DOES AZT AND ART IN AIDS PATIENTS ACHIEVE IMMUNE RESTORATION AND DOES IRIS INTIATE THE PROGRESSION OF AIDS?

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In many countries, doctors routinely prescribe antibiotics to flu patients. Flu is caused by virus while antibiotics are for killing bacteria. Antibiotics do not kill the virus. Such widespread consumption of antibiotics is not a good thing as excess antibiotics can deplete minerals in the body and also impair the healthy functioning of the mitochondria. It is good to integrate antibiotic therapy with fruit juices immediately upon completing any properly prescribed antibiotic therapy.

Like antibiotics, steroids are another class of drugs that often abused. In some countries they are frequently abused. In many countries steroids have become one of the most abused class of drugs in the field of medicine. Why is that? Firstly, many of the health problems can be traced to inflammation that is associated with pain and/or decline in cell function. Malnutrition or low antioxidant intake associated with the empty calorie syndrome can, over time, can initiate the biochemical changes in the body that lead to oxidative stress that set the stage for inflammation, causing aches, pains, and allergic reactions and increasing the long-term risk of life-threatening diseases.

Antibiotics kill both the pathogens as well as the symbiotic bacteria that are part of the natural and the healthy gut flora. About 30-40 species of bacteria normally make up most of the gut flora (University of Glasgow, 2005, The normal gut flora, Available through web archive, Accessed May 22, 2009: Michael L McCann, 2004, Bacteria for Breakfast: Probiotics for Good Health, The Annals of Pharmacotherapy: Vol. 38, No. 9, pp. 1546-1548) along with fungi but some may also have protozoa. The bacteria perform a host of useful functions, preventing growth of harmful species (Guarner and Malagelada, 2003, Gut flora in health and disease, Lancet Feb 361 (9356): 512–9) producing vitamins for the host (such as biotin and vitamin K).

The symbiotic bacteria help to keep the candida in check. Yeasts and harmful bacterial species such as Clostridium difficile, that can cause pseudomembranous colitis, are unable to proliferate due to competition from helpful gut flora species to adhere to the mucosal lining of the intestine. The decimation of symbiotic bacteria by antibiotics invariably leads to rapid growth of candida. The use of antibiotics, which kill native gut flora and harmful infectious pathogens alike, especially during childhood, is associated with inflammatory bowel disease (IBS) (Wynne AG et al, 2004, An in vitro assessment of the effects of broad-spectrum antibiotics on the human gut microflora and concomitant isolation of a Lactobacillus plantarum with anti-

Candida activities, Anaerobe June 10 (3): 165–9). Another possible cause of IBS is protozoal infection.

Symbiotic bacteria play a very useful role in the health of the human host. Symbiotic gut bacteria convert carbohydrates into short chain fatty acids (SCFAs) including acetic acid, propionic acid and butyric acid (University of Glasgow, 2005, The normal gut flora. Available through web archive: Gibson RG, 2004, Fibre and effects on probiotics (the prebiotic concept), Clinical Nutrition Supplements 1 (2): 25–31: Beaugerie and Petit, 2004, Microbial-gut interactions in health and disease, Antibiotic-associated diarrhoea, Best Pract Res Clin Gastroenterol April 18 (2): 337–52: Francois-Pierre J Martin, 2007, Probiotic modulation of symbiotic gut microbial–host metabolic interactions in a humanized microbiome mouse model, Mol Syst Biol, 2008, 4: 157).

These byproducts of symbiotic metabolism can be used by host cells, providing a major source of useful energy and nutrients for humans and in fact provide nutritional support. Acetic acid is used by muscle cells while propionic acid helps the liver produce ATP and butyric acid provides energy to gut cells and may prevent cancer (Gibson RG, 2004, Fibre and effects on probiotics (the prebiotic concept), Clinical Nutrition Supplements 1 (2): 25–31) and may help prevent leaky gut syndrome. Disturbances in the mammalian-microbial symbiosis can lead to a host of diseases, including insulin resistance and gastro-intestinal cancers, IBS, food allergies, fungal disease and ulcers (ref: Francois-Pierre J Martin, 2007, Probiotic modulation of symbiotic gut microbial–host metabolic interactions in a humanized microbiome mouse model, Mol Syst Biol, 2008, 4: 157) and such disturbances have been going on for the last fifty years with the advent of antibiotics. Hence, there is interest in probiotic medicine - interest in the impact of gut microbial activity on human health is expanding rapidly and many mammalian–microbial associations.

The expanded use of glucocorticoids (GC) in clinical practice accounts for the increasing number of fungal infections reported in the mildly or nonimmunocompromised hosts. Invasive pulmonary aspergillosis (IPA) usually occurs in severely immunocompromised patients, especially asthma patients. There are patients with opportunistic infections in whom the only immunosuppressive condition was long term treatment with high doses of GC (Carlos Agusti, 2006, Fungal pneumonia, chronic respiratory diseases and glucocorticoids, Medical Mycology September 44, S207S211). Reports of serious opportunistic pulmonary infections in patients with chronic lung diseases requiring permanent or repetitive doses of GC have been occasionally described. Glucocorticoids (GC) exert a decisive influence in the innate immune function of resident alveolar macrophages and granulocytes, the two major immunoregulatory cells in host defenses against opportunistic and bacterial infections. As a consequence, it might be expected for patients receiving long-term-high doses of GC to have depressed resistance to a

wide variety of infective agents (Berenguer J et al, 1995, Pathogenesis of pulmonary aspergillosis granulocytopenia vs cyclosporine and methylprednisone-induced immunosuppression, Am J Respir Crit Care Med, 152: 1079□1086).

The role of corticosteroid therapy as a risk factor is repeatedly found in studies involving preterm infants (Botas CM et al, 1995, Disseminated Candida infections and intravenous hydrocortisone in preterm infants. Pediatrics, 95:883-887), leukemic children (Flynn PM et al, 1993, Candida tropicalis infections in children with leukemia, Leuk Lymphoma, 70:369-376), surgical patients (Dean and Burchard, 1996, 1996, Fungal infections in surgical patients, Am J Surg, 171:374-382), and in a case-control study of a general hospital population (Wey SB et al, 1989, Risk factors for hospital-acquired candidemia, Arch Intern Med, 149:2349-2353). Numerous studies show that Curvularia, a filamentous fungi, has recently emerged also as an opportunistic pathogen that infects immunocompromised hosts (ref: Annaise E et al 1989, New spectrum of fungal infections in patients with cancer, Rev Infect Dis 11 369-378: Vartivarin Se et al, 1993, Emerging fungal pathogens in immunocompromised patients: classification, diagnosis and management, Clin Infect Dis 17:S487-91).

Risk factors for development of invasive fungal infections after blood or bone marrow transplantation include the use of broad-spectrum antibiotics, steroids, mismatched or unrelated donor transplant, right atrial catheters and prolonged or profound neutropenia (Boyle and McCann, 2002, The use of itraconazole as prophylaxis against invasive fungal infection in blood and marrow transplant recipients, Transpl Infect Dis, 2(2):72-9).

Invasive fungal sinusitis is a well-described clinical entity characterized by the mucosal infiltration of mycotic organisms and angiocentric extension into orbital and intracranial structures. The population at risk for invasive fungal rhinosinusitis is growing with the increased increased use of immunosuppressive therapies (Parnes LS et al, 1989, Mycotic sinusitis: a management protocol, J Otolaryngol, 18:176-180).

Patients with any immuno-defective conditions with oxidative stress, including cancers, anaemia, neutropenia, chronic fatigue and those with protozoal infections are at risk for invasive fungal infections when exogenous GC therapy is administered. Fungal infections are the most likely cause of persistent fevers, persisatent cough, whitish vaginal discharge and deterioration. The critically ill injured patient is immunosuppressed, invasively monitored, and exposed to microbial pathogens at the time of injury and while residing in the intensive care unit (ICU). The incidence of nosocomial infections by Candida species has surged over the past decade, from the eighth to the fourth most common cause of nosocomial bloodstream infection. Many of the classic risk factors for fungal infection in other populations are actually concomitants of injury severity and its requisite level of care in trauma patients (Beck-Sague and Jarvis, 1993, Secular trends in the epidemiology of nosocomial fungal infections in the

United States, 1980-1990: National Nosocomial Infections Surveillance System, J Infect Dis, 167:1247-1251). The drugs used to treat fungal infections are themslves toxic and add a burden to immune suppression. A powerful finding in one study reveals that there is a low rate of fungal infections in a large group of badly injured, critically ill trauma patients who do not receive antifungal prophylaxis (Beck-Sague and Jarvis, 1993, Secular trends in the epidemiology of nosocomial fungal infections in the United States, 1980-1990: National Nosocomial Infections Surveillance System, J Infect Dis, 167:1247-1251).

Fungal infection is increasingly common in critical illness with severe sepsis. Invasive fungal infection is frequent in patients with severe sepsis in surgical ICUs and is associated with excess risk for hospital mortality, longer ICU and hospital stays, and greater consumption of medical resources. Compared with the control patients with severe sepsis but without IFI, the matched patients with severe sepsis and IFI had higher hospital mortality, ICU LOS, hospital LOS and hospital costs, and received more aggressive interventions (Guo-Hao Xie1, 2008, Impact of invasive fungal infection on outcomes of severe sepsis: a multicenter matched cohort study in critically ill surgical patients, Critical Care, 12:R5). IFI is a severe clinical complication in immunocompromised patients, such as neutropenic patients, recipients of bone marrow or solid organ transplants, cancer patients receiving chemotherapy, and HIV-infected patients. However, during the past two decades, with advances in diagnostic and therapeutic interventions, critically ill patients with lesser degrees of immunocompromise, especially those in surgical and neonatal intensive care units (ICUs), have emerged as another population at high risk for IFI (Eggimann P et al, 2003, Epidemiology of Candida species infections in critically ill non-immunosuppressed patients, Lancet Infect Dis 2003, 3:685-702) which is an oportunistic infection (Fisher-Hoch and Hutwagner, 1995, Opportunistic candidiasis: an epidemic of the 1980s, Clin Infect Dis 1995, 21:897-904).

Steroids were originally reserved for the extreme emergency cases but today, they are being used on the most trivial of conditions. Secondly, and the main reason for their present common use is that steroids give the appearance of an instant miracle cure which matches or goes beyond the expectation level of the patient as they can effectively and quickly suppress the symptom and the associated pain. This quick relief has led many vets and practitioners of modern medicine to turn to steroids as the first instead of the last line of prescription against inflammations and allergies due to their anti-inflammatory and anti-allergic effects.

The body's most powerful regulator of general metabolism is steroidal in nature. Steroids mimic the action of the adrenal glands but they are not a wonder drug in the sense of a cure all. Steroids cannot cure one single condition but can present themselves as a drug for wonderful relief as they effectively suppress the symptoms. However in that process they may not promote the body's ability to express a normal response to heal itself. Occasionally this type of

suppression can give the body a chance to heal itself, especially when the diet is rich in a broad range of antioxidants. They can be useful in integrative medicine but steroid abuse can also produce fast effects that may be devastating and can cause permanent damage.

Even low daily doses of steroids may lead to health troubles. Very recently scientists reported that low daily doses of a commonly prescribed oral steroid, prednisone, can double the risk of hip fractures and cataracts. Researchers have long known of the link between higher doses of oral steroids and dangerous side effects, but the new study shows the potential for side effects at much lower doses, says Dr. John B. Wong, an associate professor of medicine at Tufts-New England Medical Center in Boston. The problem is that prednisone and other steroid medications are critical in managing diseases in which inflammation plays a painful role, Wong says. The health story rolls back to inflammation and how to manage them through clinical nutrition and daily nutrition that helps to prevent the development of inflammatory changes in cells and tissues.

Low-dose steroids are used commonly in a number of diseases, including patients with asthma or rheumatoid arthritis. Prednisone also is used to treat Crohn's disease and other inflammatory bowel disorders. Dr John Wong stressed that people who are taking this medicine should not stop doing so based just on these new findings. Modern medicine must take a new approach to slowly wean patients away from drugs with improvements in health through clinical nutrition or therapies that apply natural antioxidants. This view is part and parcel of integrative medicine.

Many patients are naturally worried about the long-term side effects of antibiotics, drugs and steroids. Patients must discuss their use with their doctors so as to maintain a position in which the benefits of the medicine might clearly outweigh the risks. There are other important reasons for discussing the benefits and risks of long-term medication by drugs as many of them are cytotoxic and might be able to suppress the immune system and may then exacerbate the problem.

An interesting piece of information is that AIDS is caused by the heavy use of corticosteroids and/or cytotoxic drugs to treat many health problems resulted from the use of illicit drugs by drug users and homosexuals. The appearance of AIDS cases in the USA in 1978 coincided with approval of corticosteroids aerosol by the US FDA in 1976. In addition, homosexual men are usually heavy users of rectal glucocorticoids. AIDS in hemophiliacs is caused by the use of corticosteroids and other immunosuppressive drugs to prevent the formation of antibodies for factors VIII and IX and to treat other health problems (Baltimore and Feinberg, 1989, HIV revealed: Toward a natural history of infection, The New England Journal of Medicine, 321(24), 1673-4).

