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The Dual Strategy of the Immune Response

A Review of Heinrich Kremer's Research on the Pathophysiology of AIDS, Cancer, and Other Chronic Immune Imbalances

BY DAVID LOWENFELS

In 1984, Bob Gallo and Margaret Heckler held a press conference in which they attributed AIDS to infection with the allegedly exogenous retrovirus, HIV. This pronouncement bypassed the scientific peer-review process and jumped straight into the hands of the media and the minds of the masses. To understand the context of this event, it is important to remember the politics of Nixon's Retrovirus-Cancer research, Bob Gallo's misleading laboratory deceptions in his thirst for fame and fortune, and the gross medical oversight of the challenges of the "fast-lane" gay lifestyle of the 1970s, which have been elaborated previously [Duesberg 1996, Crewdson 2002, Roberts 2006, Root-Bernstein 1993, de Harven 2003, Kremer 1996, 2001, 2003].

Since the time of Gallo's media announcement, many so-called "AIDS dissidents" have vociferously disputed the HIV theory of AIDS causality (Duesberg and Rasnick, The Perth Group, Root-Bernstein, Giraldo, to name but a few), but a coherent model for the pathophysiology of immune dysfunction and a corresponding nontoxic clinical therapy for disease reversal has been lacking. Mainstream HIV-centric AIDS therapies have focused on chemotoxic eradication, which at best is a stop-gap measure with ultimately grave consequences. HIV theorists continually invent convoluted explanations for how a phantom virus that can hardly be found *in vivo* (and only then by surrogate markers) could cause a total collapse of the immune system.

Most non-HIV theories of treatment revolve around drug abstinence, good nutrition, and avoidance of infections and other oxidative stressors. While

these measures are supportive to prevention and health maintenance, they have not been very useful in the actual reversal of AIDS and pre-AIDS, due to a lack of biochemical understanding of the actual disease mechanisms. The one exception that this author has encountered is the work of German doctor Heinrich Kremer MD, which is deeply grounded in modern biochemistry, immunology, and cell physiology.

This article is a summary of the pathophysiological model of chronic immune dysfunction, as elaborated by Dr. Kremer in his 2001 book, *A Quiet Revolution in Cancer and AIDS Medicine* (*Die Stille Revolution der Krebs und AIDS-Medizin*). An Italian version was published in 2003, and the translation of this monumental work into English is currently underway. Kremer and his colleagues are searching for a publishing house that can make this book available in print

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worldwide. The therapy guideline chapter [Kremer 2001 b], as well as an index with chapter summaries, are available at http://aliveandwellsf.org/kremer/.

An understanding of Kremer's model is based on three fundamental concepts, which are introduced here and will subsequently be elaborated:

- the function of nitrogen oxides and thiols (antioxidant sulfur compounds) as bioregulators of redox metabolism in cellular life forms and, particularly, the importance of nitric oxide (NO) in humans;
- the generalized functional dichotomy of the immune system and its cytokines (immunoregulatory messaging proteins), between the cell-mediated and humoral immunity, and its evolutionary interplay with NO; and
- the symbiotic nature of multicellular organisms, particularly regarding the mitochondrion, which is an endosymbiotic proteobacterium and is regulated by the intracellular redox balance.

Some of the finer points cannot be covered in this short format, nor can some of the more recent insights. However, what will be elaborated is a solid overview of the biological mechanisms and treatment of the chronic immune imbalance known as AIDS.

The Discovery of Nitric Oxide as an Endogenous Bodily Regulator

Research on the effect of nitrogen oxides in humans began in the late 1800s, when amyl nitrate and nitroglycerine were used as vasodilators in the treatment of cardiac disorders such as angina pectoralis [Brunton 1867, Fye 1986, Berlin 1987]. Over a century would pass until light was shed on the biochemical mechanism of these drugs. Research beginning in the late 1970s by the teams of Furchgott, Ignarro, and Murad led to the eventual discovery of NO as an endogenous (self-made) signaling chemical used not only in the vascular system, but also throughout the body; for this, those researchers were awarded the 1998 Nobel Prize in Physiology/Medicine.

NO is a highly reactive, but short-lived, paramagnetic radical. Due to its electrical neutrality, tiny size, and gaseous nature, NO can diffuse freely through cell membranes to foster cell-to-cell communication without need for specialized receptors – a phenomenon that was never before seen in biology. For decades, this mechanism was overlooked, as scientists were adamant that animal cells could not synthesize such a primitive molecule.

