**TOXIC EFFECTS OF ANTIVIRAL DRUGS**

U.S. officials to tout new treatment policy

By Laurie Garrett

Newsday 17 Jan. '01

U.S. officials will announce a significant change in treatment guidelines for HIV disease when top AIDS scientists gather for their annual meeting next month.

Instead of telling American physicians to "hit early, hit hard," a policy in effect since 1996 that calls for giving HIV-positive patients powerful drug cocktails before the patients actually experience any symptoms of illness, the new National Institutes of Health guidelines will call for caution and delay in treatment.

The shift, NIH scientists will explain at the annual Conference on Human Retroviruses in Chicago, is prompted by an emerging consensus on three factors. First, the cocktails-called highly active anti- retroviral therapy, or HAART-can't wipe out all the viruses in a person's body, so patients must take these drugs every day, probably for the rest of their lives. That prompts the second and third factors: toxicity and resistance. The longer people take the HAART cocktails, the greater the number of side effects they experience. And there is greater the likelihood that the efficacy of the drugs will diminish, as drug-resistant forms of HIV swarm into a patient's bloodstream.

In practical terms, the new guidelines say physicians should hold off on using HAART until a patient's vital CD4 immune system cell count drops below 350 per milliliter of blood; guidelines now in use set a level of 500. A healthy, uninfected individual has a CD4 count of more than 800.

In terms of viral levels, the soon-to-be-replaced guidelines say patients should go on HAART when tests show 10,000 HIVs per milliliter of blood. The new guidelines call for waiting until the viral load tops 30,000 (as detected with branch DNA analysis) per milliliter of blood.

In a speech to the Royal Society of Medicine in London last month, prominent AIDS physician Charles Carpenter of Brown University, a member of the AIDS advisory committee to the NIH, signaled plans to change the treatment guidelines. "In retrospect," he said, "we now realize the risk of drug toxicity is greatly enhanced by taking these drugs early."

Yesterday, in an interview with Newsday, Dr. Anthony Fauci, director of the National Institute of Allergy and Infectious Diseases, confirmed details of the new guidelines.

"It's clear we're not going to eradicate the virus with the drugs we have now," Fauci said. "And we're starting to see a greater and greater realization of the accumulation of toxic side effects."

Among the most troubling side effects seen in people taking the HAART cocktails are death of hip bone tissue, increase in blood cholesterol levels, neuropathy or loss of nerve sensations, kidney failure, radical alterations of liver metabolism, diabetes, skin rashes, pancreas failure, severe anemia, liver dysfunctions so acute as to require transplants and near-instantaneous death due to buildup of lactic acid.

Mark Harrington, leader of the activist Treatment Action Group in Manhattan, was infected 11 years ago. He held off on taking any drugs until 1996, when his CD4 count hit a low of 150. In retrospect, Harrington thinks he made the right decision because, unlike so many of his HIV-positive friends, he has been able to stay on the same drug cocktail for five years without witnessing emergence of drug-resistant strains.

Since starting the drug regimen, "I have had two kidney stone episodes" that required hospitalization, "one serious case of peripheral neuropathy, one chemical hepatitis bout, some nasty fat redistribution and a host of minor problems. And I'm lucky."

Dr. Michael Saag handles hundreds of HIV-positive patients in his clinic at the University of Alabama in Birmingham. He's worried about the rising tide of drug toxicities he sees, coupled with a change in patients' attitudes.

"I've got a lot of patients coming to me after three or four years on HAART saying, 'I just can't take it anymore,' or 'I'm tired of taking all these pills.' I think we need to keep in mind that this is a marathon, not a sprint."

Saag tells his patients that once they commence HAART, they must be prepared to live with the drugs for 20 or 30 years, or even longer. And there will be complications. He calculates that among typical, nonsmoking 35-year-old males, the odds they will have serious hypertension by age 45 are about six out of 100. But for a nonsmoking man on HAART the odds of serious hypertension by age 45 more than double to 16 per 100, largely because one group of the anti-HIV drugs boosts cholesterol counts.

New research indicates that completely effective HAART would take 70 years to kill off all HIVs in a patient's body. And few patients experience such effectiveness. Most are overcome by drug-resistant forms of the virus.

The ranks of such patients have swelled, and the FDA is considering weakening drug-testing requirements in an effort to speed more agents onto the roster of HAART drugs. That makes activists like Harrington and Gregg Gonsalves, policy analyst for Gay Men's Health Crisis in New York City, angry.

"I would argue that the drug companies and the Food and Drug Administration have been negligent, retrospectively, in not conducting or requiring long- term studies of the effects of these drugs so we can answer basic questions like these about their use," Gonsalves said. "Thousands of patients like me don't have the data to make an informed decision about when to use these agents, and the drug companies are laughing all the way to the bank."

Saag, however, feels optimistic. He is hopeful that within three to four years the details of these toxicities, and their biological causes, will be elucidated. And that, he hopes, will lead to much-needed improvements in drug therapy.

1: Lancet. 1999 Sep 25;354(9184):1112-5. Related Articles, Links

Comment in:
Lancet. 1999 Sep 25;354(9184):1046-7.
Lancet. 2000 Mar 25;355(9209):1096.

**Mitochondrial toxicity induced by nucleoside-analogue reverse-transcriptase inhibitors is a key factor in the pathogenesis of antiretroviral-therapy-related lipodystrophy.**

Brinkman K, Smeitink JA, Romijn JA, Reiss P.

Department of Internal Medicine, Onze Lieve Vrouwe Gasthuis, Amsterdam, The Netherlands. K.Brinkman@OLVG.nl

Highly active antiretroviral therapy (HAART) can induce a characteristic lipodystrophy syndrome of peripheral fat wasting and central adiposity. HIV-1 protease inhibitors are generally believed to be the causal agents, although the syndrome has also been observed with protease-inhibitor-sparing regimens. Here, we postulate that the mitochondrial toxicity of the nucleoside-analogue reverse-transcriptase inhibitors plays an essential part in the development of this lipodystrophy, similar to the role of mitochondrial defects in the development of multiple symmetrical lipomatosis.

1: N Engl J Med 1990 Apr 19;322(16):1098-105

**Mitochondrial myopathy caused by long-term zidovudine therapy.**

Dalakas MC, Illa I, Pezeshkpour GH, Laukaitis JP, Cohen B, Griffin JL

Division of Intramural Research, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD 20892.

Both infection with the human immunodeficiency virus type 1 (HIV) and zidovudine (formerly called azidothymidine [AZT]) cause myopathy. To identify criteria for distinguishing zidovudine-induced myopathy from that caused by primary HIV infection, we reviewed the histochemical, immunocytochemical, and electron-microscopical features of muscle-biopsy specimens from 20 HIV-positive patients with myopathy (15 of whom had been treated with zidovudine) and compared the findings with the patients' clinical course and response to various therapies. Among the zidovudine-treated patients, the myopathy responded to prednisone in four, to the discontinuation of zidovudine in eight, and to nonsteroidal anti-inflammatory drugs in two. Numerous "ragged-red" fibers, indicative of abnormal mitochondria with paracrystalline inclusions, were found in the biopsy specimens from the zidovudine-treated patients but not in those from the other patients. The number of these fibers appeared to correlate with the severity of the myopathy. All the patients, regardless of whether they had been treated with zidovudine, had inflammatory myopathy characterized by degenerating fibers, cytoplasmic bodies, and endomysial infiltrates consisting of CD8+ cells (mean +/- SD, 60.7 +/- 6.4 percent) and macrophages (39.2 +/- 6.4 percent) associated with Class I major histocompatibility complex (MHC-I) antigens (HLA-A, -B, and -C antigens) in the muscle fibers. The numbers and percentages of CD8+ cells and macrophages were similar in both the zidovudine-treated and the untreated HIV-positive patients. Specimens obtained on repeat muscle biopsy from two patients in whom the myopathy responded to the discontinuation of zidovudine showed remarkable histologic improvement. We conclude that long-term therapy with zidovudine can cause a toxic mitochondrial myopathy, which coexists with a T-cell-mediated inflammatory myopathy that is restricted to MHC-I antigen, and is indistinguishable from the myopathy associated with primary HIV infection or polymyositis in HIV-seronegative patients.

Comment in:
N Engl J Med. 1990 Oct 4;323(14):994

1: Ital J Neurol Sci 1992 Dec;13(9):723-8

**AZT-induced mitochondrial myopathy.**

Tomelleri G, Tonin P, Spadaro M, Tilia G, Orrico D, Barelli A, Bonetti B, Monaco S, Salviati A, Morocutti C, et al

Istituto di Neurologia, Universita di Verona.

Histochemical, electron microscopy and biochemical studies were performed on muscle biopsy specimens from 11 AIDS patients treated with zidovudine. A peculiar association of structural abnormalities and mitochondrial dysfunction was found. Focal cytochrome c oxidase (COX) deficiency was evident in muscle sections from 9 patients, 8 of whom had received long-term treatment while one had been treated for 1 month only. Electron microscopy showed changes in number, size and structure of mitochondria. Biochemical studies proved partial COX and succinate cytochrome c reductase (SCR) deficiency in 4 patients; one patient had only reduced SCR activity. Our data confirm that AZT therapy can cause toxic myopathy with mitochondrial dysfunction.

PMID: 1336487

1: Lancet 1991 Mar 2;337(8740):508-10

**Depletion of muscle mitochondrial DNA in AIDS patients with zidovudine-induced myopathy.**

Arnaudo E, Dalakas M, Shanske S, Moraes CT, DiMauro S, Schon EA

Department of Neurology, Columbia University College of Physicians and Surgeons, New York.