In addition to illicit drug and alcohol abuse, homosexuals are also heavy users of alkyl nitrites that relax the anal muscle and facilitate anal sex. It has been stated that the use of alkyl nitrites permeated the gay life by 1977. Homosexuals usually suffer from acute and chronic rectal and gastrointestinal diseases that dictate the heavy therapeutic use of rectal steroids. Among 7 selected studies that included 736 patients (97% of them were homosexual or bisexual men) who were infected with HIV and/or had AIDS.

Many individuals with AIDS have abused opioids along with alcohol and may be smokers, too. These substances have immune suppression effects that are mediated through oxidative stress with the secondary radicals producing oxidative injury to receptor sites on the surface of cells of the immune system and my depletion of vitamin C in these cells. Opioids suppress many aspects of immune responses, including antimicrobial resistance, antibody production, and delayed-type hypersensitivity. This occurs in part through the desensitization of chemokine receptors on neutrophils, monocytes, and lymphocytes (Rogers TJ et al, 2000, Birectional hetreologous desensitization of opiod and chemokine receptors, Ann NY Acad Sci, 917:19-28). Morphine decreases mitogen responsiveness and natural killer cell activity (Houghtling RA et al, 2000, Acute effects of morphine on blood lymphocyte proliferation and IL-6 levels, Ann NY Acad Sci, 917:771-777).

In addition to these direct effects, morphine could also affect immune responses indirectly through adrenergic effects, because it increases concentrations of catecholamines in the plasma (Gomez-Flores and Weber, 2000, Differential effect of buphrenorphine and morphine on immune and neuro-endocrine functions following acute administration in the rat mesencephalon periaqueductal gray, Immunopharmacology, 48:145-156). Catecholamines inhibit production of proinflammatory cytokines, such as IL-12, TNF-α, and interferon-γ, and stimulate the production of anti-inflammatory cytokines, such as IL-10 and transforming growth factor-β (Elenkov and Chrousus, 1999, Stress hormones Th1/TH2 patterns, pro/anti-inflammatory cytokines and susceptibility to disease, Trends Endrcrinol Metab, 10:359-368). Through this mechanism, systemic catecholamines can cause a selective suppression of Th1 responses and enhance Th2 responses that can depress or impair T4 cell mediated immunity (Madden KS et al, 1995, Catecholamine influences and sympathetic neural modulation of immune responsiveness, Annu Rev Pharmavol Toxicol, 35:417-448).

People with drug and alcohol abuse already have compromised or suppressed or impaired immune systems. Treatments with drugs whether for disease conditions or for attempted rehabilitation as with replacement with methadone that have immune suppression effects only compounds or adds to the problem of a depressed or impaired immune system and start off as immune compromised patients or patients with a depressed immune system.

Fauci gives detailed descriptions of the effects of corticosteroids on the immune system. These effects resemble the immune abnormalities that are found in patients suffering from AIDS or Idiopathic CD4 T cells lymphocytopnea (ICL) (Fauci AS, 1975, Mechanisms of Corticosteroid Action on lymphocyte Subpopulations I, Redistribution of circulating T and B lymphocytes to the bone marrow, Immunology 28:669-679).

Many types of infections seem to appear more often in patients treated with corticosteroids. Of the bacterial infections, staphylococcal and Gram-negative infections, as well as tuberculosis and Listeria infections, probably occur most often. Since steroids have a broad range of effects in the body, including immune suppression, it is not surprising that certain types of viral, fungal, and parasitic infections also occur often. Patients with lupus erythematous, rheumatoid arthritis, and renal transplant have more infection with steroid administration. Studies of bronchial aerosols showed that with higher doses of steroid in the aerosol, Candida infections of the larynx and pharynx occurred more often (Fauci AS et al, 1976, glucocorticosteroid therapy: Mechanisms of Action and Clinical Considerations, Annals of Internal Medicine 84: 304-15: Fauci AS et al, 1998, Harrison's Principles of Internal Medicine, McGraw-Hill Companies, Inc. New York USA, ed 14).

A review of the literature relating to the causes and the pathogenesis of AIDS worldwide revealed that approximately 90% of AIDS cases in the USA and Europe are observed in homosexual men and drug users. The regular and combined use of alcohol, heroin, cocaine, amphetamines, and alkyl nitrite cause chronic health problems of the nervous system, respiratory system, cardiovascular system, kidneys and other tissues in these individuals. All of these substances can create oxidative stress when taken on a regular or daily basis. When the oxidative stress spreads to the immune system, lowering the vitamin C and glutathione levels, health problems begin to manifest.

The majority of these health problems are usually diagnosed as idiopathic currently, and treated with high doses of glucocorticoids and/or cytotoxic drugs. In addition, homosexual men, as a group tend to be heavy users of illicit drugs, alcohol, and rectal glucocorticoids than their heterosexual counterparts.

The HIV-hypothesis states that a virus causes AIDS by killing the CD4+ T cells directly or indirectly after long incubation times (about 10 years), and the number of these cells will reach very low levels (<300/ μL) which lead to severe immune deficiency. Patients with severe immune deficiency (CD4+ T cells < 200/μL) usually suffer from opportunistic infections (viral, bacterial, fungal, yeast, and/or parasitic) and certain forms of cancer such Kaposi's sarcoma (KS) and lymphoma.

The majority of AIDS patients who participated in the four major Zidovudine (AZT) clinical trials in the US between 1987-1992 were HIV-negative prior to their treatment with AZT. Briefly, a total of 2,349 patients participated in these studies, and at least 77% of them were HIV-negative prior to their treatment with AZT. The treatment of a patient with prednisone at 60 mg per day for about three months can actually cause AIDS. This treatment and doses often given to patients suffering from lung fibrosis, thrombocytopenia, or other chemically induced chronic illnesses (Fischl MA et al, 1987, The efficacy of Azidothymmidine (AZT) in the treatment of patients with AIDS and AIDS-related complex, A double-blind, Placebo-Controlled Trial, The New England Journal of Medicine, Volume 317, number 4 (185-191): Fischl MA, 1990, A randomized controlled trial of a reduced daily dose of zidovudine in patients with the acquired immunodeficiency syndrome, The New England Journal of Medicine, Volume 323, number 15 (1009-14).

Daily doses of steroids can actually cause AIDS, more so in people with a low antioxidant dietary intake. And that may include fungal infections as well, in addition to viral and bacterial infections. "...the treatment of a patient with prednisone at 60 mg per day for about three months can actually cause AIDS. This treatment and doses is often given to patients suffering from lung fibrosis, thrombocytopenia, or other chemically induced chronic illnesses." As an acquired immune deficiency syndrome "AIDS is caused by the heavy use of corticosteroids and/or cytotoxic drugs to treat many health problems the effects of corticosteroids on the immune system." This treatment and doses often given to patients suffering from lung fibrosis, thrombocytopenia, or other chemically induced chronic illnesses clearly shows that the daily use of corticosteroids and/or cytotoxic drugs to treat many health problems. Fauci described in detail the effects of corticosteroids on the immune system. These effects resemble the immune abnormalities that are found in patients suffering from AIDS or Idiopathic CD4 T cells lymphocytopnea (ICL) which are also described by Fauci et al" (Mohammed Ali Al-Bayati, Ph.D., DABT, DAVT, HIV Does Not Cause AIDS:cf; Mercola.com).

AIDS patients receiving antiretroviral therapy (ART) tend to develop immune reconstitution inflammatory syndrome (IRIS) which is a worsening of a known condition in the patient or the development of a new condition after ART that characterizes IRIS. The overall incidence of IRIS is not known. Its underlying opportunistic infectious burden includes infections from mycobacteria, varicella voster, herpesviruses and cytomegaloviruses (CMV). Antiretroviral drug therapy (d4T, 3TC, NVP) for one month prior can induce borderline tuberculoid leprosy, with reversal reaction that in the setting of the recent Antiretroviral Therapy (ART) this is considered clinically as (IRIS) (Sujata Mehta et al, 2008, Leprosy presenting as immune reconstitution Inflammatory Syndrome, Ind J of sexually transmitted Diseases, Vol:29, Issue:2, 96-97).

A study on the incidence, clinical manifestations, risk factors and outcome of immune reconstitution inflammatory syndrome (IRIS) in South Africa University hospital-based antiretroviral therapy (ART) clinic offers some data in a total of 423 ART-naive HIV-infected South African patients who were followed for signs and symptoms IRIS during the first 6 months of ART. During the first 6 months of ART, 44 (10.4%) patients experienced IRIS for an overall incidence rate of 25.1 cases per 100 patient-years. Diagnoses included tuberculosis (18/44, 41%), abscess formation and suppurative folliculitis (8/44, 18.2%), varicella zoster (6/44, 13.6%), herpes simplex (4/44, 9.1%), cryptococcal meningitis (3/44, 6.8%), molluscum contagiosum (3/44, 6.8%), and Kaposi's sarcoma (2/44, 4.5%). Median IRIS onset was 48 days (interquartile range, 29-99) from ART initiation (Murdoch DM et al, 2008, Incidence and risk factors for the immune reconstitution inflammatory syndrome in HIV patients in South Africa: a prospective study, AIDS, Mar 12;22(5):601-10).

The immune reconstitution inflammatory syndrome (IRIS) in HIV-infected patients initiating antiretroviral therapy (ART) results from restored immunity to specific infectious or non-infectious antigens. These benefits are, in part, a result of partial recovery of the immune system, manifested by increases in CD4+ T-lymphocyte counts and decreases in plasma HIV-1 viral loads (Gea-Banacloche and Clifford Lane: Immune reconstitution in HIV infection, Aids 1999, 13 Suppl A:S25-38). After initiation of ART, opportunistic infections (OI) and other HIV-related events still occur secondary to a delayed recovery of adequate immunity (Ledergerber B et al, 1999, AIDS-related opportunistic illnesses occurring after initiation of potent antiretroviral therapy: the Swiss HIV Cohort Study, Jama 282(23):2220-2226).

The depletion of CD4 lymphocytes has been related to AIDS ever since its first description. With the dramatic reduction in number of CD4 lymphocytes, the ratio of CD4 to CD8 cells changes and it is often used as a marker of the progress of the disease.

Some patients initiating ART experience unique symptoms during immune system recovery. In these patients, clinical deterioration occurs despite increased CD4+ T-lymphocyte counts and this clinical deterioration is a result of an inflammatory response or "dysregulation" of the immune system (David Murdoch et al, 2007, Immune reconstitution inflammatory syndrome (IRIS): review of common infectious manifestations and treatment options, AIDS Research and Therapy, 4:9). This situation is considered as a paradoxical clinical worsening of a known condition or the appearance of a new condition after initiating therapy characterizes the syndrome. We need to consider this "paradox" in the context of whether there is in fact a real restored immunity upon initiating ART as indicated by increased T4 cell lymphocyte count and the resulting clinical deterioration as a result of an inflammatory response or dysregulation of the immune system.

Other researchers conducted a study development of IRIS as a part of ART over a period of 2 years. They found that twenty (22.2%) out of the 90 patients developed IRIS. Herpes zoster (HZ), herpes simplex virus (HSV), and tuberculosis (TB) were the cases of IRIS seen in the present study. They concluded that IRIS in terms of HSV/TB is known to accelerate HIV disease progression (Sharma A et al, 2008, Immune reconstitution inflammatory syndrome, Indian J Dermatol Venereol Leprol, 74(6):619-21). IRIS is known to accelerate the progression of AIDS. Drug and chemical stimulated activation of T cells cannot be considered as restoration of immune function or restoration of the immune system when such stimulation leads to thyroiditis and/or RA with new infections or other conditions setting in. There are other substances that have entered the immune system of humans through the widespread use of vaccines. Of such substance is squalene.

Squalene is a cholesterol precursor that is used as an adjuvant in vaccines. It is a stimulant that stimulates the immune system nonspecifically. One intradermal injection of this adjuvant lipid can induce joint-specific inflammation in arthritis-prone DA rats. Histopathological and immunohistochemical analyses revealed erosion of bone and cartilage, and that development of polyarthritis coincided with infiltration of ß+ T cell. This demonstrates that an autoadjuvant can trigger chronic, immune-mediated joint-specific inflammation may give clues to the pathogenesis of rheumatoid arthritis and it raises new questions concerning the role of endogenous molecules with adjuvant properties in chronic inflammatory diseases (Barbro Carlson et al, 2000, The Endogenous Adjuvant Squalene Can Induce a Chronic T-Cell-Mediated Arthritis in Rats, American Journal of Pathology, 156:2057-2065). The RA onset correlated with T cell infiltration specifically into joints.

These T cells were activated by squalene. The immunological involvement in the pathogenesis appears clear, since depletion of T cells expressing ß TcR completely abrogated the disease. In contrast, depletion of CD8+ T cells and TcR+ cells did not ameliorate the disease, which points to a pathogenic role for ß TcR+ CD4+ T cells.

