Nutrients and Foods in AIDS

Edited by Ronald R. Watson

Boca Raton, FL: CRC Press, 1998,
ISBN 0-8493-8561-X

This book is intended to enlarge and expand (rather than update) the information presented in the editor's previous volume, *Nutrition and AIDS*, published in 1994. The four sections of the book are entitled Nutrition and AIDS (Chaps. 1–6), Absorption and AIDS (Chaps. 7–11), Animal Models for Nutrition and AIDS (Chaps. 12–14), and Fruits and HIV Progression (Chaps. 15 and 16).

NUTRITION AND AIDS

Chapter 1 (Trace Elements, Free Radicals and HIV Progression by Brigitte Douset, Francois Hussenet, and Francine Belleville of Central Hospital in Nancy, France) provides a general if unfocused review of evidence that infection with the human immunodeficiency virus (HIV) is associated with micronutrient deficiencies in humans and introduces the notion that changes in the serum concentrations of selenium may predict the progression of symptomatic AIDS at least as accurately as changes in circulating CD4+ T-lymphocyte numbers. However, in Chapter 2 (Selenium and AIDS), Joel Constans (Hôpital Saint-Andre in Bordeaux, France) discusses selenium physiology in humans and disagrees with the suggestion that serum selenium concentrations reflect AIDS status.

In perhaps what should have been the lead chapter, by F. Muller, P. Aukrust, and S. S. Froland of the University of Oslo and A. M. Svardal, R. K. Berge, and P. M. Ueland of the University of Bergen, a superb review is given of the generation of reactive oxygen species (ROS), oxidative stress, and antioxidant biochemistry in HIV-infected human CD4+ T lymphocytes (Chap. 3: The Thiols Glutathione, Cysteine, and Homocysteine in Human Immunodeficiency Virus [HIV] Infection). The authors present detailed experimental evidence supporting the hypothesis that HIV infection affects human T lymphocytes by reducing their capacity to regenerate reduced glutathione (GSH) from oxidized glutathione (GSSG). In brief, Muller et al. propose that the initial infection with HIV acutely triggers increased bursts of tumor necrosis factor-α (TNF-α) production and secretion throughout the immune system, with two streams of consequences within host T-lymphocytes: 1) the generation of ROS is stimulated; and 2) the regeneration of nicotinamide adenine dinucleotide phosphate is inhibited, in turn inhibiting the activity of glutathione reductase and reducing the ability of T lymphocytes to regenerate GSH from GSSG. The resulting increased intracellular ratio of GSSG to GSH reduces the ability of the cell to metabolize ROS, and the increased generation of ROS and decreased redox capacity combine to increase cytoplasmic ROS concentrations, especially of the hydroxyl radical. High intracellular concentrations of hydroxyl radicals contribute to the activation of the cytoplasmic regulatory protein, NFκB, which ultimately results in both accelerated replication of the HIV virus within infected cells and, via suppression of interleukin-2 secretion, attenuated replication of T lymphocytes. In addition, the elevated cytoplasmic GSSG:GSH ratio interferes with the activation of tyrosine phosphatase in response to proliferative stimuli, resulting in reduced dephosphorylation of inhibitory sites on src kinase, increased cytoplasmic concentrations of activated src kinase, accelerated src kinase phosphorylation of phospholipase C-γ, reduced transmembrane calcium influx to the cytoplasm, and reduced proliferative response of T lymphocytes. Furthermore, high cytoplasmic concentration of hydroxyl radicals reduces the mitochondrial transmembrane potential, effectively partly depolarizing the mitochondrial membrane and ultimately triggering mechanisms of apoptosis of the host T lymphocyte. Supporting this scheme are observations that in vitro restoration of intracellular GSH activity in HIV-infected CD4+ T lymphocytes has restored replicative responses to proliferative stimuli.