Long-term zidovudine therapy in patients with human immunodeficiency virus (HIV) infection can cause a destructive mitochondrial myopathy with histological features of ragged-red fibres (RRF) and proliferation of abnormal mitochondria. In 9 zidovudine-treated patients with this myopathy we found severely reduced amounts (up to 78% reduction vs normal adult controls) of mitochondrial DNA (mtDNA) in muscle biopsy specimens by means of Southern blotting. In 2 HIV-positive patients who had not received zidovudine, muscle mtDNA content did not differ from that in the 4 controls. Depletion of mtDNA seems to be reversible, since 1 patient showed a substantial reduction in RRF and a concomitant pronounced increase in muscle mtDNA content after zidovudine therapy was discontinued. Depletion of muscle mtDNA is probably due to zidovudine-induced inhibition of mtDNA replication by DNA polymerase gamma and is not a secondary effect of HIV infection.

1: Lancet 1999 Sep 25;354(9184):1112-5

**Mitochondrial toxicity induced by nucleoside-analogue reverse-transcriptase inhibitors is a key factor in the pathogenesis of antiretroviral-therapy-related lipodystrophy.**

Brinkman K, Smeitink JA, Romijn JA, Reiss P

Department of Internal Medicine, Onze Lieve Vrouwe Gasthuis, Amsterdam, The Netherlands. K.Brinkman@OLVG.nl

Highly active antiretroviral therapy (HAART) can induce a characteristic lipodystrophy syndrome of peripheral fat wasting and central adiposity. HIV-1 protease inhibitors are generally believed to be the causal agents, although the syndrome has also been observed with protease-inhibitor-sparing regimens. Here, we postulate that the mitochondrial toxicity of the nucleoside-analogue reverse-transcriptase inhibitors plays an essential part in the development of this lipodystrophy, similar to the role of mitochondrial defects in the development of multiple symmetrical lipomatosis.

1: N Engl J Med 1994 Mar 17;330(11):738-43

**Evaluation of the quality of life associated with zidovudine treatment in asymptomatic human immunodeficiency virus infection. The AIDS Clinical Trials Group.**

Lenderking WR, Gelber RD, Cotton DJ, Cole BF, Goldhirsch A, Volberding PA, Testa MA

Statistical and Data Analysis Center, Harvard School of Public Health, Boston, MA 02115.

BACKGROUND. Zidovudine therapy is recommended for asymptomatic patients infected with the human immunodeficiency virus (HIV) who have fewer than 500 CD4+ cells per cubic millimeter. An analysis of the quality of life associated with therapy that integrated both the effects of adverse events and the benefits of delayed disease progression might influence this recommendation. METHODS. We applied a survival analysis adjusted for the quality of life to data from a

randomized trial conducted by the AIDS Clinical Trials Group. The trial compared treatment with 500 mg of zidovudine per day, 1500 mg of zidovudine per day, and placebo (Protocol 019) in 1338 asymptomatic HIV-infected patients. RESULTS. The average time with neither a progression of disease nor an adverse event (symptom or laboratory finding) was 15.7, 15.6, and 14.8 months for patients receiving placebo, 500 mg of zidovudine, and 1500 mg of zidovudine, respectively. The incidence of severe symptoms was 13.8 percent in the placebo group, 15.2 percent in the 500-mg group, and 19.9 percent in the 1500-mg group (P = 0.038). After 18 months, the 500-mg group gained an average of 0.5 months without disease progression, as compared with the placebo group, but had severe adverse events an average of 0.6 months sooner. The 500-mg group had more quality-of-life--adjusted time than the placebo group only if the time lived after the progression of disease was considered by a patient to have less value than the time after the occurrence of a severe symptom. CONCLUSIONS. For asymptomatic patients treated with 500 mg of zidovudine, a reduction in the quality of life due to severe side effects of therapy approximately equals the increase in the quality of life associated with a delay in the progression of HIV disease.

1: Nat Med 1995 May;1(5):417-22

**Mitochondrial toxicity of antiviral drugs.**

Lewis W, Dalakas MC

Department of Pathology and Laboratory Medicine, University of Cincinnati College of Medicine, Ohio 45267-0529, USA.

Long-term treatment with antiviral nucleoside analogue drugs, such as AZT, can give rise to delayed and at times severe mitochondrial toxicity. Although these toxic effects are manifest in many tissues, a common disease mechanism can explain the diverse clinical events. A better understanding of these disorders will shed light on genetic mitochondrial diseases and lead to the design of safer and more effective antiviral drugs.

1: J Neurol Sci 1997 Jul;149(1):19-25

Related Articles, Books

**Cellular and mitochondrial toxicity of zidovudine (AZT), didanosine (ddI) and zalcitabine (ddC) on cultured human muscle cells.**

Benbrik E, Chariot P, Bonavaud S, Ammi-Said M, Frisdal E, Rey C, Gherardi R, Barlovatz-Meimon G

Groupe d'Etudes et de Recherches sur le Muscle et le Nerf (GERMEN: ER 269 et 315, Universite Paris XII), Faculte de Medecine, Creteil, France.

Zidovudine (AZT), didanosine (ddI) and zalcitabine (ddC) are the reference antiretroviral therapy in patients with AIDS. A toxic mitochondrial myopathy can be observed in patients treated with AZT, but not with ddI and ddC. All 3 compounds can inhibit mitochondrial (mt)DNA polymerase and cause termination of synthesis of growing mtDNA strands and mtDNA depletion. The propensity to injure particular target tissues is unexplained. In our work, cultured muscle cells prepared from human muscle biopsies, were exposed to various concentrations of AZT (4-5000 micromol/l), ddI (5-1000 micromol/l) and ddC (1-1000 micromol/l) for 10 days. We evaluated cell proliferation and differentiation and measured lipid droplet accumulation, lactate production and respiratory chain enzyme activities. All 3 compounds induced a dose-related decrease of cell proliferation and differentiation.

AZT seemed to be the most potent inhibitor of cell proliferation. AZT, ddI and ddC induced cytoplasmic lipid droplet accumulations, increased lactate production and decreased activities of COX (complex IV) and SDH (part of complex II). NADHR (complex I) and citrate sinthase activities were unchanged. Zalcitabine (ddC) and, to a lesser extent, ddI, were the most potent inhibitors of mitochondrial function. In conclusion, AZT, ddI and ddC all exert cytotoxic effects on human muscle cells and induce functional alterations of mitochondria possibly due to mechanisms other than the sole mtDNA depletion. Our results provide only a partial explanation of the fact that AZT, but not ddI and ddC, can induce a myopathy in HIV-infected patients. AZT myopathy might not simply result from a direct mitochondrial toxic effect of crude AZT.

PMID: 9168161

**Hepatotoxicity development during antiretroviral therapy containing protease inhibitors in patients with HIV: the role of hepatitis B and C virus infection.**

Aceti A, Pasquazzi C, Zechini B, De Bac C; The LIVERHAART Group.

Department of Infectious and Tropical Diseases, II Faculty of Medicine, University of Rome La Sapienza, Rome, Italy. professoraceti@tiscalinet.it

To evaluate the occurrence of hepatotoxicity in patients during antiretroviral therapy (ART) that contains protease inhibitors and the role of hepatitis viruses in its development, we performed a retrospective study including 1325 HIV-infected patients treated with ART for at least 6 months. Presence or absence of hepatitis viruses, alanine aminotransferase (ALT), total bilirubin, CD4 cell count, and plasma HIV RNA levels were evaluated. Hepatotoxicity developed in a few study subjects without coinfection, whereas it was significantly higher in coinfected patients. Univariate logistic regression analysis showed that viral hepatitis coinfections are independent risk factors for hepatotoxicity. After 6 months of treatment, ritonavir was associated with higher rates of severe hepatotoxicity in the coinfected group; in fact, ritonavir seems to be the most strongly hepatotoxic agent among coinfected patients. After 12 months of therapy, hepatotoxicity occurred more frequently in patients with hepatitis C virus who did not respond to antiretroviral therapy (ART), whereas patients who did respond to ART showed decreased ALT levels. Hepatotoxicity is not exclusively an effect of drug toxicity, and the presence of hepatitis coinfection is an independent risk factor. Moreover, chronic hepatotoxicity mainly occurs in patients who did not respond to therapy. Conversely, patients who did respond to ART seemed to show improvement of chronic liver infection.

## 15) Toxicities Associated with Purine Analog Therapy

**Bruce D. Cheson**
National Cancer Institute Bethesda, Maryland

### V. Summary

The nucleoside analogs have proven to be highly effective in the therapy of lymphoid malignancies. However, they have a number of associated toxicities, some of what may be severe. Of particular concern is immunosuppression wich is uniform with standard treatment programs. Each of the nucleoside analogs is associated with a profound lymphocytopenia, with a reversal of the CD4/CD8, and opportunistic infections. Whether secondary malignancies will be a long-range complication will require observation and recording of long-term follow-up resulsts.
The frequency with wich many of the nonhematologic toxicities occur is difficult to estimate. Most studies contain small numbers of patients, in whom few, if any nonhematologic toxicities are reported. Whether that reflects the actual rarity of these events or the care with which those series was evaluated is not clear. As the clinical experience with these agents become more extensive, with longer follow-up, recognized toxicities will become better charatrized and new side effects ma be encountered. Anecdotal reports may serve to increase the sensitivity for identification of new and unusual complications.

