "How many spores does it take to kill a person?" "Can spores pass through the fabric of paper envelopes?" "What are human predisposing conditions that would make an exposed person more or less susceptible to anthrax?" "Are spores in the drinking water supplies a threat?" "Is microwaving your mail useful?" "Once they get in the air of your office building how long do spores float around?" "If spores land on your desk, or your front lawn, can they become airborne again?"

3. 1-INTRODUCTION:
a. The second sentence on "aqueous droplets" requires a reference. How about "dried spores" as a weaponized form of anthrax? (somewhat covered later in text but might need to be mentioned here as well).
b. You may like a bit of sensationalism to help sell a book. But I find it a bit distasteful. Phrases like, "...B.anthracis is the focus of many biological warfare industries....." and, "Biological warfare is an evolving research enterprise...." Are not to my personal tastes.
c. The last sentence of the first paragraph reads, "This review has examined the genome sequence of B. anthracis to describe its pathogenic strategies and we focus our discussion on the identification of novel targets for antiinfective therapies". This is a fine claim. But, from reading the rest of the work, it rings false! There is no mention of the genome sequencing work. No credit (that I could find) given to the genome sequencers (TIGR). No mention on how WELL the genome was sequenced (was it good data? complete?). No mention on "how" the genome sequence was actually "examined" by the authors. No mention on how many genes anthrax has, what classes of genes it has, what the genome

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Obesity drug inhibits prostate tumor growth

Proteomics screen identifies novel prostate cancer target

(La Jolla, California) The Burnham Institute's Jeffrey Smith, Ph.D. has discovered that orlistat, commonly prescribed as an anti-obesity drug, has a positive side-effect: it inhibits cancer growth. Dr. Smith made this discovery using an activity-based proteomics screening technique developed in his laboratory that makes it possible to identify active targets and simultaneously screen for their inhibitors. These results will be published in the journal Cancer Research on March 15.

The metabolism of a tumor cell is different from its normal counterpart cell. Scientists have long suspected that metabolism is connected to tumor progression. Dr. Smith and co-workers designed a proteomics screen based on monitoring the activity of a family of enzymes--serine hydrolyases--involved in metabolism. They used their screen to compare normal prostate cells with prostate cancer cells and discovered that the prostate cancer cells are affected by an increased activity of fatty acid synthase. Fatty acid synthase is the enzyme that converts dietary carbohydrate to fat.

The screen also identified orlistat, marketed by Roche as XenicalTM, as an inhibitor of fatty acid synthase.

These discoveries, made in vitro, held true when tested in mice. When they administered orlistat to mice bearing prostate tumors, the Smith laboratory discovered that the drug was able to inhibit tumor growth in mice. Further experiments confirmed that orlistat has no effect on normal prostate cells and no apparent side effects in the mice; it acts specifically as fatty acid synthase.

Additional screening of breast cancer and colon cancer cells revealed that fatty acid synthase activity is upregulated in these tumors, as well, presenting the possibility of designing new treatments for these cancers based on inhibiting the enzyme's activity with orlistat or a new drug based on orlistat's inhibitory activity.

Orlistat was originally developed as an inhibitor of pancreatic lipase. Pancreatic lipase is a member of the same enzyme family--the serine hyrdolases--used in Smith's screening. It is involved in processing of fats in the digestive tract, which is how the drug prevents adsorption of dietary fat.

The method developed by Dr. Smith represents a quantum leap in drug discovery. So-called "activity-based" proteomics screening is a new frontier in medical research, based on applying information gleaned from the human genome project. The ability to compile a comprehensive profile of a potential drug's activities, revealing unintended activities along with the intended behaviors targeted by the drug offers a systematic way to simulate how a drug will work, before it is actually tested in animals and humans.