Muller et al. also summarize research indicating that immunomodulating agents in combination with antiviral drugs may preserve CD4+ T-lymphocyte functions and numbers in HIV-infected individuals. In particular, several promising lines of in vitro evidence are emphasized.

- *N*-acetyl-L cysteine has been reported to inhibit both TNF-α-induced activation of NFκB and HIV replication within infected T lymphocytes.
- Cystamine and cysteamine have been reported to inhibit both proviral DNA formation and virus assembly in infected T lymphocytes.
- Selenium supplementation has been reported to increase glutathione peroxidase activity in HIV-infected T lymphocytes.
- Ascorbic acid has been reported to inhibit HIV replication (via reduction of free hydroxyl radicals and inhibition of the activation of NFκB) in HIV-infected T lymphocytes.

Unfortunately, these potential therapies have not been studied carefully in HIV-infected humans.

In Chapter 4, Mariana K. Baum and Gail Shor-Posner of the University of Miami School of Medicine address the often overlooked Nutritional Aspects of Neuropsychological Function in HIV/AIDS. They discuss possible relations between the cognitive dysfunctions common to AIDS (such as diffuse and regional encephalopathies, myelopathy, meningitis, intraaxial cranial neuropathies, and retinopathy) and the B-vitamin deficiencies commonly found among persons with AIDS. In particular, they emphasize that: 1) supplementation with vitamin B_{12} may resolve symptoms of HIV-associated dementia complex when serum vitamin B_{12} concentrations are below the normal range before supplementation; and 2) pyridoxine supplementation may improve mood in HIV-infected persons with below-normal serum pyridoxine concentrations (possibly through renormalization of serotonin production).

The controversy over appropriate dietary fat intakes in AIDS is joined in Chapter 5 (Lauric Oils as Antimicrobial Agents: Theory of Effect, Scientific Rationale, and Dietary Application as Adjunct Nutritional Support for HIV-Infected Individuals) by Mary Enig of Enig Associates. Enig argues that the caloric needs of the HIV-infected individual can be met only by diets supplying sufficient amounts of fatty acids and with a ratio of ω-6 to ω-3 fatty acids of between 4:1 and 10:1. In particular, lauric-acid-containing fats should be emphasized to realize the antimicrobial activity of monolaurin, the monoglyceride of lauric acid. Monolaurin has been shown to disrupt the lipid membranes of a number of infectious pathogens, resulting in their inactivation, including HIV, measles virus, herpes simplex virus, vesicular stomatitis virus, visna virus, cytomegalovirus, influenza virus, pneumonovirus, syncytial virus, rubeola virus, *Listeria monocytogenes*, *Staphylococcus aureus*, and *Streptococcus agalactiae* and other strepto-

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cocci, among others. This effect appears to require daily monolauric acid intakes of 20–30 g in adults and can be met with dietary use of coconut and palm kernel oils.

The results of available Experimental Studies with Antioxidants are summarized in Chapter 6 by Raxit J. Jariwalla of the California Institute for Medical Research. Studies with biological antioxidants (glutathione, cysteine, *N*-acetyl-L cysteine, superoxide dismutase, catalase, glutathione peroxidase, vitamin C, pyridoxine, riboflavin, vitamin E, β-carotene, quercitin, hesperitin, catechin, coenzyme Q_{10} [ubiquinol 10]) and synthetic antioxidants (dithiocarbamates, thiocytic acid, lipoic acid, nordihydroquaretic acid, butylated hydroxyanisole, and butylated hydroxytoluene) have shown different degrees of promise in blocking NFκB transcription factor activation, HIV replication, and cellular apoptosis in HIV-infected human T lymphocytes. Because these agents are not likely to share the same targets of action, they may eventually provide the basis for broad-spectrum antiviral therapies.

ABSORPTION AND AIDS

The loss of appetite and weight loss commonly associated with AIDS are documented in a very brief Chapter 7 (Appetite and Energy Intake in Human Immunodeficiency Virus [HIV] Infection and AIDS) by Carolyn D. Summerbell of the Royal Free Hospital School of Medicine in London. According to Summerbell, the causes of HIV-associated cachexia remain mysterious.