Clearly squalene stimulates an autoimmune response that increases CD8 and T cells that causes RA. Autoimmune diseases arise from a stimulated immune response of the body against substances and tissues normally present in the body in which the body really attacks its own cells. This may be restricted to certain organs as in thyroiditis or certain tissues as in RA. Such thyroiditis is generally caused by an autoimmune attack on the thyroid, resulting in inflammation and damage to the thyroid cells. Immune suppression as in IRIS and oxidative stress leads to the progression of AIDS.

Dr. Luc Montagnier, a Nobel Prize winner, who was credited with discovering a virus that is referred to as HIV, states in his book that oxidative stress, must be present for the progression of AIDS. In his interview with Richard A. Passwater, Ph.D. in 1995, Luc Montahnier sates that:-

> "Oxidative stress is a key factor. There is a higher free radical production in stage II of HIV infection that could be caused by several factors including the overproduction of oxygen radicals by polymorphonuclears. The key may be to reduce oxidative stress at the earliest stage of HIV infection."

It appears from his assertions that early detection of IRIS and prompt intervention to reduce or eliminate oxidative stress is important instead of continuation of highly active ART, as these drugs increase the ROS and increase the oxidative stress in the human biological system.

According to Peter Duesberg, AZT is triphosphorylated extracellularly. The triphosphorylated AZT enters the cells and attaches to the DNA and stops its synthesis - AZT is a DNA chain terminator in human cells and by doing so becomes toxic to the cells (Lauritsen J, 1990, Poison by prescription - The AZT story. New York: Asklepois Press). However, the enzymes which triphosphorylate AZT are found only intracellularly which means that AZT cannot even be triphosphorylated extracellularly. Further, it is interesting to note that the cell membrane is impermeable to the phosphorylated nucleotides (Leibman and Heidelberger, The metabolism of P32 labelled ribonucleotides in tissue slices and cell suspensions, J Biol Chem 1995; 216:823-830) so that means the extracellularly triphosphorylated AZT cannot then act as a retroviral against the HIV contained within cells. So, how does it stop the HIV from replicating?

It is stated that the HIV is an unusual virus. It is a retrovirus which means that it reverses the normal pattern of replication. Its genetic material contains only RNA instead of DNA. AZT is a DNA chain terminator not an RNA replication terminator. For it to terminate RNA replication, it must attach to the RNA but AZT attaches to DNA.

The present available data show there is no significant triphosphorylation of AZT even intracellularly, since for triphosphorylation of AZT reducing equivalents are necessary as AZT is an oxidising agent. It is through this oxidising property that it induces its toxicity, like all other oxidants inluding the peroxynitrite radical (see: Perth Group Commentary On The Rethinking of AIDS Ressponse To The Gallo et al Crtiticism of Celia Farber in harpers, 2005).

Some researchers think that since the T4 cell count improves in IRIS patients there is restoration of immunity and the body begins to fight aggressively against coexisting infection. That would be the simplistic view to hold if one fails to understand the mechanism that increases T4 (and possibly T8) cell count mediated through ART that also increases the inflammation at the same time as seen in the increased activity of cytokines like IL-2 and interferon-gamma.

It would be therefore be tragically interesting to research how the clinical deterioration in IRIS which is stated to be a result of an inflammatory response or "dysregulation" of the immune system occurs or how it is precipitated during the course of the therapy. The resulting clinical manifestations of this syndrome are diverse and depend on the infectious or noninfectious agent involved. These manifestations include mycobacterial-induced lymphadenitis, paradoxical tuberculosis reactions, worsening of progressive multifocal leukoencephalopathy (PML), recurrence of cryptococcosis and Pneumocystis jirovecii pneumonia (PCP), Cytomegalovirus (CMV) retinitis, shingles, and viral hepatitis, as well as noninfectious phenomena (ref: David MM et al, 2007, Immune reconstitution inflammatory syndrome (IRIS), review of common infectious manifestations and treatment options, AIDS Research and Therapy, 4:9). The resulting clinical manifestations that are diverse tend to follow the kind of diversity expected from immune suppression caused by oxidative stress and immune suppression.

A significant proportion of HIV/TB coinfected patients undergoing HAART have symptoms consistent with IRIS, with estimates ranging from 7–45%. The commonest clinical manifestations of TB-IRIS are fever, lymphadenopathy and worsening respiratory symptoms (Lawn SD et al, 2005, Immune reconstitution disease associated with mycobacterial infections in HIV-infected individuals receiving antiretrivirals, Lancet Infect Diseases, 5(6):361-373). Pulmonary disorders, such as new pulmonary infiltrates, mediastinal lymphadenopathy, and pleural effusions are also common (Narita et al, 1998, Paradoxical worsening of tuberculosis following antiretroviral therapy in AIDS patients, Am J Respirat Crit Care Med, 158(1):157161). Understanding the importance of host susceptibility and underlying opportunistic infections on the risk of developing IRIS in critical in looking at approaches that promote natural immune support rather than continue with immune suppression. The mechanism for IRIS involves host suppression of the immune system to these opportunistic infections, the suppression being induced by the cytotoxic drugs and/or steroids that maintain the susceptibility to the opportunistic infections. At least, 20-25% of patients in ART therapy are likely to fall in this category.

The treatment for mycobacterial-associated IRIS depends on the presentation and disease severity. Most patients present with non-life threatening presentations which respond to the institution of appropriate antituberculous therapy. However a range of life threatening presentations, such as acute renal failure and acute respiratory distress syndrome (ARDS), are described and have significant morbidity and mortality. Since the pathogenesis of the syndrome is an inflammatory one, systemic corticosteroids or nonsteroidal anti-inflammatory drugs (NSAIDS) may alleviate symptoms. Anecdotal evidence indicates that where therapy for IRIS was mentioned, the use of corticosteroids was variable effective. Therapies ranged from intravenous methylprednisolone 40 mg every 12 hours to prednisone 20–70 mg/day for 5–12 weeks. These practices reflect the lack of evidence from controlled trials for the use of anti-

inflammatory agents in IRIS. Doctors suggest that continuation of ART is desirable, although its discontinuation may be necessary in unresponsive cases or in those presenting with advanced neurological symptoms. We need to look at the randomized placebo controlled trial examining doses of prednisone 1.5 mg/kg/day for two weeks followed by 0.75 mg/kg/day for two weeks in mild moderate TB-IRIS that is currently underway in South Africa for further data.

Inflammatory stimuli reliably elicit hypothalamic-pituitary-adrenal (HPA) activation, and it is now established that the immune and HPA systems are mutually regulatory (Nola Shanks and Stafford Lightman, 2001, The maternal-neonatal neuro-immune interface: Are there long-term implications for inflammatory or stress-related disease? J. Clin. Invest. 108(11): 1567-1573). The interactions between the neuroendocrine and immune systems provide a finely tuned regulatory system required for health. Disturbances at any level can lead to changes in susceptibility to or severity of infectious, inflammatory or autoimmune diseases. Inflammation and inflammatory responses are modulated by a bidirectional communication between the neuroendocrine and immune system. Many lines of research have established the numerous routes by which the immune system and the central nervous system (CNS) communicate. The CNS signals the immune system through hormonal pathways, including the hypothalamic–pituitary–adrenal axis and the hormones of the neuroendocrine stress response, and through neuronal pathways, including the autonomic nervous system. The hypothalamic–pituitary–gonadal axis and sex hormones also have an important immunoregulatory role (Farideh E et al, 2003, Neural immune pathways and their connection to inflammatory disease, Artiritis Res Therapy, 5:251-261).

The inflammatory response is modulated in part by a bidirectional communication between the brain and the immune systems. This involves hormonal and neuronal mechanisms by which the brain regulates the function of the immune system and, in the reverse, cytokines, which allow the immune system to regulate the brain. In a healthy individual this bidirectional regulatory system forms a negative feedback loop, which keeps the immune system and central nervous system (CNS) in balance. Perturbations of these regulatory systems could potentially lead to either overactivation of immune responses and inflammatory disease, or oversuppression of the immune system and increased susceptibility to infectious diseases.

There are two major pathways by which the CNS regulates the immune system: the first is the hormonal response, mainly through the hypothalamic–pituitary–adrenal (HPA) axis, as well as the hypothalamic–pituitary–gonadal (HPG), the hypothalamic–pituitary–thyroid (HPT) and the hypothalamic–growth-hormone axes; the second is the autonomic nervous system, through the release of norepinephrine (noradrenaline) and acetylcholine from sympathetic and parasympathetic nerves. In turn, the immune system can also regulate the CNS through cytokines.

Conversely, cytokines released in the periphery change brain function, whereas cytokines produced within the CNS act more like growth factors. Thus, cytokines produced at inflammatory sites signal the brain to produce sickness-related behavior including depression and other symptoms such as fever. In addition, cytokines produced locally exert paracrine/autocrine effects on hormone secretion and cell proliferation (ref: Farideh E et al, 2003, Neural immune pathways and their connection to inflammatory disease, Artiritis Res Therapy, 5: 251-265).

The interactions between the neuroendocrine and immune systems provide a finely tuned regulatory system required for health. Disturbances at any level can lead to changes in susceptibility to or severity of infectious, inflammatory or autoimmune diseases.

On stimulation, corticotropin-releasing hormone (CRH) is secreted from the paraventricular nucleus of the hypothalamus into the hypophyseal portal blood supply. CRH then stimulates the expression and release of adrenocorticotropin (ACTH) from the anterior pituitary gland. Arginine vasopressin (AVP) synergistically enhances CRH-stimulated ACTH release ACTH in turn induces the expression and release of glucocorticoids from the adrenal glands.

Glucocorticoids (GC) are a class of steroid hormones that bind to the glucocorticoid receptor (GR), which is present on the surface of almost every vertebrate animal cell. They are synthesized in the adrenal cortex and they have an important role in glucose metabolism. Cortisol (or hydrocortisone) is the most important human glucocorticoid. It is essential for life. It in involved in the regulation of a variety of important cardiovascular, metabolic, immunologic and homeostatic functions and in the synthesis of nitric oxide. Various synthetic glucocorticoids are available which are used either as replacement therapy in glucocorticoid deficiency or to suppress the immune system. Glucocorticoids may be used in low doses in adrenal insufficiency. In much higher doses, glucocorticoids are used to suppress various allergic, inflammatory and autoimmune disorders.

Glucocorticoids regulate a wide variety of immune-related genes and immune cell expression and function. Glucocorticoids modulate the expression of cytokines, adhesion molecules, chemoattractants and other inflammatory mediators and molecules and affect immune cell trafficking, migration, maturation, and differentiation. Insufficient glucocorticoid modulation on the adhesion molecules may result in internal bleeding or platelet aggregation. Glucocorticoids cause a Th1 (cellular immunity) to Th2 (humoral immunity) shift in the immune response, from a proinflammatory cytokine pattern with increased interleukin (IL)-1 and tumor necrosis factor (TNF)-α to an anti-inflammatory cytokine pattern with increased IL-10 and IL-4. Pharmacological doses and preparations of glucocorticoids cause a general suppression of the immune system, whereas physiological doses and preparations of glucocorticoids are not completely

immunosuppressive but can enhance and specifically regulate the immune response under certain circumstances. Physiological concentrations of natural glucocorticoids (i.e. corticosterone) stimulate delayed-type hypersensitivity reactions acutely, whereas pharmacological preparations (i.e. dexamethasone) are immunosuppressive (Dhabhar and McEwen, 1999, Enhancing versus suppressing effects of stress hormones on skin function, Proc Natl Acad Sci USA, 96:1059-1064).

Several drugs decrease TSH secretion and lower serum TSH concentrations, although not to values as low as those found in patients with hyperthyroidism (Martin Surks and Rubens Sievert, 1995, Drugs and Thyroid Function, Review article, Drug Therapy, Volume 333:1688-1694 December 21, Number 25). These agents are dopamine (in doses of at least 1 µg per kilogram of body weight per minute), glucocorticoids (e.g., dexamethasone, in doses of 0.5 mg or more per day or hydrocortisone in doses of 100 mg or more per day) (Brabant A, et al, 1989, The role of glucocorticoids in the regulation of thyrotropin. Acta Endocrinol Suppl (Copenh) 121:95-100: Samuels MH et al, 1994, Effects of hydrocortisone on pulsatile pituitary glycoprotein secretion, J Clin Endocrinol Metab 78:211-215) and octreotide (in doses of more than 100 µg per day), which is a somatostatin analogue used for the treatment of acromegaly and certain other hormone-excess syndromes (Bertherat J et al, 1992, Somatostatin receptors on thyrotropin-secreting pituitary adenomas: comparison with the inhibitory effects of octreotide upon in vivo and in vitro hormonal secretions, J Clin Endocrinol Metab 75:540-546: Christensen SE et al, 1992, Long-term efficacy and tolerability of octreotide treatment in acromegaly, Metabolism 41:Suppl 2:44-50).