There are a number of unresolved issues in the use of the nucleoside analogs. The optimal schedule of administration remains unknown. A 6-month course of fludarabine has been recommnded for CLL, and a similar duration of DCF for HCL. Although a single course of CDA is generally used for HCL, repeated courses have been delivered for the other lymphoid malignancies.
Nevertheless, these regiments are empiric. An accumlating body of evidence suggests that fludarabine and CdA work by a different mechnism of action, e.g., activation of apoptosis. Therefore, we may be administering more drug than is required for biological effect (199, 200). Further study of this issue is warranted to maintain efficacy while minimizing the tocicities associated with treatment with these highly effecive nucleosid analogs. As nucleosid analogs are being combined with cytotoxic and biological agents in an attempt to increase their efficacy, care must be exercised to avoid drugs with overlapping toxicities.
Based on the published literature, the non-hematologic toxicities from the nucleoside analogs are relatively similar (Table 3), with the possible exception of the ocular toxicity, rash and increased severity of nausea and vomiting with DCF, and the relatively more prolonged period of immunosuppression with DCF and CdA. In general, however, they are relatively well tolerated. The decision as to which is the preferred nucleoside analog for a specific indication must be determined by their response rate, durability of responses, cost, toxicity profile and ease with wich they can be combined into effective combination regiments.

from: **Nucleoside Analogs in Cancer Therapy**
**edited by Bruce D. Cheson, Michael J. Keating, William Plunkett**
**Marcel Dekker Inc. New York, Basel, Hong Kong 1997**

## THERAPY

Immunol Today 1994 Dec;15(12):575-81

**The Th1-Th2 hypothesis of HIV infection: new insights.**

Clerici M, Shearer GM

Cattedra di Immunologia, Universita degli Studi, Milano, Italy.

In their earlier, much quoted, viewpoint article, Mario Clerici and Gene Shearer examined the role of T helper 1 (Th1)- and Th2-type responses in immune dysregulation associated with human immunodeficiency virus (HIV) infection. In this article, they consider the complications of a Th1-Th2 model raised by the nomenclature, discuss the issue of cytokine production by non-T cells, and compare data obtained from T-cell clones with heterogeneous populations of leukocytes from patients. They define Th-cell responses and cytokine profiles as 'type 1' and 'type 2', and reemphasize the importance of strong cellular immune responses, along with the cytokines that augment and maintain such responses, in protective immunity against HIV infection and AIDS progression. Finally, they present a model of activation-induced, cytokine-modulated, programmed cell death as a major factor in the pathogenesis of HIV infection and AIDS.

**Role of cysteine and glutathione in HIV infection and other diseases associated with muscle wasting and immunological dysfunction.**

Droge W, Holm E

Division of Immunochemistry, Deutsches Krebsforschungszentrum, Heidelberg, Germany.

The combination of abnormally low plasma cystine and glutamine levels, low natural killer (NK) cell activity, skeletal muscle wasting or muscle fatigue, and

increased rates of urea production defines a complex of abnormalities that is tentatively called "low CG syndrome." These symptoms are found in patients with HIV infection, cancer, major injuries, sepsis, Crohn's disease, ulcerative colitis, chronic fatigue syndrome, and to some extent in overtrained athletes. The coincidence of these symptoms in diseases of different etiological origin suggests a causal relationship. The low NK cell activity in most cases is not life-threatening, but may be disastrous in HIV infection because it may compromise the initially stable balance between the immune system and virus, and trigger disease progression. This hypothesis is supported by the coincidence observed between the decrease of CD4+ T cells and a decrease in the plasma cystine level. In addition, recent studies revealed important clues about the role of cysteine and glutathione in the development of skeletal muscle wasting. Evidence suggests that 1) the cystine level is regulated primarily by the normal postabsorptive skeletal muscle protein catabolism, 2) the cystine level itself is a physiological regulator of nitrogen balance and body cell mass, 3) the cyst(e)ine-mediated regulatory circuit is compromised in various catabolic conditions, including old age, and 4) cysteine supplementation may be a useful therapy if combined with disease-specific treatments such as antiviral therapy in HIV infection.

**Glutathione deficiency is associated with impaired survival in HIV disease.**

Herzenberg LA, De Rosa SC, Dubs JG, Roederer M, Anderson MT, Ela SW, Deresinski SC, Herzenberg LA

Department of Genetics, Stanford University Medical School, CA 94305-5125, USA.

Glutathione (GSH), a cysteine-containing tripeptide, is essential for the viability and function of virtually all cells. In vitro studies showing that low GSH levels both promote HIV expression and impair T cell function suggested a link between GSH depletion and HIV disease progression. Clinical studies presented here directly demonstrate that low GSH levels predict poor survival in otherwise indistinguishable HIV-infected subjects. Specifically, we show that GSH deficiency in CD4 T cells from such subjects is associated with markedly decreased survival 2-3 years after baseline data collection (Kaplan-Meier and logistic regression analyses, $P < 0.0001$ for both analyses). This finding, supported by evidence demonstrating that oral administration of the GSH prodrug N-acetylcysteine replenishes GSH in these subjects and suggesting that N-acetylcysteine administration can improve their survival, establishes GSH deficiency as a key determinant of survival in HIV disease. Further, it argues strongly that the unnecessary or excessive use of acetaminophen, alcohol, or other drugs known to deplete GSH should be avoided by HIV-infected individuals.

1: Proc Natl Acad Sci U S A 1998 Mar 17;95(6):3071-6

**Glutathione levels in antigen-presenting cells modulate Th1 versus Th2 response patterns.**

Peterson JD, Herzenberg LA, Vasquez K, Waltenbaugh C

Department of Microbiology-Immunology, Northwestern University, Medical School, Chicago, IL 60611-3072, USA.

Current thinking attributes the balance between T helper 1 (Th1) and Th2 cytokine response patterns in immune responses to the nature of the antigen, the genetic composition of the host, and the cytokines involved in the early interaction between T cells and antigen-presenting cells. Here we introduce glutathione, a tripeptide that regulates intracellular redox and other aspects of cell physiology, as

a key regulatory element in this process. By using three different methods to deplete glutathione from T cell receptor transgenic and conventional mice and studying in vivo and/or in vitro responses to three distinct antigens, we show that glutathione levels in antigen-presenting cells determine whether Th1 or Th2 response patterns predominate. These findings present new insights into immune response alterations in HIV and other diseases. Further, they potentially offer an explanation for the well known differences in immune responses in "Th1" and "Th2" mouse strains.

1: Eur J Clin Invest 2000 Oct;30(10):915-29

**N-acetylcysteine replenishes glutathione in HIV infection**

De Rosa SC , Zaretsky MD, Dubs JG, Roederer M, Anderson M, Green A, Mitra D, Watanabe N, Nakamura H, Tjioe I, Deresinski SC, Moore WA, Ela SW, Parks D, Herzenberg LA, Herzenberg LA

Stanford University, USA, University of California, Berkeley, USA, Vaccine Research Center, NIH Bethesda MD, USA, Comprehensive Cancer Center, Birmingham, USA, Medical Institute, India, University of Tokyo, Japan, Institute of Viral Research, Kyo.

[Record supplied by publisher]

BACKGROUND: Glutathione (GSH) deficiency is common in HIV-infected individuals and is associated with impaired T cell function and impaired survival. N-acetylcysteine (NAC) is used to replenish GSH that has been depleted by acetaminophen overdose. Studies here test oral administration of NAC for safe and effective GSH replenishment in HIV infection. DESIGN: Oral NAC administration in a randomized, 8-week double-blind, placebo-controlled trial followed by optional open-label drug for up to 24 weeks. SUBJECTS: HIV-infected, low GSH, CD4 T cells < 500 &mgr;L-1, no active opportunistic infections or other debilitation; n = 81. Study conducted prior to introduction of protease inhibitors. RESULTS: Whole blood GSH levels in NAC arm subjects significantly increased from 0.88 mM to 0.98 mM, bringing GSH levels in NAC-treated subjects to 89% of uninfected controls (P = 0.03). Baseline GSH levels in the placebo group (0.91) remained essentially the same during the 8 week placebo-controlled trial. T cell GSH, adjusted for CD4 T cell count and beta2-microglobulin levels, also increased in the NAC-treated subjects (P = 0.04). Adverse effects were minimal and not significantly associated with NAC ingestion. CONCLUSION: NAC treatment for 8 weeks safely replenishes whole blood GSH and T cell GSH in HIV-infected individuals. Thus, NAC offers useful adjunct therapy to increase protection against oxidative stress, improve immune system function and increase detoxification of acetaminophen and other drugs. These findings suggest that NAC therapy could be valuable in other clinical situations in which GSH deficiency or oxidative stress plays a role in disease pathology, e.g. rheumatoid arthritis, Parkinson's disease, hepatitis, liver cirrhosis, septic shock and diabetes.

**The 1996 Albert Lasker Medical Research Awards. The discovery of endothelium-derived relaxing factor and its importance in the identification of nitric oxide.**

Furchgott RF.

Department of Pharmacology, State University of New York, Health Science Center at Brooklyn, NY 11203, USA.

The discovery of endothelium-derived relaxing factor (EDRF) and its importance in the identification of nitric oxide (NO) originated with studies using rabbit aorta to examine drug-receptor interactions in vascular smooth muscle. Smooth muscle relaxation by

acetylcholine and a number of other agonists was found to be dependent on the presence of endothelial cells, which, when stimulated by the agonist, released a diffusable, very labile, nonprostanoid substance, termed EDRF, that acted on vascular smooth muscle cells to activate relaxation. The characteristics of EDRF, when released from endothelial cells, were similar to the characteristics of NO. It is now established that EDRF, either as NO or some related nitrosyl substance, has a major role in a variety of important biological processes, including the regulation of vascular tone, local blood flow, and blood pressure, inhibition of platelet aggregation and adhesion, and involvement in postischemic reperfusion, memory function, and central nervous system degenerative diseases.

1: Annu Rev Pharmacol Toxicol 1995;35:1-27

**A research trail over half a century.**

Furchgott RF.

Department of Pharmacology, State University of New York Health Science Center at Brooklyn 11203, USA.

The author describes his major research activities from the time of his PhD thesis work (1937-1940) on properties of erythrocyte membranes to the present. His involvement in research on circulatory shock during World War II led to a continuing interest in the physiology and pharmacology of smooth muscle and cardiac muscle. From 1956 to 1978, his main areas of research were photorelaxation of blood vessels, factors influencing contractility of cardiac muscle, peripheral adrenergic mechanisms, and receptor theory. The major findings of his and his collaborators in these areas are described. He then recounts how an accidental finding in an experiment in 1978 on preparations of rabbit aorta eventually led to the discovery of endothelium dependent relaxation and the endothelium-derived relaxing factor (EDRF); and how additional findings led him to propose in 1986 that EDRF is nitric oxide.