Impaired intestinal function likely to contribute to weight loss, malnutrition, deterioration of the immune system, and mortality in HIV-infected persons is explored by Michael Ott and Bernhard Lembcke of the J. W. Goethe University, Frankfurt, in Chapter 8 (Assessing the Role of Intestinal Absorption, Permeability, and Nutrition in AIDS Patients). They describe and discuss the pathogenesis of both "pathogen-positive" intestinal dysfunction (correlated with demonstrable infection with *Cryptosporidium parvum*, various species of *Microsporidia*, *Isospora belli*, *Giardia lamblia*, *Mycobacterium avium-intracellulare*, *Clostridium difficile*, *Salmonella typhimurium*, *Campylobacter jejuni*, cytomegalovirus, astrovirus, picobirnavirus, calciviruses, or adenoviruses) and "pathogen-negative" intestinal dysfunction associated with HIV infection. The importance of a clinical evaluation for intestinal malabsorption in the presence of HIV infection and diarrhea, steatorrhea, weight loss, or signs of specific nutritional deficiencies is emphasized. The evaluation should begin with analysis of stool samples for the presence of identifiable pathogenic organisms. Instead of fecal-fat analysis or carbon-dioxide breath tests, Ott and Lembcke advocate measurement of serum β-carotene concentrations as surrogate markers for assessing the efficiency of fat absorption in AIDS. Small intestinal absorptive capacity should be assessed using the 25-g D-xylose test. If the results of this test are abnormal, an upper gastrointestinal endoscopic examination should be performed. Previous recent use of antibiotics reduces the value of lactose tolerance or H_2 breath testing in this setting. Intestinal motility should be assessed using enteroclysma of the small bowel, which can provide information about intestinal transit time, mucosal edema, and, if present, ulcerations, intestinal Kaposi's sarcoma, lymphoma, and fistula.

Lawrence A. Cone of the Harbor-UCLA Medical Center describes the epidemiology, pathogenesis, clinical presentation, and malabsorption characteristic of infection with *Mycobacterium avium-intracellulare* in patients with AIDS (Chap. 9: Malabsorption of Nutrients and Drugs in Patients With AIDS and Mycobacteriosis and Their Obviation by Parenteral Therapy). Cone emphasizes that intestinal infection by this organism is the third most common opportunistic disease in HIV-infected persons and that dual infection is characterized by wasting from malabsorption. Because oral medications also are absorbed poorly by affected individuals, Cone has developed a treatment regimen of combined parenteral amikacin, rifampin, ciprofloxin, and complete nutrient mixtures.

Another pair of causative agents associated with intestinal malabsorption in HIV-infected persons, *Enterocytozoon bieneusi* and *Septata intestinalis*, are described by Cone in Chapter 10 (Malabsorption and Microsporidia). Found in up to 30% of patients with symptomatic AIDS, these organisms trigger enterocyte death, eventually resulting in villous atrophy, diarrhea, and wasting. Drug therapy targeted toward these protozoans is described.

Experience with a private food-assistance program is shared in Chapter 11 by Dorothy C. Humm and Bruce C. Oliver (The Role of Home Delivered Meals and Community-Based Medical Nutrition Therapy in HIV Care). This program delivers formally structured HIV-oriented meals to the homes of HIV-infected persons who are under home care. Although somewhat successful, the program has encountered difficulties in the areas of scheduling deliveries, patient acceptance, and food safety.

ANIMAL MODELS FOR NUTRITION AND AIDS

The book's editor, Ronald Watson, has taken advantage of his role as editor to include a brief chapter (T-Cell Receptor Peptide and Immune Modulation) that, although bearing no relation to nutrition, suggests a possible therapeutic role for TCR Vβ CDR1 peptides in AIDS. Preliminary data indicate that these peptides may selectively inhibit retrovirus-induced proliferation of HIV-infected T lymphocytes. Initial evidence for the production of autoantibodies to HIV-infected T lymphocytes in response to exposure to this family of infection-induced peptides is discussed.

