Correspondence

Anatomy of Anthrax Infection from a REDOX Perspective

After the news reports regarding Anthrax began, I did a quick Medline search – searching the words "oxidative and anthrax" and identified a few key references which are important in relation to anthrax's toxic effects. The first article was from work done at Albert Einstein University and Harvard Medical School, published in the *Journal of Molecular Medicine*, Nov;1(1): 7-18, 1994. This and a few other references provided relevant information about mechanisms and the importance of nutritional compounds.

I'll present a short background of information. Anthrax is an infectious disease caused by the gram-positive, spore-forming, rod bacteria *Bacillus anthracis*. The virulence of the organism is dependent on the presence of a poly-D-glutamic acid capsule and production of toxins. The production of the toxin and the capsule is due to the presence of two genetic plasmids (which are nucleic acids separate from the bacterial chromosome). The capsule is thought to enhance virulence by preventing the lysis of the organism by cationic host proteins.

The organism secretes a toxin made of three proteins: protective antigen (PA); edema factor (EF); and lethal factor (LF). PA binds to cell-surface receptors on the host's cell membranes. After being cleaved by a protease, PA binds to the two toxic proteins EF and LF and their pathogenic effects occur. The lethal factor shocks the immune system, the edema factor causes swelling and shock, and the protective antigen permits the bacteria to enter the host cell, and allow entry of the toxins. (*Nature.com*)

Neutrophils are disarmed by anthrax. The oxidative metabolism via the neutrophile oxidative burst is decreased due to signaling interference by the pathogen. (*Infection*, 22(4) 281-2, 1994.)

The macrophages, on the other hand, are active mediators of symptoms and death induced by the lethal toxin during anthrax infection. Cell death of macrophages can be detectable within 1 to 2 hours of exposure to lethal toxin in in vitro studies. Lesser exposures to LT are not immediately cytolytic but stimulate the production of free radicals and inflammatory cytokines, which largely account for the shock and death of anthrax patients.

In the *Journal of Molecular Medicine* study, mouse macrophages treated in vitro with high levels of lethal toxins released large amounts of superoxide anion, beginning at one hour, which correlated with the onset of cytolysis. Cytolysis could be blocked with exogenous antioxidants N-acetyl-cysteine or methionine, which promote production of endogenous glutathione. Levels of NAC–as low as l millimole–could reduce cytolysis. If we were to extrapolate to the average adult human weighing 150 pounds, then 5 grams of NAC might substantially reduce cytolysis to approximately half the original level. This number will be much higher when accounting for oral absorption. This is a provocative finding, which encourages further exploration of the benefit of oral antioxidants.

Much higher levels of antioxidants were required to reduce effects of the edema agent. Herein, doses of 50 millimole of the nutrients or higher were required to reduce edema, however in these in vitro studies, 90% or higher inhibition of cytolytic effects was achieved. However, it would be near impossible to achieve a concentration of 50 mM in vivo.

Mutant macrophages deficient in the ability to produce reactive radicals were relatively insensitive to the action of the lethal toxin, as expected from the above model. Other mutant macrophages which had increased oxidative burst potential showed elevated sensitivity to toxin-mediated macrophage damage.

Macrophages from a patient with Chronic Granulomatous disease, which is a condition wherein the phagocyte oxidative burst mechanism is inactive, was totally resistant to the toxin.

Mice pretreated with NAC or vitamin C via intravenous infusion showed partial protection against the lethal toxin. In animal studies, such IV treatment spared the lives of animals that would surely have died without the nutritional intravenous therapies. The authors conclude that reactive oxygen species are involved in both the cytolytic action of anthrax lethal toxin and the overall pathogenic process in vivo.

The authors present a warning that high prophylactic levels of antioxidants might be problematic, by reducing macrophages ability to respond to other threats. However, this sounds a bit like what we've heard from oncologists: "Don't use antioxidants" - as they will interfere with chemotherapy. Herein, we all know that potent antioxidant regimes can be developed which do not reduce immune vigilance but rather increase it. We know that at bowel tolerance levels of vitamin C, patients will exhibit a more optimum immune response, and that synergism, or at least enhanced benefits, appear to result from combination antioxidant regimes.