Glucocorticoids exert these immunomodulatory effects through a cytosolic receptor, the glucocorticoid receptor (GR). This is a ligand-dependent transcription factor that, after binding of the ligand, dissociates from a protein complex, dimerizes, and translocates to the nucleus, where it binds to specific DNA sequences (glucocorticoid response elements) to regulate gene transcription (Aranda and Pascual, 2001, Nuclear hormone receptors and gene expression, Physiol Review, 81:1269-1304). The oxidatively damaged GR can also interfere with other signaling pathways and this mechanism may be the one through which most of the anti-inflammatory actions are mediated. Increases in its damaged variants such as GRβ may be involved in several inflammatory diseases including asthma, inflammatory bowel disease/ulcerative colitis, and RA which is a measure of oxidative stress or its disruptive impact.

In addition to the HPA axis, other central hormonal systems, such as the HPG axis and in particular estrogen, also modulate the immune system. In general, physiological concentrations of estrogen enhance immune responses whereas physiological concentrations of androgens, such as testosterone and dehydroepiandrosterone (DHEA) are immunosuppressive in females with RA (Cutolo and Wilder, 2000, Different roles for androgens and estrogens in the

susceptibility of autoimmune rheumatic diseases, Rheum Dis Clin North Am, 26:825-839). Females of all species exhibit a greater risk of developing many autoimmune/inflammatory diseases, such as systemic lupus erythematosus, RA and multiple sclerosis, ranging from a 2-fold to a 10-fold higher risk compared with males (Olsen and Kovacs, 1996, Gonadal steroids and immunity, Endocr Rew, 17:369-384: Ahmed SA, 1999, Gender and risk of autoimmune diseases: possible role of estrogenic compounds, Environ Health Perspect, 107(suppl5):681-686). Knockout mouse models indicate that both estrogen receptors α and β are important for thymus development and atrophy in a gender-specific manner (Erlandsson MC, Role of Oestragen receptors aplha and beta in immune organ development and in oestrogen-mediated effects on thymus, Immunology, 103:17-25). Since estrogen is an antioxidant, it becomes depleted upon prolonged oxidative stress and long term use of drugs by females tends to disturb the estrogen-androgen balance that affects susceptibility to some of those disease conditions.

The growth hormone (GH) is also a modulator of the immune system and its effects are mediated primarily through insulin-like growth factor-1 (IGF-1). GH and IGF-1 have been shown to modulate the immune system by inducing the survival and proliferation of lymphoid cells. Thus, immune cells including T and B lymphocytes and mononuclear cells express IGF-1 receptor. After binding to these receptors, GH activates the phosphoinositide 3-kinase/Akt and NF-κB signal transduction pathways. This pathway is also important in immunity. Some of the GH effects on the immune system might be modulated through this signal transduction pathway but studies in GH knockout animals show that this hormone is only minimally required for immune function and is more important in rejuvenation.

GH might also modulate immune function directly by rejuvenating other hormonal systems and by rejuvenating the cells of the immune system directly. Short-term increases in glucocorticoids increase GH production (Veldhius JD et al, 1992, Divergent effects of short-term glucocorticoid excess on the gonadpothrohic and somatotrophic axes in normal men, Journal Clin Endorinol Metab, 74:96-102) whereas long-term high doses result in a decrease in the hypothalamic–GH axis and even growth impairment (Hochberg Z et al, 2002, Mechanisms of steroidal impairment of growth, Horm Res, 58(suppl1) 33-38). Hence long term use of glcocorticoid inhibits the hypothalamic–GH axis. Children with chronic inflammatory disease exhibit growth retardation. During the early phase of inflammatory reactions, the concentration of GH is increased. In spite of an initial rise in GH secretion, GH action is reduced because of GH and IGF-1 resistance in the inflamed tissues. The initial increases in GH by stimulation that later or subsequently inhibits its secretion may be due to a feedback mechanism. Also when corticosteroids are initially applied, they tend to give quick relief from the symptoms by suppression of the inflammation but excess or prolonged use of corticosteroids flow into the bio-feedback mechanism and the body's natural production of glucocortociods decline that leads to a flair-up in the inflammations. This

mechanism helps to impair growth and adversely affects the immune function.

As with the interaction between the HPA axis and the immune system, there is a bidirectional interaction between the HPT axis and immune system. The HPT axis has an immunomodulatory effect on most aspects of the immune system. Thyrotropin-releasing hormone (TRH), thyroid-stimulating hormone (TSH), and the thyroid hormones triiodothyronine (T3) and thyroxine (T4) all have stimulatory effects on immune cells. Glucocorticoids also have direct immunosuppressive effects on thyroid hormones possibly by participating in factors that compete in binding to receptor sites in cells of the thyroid. Inflammation caused by glucocorticoids also inhibits TSH secretion and indirectly lowers cell-mediated immunity.

In addition to direct effects of thyroid hormones on immune response, there is also interaction between the HPA and HPT axes. Hyperthyroid and hypothyroid states in rats have been shown to alter responses of the HPA axis, with hypothyroidism resulting in a reduced HPA axis response and hyperthyroidism resulting in an increased HPA axis response. In agreement with this, administration of thyroxine, inducing a hyperthyroid state, has been shown to activate the HPA axis and be protective against an inflammatory challenge in rats and hypothyroidism has been shown to cause a reduction in CRH gene expression. Chronic HPA axis activation also represses TSH production and inhibits the conversion of inactive T4 to the active T3 (Benker G et al, 1990, TSH secretion in Cushing's syndrome' relation to excess glucocortocoid excess, diabetes, goitre, and the sick eurothroid syndrome, Clin Endorinolo (Ofd) 33:777-786). This disturbance caused by excess glucocorticoids inhibit the activation of T4 cells also lowers cell-mediated immunity in the long term.

As expected a blunted HPA axis has been associated with susceptibility to autoimmune/inflammatory diseases in several animal models. The animal models for arthritis have shown a role for the HPA axis, sympathetic, parasympathetic, and peripheral nervous systems. They have shown the necessity of endogenous glucocorticoids in regulating the immune response after exposure to antigenic or proinflammatory stimuli. The severity of inflammatory/autoimmune disease or mortality increases after removal of these endogenous glucocorticoids by adrenalectomy or GR blockade.

Another condition that appears to have three common symtoms to AIDS patients with IRIS, namely fatigue, inflammation and elevated T4 cell counts is sarcoidosis. Sarcoidosis is a disease that can affect any organ in the body. The lung is the most common organ involved with sarcoidosis. The eyes, skin, and lymph glands are also commonly involved. Sarcoidosis can also affect the liver, spleen, brain, nerves, heart, bones, muscles, and joints. Sarcoidosis can also cause generalized body symptoms such as fever, weight loss, night sweats, and fatigue. The aetiology of sarcoidosis remains unclear, although it is recognized as a disease of activated T

lymphocytes (Porter N et al, 2003, Endocrine and reproductive manifestations of sarcoidosis, Q J Med 2003; 96: 553-561) and is associated with inflammations. Autoimmune disease and sarcoidosis may be related, and the association between sarcoidosis and autoimmune thyroid disease has long been recognized (Papadopoulos K et al, 1996, High Frequency of Endocrine Autoimmunity in Patients with sarcoidosis, Eur J Endocrinol 134:331–6). Excess ROs and secondary radicals and oxidants, whether the peroxynitrite or chemical oxidants like AZT can cause inflammations.

Sarcoidosis is an inflammatory disease that affects multiple organs in the body, but mostly the lungs and lymph glands. Since it is an inflammatory disease, communities with low dietary antioxidant intake and poor nutrition will have a higher incidence of this condition. In patients with sarcoidosis, abnormal masses or nodules (called granulomas) consisting of inflamed tissues form in certain organs of the body. These granulomas might alter the normal structure and possibly the function of the affected organ(s) (source: Cleveland Clinic). It is an inflammatory condition in which thyroid dysfunction occurs in sarcoidosis that activates and increases the number of T4 cells. It could be due to a earlier exposure to glucocorticoids. Thyroid disease is a frequent side effect of interferon (IFN)- therapy for hepatitis C virus (HCV) and other disorders (Carella et al, 2004, Interferon-Related Thyroid Disease: Pathophysiological, Epidemiological, and Clinical Aspects, The Journal of Clinical Endocrinology & Metabolism Vol. 89, No. 8 3656-3661).

The elevation in T4 concentrations was studied in a canine model and was found to be due to the production of anti-T4 antibody. Autoantibodies to thyroid hormones are indicative of autoimmune thyroid disease. The expression of Th1-type cytokines, such as IFN-γ, IL-18 and IL-15, was increased during the development of autoimmune thyroiditis (E-W Choi et al, 2006, Hormonal change and cytokine mRNA expression in peripheral blood mononuclear cells during the development of canine autoimmune thyroiditis, Clin Exp Immunol, October 146(1): 101–108). The increase in T4 cell level associated with increased level of inflammation is similar to seropositive AIDS patients in IRIS.

Circulating thyroid autoantibodies are present in 18% of individuals without reported thyroid disorders (Ruth M. Belin et al, 2004, Smoke Exposure Is Associated with a Lower Prevalence of Serum Thyroid Autoantibodies and Thyrotropin Concentration Elevation and a Higher Prevalence of Mild Thyrotropin Concentration Suppression in the Third National Health and Nutrition Examination Survey (NHANES III), The Journal of Clinical Endocrinology & Metabolism Vol. 89, No. 12 6077-6086) and thyroid autoimmunity occurs commonly in the United States, affecting more than 35 million Americans (Hollowell JG et al, 2002 Serum TSH, T4, and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III), J Clin Endocrinol Metab 87:489–499) a population with

probably the highest exposure to drugs in therapy and chemicals from industry. Drug administration in these people, especially drugs that are oxidants or that can increase the ROS and secondary radicals that in turn cause or aggravate inflammations may be particularly susceptible to thyroiditis and immune suppression in long terms use of drugs in therapy. Integrating natural antioxidants may be a way to optimize drug therapy while lowering the risk of inflammations and immune suppression.

The treatment of sarcoidosis has not yet been standardized. Corticosteroids are the primary medication used for the treatment of sarcoidosis. Corticosteroids effectively suppress the elevated CD4-CD8 (T4-T8) lymphocyte ratio, decrease interleukin-2 production, and inhibit collagen synthesis, all of which occur at the sites of active disease (Agbogu BN et al, 1995, Therapeutic considerations in patients with refractory neurosarcoidosis, Arch Neurol 52:875–9). Treatment is usually prolonged, exposing the patient to significant steroid-related side-effects. Many times no therapy is given for sarcoidosis because, although Corticosteroids have been shown to be of benefit in the short term, they usually are not of benefit over the long term. Since corticosteroids have many side effects, physicians sometimes believe that the "therapy" with corticosteroids may be worse than the disease.

About 5% of patients with sarcoidosis have clinical involvement of the nervous system (Stern BJ et al, 1985, Sarcoidosis and its neurological manifestations. Arch Neurol 42:909–17); however, the incidence of subclinical and undiagnosed neurosarcoidosis (NS) is much higher (James DG and Sharma OP, 1967, Neurological complications of sarcoidosis. Proc Roy Soc Med 60:1169–70). Inr 10-15 percent of affected persons, sarcoidosis is a chronic condition. Although its involvement in NS is uncommon, the hypothalamus is the most frequently involved of all the endocrine glands. Sarcoidosis, like other granulomatous diseases, infections, and metastatic tumors, commonly leads to an infiltrative process in the hypothalamo-hypophyseal region resulting in neuroendocrinological dysfunction.

Hypothalamic sarcoidosis can lead to growth hormone insufficiency/deficiency (Veseky D et al, 1977, Hypopituitarism and Possible Hypothalamic Involvement In Sarcoidosis, Am J Med 62:425–30) and an increase in catecholamines (Porter N et al, 2003, Endocrine and reproductive manifestations of sarcoidosis, Q J Med 2003; 96: 553-561). Persons on opioids also have elevated catecholamine levels that indicate depressed immune systems. Research has shown that catecholamines can cause a selective suppression of Th1 responses and enhance Th2 responses that can depress or impair T4 cell mediated immunity. Hypothalamic sarcoidosis appears similar to cases in of blunted HPA axis in animal studies that has been associated with susceptibility to autoimmune/inflammatory diseases.

In 1985 Montagnier wrote “This [clinical AID] syndrome occurs in a minority of infected persons, who generally have in common a past of antigenic stimulation and of immune

depression before LAV infection (Montagnier L, 1985, Lymphadenopathy-Associated Virus: From Molecular Biology to Pathogenicity, Ann Int Med 103:689-693). So, he makes it clear that first there must be an antigenic stimulation and immune depression for an infection to occur. Next, in 1986 Montagnier wrote "...the replication and cytopathic effect of LAV can only be observed in activated T4 cells. Indeed, LAV infection of resting T4 cells does not lead to viral replication or to expression of viral antigen on the cell surface, while stimulation by lectins or antigens of the same cells results in the production of viral particles, antigenic expression and the cytopathic effect" (Klatzmann D and Montagnier L, 1986, Approaches to AIDS therapy, Nature 1986;319:10-11). Secondly, it was made clear that the virus only replicates in activated T4 cells and only these cells the cytopathic effects of the virus can be observed.