Today, we know that NO is crucial to a massive variety of processes in the animal organism and is not just limited to the regulation of blood pressure. The body has several different enzymes used to produce NO, of the family called NO synthase (NOS). Nearly all human cell systems produce (dependent on the level of intracellular calcium) small amounts of NO from L-arginine, as part of normal and pathological processes [Moncada 1991]. A sampling of such systems includes neural, mucosal, spleen, cardiac, bone, cartilage, liver, and skin cells [Lincoln 1997]. Of particular importance to immunological discussions is the calcium-independent enzyme called inducible NOS (iNOS), which can manufacture NO in large amounts over an extended period of time.

Redox Potentials Direct Cellular Processes

From the perspective of evolutionary biology, reactive nitrogen species (RNS) – i.e., nitrogen oxides – and other reactive oxygen species (ROS) are ancient but universal methods of intracellular and cell-to-neighbor communication, which operate via manipulation of biological redox potentials [Kremer 2001]. Redox potential describes the quality of a system as electron-rich (reduced) or electron-poor (oxidized), usually measured in millivolts.

Changes in the cellular redox status in turn affect the activation of genes and transcription of proteins [Sen and Racker 1996, Marshall 2000]. In an analogous manner, the intracellular redox status influences the production of cytokines by the immune cells, which then regulates immune function [Peterson 1997, Marshall 2000].

The primary biological counterpart to oxidation by RNS and ROS is reduction (i.e., antioxidation) by thiols, also known as mercaptans. These sulfur-containing molecules are strongly nucleophilic and can donate an electron in order to quench a free radical, themselves becoming oxidized in the process. These oxidized thiols are then either excreted or recycled by other antioxidants. The ocean is the primary source of biological sulfur, and land-based life forms face continual risk for latent sulfur deficiency [Hässig and Kremer 1999]. It is therefore necessary to maintain a sufficient sulfur reservoir, or "thiol pool," in the organism to counterbalance normal regulatory and pathological oxidative processes. For example, healthy mitochondria are one of the primary sources of ROS in the human organism, and thus their maintenance is dependent on cellular antioxidants that scavenge these byproduct radicals from oxidative phosphorylation [Cardoso 1999, Sastre 2003].

Aside from the aforementioned changes in genetic transcription, alterations in the cell redox status can also manifest as alterations of sulfur-iron groups in the mitochondrial respiration chain, or as cystine (S-S) cross-linking in enzymes and proteins that contain the amino acids cysteine or methionine [Moncada 1991]. Cysteine and methionine share the feature of a sulfhydryl (S-H) group, which is a potent antioxidant. The primary intracellular antioxidant is glutathione (GSH), which is a tripeptide synthesized from cysteine, glutamate, and glycine. (Figure 2) The balance between oxidized and reduced glutathione (GSH and GSSG, respectively) can guide many important cellular processes [Sen and Racker 1996].

The Dual Strategy of the Immune Defense

An additional scientific prerequisite to Kremer's model involves an understanding of the functional dichotomy of the immune system and its cytokines, between the cell-mediated defense and the humoral defense. Cytokines (formerly known as lymphokines) are messaging proteins secreted by various immune cells. Patterns of cytokine expression form a complex and interrelated feedback network, which regulates the functioning of the immune system. (See Figure 1.)

In 1986, the research group of Mosmann and Coffman demonstrated that CD4+ T-cells could be differentiated into two distinct functional patterns, which they named Th1 and Th2 (T-helper Type-1 and Type-2, respectively) [review in Mossmann 1989]. T-cells are

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lymphocytes that, when matured and activated, can perform as effector cells to assist the immune system in carrying out its tasks. The letter *T* stands for thymus, which is where these cells are trained and matured after their birth in the bone marrow. There are several kinds of T-cells, including helper, suppressor, and cytotoxic types. The term "helper" was originally coined before the discovery of Th1 cells to explain how Th2 cells assist B-cells in antibody production. Mosmann and Coffman's groundbreaking Th1/Th2 discoveries opened up a whole new paradigm in immunology, in which scientists attempted to classify diseases based on the pattern of cytokine responses [overview with Kidd 2003]. Many other types of regulatory and suppressor T-cells have been discovered since [Mosmann 1996], but the CD4+ Th1/Th2 dichotomy will suffice for this simplified introduction. The Type-1 cytokines are associated with the cell-mediated immunity (CMI), while the Type-2 cytokines are associated with the humoral immunity. Both types of cytokines have a tendency to counteract each other (i.e., reciprocal inhibition by negative feedback.) (Figure 1)

The CMI is the front-line defense of the immune system, which responds against *intra*cellular parasites (e.g., fungi, virii, and mycobacteria). The macrophages, natural killer (NK) cells, and Th1 cells primarily carry out this function, which is regulated by Type-1 cytokines. The CMI is also involved in cancer defense, delayed-type hypersensitivity (DTH) reactions, and homeostatic cellular "housekeeping" of dead or damaged cells.