If antibiotics were to become unavailable, then IV vitamin C and IV glutathione therapy could be life saving. It is generally believed that if antibiotic treatment is not initiated well before symptoms occur, that there is a high mortality rate associated with antibiotic treatment. In such situations it could be life saving to accompany antibiotic therapy with IV C and IV glutathione. The IV nutrients could slow and even block free radical and cytokine production, and "buy time" for the antibiotics to work on the infection.

I came across another interesting article suggesting that DHEA and melatonin may be protective. (*Cell Biology and Toxicology,* 16:165-174, 2000.) Studies have demonstrated that DHEA and melatonin play a role in immunomodulation, and as antioxidants in animals and humans, which lead the authors to test DHEA and melatonin in in vitro testing of anthrax-induced macrophage damage.

DHEA, when applied to mouse macrophages, significantly inhibited tumor necrosis factor alpha (TNFa) caused by the lethal anthrax toxin. In addition, exposure of melatonin to lethal toxin-treated macrophages also decreased TNFa. Physiological concentrations of DHEA (10^{-8} mol/L), and concentrations ten times higher protected macrophages by 35%. These observations along with others, demonstrate that DHEA might play a role as a regulator of the production of various cytokines in macrophages, including anthrax lethal toxin-induced cytokines. DHEA also appears to act as a cytokine buffer to insure homeostasis of the cell during the alteration in cytokine production. From my calculations, 1 to 10 mg might be the right range, but this would have to be determined. Melatonin may inhibit TNF alpha via its antioxidant or immunostimulatory activity. Previous results suggest that 10^{-7} mol/L could inhibit TNFa in monocytes. In this study, concentrations ranging from 10^{-8} to 10^{-9} mol/L reduced TNFa by about 50%. Including all this data together, and accounting for extensive loss due to absorption, the range would be from 100 mcg to 10 mg of melatonin. Research would have to determine dosages required to maintain these tissue concentrations. An accurate extrapolation would require determination of oral dosing in relationship to blood and tissue levels of melatonin and DHEA. This is important because a limited therapeutic range exists, outside of which protection failed.

Another study with mice (*Proc. Soc Exp. Biol Med* 216, 1997) finds that stress due to retrovirus infection caused a decrease in immune function, an increase in oxidative stress, and an increase in TNF. These responses were prevented by providing much higher levels of DHEA at the human equivalent of 1500 mg per day. At these doses, the level of IL6 and tumor necrosis factor, and the increase in oxidative stress were suppressed.

Clearly we need a greater focus on the potential use of nutrients in relation to anthrax. More exact data on melatonin, DHEA, N-acetyl-cysteine, and vitamin C, are required to determine oral and/or intravenous doses. Lives could be saved by combining such therapy with antibiotics. Lives could be saved if antibiotics were not available.

–Stephen Levine, Ph.D.
Allergy Research Group
30806 Santana St., Hayward
CA 94544

Antipsychotic Drugs and Addiction

I am writing in response to the Editorial, (JOM 16.3.01) "Are Modern Tranquillizers Addictive?"I remember Dr. Hoffer once said to me that the drugs of the future will be able to do exactly what we want them to do. I think I responded "I don't believe it," at the time. The reality is, you never get something for nothing, there's no such thing. Everything I have learned about the problem of schizophrenia shows a need for an accounting, an investigation. Without it, only so much will be achieved, in terms of shifting the problem.

With respect to the newer antipsychotics and your observations about them, I'd like to say this. First of all, my experience of taking these newer drugs is minimal, yet enough to confirm your findings. I had very bad extra-pyramidal side effects coming off them, I couldn't walk properly.

With the older drugs this never happened. I find the cool symptoms of schizophrenics, the flatness, disconnection, disinterest and self-absorption, are in fact the addictive behavior. That is, schizophrenics are addicted to the way of relating. They are habitually disinterested.