To summarize:-

1. First there must be an antigenic stimulation and immune depression for an infection to occur, and

2. Secondly, the virus only replicates in activated T4 cells and only these cells the cytopathic effects of the virus can be observed.

So it is not what the HIV hypothesis states; that a virulent and pathogenic virus targets the T4 cells and kills them thereby causing immune suppression that leads to the destruction of the immune system.

In the same year Gallo and his associates reported experiments where they prepared T-cell cultures (which contained 34% T4 cells), from normal donors.

Cultures were stimulated with PHA and were (i) "infected" with HIV; (ii) left uninfected. Control cultures remained both unstimulated and uninfected. After 2 days of culture, the proportion of T4 cells in the stimulated-uninfected and stimulated-infected cultures was 28% and 30% respectively, while at 6 days the number was 10% and 3%; the controls not changing significantly. Thus, stimulation is sufficient to cause a decrease in T4 cells and “infection” with HIV makes no significant difference. Stimulation was essential and it did not matter whether the stimulated cells were infected or not as the difference in the proportion of T4 cells (ie 30 % minus 28%) is of negligible significance or importance. Stimulation was the key. Infection with the virus is of no significance impact at all.

The most critical piece of information rests in the controls, namely data from the “infected” but unstimulated cell cultures which he stated as "controls not changing significantly". I would suppose that in these infected but unstimulated cell cultures, there was no infectivity, which is why other researchers have reported that the particles are not infective. However, they did write "the expression of HTLV-III was always preceded by the initiation of interleukin-2

secretion, both of which occurred only when T-cells were immunologically [PHA] activated. Thus, the immunological stimulation that was required for IL-2 secretion also induced viral expression, which led to cell death" (Zagury D, Bernard J, Leonard R, Cheynier R, Feldman M, Sarin PS, et al, 1986, Long-Term Cultures of HTLV-III-Infected T Cells: A Model of Cytopathology of T-Cell Depletion in AIDS, Science 231:850-853).

Luc Montagnier has stressed the importance of cofactors in the development of the AIDS condition and by 1986 Montagnier and Gallo were in agreement that:

1. HIV by itself but no stimulation → No T4 cell destruction.

2. HIV plus stimulation → T4 cell destruction.

3. Stimulation by itself without HIV → T4 cell destruction.

4. No HIV and no stimulation → No T4 cell destruction

(see:Eleni Papadopulos-Eleopulos et al, 2008, Montagnier, T4 cells (acquired immune deficiency)and our oxidative theory of “HIV”/AIDS”, The Perth Group).

Their own reported experiments prove that it is an immunologic stimulation and not a virus that is the cause of AIDS. They state that oxidative stress is essential for the progression of AIDS. In 1988 Eleni Papadopulos-Eleopulos became the first to propose the oxidative stress theory as the cause of AIDS, induced by specific agents to which the risk groups are exposed (Papadopulos-Eleopulos E, 1988, Reappraisal of AIDS: Is the oxidation caused by the risk factors the primary cause? Med Hypotheses 25:151-162).

This "HIV" phenomena cannot occur unless the cells are stimulated by oxidizine agents like toxic drugs (Klatzmann and Montagnier (1986) Approaches to AIDS therapy. Nature 319:10-1: Zagury et al, 1986, Long term cultures of HTLV-III-infected T cells: A model of cytopathology of T-cell depletion in AIDS. Science, 231:850-853). Five years later, researchers including Anthony Fauci, showed that when stimulated cell cultures are treated with reducing agents such as antioxidants, this greatly suppresses the appearance of such phenomena (Fauci et al, 1991, Suppression of human immunodeficiency virus expression in chronically infected monocytic cells by glutathione, glutathione ester and N-acetyl cysteine, Proc. Natl. Acad. Sci, USA 88:896-990). They proved that immunological stimulation under conditions of oxidative stress triggers the “HIV” phenomenon – nothing else.

So how does this oxidative stress works in the initiation and development of AIDS? From the available information, it is obvious that oxidative stress depresses the immune system but that that alone is insufficient for infection and progression of AIDS. In an internal environment,

where the body is under oxidative stress due to poor and chronic malnutrition or due to drug and chemical and/or alcohol abuse, when there also occurs some immunological stimulation that results in an increase in activated T cells as in the case of thyroiditis and RA by glucococortoids and AZT and ART, these new cells become infected with viruses and die. It is said that these drug/chemically stimulated T4 cells have highly permeable cell membranes that allows infection.

"Infection of resting T4 cells does not lead to viral replication or to expression of viral antigens on the cell surface, while stimulation by lectins or antigens of the same cells results in production of viral particles, antigenic expression and the cytopathic effect" (Klatzmann and Montagnier, 1986, Klatzmann and Montagnier (1986) Approaches to AIDS therapy, Nature 319:10-1). If so, the entry of viruses into these newly activated T cells reduces the overall viral load which is again misread as a positive effect of a toxic therapy. In the meantime, these drugs generate more oxidative stress that further suppresses the immune system and opens it up for opportunistic infections. In the infected T cells, viruses replicate and when they die, the T cell counts begin to decline but such decline is not the perfect marker of AIDS progression. It is the antioxidant and the immune systems when they are sufficiently depressed that few new T cells are formed by activation in the thyroid while aggressive use of ART continues its toll on the immune system through aggravated oxidative stress and glutathione levels continue to decline as the p24 levels increase until the glutathione levels drops to the point of no return and death occurs.

Glutathione levels are depleted by oxidative stress caused by aggressive use of toxic drugs and drugs that cause a chronic stimulation of the immune system and with its decline the whole natural antioxidant defense mechanism of the body deteriorates while the AIDS condition, in this state of oxidative stress progresses. The actins that are produced by the stressed white blood cells cleave, due to breaks caused by free radicals yielding more and more of p24. “In conclusion, our data show that chronic immune activation and the size of the CD4 T cell pool are critical factors in HIV-1 pathogenesis, even when measured before seroconversion" (Hazenberg MD et al, 2003, Persistent immune activation in HIV-1 infection is associated with progression to AIDS, AIDS 17:1881-8). Here again, it can be noted that persistent immune activation is the immunologic stimulation by toxic drugs that triggers AIDS. And daily doses of AZT and ART provides that persistent or chronic stimulation of the immune system to precipitate AIDS that initially yields T4 cells as in thyroiditis which is misread as a restoration of the immune system but in fact it precipitates IRIS and initiates AIDS progression through oxidative stress – just like Luc Montagnier said: :oxidative stress aids the progression of AIDS.” It is an drug/chemical induced disease or oxidant-induced disease condition by persistent or chronic immunologic stimulation of the immune system .

Hence, oxidative stress may lead to some disease condition or other conditions may be treated by glucocortocoids that stimulate the system to activate T cells. Excessive use of steroids can sufficiently depress the immune system that begins to show signs of AIDS and when it is followed by ART, the patient may progress into IRIS and aggressive use of drugs to treat the opportunistic infections in IRIS patients leads to clinical deterioration and eventually death ensues. In cases of chronic malnutrition, the depression of the immune system and the body's antioxidant system leads to glutathione depletion and the emergence of p120, p160 etc and p24 and they are not virus-specific. With chronic inflammations on account of the prolonged oxidative stress, and glutathione depletion, the body opens up for opportunistic infections to take root.

Cells possess a highly efficient enzyme system responsible for the bulk of free radical scavenging and quenching of the oxygen free radical (OFR) that is a natural byproduct of metabolism in mitochondria. This system represents the primary defense against oxygen free radicals and function to reduce the superoxide radical, the first product of the monoelectric oxygen reduction, to water and oxygen in a step-wise process. First, the superoxide dismutase (SOD) converts the superoxide radical (OFR) into hydrogen peroxide (H2O2); next catalase and glutathione convert the hydrogen peroxide into water and oxygen. It is an ingenious biochemical system that requires organic minerals for its catalytic enhance efficiency that can go wry if these antioxidant enzymes and minerals are depleted by excess drug consumption as their metabolism generates excess hydrogen peroxide. In such a situation, the excess hydrogen peroxide will react with the superoxide to yield secondary radicals like the hydroxyl and excess superoxide will react with nitric oxide to yields the highly reactive oxidant called the peroxynitrite. In a healthy state, there should be no such secondary radicals and oxidants.

Glutathione peroxidase (GPx), is primarily a critical antioxidant in this system but it can also conjugate with drug metabolites for excretion. Glutathione conjugates are commonly secreted in bile (Gibson and Skett, 1999, Pathways of drug metabolism, in Introduction to Drug Metabolism, pp 1-34, Stanley Thornes Publishers, Athenaeum Press Ltd., London.) If the glutathione conjugate leaves the liver via the blood, it is rapidly converted to the cysteine conjugate which is eliminated in urine (Fischer LJ et al, 1985, Studies on the fate of the glutathione and cysteine conjugates of acetaminophen in mice, Drug Metabolism and Disposition, Volume 13, Issue 2, pp. 121-126, 03/01).

Glutathione (GSH) is a tripeptide composed of L-glutamic acid, L-cysteine, and L-glycine. Glutathione is one of the most important molecules in the cellular defense against chemically reactive toxic compounds or oxidative stress. This protective function is due in part to its involvement in conjugation reactions (Abdul Mutalib et al, 2000, Disposition of Glutathione Conjugates in Rats by a Novel Glutamic Acid Pathway: Characterization of Unique Peptide

Conjugates by Liquid Chromatography/Mass Spectrometry and Liquid Chromatography/NMR, The Journal of Pharmacology And Expt Therapetics, Vol. 294, No. 2). Gultathione conjugates with reactive metabolites of drugs to render them harmless and are excreted.

Glutathione-conjugated xenobiotics and GSH-conjugated metabolites must be exported from the cells in which they are formed before they can be eliminated from the body. This efflux is often mediated by the multidrug resistance protein 1 (MRP1) transporter protects normal cells from toxic insults but MRP1 also confers drug resistance to tumour cells (Cole and Deeley, 2006, Transport of glutathione and glutathione conjugates by MRP1, Trends Pharmacol Sci, Aug;27(8):438-46. Epub 2006 Jul 3). Hence, the more drugs are metabolized, accordingly more GSH-conjugation takes place and more MRP1 is produced that begins to confer drug resistance to tumor cells. So, ironically, the drug itself triggers the biochemical pathways that lead to the production of a protein that confers drug resistance to tumor cells. At the same time, with more drugs, more of the antioxidant enzyme is lost through conjugation and the depletion weakens the antioxidant system fomenting the onset of chronic oxidative stress. Severe oxidative stress in cancer patients and severe drug-induced oxidative stress can lead to sleep disturbances, disruption of the endocrine system, breathing difficulties, depressed liver function and heart failure.

Elevations in ROS in the kidney and the liver could lead to earlier and more extensive damage in both of these organs, thus potentially leading to disruption in healthy cell function and the development of disease states or accelerating the aging process and ultimately leading to premature mortality. Maintenance of good health by eliminating ROS is also managed through the growth hormone that is secreted during sleep. So, there need to be in place some mechanism to manage a tricky balance between HGH and the enzymes in the system that convert the superoxide into water and oxygen. Nature's ingenuity, perhaps may be found in how it acts during sleep.

During sleep, the light-sensitive portion of the brain (pineal gland) responds by increasing the secretion of the hormone melatonin. Rising levels of melatonin cause the pituitary gland to begin production of prolactin and growth hormone.

The magic of sleep lies in the fact that as melatonin levels increase during sleep, a squirt of HGH (at about 1-2am) is released to slow down the metabolic rate. This slowing down of the metabolic rate serves to reduce the overall H2O2 production, followed by increases in melatonin yields. Melatonin is a brain-body antioxidant that works synergistically with L-ascorbic acid to scavenge free radicals. In this process it supports the body’s SOD-glutathione-catalse system. Then this process kicks in again at about 3.30-5 am. When this process is effective it heals through strong free radical scavenging activity that also supports biological

repair and reduces or eliminates inflammation. With the elimination of inflammation, the type 1 immune system is deactivated in favor of cell-mediated (Th1) immune system. When it functions effectively, the body wakes up feeling fresh after a restful sleep. It is a well coordinated therapeutic mechanism that occurs only during sleep. Unfortunately, drugs can disrupt the sensitive regulatory processes coordinated by the endocrine system through oxidative stress and glutathione depletion and disrupt the therapeutic effects of sleep.

Sleep is considered to strengthen immune defense (Tanja Lange et al, 2006, Shift of Monocyte Function Toward Cellular Immunity During Sleep, Archives of Internal Medicine, Vol. 166 No. 16, September 18) that shifts monocyte cytokine production to type 1 cytokines (interleukin IL-2, interferon-, and IL-12), as a prerequisite for a sleep-associated predominance of helper T-cell 1 (TH1)–mediated adaptive immune defense and improves cell-mediated immunity and supports the view that sleep coordinates adaptive immunity (Romagnani S, 1996, Development of Th 1– or Th 2–dominated immune responses: what about the polarizing signals? Int J Clin Lab Res, 26:83-98: Marshall and Born, 2002, Brain-immune interactions in sleep, Int Rev Neurobiol, 52:93-131). Antioxidants tend to reduce inflammatory markers that promotes the shift from type 1 immune defense systems to boost cell-mediated immunity.

