

~ Glutathione and N-Acetyl-Cysteine (NAC) ~ © 2001 Lark Lands, Ph.D.

Research has shown that higher glutathione levels clearly correlate with increased survival in HIV+s. Unfortunately, research has also shown that cellular levels of glutathione go downhill as HIV disease progresses and that levels in plasma, lung fluid, and T cells are frequently deficient, even in very early disease stages. This may result from a combination of increased oxidative stress in the body and decreased synthesis of glutathione in the liver. Proper glutathione levels are critical to immune function because it is the most important intracellular water-soluble antioxidant. It is a cofactor for the antioxidant enzymes glutathione peroxidase and glutathione transferase. It is also necessary for competent lymphocyte function, including the activity of cytotoxic T cells. In addition, the liver uses glutathione for the detoxification of drugs. When levels of glutathione in the liver are too low, its ability to properly break drugs down may be compromised. Optimal levels of glutathione are also necessary for the immune defenses of the lungs. Glutathione deficiencies may increase the risk of lung infections. Studies done at Stanford University, the National Institutes of Health, and a number of European research institutes have shown that N-acetyl-cysteine (NAC) works both directly and indirectly as an antioxidant, helping to raise glutathione levels back toward normal. Glutathione itself has been shown to exert inhibitory effects on HIV similar to that of NAC. Although most of the discussion of glutathione in the HIV community has focused on NAC, the use of vitamin C, alpha-lipoic acid, and L-glutamine are also very important to give the body what it needs to fully replenish glutathione in all the places that it is required and maintain optimal levels over time. Restoring and maintaining glutathione levels may be one of the very most important things you can do for long-term survival.<sup>1</sup>

Researchers believe that restoring glutathione levels can reduce oxidative damage, inhibit HIV stimulation by inflammatory cytokines such as tumor necrosis factor, and block viral production. *In vitro* research done at Kumamoto University in Japan has shown that NAC significantly depresses both HIV Tat activity and HIV infectivity, and is active in both acute and chronically infected cells.<sup>2</sup> It may also help restore the function of T cells, reduce the wasting often seen in later stages, and prevent apoptosis. The latter may be particularly important since this programmed cell death is thought by some researchers to be a major cause of the loss of CD4 cells. Drs. Paul Sandstrom (Retrovirus Diseases Branch, Centers for Disease Control and Prevention, Atlanta, Georgia), Thomas Buttke (Department of Microbiology and Immunology, East Carolina University School of Medicine, Greenville, North Carolina) and their colleagues have produced substantial research showing that oxidative stress may induce apoptosis and that antioxidants such as glutathione and NAC may block this process.<sup>3</sup> Glutathione is important to immune function in a number of ways, including its effects on the synthesis and turnover of interleukin-2 receptors.<sup>4</sup> Those receptors are, of course, critical to the use of interleukin-2, the body's natural growth hormone for T cells. For that reason, the use of glutathione-raising supplements in conjunction with IL-2 therapy is probably very important. [See discussion in *Chapter Seven, Interleukins.*] Several researchers have strongly suggested that glutathione replacement therapy may be effective in slowing disease progression and delaying development of opportunistic infections.<sup>5</sup> A number of very important papers on glutathione were presented

at a conference held at the National Institutes of Health, (*Conference on Oxidative Stress in HIV/AIDS*, National Institutes of Health, Bethesda, Maryland, November 8-10, 1993). The scientists there reported that glutathione is decreased in all T cells in HIV+ people, averaging only 63% of normal in CD4's and 62% of normal in CD8's, and that this decrease in glutathione levels begins in the first weeks of infection and grows worse over time. Dr. Leonard Herzenberg of Stanford University underscored the importance of this by his statement that even a 5% decrease in glutathione yields a significant decrease in immune effectiveness, even in those with still-high (even normal) CD4 counts. It's thought that this decrease in glutathione causes increased susceptibility to oxidants and inflammatory stimulations. This is very likely part of the cause of the intestinal inflammation that blocks uptake of nutrients.

In addition, glutathione helps to regulate the release of cytokines like tumor necrosis factor (TNF), elevated levels of which are a known cause of wasting. Interestingly, it was reported by a number of researchers that one of the results seen in various studies of glutathione supplementation was weight gain. In addition to its role in increasing glutathione, NAC supplementation may also be important for preventing wasting for another reason. Cysteine is one of the building blocks of body proteins so the low levels of cysteine that people with HIV have (because of the high levels of oxidative stress) may prevent proper building of proteins. A direct mechanism of wasting, even in the absence of HIV infection, is the result of the priority the body places on maintenance of the enzyme trypsin which requires cysteine for its production. When dietary cysteine sources are low, the body will rob other body protein in an attempt to maintain this important enzyme.<sup>6</sup> This is obviously a problem because in HIV infection the body turns to protein as an energy source and starts, in essence, burning up the muscles. Then the low levels of cysteine may be one of the factors that keeps the body from being able to restore that protein. The end result is loss of the body's protein stores. Supplementation with NAC may help provide one of the needed building blocks to restore protein. [Of course, a plentiful intake of protein in your diet is also important; see *Chapter Three*; a plentiful supply of glutamine is also crucial; see above.] Dr. Rene Olivier, of the Pasteur Institute, also reported that research has shown that after two to six months of NAC therapy, there is a disappearance of apoptotic cells and an increase in cell viability, obviously exciting since apoptosis is thought to be a major factor in HIV-induced cell death. Last but not least, cysteine is a component of metallothionein, the protein that regulates serum levels of copper and zinc. Thus, a deficiency of cysteine may have a negative impact on the body's ability to maintain normal levels of copper and zinc.<sup>7</sup> Supplementation may be very important for this reason, also.