The humoral immunity is the second-line of defense, which blocks *extra*cellular parasites (e.g., bacteria and worms) from entering cells, via antibodies. The B cells (*B* for maturation in the bone marrow) and Th2 cells primarily carry out this function, which is regulated by Type-2 cytokines. The humoral arm of the immune system is responsible for the manufacture of antibodies, as well as allergic and autoimmune reactions.

Th1 Cells Can Synthesize Large Amounts of NO Gas, While Th2 Cells Cannot

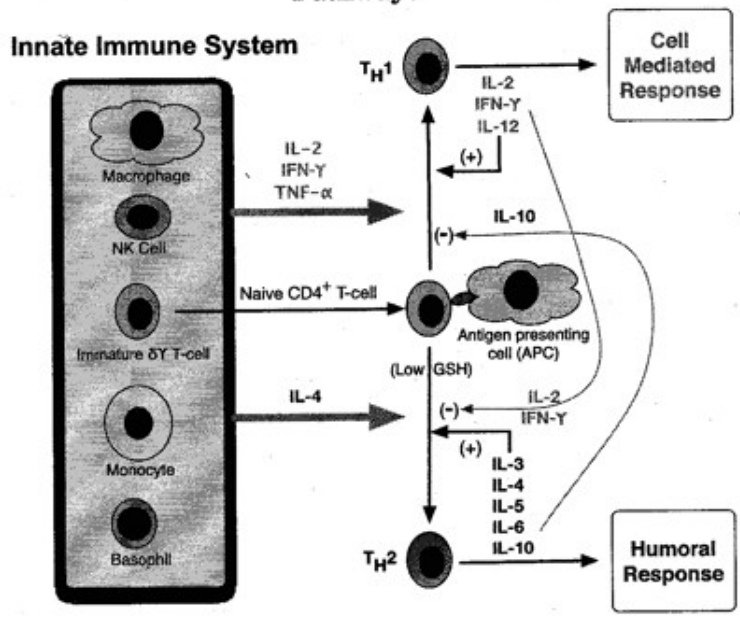
While the body has several enzymes for producing NO under different circumstances and in different cell systems, the inducible form (iNOS) is of crucial importance to the immune system. Inducible nitric oxide synthase (iNOS) is used by the cell-mediated immunity (CMI) to create clouds of cytotoxic (cell-killing) NO gas. The humoral Th2 cells do not have this ability to manufacture large amounts of NO gas. The cytotoxic NO gas spray is an integral weapon in the defense against intracellular pathogens (e.g., fungi, viruses, and mycobacteria). (Table 1) Macrophages, NK, and Th1 cells use this gas to disrupt and/or kill intracellular microbes, via inhibitory binding to their metalloenzymes and thiopeptides crucial for metabolism [Kröncke 1995]. In the process, the infected cells are also destroyed and, depending on the severity of the assault, sometimes innocent "bystander" cells are as well.

The Thiol Depletion Sensor Regulates the Cytokine Synthesis

The question remains: how does the immune system know whether to activate Type-1 or Type-2 cytokines? The answer stayed a mystery until a major discovery at Stanford in 1998 when researchers there found that the level of GSH in antigen-presenting cells (APCs) – i.e., macrophages, dendritic cells, and B lymphocytes – controls the switching between synthesis of Type-1 or Type-2 cytokines [Peterson 1998, Murata 2002].

In other words, a decline in the GSH:GSSG ratio signals the APCs to manufacture Type-2 cytokines, which then instruct naíve Th0-cells to mature into the Th2 type. The abundance of Type-2 cytokines causes reciprocal downregulation of Type-1 cytokines, which in turn inhibits any further

Figure 1: Diagram of Cytokine Regulation and Feedback Pathways.