**Nitric oxide donors and cardiovascular agents modulating the bioactivity of nitric oxide: an overview.**

Ignarro LJ, Napoli C, Loscalzo J.

Nitric Oxide Research Group (L.J.I.), Molecular and Medical Pharmacology, Center for the Health Sciences, University of California, Los Angeles.

Nitric oxide (NO) mediates multiple physiological and pathophysiological processes in the cardiovascular system. Pharmacological compounds that release NO have been useful tools for evaluating the pivotal role of NO in cardiovascular physiology and therapeutics. These agents constitute two broad classes of compounds, those that release NO or one of its redox congeners spontaneously and those that require enzymatic metabolism to generate NO. In addition, several commonly used cardiovascular drugs exert their beneficial action, in part, by modulating the NO pathway. Here, we review these classes of agents, summarizing their fundamental chemistry and pharmacology, and provide an overview of their cardiovascular mechanisms of action.

PMID: 11786514 [PubMed - in process]

**Glutamine-antioxidant supplementation increases body cell mass in AIDS patients with weight loss: a randomized, double-blind controlled trial.**

Shabert JK, Winslow C, Lacey JM, Wilmore DW.

Department of Obstetrics and Gynecology, Harvard Medical School, Boston, Massachusetts, USA.

Loss of body cell mass, the active functioning tissue of the body, commonly occurs in patients

with human immunodeficiency virus (HIV) infection, and the extent of wasting is related to the length of survival. We evaluated the anabolic role of the amino acid L-glutamine (GLN) and antioxidants in a double-blind, placebo-controlled trial in 26 patients with > 5% weight loss since disease onset. Subjects received GLN-antioxidants (40 g/d) in divided doses or glycine (40 g/d) as the placebo for 12 wk. Throughout the study, the subjects were seen weekly by a nutritionist, and body weight, bioelectric impedance assessment, and nutritional counseling were performed. Twenty-one subjects completed the study, and the groups were well matched. The 5 patients excluded from analysis all met a priori exclusion criteria. Over 3 mo, the GLN-antioxidant group gained 2.2 kg in body weight (3.2%), whereas the control group gained 0.3 kg (0.4%, P = 0.04 for difference between groups). The GLN-antioxidant group gained 1.8 kg in body cell mass, whereas the control group gained 0.4 kg (P = 0.007). Intracellular water increased in the GLN-antioxidant group but not in the control group. In conclusion, GLN-antioxidant nutrient supplementation can increase body weight, body cell mass, and intracellular water when compared with placebo supplementation. GLN-antioxidant supplementation provides a highly cost-effective therapy for the rehabilitation of HIV+ patients with weight loss.

**L-carnitine deficiency in AIDS patients.**

De Simone C, Tzantzoglou S, Jirillo E, Marzo A, Vullo V, Martelli EA.

Dipartimento di Medicina Sperimentale, Universita dell' Aquila, Italy.

OBJECTIVE: To evaluate carnitine (3-hydroxy-4-N-trimethyl-ammoniobutanoate) deficiency in AIDS patients by measuring serum total, free and short-chain carnitine concentrations. DESIGN: We conducted an open study. SETTING: All patients were seen at the Infectious Diseases Clinic, Universita 'La Sapienza', Rome, Italy. PATIENTS, PARTICIPANTS: Twenty-nine AIDS patients, aged 27-41 years, with a previous history of drug use; and 14 healthy age- and sex-matched controls were studied. INTERVENTIONS: Study subjects were administered 500-800 mg zidovudine daily for 2 to 28 months (8 +/- 6 months). MAIN OUTCOME MEASURES: Carnitine deficiency was suspected in study participants prior to data collection because of previously reported cardiac symptoms, muscle weakness, hypometabolism and/or cachexia. RESULTS: A marked decrease in total and free carnitine was observed in 21 (72%) subjects. Nine of these patients also had low levels of short-chain carnitine. CONCLUSIONS: AIDS patients may become carnitine-depleted and therefore at risk for alterations in fatty-acid oxidation and energy supply.

PMID: 1558717 [PubMed - indexed for MEDLINE]

**Cystine levels, cystine flux, and protein catabolism in cancer cachexia, HIV/SIV infection, and senescence.**

Hack V, Schmid D, Breitkreutz R, Stahl-Henning C, Drings P, Kinscherf R, Taut F, Holm E, Droge W.

Department of Immunochemistry, Deutsches Krebsforschungszentrum, Heidelberg, Germany.

Patients with skeletal muscle catabolism (cachexia) fail to conserve the skeletal muscle protein and release large amounts of nitrogen as urea. Previous studies suggest that the threshold for the conversion of amino acids into other forms of chemical energy and the concomitant production of urea are regulated by the plasma cystine level and hepatic cysteine catabolism. Studies of plasma amino acid exchange rates in the lower extremities now show that healthy young subjects regulate their plasma cystine level in a process that may be described as controlled constructive catabolism. The term controlled describes the fact that the release of cystine and other amino acids from the peripheral tissue is negatively correlated with (certain) plasma amino acid levels. The term constructive describes the fact that the release of cystine is correlated with an increase of the plasma cystine level. The regulation of the plasma cystine level is disturbed in conditions with progressive skeletal muscle catabolism including cancer, HIV infection, and old age. These conditions show also a low plasma glutamine:cystine ratio indicative of an impaired hepatic cystine catabolism. In HIV+ patients and SIV-infected macaques, a decrease of the plasma cystine level was found to coincide with the decrease of

CD4+ T cells.

PMID: 9034170 [PubMed - indexed for MEDLINE]

**Abnormal glutathione and sulfate levels after interleukin 6 treatment and in tumor-induced cachexia.**

Hack V, Gross A, Kinscherf R, Bockstette M, Fiers W, Berke G, Droge W.

Division of Immunochemistry, Deutsches Krebsforschungszentrum, Heidelberg, Germany.

Excessive urea excretion associated with a negative nitrogen balance and massive loss of skeletal muscle mass (cachexia) is a frequent life threatening complication in malignancies and HIV infection. As these patients have often elevated interleukin-6 (IL-6) and abnormally low cystine levels, we have now determined the intracellular levels of glutathione and other cysteine derivatives in the liver and muscle tissue of IL-6-treated or tumor-bearing C57BL/6 mice. IL-6 treatment or inoculation of the MCA-105 fibrosarcoma caused a significant increase in hepatic gamma-glutamyl-cysteine synthetase activity and a decrease in the sulfate level, glutamine/urea ratio, and glutamine/glutamate ratio, suggesting that a decrease of the proton generating cysteine catabolism in the liver may increase carbamoyl-phosphate synthesis and urea formation at the expense of net glutamine synthesis. Treatment with cysteine, conversely, caused an increase in sulfate, glutamine/urea ratios, and glutamine/glutamate ratios and may thus be a useful therapeutic tool in clinical medicine. In contrast to the liver, muscle tissue of tumor-bearing mice showed decreased glutathione and increased sulfate levels, suggesting that the cysteine pool may be drained by an increased cysteine catabolism in this tissue. The findings indicate that tumor cachexia is triggered initially by IL-6 and is later sustained by processes driven by an abnormal cysteine metabolism in different organs.-Hack, V., Gross, A., Kinscherf, R., Bockstette, M., Fiers, W., Berke, G., and Droge, W. Abnormal glutathione and sulfate levels after interleukin 6 treatment and in tumor-induced cachexia.

**Lymphocyte function in anergic patients.**

Rode HN, Christou NV, Bubenik O, Superina R, Gordon J, Meakins JL, MacLean LD.

The lymphocyte function of anergic surgical patients who are at increased risk for sepsis and mortality was studied. In vitro lymphocyte responses appear to be normal in most instances, in that over 80% of patients showed a normal response in a standardized mixed leucocyte culture reaction. Similarly, 56% of the lymphocytes from anergic patients showed a positive in vitro proliferative response with PPD. The ability of in vitro-activated lymphocytes to elicit a skin reaction was determined by culturing the cells of anergic patients with PPD and then reinjecting the lymphocytes or their supernatants intradermally into the original donor. When there was a positive proliferative response to PPD in vitro, the reinjected cells or supernatant elicited a positive skin reaction in 79% of the anergic patients. In contrast, a skin reaction was obtained in less than 20% of the instances when there was no in vitro proliferation to PPD or when the cells were cultured without antigen. These results suggest that one of the acquired immune defects in these anergic patients is an in vivo block of lymphocyte activation.

**The possible role of glutamine in some cells of the immune system and the possible consequence for the whole animal.**

Newsholme EA.

Department of Biochemistry, University of Oxford, United Kingdom.

Glutamine is important for the function of lymphocytes and macrophages. A role for the high rate of glutamine utilisation by these cells is presented. Since muscle syntheses, stores and releases glutamine, this tissue may play a role in the immune response. Since the number of immune cells utilising glutamine may be large, the demand for glutamine from muscle, especially during trauma, sepsis or burns, may be very high. A speculative suggestion is put

forward that this requirement for glutamine from muscle may play a role in cachexia under some of these conditions.

**Dehydroepiandrosterone sulfate (DHEAS) and testosterone: relation to HIV illness stage and progression over one year.**

Ferrando SJ, Rabkin JG, Poretsky L.

Department of Psychiatry, Cornell University Medical College, New York, New York, USA.