Growth hormone (GH) levels in the human, as well as in experimental animals, decline dramatically with increasing age (Iranmanesh A et al, 1991, Age and relative obesity are specific negative determinants of the frequency and amplitude of growth hormone (GH) secretion secretory bursts and the half-life of endogenous GH in healthy men, J Clin Endocrinol Metab 73:1081-1088: Muller EE et al, 1993, Aspects of the neuroendocrine control of growth hormone secretion in ageing animals, J Reprod Fertil 46: (suppl) 99-114). This age-related decline and deficiency in GH is associated with increased adiposity (Hoffman DM et al, 1995, Adults with growth hormone deficiency have abnormal body composition but normal energy metabolism, J Clin Endocrinol Metab 80:72-77), elevated blood lipids (de Boer H et al, 1995, Clinical aspects of growth hormone deficiency in adults, Endocr Rev 66:63-86), and a loss of lean body mass (Corpas E et al, 1993, Human growth hormone and human aging, Endocrine Rev 14:20-38). Increased risk of cardiovascular disease and early mortality have also been reported in patients with GH deficiency (Rosen and Bengsson, 1990, Premature mortality due to cardiovascular disease in hypopituitarism, Lancet 336:285-288) but this mortality is modified by the nature of treatments.

GH has also been shown to exert effects that can be considered beneficial in animal models as well as humans, which has led to its clinical use in elderly patients. In rats, GH administration elevates both CAT activity and glutathione content, which would presumably reduce ROS and ROS-mediated damage. In humans, GH administration has been shown to reverse the declines associated with GH deficiency and improve overall health. These include increased lean muscle

mass and decreased adiposity, decreased blood lipids, and improved cardiac function.

Elevated levels of antioxidative enzymes in liver tissues are present in the Ames dwarf, a growth hormone (GH)-deficient mouse that lives more than 1 year longer than wild-type mice from the same line. In contrast, transgenic mice that overexpress GH exhibit depressed hepatic levels of catalase and have significantly shortened life spans (Holly M. Brown-Borg, et al, 2002, Effects of Growth Hormone and Insulin-Like Growth Factor-1 on Hepatocyte Antioxidative Enzymes, Experimental Biology and Medicine 227:94-104). Healthy biochemistry is an intricate balance that is maintained by natural antioxidants in the L-form biochemical system. It is complex web of interlinking biochemical pathways involving many biomolecules, not drugs and chemicals.

Melatonin shows an outstanding functional versatility by exhibiting antioxidant (Beni SM et al, 2004, Melatonin-induced neuroprotection after closed head injury is associated with increased brain antioxidants and attenuated late-phase activation of NF-B and AP-1, FASEB J, 18:149–151), oncostatic (Blask DE et al, 2004, Melatonin uptake and growth prevention in rat hepatoma 7288CTC in response to dietary melatonin: melatonin receptor-mediated inhibition of tumor linoleic acid metabolism to the growth signaling molecule 13-hydroxyoctadecadienoic acid and the potential role of phytomelatonin, Carcinogenesis 25:951–960), antiaging (Reiter RJ, 1992, The ageing pineal gland and its physiological consequences, Bioessays 14:169–175) and immunomodulatory (Guerrero and Reiter, 2002, Melatonin-immune system relationships, Curr Top Med Chem 2:167–179) properties. Melatonin in vivo administration usually promotes stimulation of the immune system (Guerrero and Reiter, 2002, Melatonin-immune system relationships, Curr Top Med Chem 2:167–179).

Many researchers have demonstrated the direct effects of melatonin on T and B lymphocytes (García-Mauriño et al, 1997, Melatonin enhances IL-2, IL-6, and IFN production by human circulating CD4+ cells: a possible nuclear receptor-mediated mechanism involving T helper type 1 lymphocytes and monocytes. J Immunol 159:574–581: Topal T et al, 2004, Exogenously administered and endogenously produced melatonin reduce hyperbaric oxygen-induced oxidative stress in rat lung, Life Sci 75:461–467). Regarding the effects of melatonin on immune system, in vivo studies have revealed that pinealectomy promotes thymic disorganization as well as inhibition of IL-2 production and natural killer cell activity in rodents whereas melatonin treatment or pineal grafting prevents thymic involution in very old mice (Ref: Antonio Carrillo-Vico et al, 2005, Human Lymphocyte-Synthesized Melatonin Is Involved in the Regulation of the Interleukin-2/Interleukin-2 Receptor System, The Journal of Clinical Endocrinology & Metabolism Vol. 90, No. 2 992-1000).

A critical factor is that "human lymphocyte-synthesized melatonin plays a fundamental intra-, auto-, and/or paracrine role in cell activation through regulation of the IL-2/IL-2R system and, probably, other cytokine and immunological mediators" (Antonio Carrillo-Vico et al, 2005, Human Lymphocyte-Synthesized Melatonin Is Involved in the Regulation of the Interleukin-2/Interleukin-2 Receptor System, The Journal of Clinical Endocrinology & Metabolism Vol. 90, No. 2 992-1000) and this factor is potentially important for understanding hormonal control of immune activation. The majority of interleukins are synthesized by helper CD4+ T lymphocytes, as well as through monocytes, macrophages, and endothelial cells. They promote the development and differentiation of T, B, and hematopoietic cells

Interleukin 24 (IL-24) is a cytokine that controls cell proliferation and is a tumor suppressing protein. It is predominantly released by activated monocytes, macrophages and T helper 2 (Th2) cells (Poindexter et al, 2005, Cytokine induction of interleukin-24 in human peripheral blood mononuclear cell, Journal of Leukocyte Biology, Volume 78, pages 745-752) and acts on non-haematopoietic tissues such as skin, lung and reproductive tissues. IL-24 performs important roles in wound healing, psoriasis and cancer (Wang and Liang, 2005, Interleukin-24 and its receptors, Immunology, Volume 114, pages 166-70). IL-28 and IL-29 play a role in host immune defense against viruses and microbes. Il-1 produced by B cells have a role against inflammations. IL-6 produced in T2 cells and macrophages are involved in antibody response and against inflammation. IL-21 from T helper cells helps NK cells to target cancer cells and regulates proliferation of CD8 cells. IL-4 from T4 cells direct production of IgG1 and IgGE synthesis and play an important role in allergic reactions.

Interleukin 24 (IL-24) is a cytokine that is a tumor suppressing protein. Treatment of ovarian cancer cells with mda-7/IL-24 results in growth suppression both in vitro and in vivo (Began Gopalan et al, 2007, MDA-7/IL-24 suppresses human ovarian carcinoma growth in vitro and in vivo, Molecular Cancer, 6:11). It is an interesting protein because it induces apoptosis selectively in cancer cells (Lebedeva IV, 2002, The cancer growth suppressing gene mda-7 induces apoptosis selectively in human melanoma cells, Oncogene 21: 708-718). Adenoviral-mediated delivery of mda-7/IL-24 causes growth suppression and apoptosis in a wide spectrum of cancer cells, including prostate, without harming normal cells (Irina V. Lebedeva, 2003, Melanoma Differentiation Associated Gene-7, mda-7/Interleukin-24, Induces Apoptosis in Prostate Cancer Cells by Promoting Mitochondrial Dysfunction and Inducing Reactive Oxygen Species, Cancer Research 63, 8138-8144, December 1).

This cytokine is predominantly released by activated monocytes, macrophages and T helper 2 (Th2) cells (Poindexter et al, Cytokine induction of interleukin-24 in human peripheral blood mononuclear cells. Journal of Leukocyte Biology 2005, Volume 78, pages 745-752). In vitro, IL-19, IL-20 and IL-24 were produced not only by activated immune cells, particularly monocytes,

but also to a similar extent by keratinocytes (Kunz S et al, 2006, Interleukin (IL)-19, IL-20 and IL-24 are produced by and act on keratinocytes and are distinct from classical ILs, Exp Dermatol, Dec;15(12):991-1004). The keratinocyte is the major constituent of the epidermis, constituting 95% of the cells found there (McGrath JA et al, 2004, Rook's Textbook of Dermatology (Seventh Edition), Blackwell Publishing. Pages 3.7). Il-24 has important roles in wound healing, psoriasis and cancer (Wang M, Liang P. Interleukin-24 and its receptors. Immunology, 2005, Volume 114, pages 166-70).

Since Il-24 is found to suppress tumor growth and also inhibited tumor vascularization, it is thought to have potential therapeutic value (Chen WY et al, 2005, IL-24 inhibits the growth of hepatoma cells in vivo) for hepatoma, Genes Immun, Sep;6(6):493-9). Its analogue, however, may trigger health problems. Analogues tend to induce thyroiditis and exploiting its therapeutic potential lies not in producing its analogue but in inducing greater yields in a constant manner and attempting to harness the keratinocyte for such a process appears paramount, if not critical. The skin is the largest human organ comprising about one sixth of total body weight.

The "holy grail" of cancer therapy is to identify and exploit genetic elements and signal transduction pathways capable of selectively destroying tumor cells without eliciting harmful effects in normal cells or tissues. Il-24 localizes to the ER/Golgi compartments, whether or not the protein contains a secretory signal and its accumulation in this compartment of the cell triggers apoptosis that could apparently involve induction of pathways described currently as ER stress. Additionally it acts indirectly on mitochondria to generate reactive oxygen species (Paul B. Fisher, 2005, Is mda-7/IL-24 a "Magic Bullet" for Cancer? Cancer Research 65, 10128-10138, November 15).

Reactive oxygen intermediates are considered central to the inflammatory processes (Vassilakopoulos T et al, 2003, Antioxidants attenuate the plasma cytokine response to exercise in humans, J Appl Physiol, 94:1025–1032) when their oxidative stress affects the cell wall and oxidative stress is closely linked to apoptosis in various cells (Taniyama and Griendling, 2003, Reactive oxygen species in the vasculature: molecular and cellular mechanisms, Hypertension, 42:1075–1081) when the quick and elevated stress occurs within the mitochondria. The idea is to provoke direct killing of cancer cells using a natural yield from healthy cells. The selective killing in cancer cells can be augmented by agents that enhance mitochondrial dysfunction and induce ROS production and such mitochondrial dysfunction through induction of ROS leading to apoptosis can be induced by mda-7/IL-24 (see:Irina V. Lebedeva, 2003, Melanoma Differentiation Associated Gene-7, mda-7/Interleukin-24, Induces Apoptosis in Prostate Cancer Cells by Promoting Mitochondrial Dysfunction and Inducing Reactive Oxygen Species, Cancer Research 63, 8138-8144, December 1).

Since the most intriguing property of mda-7/IL-24 is preferential induction of apoptosis in cancer cells of diverse origin without harming normal cells, research must focus on how to trigger Il-24 production and how to enhance its yields. It may turn out to be a tricky business as it may the linked to glutathione levels in cells. Glutathione is the most abundant nonproteinous tripeptide containing a sulfhydryl group in virtually all cells, and it plays a significant role in many biological processes. It also constitutes the first line of the cellular defense mechanism against oxidative injury and is the major intracellular redox buffer in ubiquitous cell types (Meister A, 1989, Molecular Properties and Clinical Applications Glutathione Centennial Academic Press). The depletion of glutathione that alters the redox balance can induce IL-12 (Mitsuyoshi Utsugi et al, 2002, Glutathione redox regulates lipopolysaccharide-induced IL-12 production through p38 mitogen-activated protein kinase activation in human monocytes: role of glutathione redox in IFN- priming of IL-12 production, Journal of Leukocyte Biology. 2002;71:339-347) but cancer markers may be the only trigger for the priming of T cells that will produce Il-24 and mineral suplementation from organic sources may be necessary to enhance Il-24 yields against the cancer cells while excess exogenous antioxidant may suppress inflammation that may then inhibit Il-24 yields instead of enhancing it. Chemo-drugs, on the other hand may slow down the priming of T cells that are primed for producing Il-24.

One of the symptoms of AIDS patients is fatigue or chronic fatigue. In many cases this may be linked to disruption on the functioning of the endocrinal system. Many factors impact or impinge on the HPA axis such as lack of exercise, oxidative stress leading to sleep disturbance, psychiatric comorbidity, and medications, and there is growing interest on how HPA axis disturbance leads to chronic fatigue syndrome. Chronic fatigue syndrome (CFS) invloves a lowering of ATP yields and lower levels of CoQ10, an antioxidant enzyme that is involved in the utilization of energy released from ATP. Oxidative stress in the adrenal gland can lead to a decline in cortisol levels. Cortisol is a natural corticosteroid hormone or glucocorticoid produced by the adrenal cortex. Cortisol is synthesized from cholesterol. The amount of cortisol present in the blood undergoes diurnal variation, with the highest levels present in the early morning, and the lowest levels present around midnight or 3–5 hours after the onset of sleep. It comes under some endocrinal regulatory control in the healthy individual. It is involved in a wide range of biochemical pathways including, carbohyrate metabolism, collagen formation and MT protein synthesis, inhibiting these when in excess, etc and it promotes the conversion of lipids into glucose. Excess and unregulated cortisol can weaken the activity of the immune system. Hence, therapy ought to focus on restoration of the healthy biochemical pathways and the regulatory mechanisms which can be a difficult process with drugs and inhibitors and blockers.