IL = Interleukin
IFN = Interferon
TNF = Tumor Necrosis Factor
NK cell = Natural Killer cell

Table 1: Pathogens and Cellular Targets of NO

Viruses
Herpes simplex virus (a,d)
Coxsackie virus (a)
Vaccinia virus (d)
Ectomelia virus (d)

Bacteria
Francisella tularensis (a)
Mycobacterium tuberculosis (a,e)
Mycobacterium bovis (f)
Mycobacterium leprae (a,b)
Mycobacterium avium (e)
Listeria monocytogenes (a)
Chlamydia trachomatis (a)

Fungi
Cryptococcus neoformans (a,b)
Histoplasma capsulatum (g)

Parasites
Leishmania species (a,b,c)
Trypanosoma cruzi, musculi and *brucei* (a,c)
Plasmodium falciparum (a,c), *chabaudi* (h)
Toxoplasma gondii (b,c)
Schistosoma mansoni (b,c)
Entamoeba histolytica (a,i)

Mammalian cells
Tumour cells (a)

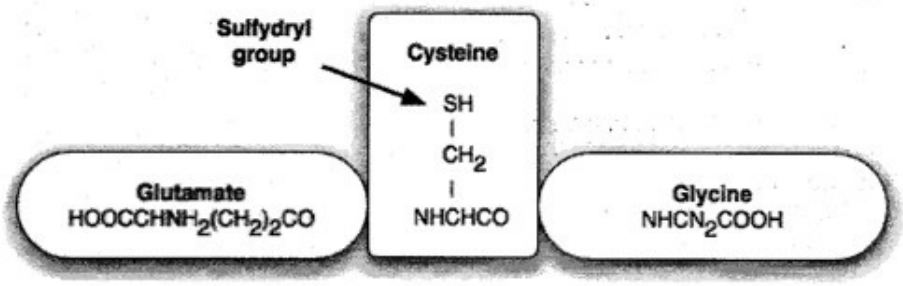
Pathogens that have been shown to induce the expression of type II NOS either *in vitro* or *in vivo* and are subject to the toxic effects of NO. Selected references are indicated in parentheses.

(a) Lowenstein, Dinerman & Snyder, 1994;
(b) Langrehr *et al.*, 1993;
(c) James, 1995;
(d) Nathan, 1995;
(e) Greenberg *et al.*, 1995a;
(f) Yang *et al.*, 1995;
(g) Zhou *et al.*, 1995;
(h) Jacobs, Radzioch & Stevenson, 1995;
(i) Lin *et al.*, 1995.

Excerpted from: Burnstock G, Hoyle C, Lincoln G. *Nitric Oxide in Health and Disease: Biological Research Topics 1.* London: Cambridge Univ. Press, 1997.

synthesis of NO. (Figure 1) This event is called the Th1-to-Th2 switch, or a shift towards Type-2 cytokine dominance. The outcome is the hyperactivation of antibody production at the expense of inhibited cell-mediated immunity. In most cases, this shift is temporary. However, if a long-lasting shift occurs, the weakness of the CMI can invite intracellular opportunistic infections (OIs, the hallmark of "HIV"/AIDS). (Table 2) A simple and reliable measurement for Th2 dominance with Type-1 cytokine inhibition is the DTH skin test (originally used in sepsis research): an anergic result is an indicator for strong risk of OI due to insufficient Interleukin-2 (IL-2) [overviews with Christou 1995 and Kremer 2001].

Figure 2: The Molecular Structure of Glutathione (GSH)



Self-Protection from Oxidative Damage.

The reason for the inhibitory switching of NO lies in an ancient evolutionary program for self-protection from oxidative damage. GSH can be seen as the "gas mask" for the Type-1 immune cells used to protect them from oxidative damage by NO [Kremer 2001]. However, reduced thiols are only available in a finite supply, dependent on the nutritional intake of cysteine/methionine and other antioxidants. The unfortunate side effect of using NO is that the immune cells themselves can become severely oxidized. If the initial CMI response is not effective against an invader, the immune system is in danger of harming itself with the double-edged sword of NO gas. This can also happen if the CMI response is excessive (perhaps due to multiple co-infections) or long-lasting (due to chronic infection). In fact, any of the myriad forms of oxidative and/or nitrosative stress can contribute to the Th2 shift by systemic antioxidant depletion. These prooxidative factors can be any combination of infectious, traumatic, psychoemotional, chemotoxic, or nutritional stressors [Hässig 1997].