This study explored associations between serum dehydroepiandrosterone sulfate (DHEAS), free and total testosterone levels, and HIV illness markers, including viral load, and the behavioral problems of fatigue and depressed mood. Subjects were 169 HIV-positive men evaluated at baseline, 6, and 12 months for levels of DHEAS, total and free testosterone, HIV RNA, CD4, HIV symptoms, opportunistic illnesses, fatigue, and depression. Men with AIDS (N = 105), compared with men with less advanced illness, had lower mean levels of DHEAS. Baseline DHEAS was positively correlated with CD4 count, HIV symptom severity, and was inversely correlated with HIV RNA. Baseline DHEAS below the laboratory reference range (96 microg/dl) was associated with history of opportunistic infections and malignancies (adjusted odds ratio [OR], 4.4; 95% confidence interval [CI], 1.9-10.4) and with incidence of these complications or death over 1 year (adjusted OR, 2.6; 95% CI, 1-7.2). Initiating protease inhibitor combination therapy was associated with an increase in DHEAS over 6 months. Free testosterone was inversely correlated with HIV RNA, but there were no other significant associations between testosterone and HIV illness markers. No hormone was related to fatigue or depression. This study confirms that low serum DHEAS is associated with HIV illness markers, including viral load, and carries negative prognostic value. Further, protease inhibitor therapy may result in increased circulating DHEAS.

## ETIOLOGY

Immunol Today 1994 Dec;15(12):575-81

**Circadian variations in plasma levels of hypophyseal, adrenocortical and testicular hormones in men infected with human immunodeficiency virus.**

Villette JM, Bourin P, Doinel C, Mansour I, Fiet J, Boudou P, Dreux C, Roue R, Debord M, Levi F

Unite d'Hormonologie, Laboratoire de Biochimie, Hopital Saint-Louis, Paris, France.

Alterations in the circadian time structure of the secretion of several hormones were investigated in 13 male patients infected with human immunodeficiency virus (HIV). Seven were asymptomatic (classified CDC II, according to the criteria of the Atlanta Centers for Disease Control), and 6 had acquired immunodeficiency syndrome (CDC IV). Ten healthy males volunteered as controls. Plasma levels of dehydroepiandrosterone (DHEA) and its sulfate (DHEA-S), cortisol, testosterone, ACTH, and beta-endorphin were determined by RIA in blood samples obtained every 4 h from 0830-0830 h the next morning. Data were analyzed both by two-way analysis of variance and the cosinor method. Circadian rhythms were statistically validated for each of the six hormones in each of the three groups of subjects. Compared with the control subjects, mesors (24-h adjusted means) were significantly higher for cortisol and lower for DHEA, DHEA-S, and ACTH (P less than 0.001 for all four hormones) in all HIV-infected patients. Plasma testosterone mesors were similar in controls and CDC II patients, but decreased significantly in the CDC IV patient group (P less than 0.05). Analysis of the circadian rhythms of plasma hormone levels clearly indicated an altered adrenal hormonal state in HIV-infected male patients, even during the asymptomatic period of the infection.

For instance, plasma cortisol at 0430 h was more than twice as high in HIV-infected patients as it was in time-qualified controls. Although patients already had elevated plasma cortisol and lowered adrenal androgen levels at this stage, hypogonadism was not observed, as gauged by plasma testosterone concentrations. We speculate that the primary hormonal defect in HIV-infected patients is increased cortisol secretion resulting from circadian-varying stimulation of the adrenal cortex by a factor other than pituitary ACTH. This factor might be a stimulating substance secreted primarily by infected immune cells. Excess cortisol would lower adrenal androgen secretion by shifting adrenal steroid biosynthesis toward glucocorticoids and decreasing pituitary ACTH secretion via a negative feedback mechanism.

1: Am J Psychiatry 1995 Apr;152(4):543-50

**Stress-associated reductions of cytotoxic T lymphocytes and natural killer cells in asymptomatic HIV infection.**

Evans DL, Leserman J, Perkins DO, Stern RA, Murphy C, Tamul K, Liao D, van der Horst CM, Hall CD, Folds JD, et al

Department of Psychiatry, University of Florida College of Medicine, Gainesville 32610-0256.

OBJECTIVE: Previous research has documented a possible relation of stress and depression to cell-mediated immunity. The authors examined how stressful events and depression may affect key parameters of cellular immunity in subjects with and without HIV infection. METHOD: Data were collected on 99 asymptomatic HIV-positive and 65 HIV-negative homosexual men as part of an ongoing, longitudinal study. Criticisms of previous studies of psychoimmunity were addressed by 1) using a comprehensive, semistructured interview to measure the objective context of stressful events, 2) double labeling of lymphocytes with monoclonal antibodies to measure subsets of cytotoxic/suppressor T lymphocytes and natural killer (NK) cells, and 3) controlling for circadian effects and methodological factors. RESULTS: In the HIV-positive men, severe stress was significantly associated with reductions in NK cell populations and a subset of T cells thought to represent cytotoxic T effector cells, particularly the CD8+ T cells expressing the CD57 antigen. In the HIV-negative men, no clear and consistent relation between stress and immune system measures was found. Depression was not correlated with any variables in either of the groups, perhaps due to the low levels of depressive symptoms. CONCLUSIONS: The findings suggest that stress is associated with reductions in killer lymphocytes (decreased NK cell and cytotoxic T lymphocyte phenotypes). The data provide evidence that stress may alter cell populations that provide cytotoxic defense against infection in HIV-positive men and indicate that the clinical significance of stress-related changes in cytotoxic T lymphocytes and NK cells in HIV infection warrants further study.

1: Am J Med Sci 1993 Feb;305(2):79-83

**The relationship of serum DHEA-S and cortisol levels to measures of immune function in human immunodeficiency virus-related illness.**

Wisniewski TL, Hilton CW, Morse EV, Svec F

Department of Medicine, Louisiana State University Medical Center, New Orleans.

Human immunodeficiency virus (HIV) is a major cause of immunoincompetence. Whether the virus, itself, accounts for all the deficiency remains in question. Steroids can also influence immune function; glucocorticoids cause

immunoincompetence while dehydroepiandrosterone (DHEA) enhances immune function. Changes in the levels of such hormones during the course of HIV illness might result in significant changes in immune competence. The purpose of this study is to investigate whether dehydroepiandrosterone-sulphate (DHEA-S) or cortisol levels correlate with absolute CD4 lymphocyte levels. Plasma for cortisol and DHEA-S was drawn from 98 adults with HIV. Of these, 67 had simultaneous CD4 levels. Cortisol levels were 12.4 +/- 4.6 micrograms/dl, DHEA-S 262 +/- 142 micrograms/dl, and CD4 levels were 308 +/- 217/mm3 (mean +/- SD). Correlational analysis revealed a significant relationship between DHEA-S and CD4 levels ($r = 0.30$; $p = 0.01$) but not between CD4 levels and cortisol ($r = 0.11$; $p = 0.36$) or cortisol/DHEA-S ratios ($r = 0.17$; $p = 0.16$). When analyzed by clinical subgroups, significant differences were also found with a decrease in DHEA-S levels seen in persons with more advanced illness. The data exhibit a positive relationship between the immune status of patients with HIV-related illness and DHEA, leading to the hypothesis that DHEA deficiency may worsen immune status.

1: Immunol Today 1994 May;15(5):209-13

**Oxidative stress and apoptosis in HIV infection: a role for plant-derived metabolites with synergistic antioxidant activity.**

Greenspan HC, Aruoma OI

LGD Biomedical Group, Annandale, NJ 08801.

The cascade of events resulting from 'oxidative stress' is markedly similar to that which can initiate apoptosis, a possible mechanism of immune-cell loss in patients with HIV infection and AIDS. Since primary and secondary metabolites found in plants can act as synergistic antioxidants, and can prevent oxidation-induced cell death, Howard Greenspan and Okezie Aruoma ask whether or not these compounds can be useful in inhibiting viral activation and the death of immune cells in HIV/AIDS.

1: J Leukoc Biol 1992 Jul;52(1):111-4

Related Articles, Books, LinkOut

**The role of oxidative stress in disease progression in individuals infected by the human immunodeficiency virus.**

Baruchel S, Wainberg MA

Department of Pediatrics, Montreal Children's Hospital, Quebec, Canada.

This review describes the potential role of oxidative stress as a cofactor of disease progression from asymptomatic human immunodeficiency virus (HIV) infection to the acquired immunodeficiency syndrome (AIDS). Oxidative stress is a known activator of HIV replication in vitro through the activation of a factor that binds to a DNA-binding protein, NF-kappa B, which in turn stimulates HIV gene expression by acting on the promoter region of the viral long terminal repeat. Tumor necrosis factor alpha (TNF-alpha), an essential cytokine produced by activated macrophages, is also involved in the activation of HIV infection through similar mechanisms. TNF-mediated cytotoxicity of cells exposed to this substance is related to the generation of intracellular hydroxyl radicals. An indirect argument in favor of the role of oxidative stress in HIV-associated disease progression is the consumption of glutathione (GSH), a major intracellular antioxidant, during HIV infection and progression. GSH is known to play a major role in regulation of T cell immune functions. Oxidative stress may also play an important role in the genesis of cellular DNA damage and, in this context, may be related to

HIV-associated malignancies and disease progression. Finally, the role of antioxidants as components of therapeutic strategies to combat HIV disease progression is discussed.

1: Immunol Today 1995 Apr;16(4):187-91

**Immune activation is a dominant factor in the pathogenesis of African AIDS.**

Bentwich Z, Kalinkovich A, Weisman Z

R. Ben-Ari Institute of Clinical Immunology, Kaplan Hospital, Hebrew University Hadassah Medical School, Rehovot, Israel.

The AIDS epidemic in Africa is very different from the epidemic in the West. As suggested here by Zvi Bentwich, Alexander Kalinkovich and Ziva Weisman, this appears to be primarily a consequence of the over-activation of the immune system in the African population, owing to the extremely high prevalence of infections, particularly helminthic, in Africa. Such activation shifts the cytokine balance towards a T helper 0/2 (Th0/2)-type response, which makes the host more susceptible to infection with human immunodeficiency virus (HIV) and less able to cope with it.