The research presented at the NIH conference indicates that somewhat higher levels of NAC than those commonly used in the past may be necessary for the best results. Based more on rumor than research, many people have been taking doses of 1200-3000 mg per day during the last several years. Drs. Leonard and Leonore Herzenberg, full professors at Stanford University and among the world's experts on NAC, have completed a trial through their lab using an initial dosage of 8000 mg per day, given orally.<sup>8</sup> Many people in their trial had to decrease this dosage because of perceived side effects (although about as many in the placebo group as in the treated group decreased their dosages, indicating that the NAC itself may not really have been the problem), with the majority ending up at 4000 mg per day. The study's results have clearly established that NAC does raise glutathione levels in whole blood. Since the study was

not designed as a dose-ranging trial, it is still not clear what the optimal dose would be for normalizing glutathione levels in most people. The best guess at this time is a dose of 2000-4000 mg per day.

Although the fact that NAC raised glutathione levels was quite predictable, other findings from this study have surprised many. Of the 97 people with CD4 counts under 200 whose glutathione levels were tested at the beginning of the study, only 37 entered the trial where NAC was given. The remaining 60 people were followed over time in order to see whether the initial differences in glutathione levels correlated with differences in survival. And correlate they did. The finding that startled even those among us who are great believers in antioxidants was a highly significant difference in survival between those who had low levels of glutathione when initially tested and those who had higher levels. The group with higher initial levels of glutathione (26 people) had approximately 85 percent survival after three years, whereas those with low initial levels (34 people) had only 18 percent survival after three years, a truly remarkable difference. [The exact percentages are not yet known because at the time of this writing, a few people have not yet reached the three-year point; however, the percentages are not expected to change much from these.]

Again, this survival difference was not related to treatment with NAC since these were the people who didn't continue in the study. Interestingly, although the trial in which people were given NAC was not designed to detect survival differences (and was too small and too short-term to do so), a retrospective look at those taking NAC versus a matched group who did not take it did find a statistically significant difference in survival. Those taking NAC appeared to gain about a year of additional survival compared to those who didn't. Thus, although the design of the study precludes saying that low glutathione in the body "causes" poorer survival, all the findings from this study certainly do support that informal conclusion. You don't have to go very far out on a limb to say that HIV+s with higher levels of glutathione may well survive substantially longer. For those only interested in pure science, additional research will be required to "prove" this.

In the meantime, for those interested in survival, using all the possible approaches to raising the levels of glutathione in the body, as well as the levels of the other antioxidants which recycle and regenerate it, seems like a very good idea. As discussed in the preceding entry, the use of L-glutamine is particularly crucial; read that entry! In addition, using optimal levels of vitamin C is very important for maintaining glutathione levels. As well, the use of alpha-lipoic acid to regenerate glutathione is extremely important. German researchers have found that supplementation with alpha-lipoic acid results in increases in blood levels of both glutathione and vitamin C, as well as increases in CD4 cells and decreases in the body compounds that result from oxidative stress.<sup>9</sup> Research carried out by Dr. Lester Packer at the University of California at Berkeley has shown that alpha-lipoic acid may, in fact, be the best way to raise glutathione levels in people living with HIV; read that entry below! As to the use of glutathione itself, old research had led to questions about how well glutathione absorbs orally. However, later research countered that, showing that it is effective to take it by mouth.<sup>10</sup> Thus, although most research is still centered on the use of NAC to raise glutathione, the far better approach is to use the combination of all the nutrients important for glutathione synthesis and recycling, including NAC, oral glutathione, vitamin C, alpha-lipoic acid, and L-glutamine. Down the line there may be other

products also available to increase glutathione. Two that are currently being researched include a drug called Pro-Cysteine and a whey protein product currently being studied in Canada.<sup>11</sup>

Because NAC can irritate the stomach, the best approach to its use is to begin with one capsule with each meal and then increase by one capsule every couple of days until you're taking 2-3 with each meal. At any point, if you feel stomach irritation, cut back to the next lower dose. In terms of the form of NAC to use, note that an incorrect statement given out by a researcher at the 8th International Conference on AIDS in Amsterdam in 1992 and a misinterpretation of the findings of an NIH study done years ago had led to the false belief that NAC is not very bioavailable and not well-absorbed when taken orally. The Drs. Herzenberg have corrected this misinformation, stating that NAC is very bioavailable and that, in fact, it is best taken orally, rather than intravenously. The Herzenberg study mentioned above used oral NAC which worked well to raise glutathione levels. [See the separate entries on the other glutathione-promoting nutrients for suggestions on their use.]

Food sources of cysteine include poultry, yogurt, oats, wheat germ and the sulfur foods that contain cysteine and/or methionine (a precursor to cysteine production in the body) such as egg yolks, red peppers, garlic, onions, broccoli, and Brussels sprouts.

[2000-4000 mg/day of NAC, taken with meals, possibly with the addition of 450-1500 mg/day of glutathione, may be beneficial. NAC can cause stomach irritation when taken on an empty stomach so always take with food; there is no competitive absorption problem between NAC and other amino acids and, thus, no reason to take it on an empty stomach; this is an incorrect myth that keeps being repeated by those who don't understand the biochemistry here.]

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