A "Fire Alarm" for Extreme Prooxidative Threat

The Th1-to-Th2 switch evolved as a "fire alarm" for extreme prooxidative threat. From an evolutionary biological perspective, the Th1 cell is first seen in simple invertebrates, like sponges. The Th2 cell appears later during the early evolution of vertebrates like amphibians and the bony fish [Roitt 1985]. Evidence suggests that the development of Th2 cells and antibodies was an evolutionary solution to parasitic colonization by other invertebrate organisms. Bony fish have a complex circulatory system, which makes them susceptible to invasion by multicellular parasites such as worms. Imagine the tiny Th1 cells attacking a large worm – that would be like using firecrackers to attack a giant monster. In that case, an excessive Th1 response using NO gas would not defeat the worm, but would instead cause harm to the fish via extreme tissue oxidation and inflammation. A backup system is needed for this emergency, and over time, Mother Nature equipped the more complex animals with such a solution: the Type-2 cytokine switch [Kremer 2001]. A Th2 dominance is generally an effective defense against prevention and healing of worm infections [Mosmann 1996].

In pre-Industrial times, humans with an aggressive Type-2 switch had a survival advantage, because they could successfully fight off worms and bacteria. Humans in those times also were not exposed to the oxidative stressors in the environment, food, and medicine now present in modern civilization. (See Sidebar.) In addition, the modern practice of vaccination also leads to more aggressive Type-2 switching. Today, these additional stress burdens flip the Type-2 switch too easily. The net result is a population-wide increase in chronic immunological diseases such as allergies, atopic skin disorders, asthma, autoimmune conditions, and cancer [Kremer 2001].

AIDS Patients and Type-2 Cytokine Dominance

Immunological observations of AIDS patients demonstrate a Type-2 cytokine dominance. The initial findings of AIDS clinics noted DTH anergy, reduced T-cell proliferation after stimulation, increased B-cell activity, and specific antibody production, all of which glaringly point towards the shift to Type-2 cytokine dominance (a.k.a. Type-2 counter-regulation) [Gottlieb 1981, Masur 1981, Mildvan 1982].

The immunological response of AIDS patients is not new, as the Th2 switch has existed in animals for millennia. Rather, the unprecedented

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Table 2: Clinical Pictures of Th1 vs Th2 Response

Th1 (NO gas)	Mixed Th1/Th2	Th2 (antibody)
Tuberculosis (localized)		Tuberculosis (systemic)*
Leprosy (tissue-destroying tuberculoid form)		Systemic Lepromatosis
Primary Syphilis	Secondary Syphilis	Tertiary Syphilis (malignant)
(N/A)		Worm Infection
Leishmaniasis (self-limiting)		Leishmaniasis (Kalaazar)
Candidiasis (localized)		Candidiasis (systemic)*
Toxoplasmosis (self-limiting)		Toxoplasmosis (brain and lymph)*
Salmonella (self-limiting)		Salmonella sepsis*
Pneumocysts w/o illness (ubiquitous in inhaled air)		Pneumocystis pneumonia*
Infertility/Miscarriage		Successful Pregnancy

(*clinical AIDS)

collective exposure to oxidative stressors precipitated the relabeling of the symptoms of the counter-regulatory Th2 switch as "AIDS." Among other things, the primary prooxidative factors involved in gay men include combinations of nitrite inhalation ("poppers"), consumption of immunotoxic medicines and recreational drugs (including Septra/Bactrim, AZT, and, recently, Viagra), and exposure to antigens and endotoxins via repeated infections. All these factors induce the synthesis of NO gas, ultimately leading to exhaustion of the thiol pool. Protein malnutrition seen in the Third World can also lead to a long-term functional inhibition of NO synthesis [Kremer 2001].

Results from research on seropositive patients showed Th1 cell impairment even in asymptomatic individuals with normal T-cell counts [Giorgio 1987, Miedema 1988, Clerici 1989 a, 1989 b]. In 1989, it was observed that asymptomatic "HIV"-seropositive individuals are systemically deficient in glutathione [Buhl 1989]. In 1993, Clerici and Shearer were the first to hypothesize about Th2 dominance in AIDS patients, which remained a tantalizing but controversial topic for many years until the Peterson group's 1998 breakthrough [Clerici 1994, Mossmann 1994, Fakoya 1997, Klein 1997].