The lack of engagement in relationships and connectedness makes one vulnerable to the hot symptoms of the psychotic state which require drugs. My own belief of the cool symptoms, as I was engaged in them, was that they were inconsequential. Similar to how it is possible for a cigarette smoker to rationalize, arguing that they don't believe smoking causes cancer, and continue smoking. It's denial.

Another example, the same argument about the cool symptoms goes something like this: "I don't believe brushing one's teeth prevents cavities, because when I have a cavity and then brush my teeth, the cavity doesn't go away. Therefore, I conclude that brushing the teeth does not prevent cavities, and also, I am not going to brush my teeth!" It's all very logical. But, it's also nonsense. The fact is, cavities won't happen when a person brushes, properly and responsibly. It's also not really possible to explain this to someone, unless they try! They have to try it for a while, no less! On faith! See what happens. Everyone struggles with these issues. They are part of the human experience, inseparable from it. One of the properties of addictions is that, without dealing with the underlying cause(s), you may transfer the addiction to another thing or substance, but you will remain addicted to something. When you remove the new anti-psychotics in these cases, then it follows that the patient is looking for something else to attach to at that time, seeking to replace what was removed, which they had been leaning on up to this point. The psychosis is familiar territory.

–Anonymous

Schizophrenia, Thyroid Hormones and Selenium

According to Hoffer and Osmond,[1] A large number of workers have shown that thyroid hormone either in the form of dried gland or as the pure hormone triiodothyronine does improve cure rates [for schizophrenia] much above the natural untreated rates and other standard treatments used, including the tranquilizers". Such improvement with thyroid treatment is thought to occur because the majority of schizophrenics are, for genetic reasons,[2] unable to rid themselves of the hallucinogenic oxidized derivative of adrenalin,

adrenochrome.[3] Adrenochrome appears antagonistic to thyroid hormone, most probably to triiodothyronine (T3). It is likely, therefore, that a treatment protocol that provides T3 will reduce the negative impacts of excess adrenochrome while simultaneously helping to restore normal functioning of this thyroid hormone.

The geographical evidence strongly suggests that any benefit in schizophrenia from thyroid hormone supplementation must be coming from triiodothyronine (T3) not thyroxine (T4). To illustrate, in 1988 this author[4] published the results of a study which involved correlation of 219 environmental variables with the prevalence of schizophrenia, in the United States, in 1965. The strongest positive correlation was with selenium deficient fodder crops (r= 0.58497, p=0.0001). Although the computer database also included information on the spatial distribution of soil iodine in the United States, no statistically significant correlation was discovered between this trace element and schizophrenia. Neither was there any significant correlation between the distribution of goitre and this mental illness.[5] Subsequently, Brown[6] examined the selenium-schizophrenia relationship in more detail, demonstrating that nine surveys, conducted in the United States during the period 1880 to 1963, all indicated a negative relationship between selenium levels in fodder crops and schizophrenia prevalence. Simply put, there is nothing to suggest that the number of schizophrenics in the United States is influenced by levels of iodine in soils or foods, but there is good evidence that this illness is, and has always been, strongly negatively correlated with the intake of selenium. Indeed, variations in the prevalence of schizophrenics in U.S.A. state and county mental hospitals suggests a selenium-related relative risk[7] of 1.77:1.

Selenium plays a key role in the production of triiodothyronine, but not of thyroxine. Researchers at the Hahn-Meitner Institute in Berlin,[8] for example, discovered that selenium is necessary to produce deiodinase, the enzyme required to convert thyroxine into triiodothyronine. If there is a selenium deficiency, deiodinase is depleted and adequate quantities of triiodothyronine cannot be produced. Naturally, this is most likely to occur when diet is low in selenium, reflecting a soil deficiency.

It would appear that the abnormally high adrenochrome levels in many schizophrenics increases their requirements for both selenium and triiodothyronine. The former is needed to produce deiodinase which is essential for the conversion of thyroxine to triiodothyronine. It follows, therefore, that any treatment protocol for such patients should include supplements which contain above normal levels of both selenium and either dried thyroid gland or the pure hormone triiodothyronine.

–Harold D. Foster, PhD
Dept of Geography
University of Victoria
P.O. Box 3050
Victoria, BC V8W3P5

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