Excess cortisol can inhibit the synthesis of MT proteins. These are very small molecules that easily move across membranes. They sequester minerals and become activated to bind the

hydroxyl radical from within the mitochondria that is under chronic oxidative stress. Under oxidative stress ATP and coQ10 production decline. The decline of synthesis of MT proteins compromises and later on impairs this role and the mitochondria leading to its death. Such impact on mitochondria can precipitate chronic fatigue and can trigger mitochondrial origin of cancers.

Excess cortisol prevents proliferation of T-cells by rendering the interleukin-2 producer T-cells unresponsive to interleukin-1 (IL-1), and unable to produce the T-cell growth factor (Palacios and Sugawara, 1982, "Hydrocortisone abrogates proliferation of T cells in autologous mixed lymphocyte reaction by rendering the interleukin-2 Producer T cells unresponsive to interleukin-1 and unable to synthesize the T-cell growth factor", Scand J Immunol 15 (1): 25–31). Cells of the immune system can take over their own regulation. Glucosteroid-activated T cells and ART-activated T cells may also start to secrete glucosteroid response modifying factor (GRMF or GAF) as well as IL-1, both of which increase the amount of cortisol required to inhibit almost all the immune cells (see: Fairchild et al, 1984, T cell-derived glucosteroid response-modifying factor (GRMFT): a unique lymphokine made by normal T lymphocytes and a T cell hybridoma, J. Immunol, 132 (2):821–7). So, this could be another mechanism through which glucosteroids and ART first function as stimulants to increase the number of T cells, that appears as immune restoration, but ends up in immune suppression that precipitates IRIS and opens the body for opportunistic infections or the failure of the host to develop an effective immune response against invading microorganisms due to immunosuppression .

The primary control of cortisol lies in the pituitary gland. The synthesis of cortisol in the adrenal gland is stimulated by the anterior lobe of the pituitary gland with adrenocorticotropic hormone (ACTH, which is a peptide. This peptide increases the concentration of cholesterol in the inner mitochondrial membrane where the cholesterol is converted to the biologically inert pregnenolone and later to the biologically active molecule - cortisol. The medulla of the adrenal gland lies under the cortex and mainly secretes the catecholamines. Hence, oxidative stress that damages the peptide (ACTH) will disrupt the concentrations of cholesterol in the mitochondria for conversion into cortisol. Oxidative stress in the adrenal glands can lead to a dysfunction in which the amount of catecholamines produced increase as in drug abusers.

The recent interest in the role of the HPA axis in CFS developed from the observations of the conditions in which there is low circulating cortisol. Such low levels were thought to be characterized by debilitating fatigue. These observations led to the hypothesis that fatigue in CFS is mediated by low circulating levels of cortisol. It was thought that if low circulating cortisol mediates some or all of the symptoms in CFS, replacement of the hypothesized deficiency should lead to improvements in those symptoms but there was significant adrenal suppression in 12 of 33 patients on hydrocortisone. Hydrocortisone, the analogue, is the pharmaceutical

term for cortisol used for oral administration, intravenous injection, or topical application. It is used as an immunosuppressive drug and with much lower doses of hydrocortisone, there was no significant adrenal suppression and there were no serious adverse effects. The use of analogues almost invariably interrupts the biochemical pathways to various extents in the L-form biochemistry in the mammalian biological systems. Their use makes it very difficult to restore the intricate and complex balance found in healthy biochemistry of the human biological system.

Antioxidants have been studied by many researchers for their ability to prevent cancer in humans. Dietary and endogenous antioxidants prevent cellular damage by reacting with and eliminating oxidizing free radicals only when they enter cells. Since, in the treatment of cancers, the mode of action of certain chemo-agents involves the generation of free radicals to cause cellular damage and necrosis of malignant cells, a concern has logically developed as to whether exogenous antioxidant compounds taken concurrently during chemotherapy could reduce the beneficial effect of chemotherapy on malignant cells. For this to happen, it must be shown that these antioxidants can enter cancer cells and can move across the cancer cell membrane that has a high cell membrane potential. The concern that antioxidants might reduce oxidizing free radicals created by radiotherapy and chemo-drugs and result in decreasing the effectiveness of the therapy must be investigated from this perspective as well as the result of metabolism of the antioxidant within the cancer cell. Also natural antioxidants when applied to the skin in paste form might help to increase keratinocyte yields of Il-24 in cancer patients. This needs special investigation. Ayurvedic therapies include applying antioxidant pastes and oils to the skin.

"Evidence reviewed demonstrates exogenous antioxidants alone (not endogenous) produce beneficial effects in various cancers, and except for a few specific cases, animal and human studies demonstrate no reduction of efficacy of chemotherapy or radiation when given with antioxidants" (Davis W. Lamson et al, Antioxidants in Cancer Therapy; Their Actions and Interactions With Oncologic Therapies) and in fact, considerable data exists showing increased effectiveness of many cancer therapeutic agents, as well as a decrease in adverse effects, when given concurrently with antioxidants, Altern Med Rev 1999;4(5):304-329). The toxic anti-cancer drugs create substantial DNA damage, resulting in cell necrosis. Recent evidence indicates a sizeable amount of chemotherapy damage is by other mechanisms, which trigger apoptosis (Schmitt and Lowe, 1999, Apoptosis and therapy, J Pathol 1999;187:127-137) and antioxidants have been shown to enhance cytotoxicity of such drugs (Chinery R et al, 1997, Antioxidants enhance the cytotoxicity of chemotherapeutic agents in colorectal cancer: a p53-independent induction of p21 via C/EBP-beta, Nat Med 3:1233-1241: Mediavilla MD et al, 1999, Melatonin increases p53 and p21WAF1 expression in MCF-7 human breast cancer cells in vitro. Life Sci 1999;65:415-420) but the mechanism may be mediated through Il-24 that leads to excess ROS

in the mitochondria and dysfunction and disruption of the alcohol pathway that starves the cancer cell of its energy molecule and it dies.

Melatonin has also been found to have some interesting anti-tumor properties in vitro, suggesting that its metabolism in cancer cells yields toxic metabolites whereas, on the other hand it is also known to modify many cytokines, including TNF, IL1, IL-2, IL-6, and gamma-interferon, in ways consistent with increased host defense against cancers (Neri B et al, 1998, Melatonin as biological response modifier in cancer patients, Anticancer Res 1998;18:1329-1332). In another phase II study, melatonin (20 mg/day) led to a normalization of platelet counts in nine of twelve breast cancer patients who acquired thrombocytopenia during epirubicin therapy. Objective tumor regression was noted in five of the 12 patients (Lissoni P et al, 1994, A randomized study with subcutaneous low-dose interleukin 2 alone vs. interleukin 2 plus the pineal neurohormone melatonin in advanced solid neoplasms other than renal cancer and melanoma, Br J Cancer 69:196-199).

A modulatory influence of melatonin on cell response to glucocorticoids has already been reported (Aoyama Mori and N. Mori, 1986, Anti-glucocortocoid effects of melatonin in young rats, Acta Pathol, Jpn 36: 423-428: Mori W, et al, 1984, Melatonin protects rats from injurious effects of a glucocorticoid, dexamethasone, Jpn, J. Exp. Med., 54: 255-261).

Vitamin E succinate (VES, alpha tocopherol succinate also demonstrated growth inhibition of human B-cell lymphoma77 and estrogen receptor-negative breast cancer78 cell lines in vitro whereas treatment with vitamin E and omega-3 fatty acid resulted in improvement in T-helper/suppressor ratio (Gogoss CA et al, 1998, Dietary omega-3 polyunsaturated fatty acids plus vitamin E restore immunodeficiency and prolong survival for severely ill patients with generalized malignancy. Cancer 82:395-402). Vitamin E supplementation at high doses decreases inflammatory markers (Jialal et al, 2002, Oxidative stress, inflammation, and diabetic vasculopathies: the role of alpha tocopherol therapy, Free Radic Res, 36:1331–1336).

Dr. Cameron has noted that a small percentage of cancer patients will respond to vitamin C with rapidly proliferating and disseminating tumors (Cameron and Campbell, 1974, The orthomolecular treatment of cancer, II. Clinical trial of high-dose ascorbic acid supplements in advanced human cancer, Chem Biol Interactions 1974;9:285-315). Treatment with ascorbic acid was not associated with decreased effect of doxorubicin but was associated with an increased life span compared with doxorubicin treatment alone (Shimpo K et al, 1991, Ascorbic acid and adriamycin toxicity, Am J Clin Nutr 54:1298S-1301S). Vitamin C at 1 mM increased the activity of doxorubicin, cisplatin, and paclitaxel in human breast carcinoma cells in vitro. This effect was particularly marked and synergistic with doxorubicin. The authors note that since vitamin C has already shown an ability to reduce the cardiotoxicity of doxorubicin, ascorbic acid and doxorubicin are an attractive future treatment for breast cancer (Kurbacher CM et al, 1996,

Ascorbic acid (vitamin C) improves the antineoplastic activity of doxorubicin, cisplatin, and paclitaxel in human breast carcinoma cells in vitro, Cancer Lett 103:183-189).

Vitamin C seems to prevent resistance of cancer cells to drugs like doxorubicin (Wells WW et al, 1995, Ascorbic acid and cell survival of adriamycin resistant and sensitive MCF-7 breast tumor cells, Free Rad Biol Med 18:699-708). On the other hand, combined intraperitoneal administration of vitamin C (1g/kg) and vitamin K (10 mg/kg) given prior to chemotherapy increased survival and the effect of several chemotherapeutic agents (cyclophosphamide, vinblastine, doxorubicin, 5-fluorouracil, procarbazine, and asparaginase) in a murine ascitic liver tumor model. The vitamin combination did not increase the toxicity of these agents to healthy tissue. Splenic and thymic weights of the vitamin-treated animals were higher than those receiving cytotoxic treatment alone, suggesting an immune-stimulating action of the vitamins (Taper HS et al.1987, Non-toxic potentiation of cancer chemotherapy by combined C and K3 vitamin pre-treatment, Int J Cancer 1987;40:575-579). This role of vitamin C may be due. In fact, to its ability to recycle glutathione and the change in redox balance lowers the production of the efflux protein MRT1, which is the protein that confers resistance to cancer cells.

In a randomized trial of oral vitamin A (1.5 million IU/day) plus radiotherapy for advanced cervical cancer, vitamin A plus radiotherapy significantly increased T-cell response and non-significantly reduced relapse rates compared with those undergoing radiotherapy only (Duchesne and Hutchinson, 1995, Reversible changes in radiation response induced by all-trans retinoic acid, Int J Radiat Oncol Biol Phys 1995;33:875-880). A pilot human study of cis-retinoic acid (cRA) with radiotherapy and interferon-a2a on locally advanced cervical cancer noted a 47-percent tumor response and 33-percent complete remission rate, with no grade 3 or 4 toxicity noted. Historical controls without cRA treatment had a 42-percent tumor response rate and only 17-percent complete remissions (Park TK et al, 1998, Interferon-alpha 2a, 13-cis-retinoic acid and radiotherapy for locally advanced carcinoma of the cervix: a pilot study, Eur J Gynaecol Oncol 19:35-38). The ability of

Vitamin A tends to increase tumor response to radiation while reducing toxicity and has been theorized to be due to the stimulation of immune response to tumor tissue (Tannock IF et al, 1972, Vitamin A and the radiation response of experimental tumors: an immune mediated effect, J Natl Cancer Inst 48:731-741). Studies have shown patients treated with antioxidants, with or without chemotherapy and radiation, have many benefits. Patients have been noted to tolerate standard treatment better, experience less weight loss, have a better quality of life, and most importantly, live longer than patients receiving no supplements (Davis W. Lamson et al, Antioxidants in Cancer Therapy; Their Actions and Interactions With Oncologic Therapies).

“Extensive research within the last two decades from our laboratory and others has indicated that there are phytochemicals present in spices that may prevent various chronic illnesses

including cancerous, diabetic, cardiovascular, pulmonary, neurological and autoimmune diseases. For instance, the potential of turmeric (curcumin), red chilli (capsaicin), cloves (eugenol), ginger (zerumbone), fennel (anethole), kokum (gambogic acid), fenugreek (diosgenin), and black cumin (thymoquinone) in cancer prevention has been established" (Aggarwal BB et al, 2008, Potential of spice-derived phytochemicals for cancer prevention, Planta Med, Oct;74(13):1560-9, Epub 2008 Jul 8).