In 2000, Breitkreutz et al. reported that asymptomatic seropositive patients showed a "massive loss" of approximately 10 g of sulfur compounds via daily urination, leading to an "an alarming negative balance of approximately 2 kg of cysteine per year" [Breitkreutz 2000]. Such a cumulative loss of thiols would obviously lead to chronic Type-2 counterregulation, the consequences of which include rising levels of antibodies (hypergammaglobulinemia) over time, leading to allergic and autoimmune complications, as well as a progressive diminishment in the CMI response, creating susceptibility to intracellular "opportunistic" infections. All these sequelae are characteristic of the progression to AIDS and are the direct result of the inhibition of NO gas synthesis due to thiol depletion.

It has been reported that hypergammaglobulinemia precedes "HIV"-antibody seroconversion in hemophiliacs [Brenner 1991]. The Perth Group also has pointed out that "studies conducted in drug users show that the decrease in T4 cells precedes a positive antibody test" [Papadopolous 2004]. Further evidence for acquired immunodeficiencies (AIDS) of the CMI, without the manifest syndrome of OIs, in both "HIV+" and "HIV-" individuals from risk groups, is discussed in Root-Bernstein 1993. The entirety of evidence convincingly suggests that the shift towards Th2 dominance begins long before seroconversion.

"HIV" Cellular Characteristics and the Depletion of Reduced Thiols

Many researchers have argued that the immune weaknesses in risk groups simply leads to greater susceptibility to putative "HIV infection." According to Kremer, this is a gross confusion of cause and effect. The characteristics attributed to HIV in cell cultures, namely reverse transcription, "virus-like" particles, and catabolic cellular debris, are part of the evolutionary response against pro-oxidation.

Reverse transcription is a well-known factor in the repair of oxidatively damaged nuclear DNA [Kremer 2001]. Cell cultures of HIV are necessarily subjected to unusual oxidative and mitogenic stressors (including hydrocortisone), in order to express the "HIV proteins" [Barre-Sinnousi 1983, Popovic 1984, Gallo 1984]. The genetic expression of pathological proteins (e.g., HIV1 TAT) by dysfunctional cells is just another symptom of systemic imbalance. Because it is the oxidative mechanisms which result in unusual gene transcription, HIV researchers are confusing cause and effect.

The inflammatory Th1 cytokines, interferon-gamma and tumor necrosis factors, activate the production of oxygen radicals that can lead to increased cell death by apoptosis (programmed cell death) and necrosis (unprogrammed cell death). Necrosis exposes intracellular proteins to the extracellular matrix, which activates autoimmune reactions in both Th1 and Th2 cells [Kremer 2001].

A widely overlooked fact by AIDS researchers is that everyone has "HIV proteins" in small amounts; those stigmatized as "HIV+" simply have higher amounts than the arbitrary threshold of the "HIV [auto]antibody" ELISA test kit, which calls for unusually high serum dilution [Giraldo 1998, Kremer 1998, 2002, 2003]. Therefore, an "HIV+" test result is pathognomonic (a distinctive indicator) for reduced thiol insufficiency (i.e., cysteine deficiency) and resultant cellular catabolism.

Glutathione

Glutathione (GSH) is a tripeptide made of cysteine, glutamate, and glycine. GSH plays important roles in cell and liver detoxification, mineral metabolism, antioxidant quenching of free radicals, and regulation of mitochondrial symbiosis. Due to its large size, GSH usually must be synthesized from components inside the cell, with cysteine and its antioxidant sulfhydryl group (sulfur-hydrogen bond) being the rate-limiting factor. One of the safest ways to boost systemic glutathione is oral N-acetylcysteine (NAC). Modern stressors which consume reduced gluathione (GSH) include the following:

- All manners of oxidative stress
- Chemical poisoning, via environment or via food/water
- Carcinogens
- Synthetic pharmaceuticals
- UV and X-rays (ionizing radiation)
- Electro-smog (non-ionizing radiation)
- Oxygen, under- and oversupply
- Infections
- Overexertion from sports
- Questionable nourishment
- Heavy metal intoxication
- Free-radical reactions
- Chronic illnesses

Oxidized GSSG is reduced back to GSH by the enzyme glutathione reductase and the coenzyme NADPH. However, this reduction depends on a well-functioning status of the enzyme glutathione reductase and sufficient coenzyme NADPH. Both enzyme and coenzyme are damaged via electrophilic bonding with toxins. With a burden of frequent detoxification, they can no longer perform their task; too much oxidized glutathione (GSSG) remains, and the vital balance of (GSH):(GSSG) becomes disturbed from its approx. 400:1 ratio. Thereby, the redox regulation so dependent on this balance is interrupted.

(Translated from German by Dr. Gerhard Ohlenschlaeger, 2003.)