**Nutrition and Immunity**
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**History of nutritional immunology: introduction and overview.**

Beisel WR.

Department of Immunology and Infectious Diseases, School of Hygiene and Public Health, Johns Hopkins University, Baltimore, MD 21205.

Nutritional immunology is a newly recognized subdiscipline of vast clinical and public health importance. Its history began in 1810 with recognition of lymphoid tissue atrophy due to malnutrition. Discovery of vitamins in the early 1900s was followed by reports on their contribution to immunity and other host defenses. A hiatus in immunonutritional progress occurred during World War II and the "antibiotic era," but a worldwide rebirth of interest began in the 1960s and early 1970s. The current logarithmic growth of nutritional immunology was triggered by increased medical interest, plus the introduction of new concepts and investigative research methodologies from both parent sciences.

1: J Nutr 1996 Oct;126(10 Suppl):2611S-2615S

Related Articles, Books, LinkOut

**Nutrition in pediatric HIV infection: setting the research agenda.**
**Nutrition and immune function: overview.**

Beisel WR.

Department of Immunology and Infectious Diseases, Johns Hopkins University, School of Hygiene and Public Health, Baltimore, MD, USA.

Malnutrition can have adverse, even devastating effects on the antigen-specific arms of the immune system and on generalized host defensive mechanisms. Protein/energy malnutrition and/or deficiencies of single nutrients that assist in nucleic acid metabolism generally lead to atrophy of lymphoid tissues and dysfunctions of cell-mediated immunity. Deficiencies of single nutrients can impair production of key proteins. Trace element deficiencies are often multifactorial. Essential fatty acid

deficiencies can reduce or perturb the synthesis of cytokine-induced eicosanoids. Arginine deficiency can diminish the production of nitric oxide, and deficiencies of antioxidant nutrients can allow increases in the damaging effects of free oxygen radicals. Humoral immunity continues to be maintained, although new primary responses to T-cell-dependent antigens are generally subnormal in both magnitude and quality. Immunological dysfunctions associated with malnutrition have been termed Nutritionally Acquired Immune Deficiency Syndromes (NAIDS). Infants and small children are at great risk because they possess only immature, inexperienced immune systems and very small protein reserves. The combination of NAIDS and common childhood infections is the leading cause of human mortality. NAIDS can generally be corrected by appropriate nutritional rehabilitation, but from a viewpoint highly important to this Workshop, AIDS and NAIDS are intensely synergistic. AIDS-induced malnutrition can lead to the secondary development of NAIDS, with its much broader array of additional immunological dysfunctions. The complex and far reaching insults to the immune system caused by NAIDS, and the synergistic combination of NAIDS and AIDS, thereby hasten the demise of many victims of AIDS. Aggressive nutritional support for children with HIV infections could delay, or lessen, the development of NAIDS and avoidance of NAIDS would improve both quality and length of life.

**Fatal infections in protein-calorie malnourished children with thymolymphatic atrophy.**

Comment in:
J Infect Dis. 1995 Feb;171(2):502-4

Purtilo DT, Connor DH.

The clinicopathological features of 25 children who died with protein-calorie malnutrition were studied. All but four subjects were found at necropsy to have nutritional thymectomy and all but 3 died of infectious diseases. The infectious agents were chiefly intracellular micro-organisms including miliary tuberculosis, Herpes simplex, varicella, measles, Pneumocystis carinii, and Plasmodium falciparum. Staphylococcal infections, salmonellosis, shigellosis, strongyloidiasis, and hookworm were other significant infectious agents. Nutritionally acquired defective immunity, especially cell-mediated immunity, probably permitted these infectious agents to multiply and to disseminate widely.

PMID: 805568 [PubMed - indexed for MEDLINE]

**Induction of antibody to asialo GM1 by spermatozoa and its occurrence in the sera of homosexual men with the acquired immune deficiency syndrome (AIDS).**

Witkin SS, Sonnabend J, Richards JM, Purtilo DT.

Compared to healthy homosexual and heterosexual men, homosexual men with acquired immune deficiency syndrome (AIDS) possessed significantly higher levels of IgG antibody to the neutral glycolipid asialo GM1 (ganglio-N-tetraosylceramide) (P less than 0.01). Of 31 homosexuals with AIDS, 36% possessed levels of this antibody that were at least two standard deviations above the mean of the healthy men. Furthermore, asialo GM1 antibody could be removed from serum by adsorption with spermatozoa. Weekly rectal insemination of male rabbits with rabbit semen also led to the appearance of antibody to asialo GM1 by 15 weeks. These results suggest that asialo GM1 is a component of ejaculated spermatozoa and demonstrate that rectal insemination by itself can lead to the production of antibodies to this glycolipid in the rabbit. In addition, asialo GM1 antibodies may be of value as a serological marker for the early detection of individuals with AIDS.

PMID: 6652964 [PubMed - indexed for MEDLINE]

**Acquired immunodeficiency syndrome, opportunistic infections, and malignancies in male homosexuals. A hypothesis of etiologic factors in pathogenesis.**

Sonnabend J, Witkin SS, Purtilo DT.

The acquired immunodeficiency syndrome (AIDS) occurs in a subgroup of male homosexuals having sexual contact with a large number of partners. Uncommonly, AIDS has also been diagnosed in Haitians, hemophiliacs, and intravenous drug users and their infants. Manifestations include autoimmune disturbances, opportunistic infections, Kaposi's sarcoma, chronic lymphadenomegaly, non-Hodgkin's lymphoma, or squamous cell carcinoma. The hypothesis receiving most consideration is that a yet-to-be-identified virus causes AIDS. An alternative view is that repeated sexual involvement with multiple partners, in a subgroup of male homosexuals, exposes the men to the immunosuppressive impact of cytomegalovirus (CMV) and allogeneic semen. Antibody to asialo-Gm1 and other antigens on sperm react with and impair lymphoid cells. We propose a biphasic process. First, a reversible acquisition phase of impaired T-cell immunoregulation permits reactivation of Epstein-Barr virus (EBV), and autoantibodies are produced by the activated B cells. If sexual activity continues at a high level, accumulating immune defects, including destruction of thymic epithelium, lead to a second, self-sustaining phase wherein cytotoxic lymphocytes fail to eliminate herpesvirus-infected cells. Evidence is mounting that Kaposi's sarcoma is caused by CMV and that EBV is responsible for the B-cell lymphomas in these patients. Multiple factors, rather than a novel virus, probably induce AIDS in male homosexuals. If this hypothesis is correct, then rational bases for prevention and intervention can be designed.

PMID: 6300480 [PubMed - indexed for MEDLINE]

**The role of Antibiotics**

Geoffrey Cannon: Superbugs, Nature's Revenge

Virgin Publishing Ltd., London 1995

Part Four: Apocalypse Now: How Antibiotics Breed Disease

Chapter 15: Nature's Most Malicious Trick?
Reasons to be careful- Immunosuppression - a link with AIDS? -Increasing risk of colon cancer.

Reasons to be careful

Once you know, that you need the resident bacteria in your gut to protect your health, and that antibiotics especially when overused may eventually not only devaste these friendly flora but also may strip away the outer immune defences in your gut, it is easy to see that prolonged course of antibiotics can in time lay you open to all sorts of infections and also non-infectious diseases.
Many diseases, some serious, have evidently become more common in countries like UK and the USA in the last 50 years. They may in part be caused by medical treatment. Infants and children are vulnerable to repeated ear, nose and throat infections. Girls and women are vulnerable to repeated cysteitis and to fungal superinfection, which can become invasive. Antibiotics are certainly one cause of this diseases and may be one cause of a variety of bowel diseases and some forms of arthritis. And the serious general malaise known as chronic fatique syndrome may be in part a complication of invasive fungal infection. Young children and old people are especially at risk, as are the chronically ill. This in addition to the known immediate or acurate ill-effects of antibiotics already described.
Once again, these are not reasons to always avoid antibiotics. To repeat, they are a presicous resource: in case of reliably diagnosed serious invasive bacterial infetions their benefits far outweight their risks. But risks there are: and many of the ill-effects of antibiotics are insidious, quite likely not to be linked with the drug either by victims or their doctors.

Immunosuppression

Our resident gut flora have another vital function not mentioned so far. They stimulate the production of immunoglobulins, proteins in the blood integral to the body's inner immune defences. Experiments show that animals with all their gut flora removed, make only about one-fiftieth as much immunoglobuline as normal animals. Commenting on this finding, the standard textbook 'Immunology' states: "If the commensal organisms of the gut are removed by antibiotics, pathogenic organisms can readily gain a foothold", and emphasises the importance of not disturbing the relationship between the host and its indigenous flora.
Does this mean that antibiotics are immunosuppressant drugs? This is an explosive question. Drugs generally classified as immunosuppressants are very dangerous. They are used only on people with cancer, and also after organ-transplants. They greatly increase the risk of serious bacterial and viral infection, and also of cancer, and are used only when patients are otherwise likely to die.
In ordinary circumstances, antibiotics are nothing like as dangerous as these drugs. As already stated, one course of antibiotics destroys the bacteria in the gut but not utterly, and a healthy balance of resident bacteria is usually restored soon after antibiotic therapy.
The only class of antibiotic that is commonly identified as immunosuppressive is tetracycline, because of its profound destruction of so many species of resident gut flora. And in a sense allergic reactions are reassuring because as mentioned, they show, that the body's inner immune defences are beeing irritated, and therefore obviously in working order. Basically healthy people are very unlikely to disrupt their inner immune defences by taking just one course of antibiotics.
Nevertheless, antibiotics do have a suppressive effect on our defences against infection. Given that our outer defences, including resident bacteria and the mucosal lining of the body's inner passages, are an integral part of our immune system, it follows inescapably that all antibiotics are by their nature immunosuppressants -mildly so, no doubt, compared with the drugs used on cancer and organtransplant patients, but immunosuppressive none the less.
How much this matters depends on the general state of the health of the individual, the type of antibiotic and the strength and length of the course. As ever, babies and little children, old people, hospital patients and anybody else who is generally weak or ill are at greatest risk, and this includes many, if not most people on the antibiotic treadmill, taking more and more courses for recurrent infections.
Most vulneralbe of all are people who are already immunosuppressed. But which came first; immunosuppression or antibiotics?
Here ist the view of Professor Sandy Raeburn, head of the departement of clinical genetics at Nottingham University, a specialist in disease of young children. In 1972 he wrote a paper for the Lancet, on "Antibiotics and Immunodeficiency":

"Immunological-deficiency syndromes were not observed before 1952. A possible explanation is that some of these conditions are produced by administration of antibiotics to certain individuals at a critical point in the development of immune responses."