A wide variety of phenolic substances derived from spice possess potent antimutagenic and anticarcinogenic activities. The chemopreventive effects exerted by these phytochemicals are often associated with their antioxidative and anti-inflammatory activities. Cyclo-oxygenase-2 (COX-2) has been recognized as a molecular target of many chemopreventive as well as anti-inflammatory agents. The molecular mechanisms underlying chemopreventive effects of the aforementioned spice ingredients involve NF-kappaB and mitogen-activated protein kinases (Surh YJ, 2002, Anti-tumor promoting potential of selected spice ingredients with antioxidative and anti-inflammatory activities: a short review, Food Chem Toxicol, Aug;40(8):1091-7). Improper up-regulation of COX-2 and/or iNOS has been associated with pathophysiology of certain types of human cancers as well as inflammatory disorders. Since inflammation is closely linked to tumor promotion, substances with potent anti-inflammatory activities are anticipated to exert chemopreventive effects on carcinogenesis, particularly in the promotion stage. Examples are curcumin, a yellow pigment of turmeric (Curcuma longa L., Zingiberaceae), the green tea polyphenol epigallocatechin gallate (EGCG), and resveratrol from grapes (Vitis vinifera, Vitaceae) that strongly suppress tumor promotion. Curcumin, EGCG and resveratrol have been shown to suppress activation of NF-kappa B (Surh YJ et al, 2001, Molecular mechanisms underlying chemopreventive activities of anti-inflammatory phytochemicals: down-regulation of COX-2 and iNOS through suppression of NF-kappa B activation, Mutat Res, Sep 1;480-481:243-68).

Vitamin C is accumulated in millimoles/liter concentration in neutrophils, lymphocytes, monocytes, and platelets, suggesting that it may be important for the functioning of the immune system. Although the mechanisms whereby vitamin C affects the immune system are poorly understood, there are studies that suggest that phagocyte function, T cell proliferation, and production of inflammatory cytokines are affected by vitamin C status. During infection, activated phagocytes produce oxidizing agents that have antimicrobial effects but if released into the extracellular medium, can be harmful to the host. To neutralize the effects of the increased presence of oxygen radicals, the cells utilize a variety of antioxidative mechanisms, including antioxidant enzymes and antioxidant nutrients such as vitamin C. Vitamin C is synthesized from glucose in the liver of most mammalian species, except for humans, apes, nonhuman primates, guinea pigs, and some fruit bats. The loss of this glucoronic pathway during the course of evolution, itself is a health problem for humans.

Vitamin C is an important nutrient for adequate immune function and limitation of pathogenesis following influenza virus infection. As shown for other antioxidant nutrients, such as selenium and vitamin E, vitamin C may be important in limiting the increased oxidative stress that occurs during an influenza infection, thus lowering tissue inflammation (Ref: Wei Li et al, 2006, Vitamin C Deficiency Increases the Lung Pathology of Influenza Virus–Infected Gulo–/– Mice, American Society for Nutrition J, Nutr., 136:2611-2616, October 2006). It depletion during toxic therapies in the lungs leads to infections in the lungs.

Vitamin C supplements have been shown to alter many different indexes of human immune responses, and the concentration of vitamin C is high in activated neutrophils and macrophages (Campbell JD ET AL, 1999, Ascorbic acid is a potent inhibitor of various forms of T cell apoptosis, Cell Immunol 194: 1-5, 1999: Jacob RA ET AL, 1991, Immunocompetence and oxidant defense during ascorbate depletion of healthy men, Am J Clin Nutr 54, Suppl: 1302S-1309S: Schwager and Schulza, 1998, Modulation of interleukin production by ascorbic acid. Vet Immunol Immunopathol 64: 45-57: Washko P ET AL, 1991, Rotrosen D, and Levine M. Ascorbic acid in human neutrophils. Am J Clin Nutr 54, Suppl: 1221S-1227S: Wolf G, 1993, Uptake of ascorbic acid by human neutrophils, Nutr Rev 51: 337-338). ROS generation and antioxidant status may be linked to immune alterations after exercise, including cell adhesion, inflammation, and lymphocyte proliferation, and conversely, certain immune changes may contribute to oxidative stress (Chen CY ET AL, 1998, Association between oxidative stress and cytokine production in nickel-treated rats, Arch Biochem Biophys 356: 127-132).

Increased dietary vitamin A intake at the time of acute pneumonia infection had greater salivary immunoglobulin (Ig)A responses. In contrast, the serum IgG response was higher in the control group (324 ± 158 mg/L) than in the high level group (225 ± 95 mg/L) (P = 0.028). The production of interferon- (IFN-), a Th1 cytokine, was lower in the high level diet group (median, 0.153 μg/L) compared with the control group (median, 0.839 μg/L) (P = 0.014), whereas the production of interleukin-10 (IL-10), a Th2 cytokine, was higher with the high level diet (median, 0.304 μg/L) than with the control (median, 0.126 μg/L) (P = 0.022) (Dongming Cui et al, 2000, High-Level Dietary Vitamin A Enhances T-Helper Type 2 Cytokine Production and Secretory Immunoglobulin A Response to Influenza A Virus Infection in BALB/c Mice, Journal of Nutrition,130:1132-1139). The body's immune responses change in accordance with the levels of dietary antioxidants and their

levels in cells of the immune system. High dose vitamin A supplements may enhance Th2-mediated immune responses (Dongming Cui et al, 2000, High-Level Dietary Vitamin A Enhances T-Helper Type 2 Cytokine Production and Secretory Immunoglobulin A Response to Influenza A Virus Infection in BALB/c Mice, Journal of Nutrition,130:1132-1139).

Colorectal cancer patients with advanced disease have reduced numbers of CD4+ T cells leading to a decreased CD4:CD8 ratio (Arista MC et al, 1994, Flow cytometric study of lymphocyte subsets in patients at different stages of colorectal carcinoma, Dis. Colon Rectum, 37: S30-S34). Short-term supplementation with high doses of dietary vitamin E leads to increased CD4:CD8 ratios and to enhanced capacity by their T cells to produce the T helper 1 cytokines interleukin 2 and IFN-. In 10 of 12 patients, an increase of 10% or more (average, 22%) in the number of T cells producing interleukin 2 was seen after 2 weeks of vitamin E supplementation and dietary vitamin E may be used to improve the immune functions in patients with advanced cancer, as a supplement to more specific immune interventions (Karl-Johan Malmberg et al, 2002, A Short-Term Dietary Supplementation of High Doses of Vitamin E Increases T Helper 1 Cytokine Production in Patients with Advanced Colorectal Cancer, Clinical Cancer Research Vol. 8, 1772-1778, June).

Vitamin E may be used as an adjuvant to more specific immunotherapy that is dependent on a functional Th1 response. Supplementation with antioxidant vitamins especially has been associated with an enhancement of immune function in various animal models (Bendich A, 1990, Antioxidant micronutrients and immune responses, Ann N Y Acad Sci 1990;587:168–80). More specifically for vitamin E, it has been shown that supplementation with a megadose (greater than the recommended dietary allowance) has a stimulatory effect on humoral and cell-mediated immunity (Tengerdy RP, 1989, Vitamin E, immune response and disease resistance, Ann N Y Acad Sci, 570:335–44). The immune enhancing mechanism of natural vitamin E is primarily through increasing interleukin production. IL-2 production showed a trend toward increased responsiveness with increasing dose of vitamin E. However, IFN- production decreased whereas IL-4 (a typical Th2 cytokine) production increased in the groups receiving vitamin E (Esther Pallast, 1999, Effect of 50- and 100-mg vitamin E supplements on cellular immune function in noninstitutionalized elderly persons, American Journal of Clinical Nutrition, Vol. 69, No. 6, 1273-1281, June).

Il-4 decreases with stress (Uchakin PN et al, 2001, Immune responsiveness following academic stress in first-year medical students, J Interferon Cytokine Res, 21:687–94) Il-6 is produced by macrophages, TH2-cells, B cells, astrocytes and in the endothelium. It targets T cells and activated B cells. Il-6 increases with pathogenic stress. Il-6 synthesis is regulated in part by oxidative stress (Jennifer Sacheck, 2006, Age-related loss of associations between acute exercise-induced IL-6 and oxidative stress, Am J Physiol Endocrinol Metab 291: E340-E349). Oxidative stress from drugs could reduce IL-6 production and thereby compromise the functioning of T cells and activated B cells in immune response.

Interferon is a synthetic analogue of a key protein component of the human immune system, normally present in the body in several forms. It is used to treat some forms of cancers,

leukemia, Karposi sarcoma, human papilloma virus, viral hepatitis B and C; Herpes zoster and HIV-seropositive individuals. Its side-effects include fFlu-like symptoms, low grade fever, runny nose, muscle pain, depression, low white blood count, low platelet count and anemia. Interferon therapy causes immunosuppression through neutropenia and can result in some opportunitis infections as well (see: Bhatti and Berenson, 2007, Adult systemic cat scratch disease associated with therapy for hepatitis C, BMC Infect Dis 7: 8). Interferon can cause thyroiditis. So, an immunosuppressive substance is used to treat autoimmune conditions that are themselves inducible through stimulation of the immune system by oxidants.

In the body, interferons (IFNs) are produced as its natural cell-signaling proteins. These interferons are produced by the cells of the immune system of most vertebrates in response to challenges such as viruses, parasites and tumor cells. Interferons belong to the large class of glycoproteins known as cytokines. Interferons are produced by a wide variety of cells in response to the presence of double-stranded RNA and assist the immune response by inhibiting viral replication within host cells and in macrophages, increasing antigen presentation to lymphocytes thereby induce resistance of host cells to viral infection. These natural inteferons also activate natural killer cells.

Phorbol is an alcohol that is cocarcinogenic. The diesters of phorbol found in croton oil. The hydrocarbon skeleton is a cyclopropabenzazulene. The phorbol esters mimic 1,2-diacylglycerol as activators of protein kinase C. These esters are widely used as experimental tumor promotors because they act by directly stimulating protein kinase C. Interferon can be produced by phorbol-stimulation of lymphocytes. Such interferon produced by phorbol-stimulated lymphocytes was reduced 70% in the group that consumed a commercially available encapsulated fruit and vegetable juice powder concentrate (FVJC). By day 77 there was a 30% increase in circulating -T cells and a 40% reduction in DNA damage in lymphocytes in the FVJC group relative to the placebo group.

Plasma levels of vitamin C and of ß-carotene, lycopene, and lutein increased significantly from baseline in the FVJC group as did plasma oxygen radical absorptive capacity (50%) and an increase in circulating-T cells (Meri Nantz et al, 2006, Immunity and Antioxidant Capacity in Humans Is Enhanced by Consumption of a Dried, Encapsulated Fruit and Vegetable Juice Concentrate, Am J. Nutr. 136:2606-2610, October). Plasma vitamin C concentrations in the FVJC group appeared to reach a steady state by day 35, as described in a review (Padyatty et al, Vitamin C as an antioxidant: evaluation of its role in disease prevention. J Am Coll Nutr. 2003;22:18–35), where vitamin C levels reach a plateau at doses of 200 mg/d and higher. The formulation of the FVJC was effective in raising carotenoid levels, ascorbic acid levels, and plasma antioxidant capacity and was associated with a greater percentage of -T cells and the tendency for a reduced number of symptoms and duration of illness (Meri Nantz et al, 2006,

Immunity and Antioxidant Capacity in Humans Is Enhanced by Consumption of a Dried, Encapsulated Fruit and Vegetable Juice Concentrate, Am J. Nutr. 136:2606-2610, October). Quite naturally, as the interferon produced by phorbol-stimulated lymphocytes was reduced 70% in the FVJC group, other cytokines (IL-4, IL-6, transforming growth factor ß) were unchanged relative to treatment or time showing that when the natural antioxidant defense mechanism can kick in a strong response and when the toxic stimulation is well controlled, the reduction in inflammation may alter a shift in the immune response by the body from interleukins to immune cell-mediation.

An integrative approach to treatment of cancers in AIDS patients may use chemo-drugs together with suitable antioxidants.

One new approach in therapy in the immune suppressed patient is to consider the use of natural antioxidants, whether taken orally or applied onto the skin to:-

1. increase the interleukin production, especially Il-24, and

2. maintain a healthy condition of the skin as an organ, and

3. increase the melatonin secretion, and

4. reduce the cell membrane potential, ie inflammation, and

5. produce ROS within the cancer cells by phytochemicals from edible plants, especially antioxidants, and

6. avoid persistent or chronic stimulation of the immune system by oxidants or toxic drugs and chemicals.

These findings and review research indicates a need to the development of novel therapies based on nutrition that promotes healthy biochemistry driven by dietary antioxidants whereas, on the other hand, the use of glucorticoids tend to promote the suppression of the immune system. The short-term use of glucocorticoids has been clearly shown to give a false sense of immune restoration as misread from the initial increases in T4 cell levels which are not due to immune restoration but due to the trigger of RA factors and thyroiditis. It is better to look for immune restoration in dietary antioxidants and organic minerals that are bioavailable to the body and through "functional foods.”