Mitochondrial Symbiosis Depends on Reduced Thiols and NO

The final nail in the coffin for the HIV theory is that the cell types used to derive "HIV proteins" (Gallo used cancer cells, and Montagnier used embryonic cells) all have altered mitochondrial bioenergetics that predispose them for Type-2 counterregulation [Barre-Sinnousi 1983, Gallo 1984, Kremer 2002].

Fueled by oxygen, mitochondria are the energy powerhouses that generate nearly all the ATP used for cellular processes. Currently accepted theory maintains that the mitochondria are endosymbiotic bacteria, long ago incorporated into eukaryotic cells [Margulis 1981]. The strongest evidence for this is that mitochondria have their own genome (mtDNA). Because the mitochondria are themselves relatives of bacterial organisms, they are also susceptible to suffocation by nitrogen oxides when present in cytotoxic concentrations [Kremer 2001].

Mitochondria are responsible for regulating cellular metabolism, including the initiation of apoptosis [Green 1998, Desagher 2000]. Laboratory research is currently lacking on the exact mechanisms that maintain the mitochondrial symbiosis. As mentioned earlier, normal mitochondrial respiration is the leading source of oxidative radicals in the cells. For this reason, a continual supply of antioxidants are needed to mop up these radicals, the primary one being glutathione peroxidase (GSH-Px), which contains both selenium and GSH. AIDS researchers in the past decade have noted deficiencies in selenium, which was erroneously postulated as excess transcription of GSH-Px by HIV [Look 1997, Taylor 1997, Foster 2000]. The GSH deficiencies that cause the inhibition of NO synthesis also lead to the dissolution of the mitochondrial symbiosis (a.k.a. "Warburg Phenomenon") [Kremer 2001].

Not surprisingly, disturbances of the mitochondria are evident even in asymptomatic seropositive individuals [Cote 2002]. This problem is made worse by the administration of nucleoside analogues such as AZT, which suffocate mitochondrial respiration enzymes and interfere with the synthesis of mtDNA via inhibition of polymerase-gamma [Cherry 2003]. Other AIDS drugs can deplete systemic GSH by liver toxicity. It is imperative to focus on restoring the mitochondrial symbiosis as a primary goal of AIDS therapy [Kremer 2001, 2003], and current research in China substantiates this paradigm [Miao 2005].

Mitochondrial dysfunction is also tied to cancer, as demonstrated by Nobel Laureate Otto Warburg, who showed that a breakdown of oxidative cell respiration and increase of lactic acid fermentation was a precursor to cancer [Warburg 1966, Kremer 2003]. Stimulated by Kremer, cutting-edge cancer research in Germany and Spain is currently corroborating Warburg's theories [Isidoro 2005, Schulz 2006].

The Case of the Missing T-Cells

A paradox overlooked by the initial AIDS researchers was that an "unknown agent" was supposedly killing the T-helper cells, yet the antibody production of the B-cells and antibodies remained intact. Another paradox is that AIDS researchers could find the nonspecific laboratory artifacts that indirectly implicated a retrovirus only amongst Th2 cell clones but not Th1 clones [Maggi 1994, Chehimi 1995, Abbas 1996, Lucey 1996]. "How can a killer be responsible for murder if it was never even at the scene of the crime?" [Kremer 2001]

Though HIV-theorists have come up with many imaginative explanations for this conundrum, the logical solution is that the decline of T-cells seen in the peripheral blood is not due to any postulated "HIV-mediated cell killing," but rather is another consequence of the thiol-mediated cytokine shift.

A predominance of Type-2 cytokines leads to the production of Th2 cells, which reside primarily in the bone marrow (where they can contact the B-cells) and out of view from peripheral blood counts. To cite an analogy given by Kremer: the "police officers" of the bloodstream are missing from the streets, not because gangsters have killed them, but instead because they have taken desk jobs [Kremer 2001].

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Immune Response

The bone marrow disruption that occurs with highly active antiretroviral therapy (HAART) is responsible for damage to the maturation of B-cells. As a result, the Th2 cells cannot make contact with mature B-cells and so return to circulation in the peripheral bloodstream. This toxic disruption explains the transient increase of CD4+ blood counts seen with nucleoside inhibitors [Kremer 2001, 2003]. The cell-count increase is misleading because Th2 cells cannot produce cytotoxic NO gas and are therefore lame against preventing OIs. Because Th1 and Th2 cells cannot be differentiated by their surface proteins, the only way to get reliable information on immune function is by cytokine profiling or DTH skin testing.