Dr Raeburn gave examples of immunodeficiency diseases suffered mostly by babies and young children. Combined immunodeficiency (DIC) lays infants open to diarrhoea, thrush, pneumonia and other infections, and may increase the chance of cancer. Chronic granulomatous disease (CGD) also makes babies more vulnerable to bacterial infections.
"This diseases were not described before the antibiotic era" said Dr. Raeburn, "and the usual view is that modern therapy has enabled affected patients to survive longer. An alternative explanation, however, is that antibiotics have actually led to immunodeficiency states -diseases which did not previously exist".
He supports this proposal by three lines of argument. First, since one of the main purposes of the immune system (including the bacteria that have evolved with us) is to protect the body against invading micro-organisms, 'removal of bacteria by other means, such as rapidly effective antibacterial therapy, could have profound effects - for exaple, in infancy, during immunological development.' Later in life, antibiotics might provoke bacteria, even the friendly flora, into producing poisons that the immune system cannot handle. "The rarest clinical effects will emerge sooner or later because antibiotics are so widely used".

Second -and here Dr. Raeburn draws on his own clinical experience -while antibiotics work well for previous healthy people with an acute infection, they usually don't work for patients who are immunodeficient.

"Failures of antibiotic therapy are often excused by an assumption that host resistance was impaired. Could it be that infection persisted because the antibiotics interfered with host resistance in a susceptible patient? I have seen several patients whose infections progressed while they were receiving seeminly appropriate antibiotics.

Third, he cited the laboratory evidence showing that antibiotics make experimental animals more vulneralbe to infections by suppressing their immune responses -some very much mor than others. Those at greatest risk of

immunodeficiency diseases caused by antibiotics will include: those born vulnerable; babies and young children; people who are suffering from other diseases; and anybody taking regular heavy doses of antibiotics. He concluded: "If this theory is substantiated, it follows that antibiotics shoud be reserved for life-threatening infections, until the risk of immunotoxicity ist excluded in each patient".
I wrote to Dr. Raeburn asking him if, in the twenty years since he had published tha Lancet paper, he had changed his view. He wrote back saying: "Since I published that paper, there has been a vast amount of work on the interaction between antibiotics and the immune system. Much of it bears my own original hypothesis... When a patient receives antibiotic treatment, the beneficial effects due to antibacterial activity could be reduced or even negated by deleterious effects on the immune system". Overall, he said, antibiotics are beneficial, "but in my special area of medical genetics, we might well see patients in which the balance is set differently -for exaple in cystic fibrosis".
In 1984, a dozen years after Dr. Raeburn's Lancet paper., Dr William Hauser of the Bosten University Medical Center and Dr. Jack Remington of the Palo Alto Medical Foundation, both specialists in infectious disease, published a review of the scientific literature on the "Effect of Antimicrobial Agents on the Immune Response" in the textbook Antimicrobial Therapy. Antibiotics listed as having ill-effects on the human immune response include: some aminoglycosides (gentamicin, tobramycin); a cephalosoprin (cephalotin); chloramphenicol; a lincosamide (clindamycin), ;various sulphonamides, and co-trimoxazole; various tetracyclines; sodium fusidate; and a number of anti-fungal and ant-tubercular drugs. Penicillins are not included, and evidently do not have ill-effects on the body's inner immune defences.

Hauser and Remington comment:
There is clearly a need for a better understanding of the potentail beneficial and deleterious effects of antibiotic therapy on the host's immune defences, especially in the immunosuppressed patient.
Indeed there is. But when antibiotics suppress our immune defences against disease, as evidently they may do, then people given constant courses of antibiotics to drive out infection will be not so much on a drug treadmill as caught in vortes pulling them down deeper into disease.
Here is an appalling prospekt. A child suffers middle-ear inflammation, treated with antibiotics, which then recurs because of antibiotics. A woman suffers cystitis, which is cleared up with antibiotics, but which then recurs in a more invasive form because of antibiotics. These infections occured in the first place because of antibiotics taken in infancy and childhood. Then people of all ages and both sexes suffer a cascade of diseases of the gut, each stage accelerated by antibiotics, which eventually cause irreversible infections carried by bacteria and by viruses that easily break thrugh weakened immune defences. At some stage in this cascade, the victims become chronically immunosuppressed, vulneralbe to invasion by any infectious agend around..
The idea that medicine can cure illness immediately and yet cause illness later may seem strange. But in other areas of life we know that gain now can mean loss later -this, after all, is one of the tenets of the Christian religion. Or, to take two familiar analogies, we knwo we can drive to destinations faster by breaking the speed limit, and we know we can spend our way out of immediate trouble by running up and overdraft. We also know we are running the risk of wrecking our car or our finances. A friendly garage mechanic or bank manager will advise us to be careful.

A link with AIDS

When Professor Raeburn wrote his paper, chronic fatigue syndrome was obscure, and AIDS was unknown. When Drs Hauser and Remington wrote their review, neither disease was common. While AIDS kills and CFS does not, the two diseases are in some ways rather similar. Both are new, epidemic, afflict young people, have no known cure, take many clinical forms and cause profound debility. In the case of AIDS it is generally but not universally agreed that the infectious agent ist the HIV retrovirus. In the case of CFS there is a growing belief, that an enterovirus is involved.

As Professor James Mowbray has said of CFS, why has the immunity of people who suffer AIDS broken down?What is it that some people who are exposed to the disease remain untouched while other become infected with HIV? Why is it that some pople who test HIV positive remain in good health for many years, perhaps never suffering full blown AIDS, while others die rapidly?
Because AIDS is a new disease, is deadly and is an accelerating epidemic with in 1990 alone an estimated one million new cases of people worldwide infected with the HIV virus, other sexually transmitted diseases seem less important now. But at the end of 1990, the World Health Organisation announced that more than 250 million new cases of sexually transmitted diseases are reported every year. According to WHO Director-General Dr. Hiroshi Nakajima, "they have reached epidemic proportion globally, and if sexual behaviour is not modified and effectiv new prevention programmes are not implemented immediately the resulting disease and mortality rates will be even more staggering".
In 1990, 25 million new cases of gonorrhoea and 3,5 million new cases of syphilis were reported worldwide. Gonorrhoea is now often very resistant to penicillin, the original durg of choice, in which case, treatment is

either with massive doses of penicillin, or other antibiotics including aminoglycosides, sulphonamides or co-trimoxazole. Penicillin usually still works on symphilis; an alteernative drug is tetracycline. In the last half-century, other sexually transmitted diseases have become more common. These include genital ulcers, treated with sulphonamides or tetracyclines; chlamydia, with tetracyclines, chancroid, with co-trimoxazole, trichomoniasis, with metronidazole; and genital herpes, a viral disease.
More than any other community, people whose lifestyle involves very many sexual partners are almost certain to suffer combinations and permutations of sexuelly transmitted diseases, which when bacterial are treated with constant courses of antibiotics, often broad-spectrum and/or cocktails. Such treatment over time provokes superinfection and drug-resistant superbugs -so more antibiotics are used, often more toxic in their effect. On such a drug treadmill, people who have constantly quenched their sexually transmitted diseaes with antimicrobial drugs are more vulneralbe to any infection, whether bacterial, fungal or viral, and once infected, are more likely to be overwhelmed.

In his book "The Plague Maker, Dr. Jeffrey Fisher states that Dr. Luc Montagnier of the Pasteur Institute in Paris, co-discoverer of HIV, believes that gross overuse of antibitocs may be a co-factor with HIV development of full-blown AIDS. This theory, sensation only because AIDS is the great deadly plague of our time, is also believed by some homoeopaths. Can it be true?
It makes microbiological sense: there is some experimental evidence suggesting that tetracycline has a side-effect of mutating mycoplasmas, including M. pirium and M. fermetans, into virus-type micro-organisms that can invade T-lymphocyte cells, whose function is crucial to the body's inner immunity against infectious diseases. The Theory goes on to propose that if these cells are also already invaded by HIV, the mutated mycoplasmas effectively feed the HIV, activating them and enabling them to destroy T-lymphocyte function, thus laying the victim open to a great range of infections identified as full-blown AIDS.
On a separate point, Dr. Fisher quotes other research scientists who confirm the findings of Drs. Hauser and Remington, and who state that various antimicrobial drugs, including sulphonamides, cephalosporins, antifungals and antiparastics are directly immunosuppressive in different ways and, when overused, themselves increase vulnerability to infectious diseases.
If the mycoplasma theory is ture, it would follow that pople who test positive for presence of the HIV virus in their bodies, but whose lifestyles have not led them to gross overuse of antibiotics, will be less likely to develop full-blown AIDS. And indeed, haemophiliacs and others frequently show no signs of illness for ten or fifteen years after beeing accidentally treated or transfused with clotting factors or blood infected with HIV.
If the mycoplasma theory turns out not to be supported by evidence from other researchers, it remains true that destruction of gut flora and damge to the body's immunological defences by continual courses of antibiotics lays the body open to all sorts of bacterial, fungal and viral infections, including those most commonly associated with AIDS.
For men, the dream of sexual liberation began in the 1940ies. American Gis believed that because of penicillin they could go on the rampage with European and Asian women during World War II, and then during the Korean and Vietnam wars, without risk to themselves. The result is multi drug-resitant gonorrhoea. But antibiotics retained their reputation as magic bullets throughout the 1970s and 1980s, enabling incresingly wild liefestyles. In the USA and other rich countries, this is the context of AIDS. It can be said, that AIDS is a disease that was waiting to happen.