Antioxidants Improve Immune Function

It must be underscored that there is a direct connection between the uptake of antioxidants – from food or supplements – and the levels of GSH in the immune cells. Therefore, there are two general ways in which antioxidant depletion and the corresponding immune imbalances can occur. The first way is through a lack of antioxidant intake, in other words, malnutrition or starvation. The second way is through redox overload due to prooxidative stressors (toxic, infectious, psychoemotional, etc.) which, alone or in combination, exceed the capacity of cellular antioxidant supply. The end result of both these situations is a systemic starvation for freely available electrons, corresponding with deficiencies of thiols and other reducing substances, which ultimately triggers the biologically evolved program of Type-2 counter-regulation.

A very wide range of antioxidants have been claimed to inhibit "HIV infection" *in vitro* [Schreck 1992, Jaruga 2002]. In fact, many of the newer AIDS drugs have potent antioxidant capacity [ScienceBlogs 2006], either directly via their metabolites or indirectly via inhibition of enzymes, like cytochrome P450. Over the long-term, the enzymatic inhibition that these drugs cause is quite toxic, particularly due to the disruption of mitochondrial replication and repair [ScienceBlogs 2006, Cherry 2003]. As early as 1989, a lack of cysteine was noticed in AIDS patients. This lack could have suggested a non-toxic supplemental therapy, if researchers were not blinded by the glamour of virus-hunting [Dröge 1989]. The replenishment of thiols in AIDS prevention by the GSH pro-drug, n-acetylcysteine (NAC), was first suggested by Dröge in 1993 [overview with Kelly 1998]. Clinical trials in subsequent years proved astounding results, and NAC is universally recommended for seropositive patients [Dröge 1997, De Rosa 1997, Herzenberg 1997, Breitkreuitz 2000]. Given the knowledge of this enormous benefit, it is troubling that doctors are not prescribing NAC to their patients; presumably its lack of popularity is due to the lack of patentability (i.e., profitability) of an endogenous (bodily-made) substance derived from a simple amino acid. Mainstream AIDS-drug "cocktail" therapy cannot possibly address this massive cysteine deficiency. In fact, the Herzenberg study showed that individuals taking HAART therapy generally had the worst levels of intracellular GSH and thus benefited most from NAC supplementation.

Kremer's Approach to Healing Immune Dysfunction

This article has provided an outline of Kremer's theory behind the immune dysfunction seen in AIDS, as explained by the shift to Th2 dominance. It has only briefly touched on the therapy, which is outlined elsewhere [Kremer 2001 b, de Fries 2005]. There is no "magic bullet" solution to this disorder, since there is no actual HI-Virus to be eradicated. Even if HIV were to actually exist, the laws of evolutionary biological immunology would still call for an identical thiol-replenishing treatment rationale. The process of reversing Th2 dominance is complex and highly individual; it requires time, patience, and the help of a truly knowledgeable physician. Excerpted from Kremer's book, here is the general strategy for healing the Th1/Th2 imbalance:

- Minimization of prooxidative stress
- Replenishment of thiol deficiency
- Balancing of amino acid dysregulation
- Liver protection to lighten the burden of systemic thiol deficiency
- Modulation of Type-2 counter-regulation
- Micronutrient replenishment
- Fortification of the extracellular matrix
- Mitochondrial revitalization
- Attenuation of stress hormones
- Fear reduction and psychological assistance (i.e., *de-hexing*) [Kremer 2001].

This author hopes you share his excitement for the English publication of Kremer's book. There is still much to be discovered regarding the healing powers of orthomolecular cell-symbiosis compensation therapy for AIDS. However, the therapy's scientific basis is solid, and the clinical application continues to demonstrate immense benefit. My deepest gratitude goes out to Dr. Kremer and his German-speaking colleagues, who have gifted us greatly in our understanding of health and disease. Please visit the website aliveandwellsf.org to keep up-to-date on the status of the publication of Kremer's work in English.

David Lowenfels is a scientist, engineer, and musician, with Master's degrees from MIT and Stanford. He began questioning the "HIV=AIDS" model in 1999 and encountered Dr. Kremer's work in 2003. He is greatly excited by the emerging paradigm of future medicine: moving beyond the current strategy of eradication and suppression, beyond "complementary alternative" therapy, and into new realms of biological understanding which yield methods for guiding and balancing the body's innate healing processes.

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