EPIDEMIOLOGY
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**Heterosexual transmission of human immunodeficiency virus (HIV) in northern California: results from a ten-year study.**

Padian NS, Shiboski SC, Glass SO, Vittinghoff E.

Department of Obstetrics, Gynecology and Reproductive Sciences, University of California, San Francisco, USA.

To examine rates of and risk factors for heterosexual transmission of human immunodeficiency virus (HIV), the authors conducted a prospective study of infected individuals and their heterosexual partners who have been recruited since 1985. Participants were recruited from health care providers, research studies, and health departments throughout Northern California, and they were interviewed and examined at various study clinic sites. A total of 82 infected women and their male partners and 360 infected men and their female partners were enrolled. Over 90% of the couples were monogamous for the year prior to entry into the study; < 3% had a current

sexually transmitted disease (STD). The median age of participants was 34 years, and the majority were white. Over 3,000 couple-months of data were available for the follow-up study. Overall, 68 (19%) of the 360 female partners of HIV-infected men (95% confidence interval (CI) 15.0-23.3%) and two (2.4%) of the 82 male partners of HIV-infected women (95% CI 0.3-8.5%) were infected. History of sexually transmitted diseases was most strongly associated with transmission. Male-to-female transmission was approximately eight-times more efficient than female-to-male transmission and male-to-female per contact infectivity was estimated to be 0.0009 (95% CI 0.0005-0.001). Over time, the authors observed increased condom use ($p < 0.001$) and no new infections. Infectivity for HIV through heterosexual transmission is low, and STDs may be the most important cofactor for transmission. Significant behavior change over time in serodiscordant couples was observed.

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**Redefining the growth of the heterosexual HIV/AIDS epidemic in Chicago.**

Murphy JT, Mueller GE, Whitman S.

Epidemiology Program, Chicago Department of Public Health, Illinois 60604, U.S.A.

A dramatic shift in the relative distribution of the five categories of heterosexual transmission for AIDS cases diagnosed in Chicago since 1991 prompted a mode-of-transmission validation study of what had become the most frequently reported heterosexual exposure: heterosexual relations with a person with AIDS (PWA) or documented HIV infection whose risk is not specified. METHODS: For 395 cases with originally reported heterosexual exposure, one or more of three supplemental data sources were employed: medical records were reviewed, medical providers were interviewed, and patients or proxies (i.e., spouse, significant other, or family member) were interviewed when possible. When reported HIV exposure could not be validated or reclassified, the transmission category employed was "no identifiable risk" (NIR). RESULTS: Eighty-five percent (336 of 395 cases) were reclassified into different transmission categories. Most notably, 69% (272 of 395 cases) were reclassified into transmission categories that did not involve heterosexual contact, including NIR. The cumulative percentage of cases attributable to heterosexual contact declined from 8% to 5% as a result of reclassification. Additionally, reclassification resulted in a reduction of nearly 50% in the number of AIDS cases attributable to heterosexual contact diagnosed in 1993 and 1994. CONCLUSIONS: In Chicago, an emerging problem in AIDS surveillance appears to be the use of an ambiguous heterosexual exposure category as a default when other information is not readily available. This study has found the growth in AIDS cases among persons exposed to HIV through heterosexual contact to be much slower than previously perceived. This finding may have important implications for the national debate over the extent to which heterosexual people are being infected and how funding and prevention strategies should be prioritized.

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HIV- ANTIBODY TESTS
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**Binding of glycoprotein 120 and peptides from the HIV-1 envelope by autoantibodies in mice with experimentally induced systemic lupus erythematosus and in patients with the disease.**

Bermas BL, Petri M, Berzofsky JA, Waisman A, Shearer GM, Mozes E.

Experimental Immunology Branch, National Cancer Institute, NIH, Bethesda, Maryland 20892.

Systemic lupus erythematosus (SLE) and infection with the human immunodeficiency virus type 1 (HIV) are diseases that are characterized by immune dysregulation and autoantibody production. In this article we identify and characterize IgG antibodies from mice with SLE and SLE patients that bind HIV gp120 and HIV envelope-derived peptides. SLE can be induced in susceptible mouse strains by immunization with a human monoclonal anti-DNA antibody that bears a common idiotype designated 16/6 Id. We tested sera from various strains of mice in which experimental SLE was induced by this method, as well as from 93 patients with SLE and 31 controls (17 healthy controls, 14 patients with other autoimmune diseases) for the presence of antibodies reactive to gp120 by an ELISA. Antibodies reactive with gp120 were produced by BALB/c, C3H.SW, AKR, and DBA/2 mice, all of which were 16/6 Id immunized and had experimental SLE. C57BL/6 mice, which are resistant to induction of SLE by this method, did not produce antibodies reactive with gp120 despite 16/6 immunization. Forty-three percent of SLE patients made antibodies that bound to gp120 at titers greater than 1:40, whereas 12% of healthy control sera ($p < or = 0.02$) and 14% of patients with other autoimmune diseases contained such antibodies ($p < or = 0.05$). We delineated the specificity of this antibody activity by testing for reactivity to six HIV envelope peptides. In both mice and SLE patients, sera reactive with gp120 recognized the same three envelope peptides. Removal of the anti-DNA antibodies from the sera by DNA-agarose affinity purification did not change anti-gp120 specificity.

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**Infection with human immunodeficiency virus type 1 (HIV-1) and human T cell lymphotropic viruses among leprosy patients and contacts: correlation between HIV-1 cross-reactivity and antibodies to lipoarabinomannan.**

Kashala O, Marlink R, Ilunga M, Diese M, Gormus B, Xu K, Mukeba P, Kasongo K, Essex M.

Department of Cancer Biology, Harvard School of Public Health, Boston, Massachusetts 02115.

To determine the association between leprosy and human retroviral infections, 57 leprosy patients, 39 leprosy contacts, and 500 pregnant women were investigated serologically for antibodies to human immunodeficiency virus type 1 (HIV) and human T cell lymphotropic virus (HTLV) types I and II. Antibodies to Mycobacterium leprae phenolic glycolipid I (PGL-I), and lipoarabinomannan (LAM) were also analyzed. A low prevalence of HIV-1 infection was observed among leprosy patients (3.5%), leprosy contacts (0), and pregnant women (3.6%). Antibodies to HTLV-I but not -II were found more often in leprosy patients (8.7%) and contacts (12.8%) than in pregnant women (0). Sera from leprosy patients and leprosy contacts were often false-positive for HIV-1 by ELISA and were indeterminate by Western blot. LAM IgM and PGL-I IgM antibodies in sera from leprosy patients yielded significant cross-reactivities with HIV-1 pol and gag proteins. These data suggest that mycobacterial cell wall antigens may share common epitopes with HIV. Caution should be exercised when interpreting HIV-1 ELISA and Western blot data from regions where leprosy or other mycobacterial diseases are endemic.

PMID: 7906291 [PubMed - indexed for MEDLINE]

**Studies with canine sera that contain antibodies which recognize human immunodeficiency virus structural proteins.**

Strandstrom HV, Higgins JR, Mossie K, Theilen GH.

College of Veterinary Medicine, Helsinki, Finland.

In a serological survey, using the immunoblotting technique, we found that substantial numbers of dog sera from both normal and diseased dogs, including dogs with neoplasia, reacted with one or more human immunodeficiency virus (HIV) recombinant proteins. A total of 144 dog sera were tested, and 72 (50%) of them reacted with one or more HIV recombinant structural proteins. Ten dog sera were also tested for reactivity with simian immunodeficiency virus (SIV), feline immunodeficiency virus (FIV), and caprine arthritis encephalitis virus (CAEV). Six dog sera reacted with at least the major core protein of HIV, while one of the dog sera tested reacted with SIV core protein, and there were no reactions with the viral proteins of either FIV or CAEV. Cell extracts from canine peripheral blood lymphocytes cocultivated with human cells and an extract of human cells infected with HIV were immunoblotted against dog sera which previously tested positive or negative on HIV recombinant protein commercially available Western blot strips. Two lymphocyte lysates and the HIV-infected Hut cell lysate reacted with the Western blot strip-positive dog serum; however, no reactions were seen with the Western blot strip-negative dog serum.

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**VIRAL LOAD**

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**T cell telomere length in HIV-1 infection: no evidence for increased CD4+ T cell turnover.**

Wolthers KC, Bea G, Wisman A, Otto SA, de Roda Husman AM, Schaft N, de Wolf F, Goudsmit J, Coutinho RA, van der Zee AG, Meyaard L, Miedema F.

Department of Clinical Viro-Immunology, Central Laboratory of the Netherlands Red Cross Blood Transfusion Service, Amsterdam, The Netherlands. clbkvi@xs4all.nl

Progression to acquired immunodeficiency syndrome (AIDS) has been related to exhaustion of the regenerative capacity of the immune system resulting from high T cell turnover. Analysis of telomeric terminal restriction fragment (TRF) length, a marker for cellular replicative history, showed that CD8(+) T cell TRF length decreased but CD4(+) T cell TRF length was stable during the course of human immunodeficiency virus type-1 (HIV-1) infection, which was not explained by differential telomerase activity. This observation provides evidence that turnover in the course of HIV-1 infection can be increased considerably in CD8(+) T cells, but not in CD4(+) T cells. These results are compatible with CD4(+) T cell decline in HIV-1 infection caused by interference with cell renewal.

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