The predominant role of oxidative stress in the transition from asymptomatic to symptomatic AIDS is emphasized by Zhen Zhang, Paula Inserra, and Ronald R. Watson of the University of Arizona and by Bailin Liang of the Yale University School of Medicine in Chapter 13 (Antioxidants and AIDS). They focus on the cascade of events that lead from HIV infection to oxidation of cellular membranes, alteration of metabolic pathways, disruption of electron transport systems, depletion of intracellular ATP reserves, loss of intracellular calcium homeostasis, activation of endonucleases, fragmentation of chromatin, and apoptosis of CD4+ T lymphocytes. As additional supportive evidence, they cite the hypothesis of the authors of Chapter 3 (HIV infection $\rightarrow$ TNF-α secretion $\rightarrow$ generation of ROS $\rightarrow$ activation of NFκB $\rightarrow$ activation of the promoter region of the viral long terminal repeat $\rightarrow$ replication of HIV $\rightarrow$ TNF-α secretion $\rightarrow$ generation of ROS, etc.). Most of the data on antioxidants presented in this chapter repeats those presented in earlier chapters. However, some additional data are provided concerning the potential therapeutic value of diethyldithiocarbamate, desferrioxamine, quercitin (as an inhibitor of protein-kinase-C-induced phosphorylation of the IκB enzyme that activates NFκB), benzopyrones, spermine, putrescine, and cadaverine.

The specific roles of vitamin E in anti-AIDS regimens are explored by James Y. Wang of the University of Minnesota Medical School and Bailin Liang in Chapter 14 (Vitamin E Supplementation Retards the Development of Acquired Immune Deficiency Syndrome). They conclude that vitamin E is an immunomodulating and antioxidant agent that acts via immunoenhancement, modulation of signal transduction, improvement of undernutrition, and free radical scavenging. Daily intakes of up to 2000 IU are recommended to maximize CD4+ T-lymphocyte populations, total lymphocyte numbers, activity of cytotoxic cells and natural killer cells, phagocytosis of macrophages, responsiveness of lymphocytes to mitogens, and leukocyte bactericidal activity and inhibit the rate of HIV replication. HIV-infected individuals receiving therapeutic daily doses of vitamin E may obtain four benefits: 1) enhancement of immune defenses against opportunistic infections; 2) reduction of required drug dosages, thereby decreasing risks of toxicity, and production of drug-resistant

strains of HIV; 3) enhancement of the effectiveness of chemotherapy and reduction of the severity of chemotherapy-induced immune suppression; and 4) extending the period between infection with HIV and the appearance of clinical symptoms of AIDS.

FRUITS AND HIV PROGRESSION

The final two chapters (both by Jeongmin Lee and Ronald Watson of the University of Arizona) present a charming approach to the consideration of the therapeutic potential of pomegranates (Pomegranates: A Role in Health Promotion and AIDS) and cranberries (Cranberry: A Role in Health Promotion). It appears that alkaloids and tannic compounds extracted from pomegranate root cortex can inhibit the growth of *E. histolyca* and *E. invadens*; extract of pomegranate rind has been reported to inhibit the growth of powdery mildew fungus; and mixtures of these extracts have suppressed the in vitro infectivity of poliovirus, herpes simplex virus, and HIV. Although there are no reports of antiviral cranberry activity, cranberry and other members of the genus *Vaccinium* (such as bilberry, lowbush blueberry, and lingonberry) contain antioxidant and antibacterial flavonoids.

Overall, the book has accomplished the goal of expanding on the information provided by its predecessor. However, actual dosages or recommended intakes usually are missing, thus severely diminishing the value of the material (and requiring tedious research of the literature by the interested clinician). This lack is most unfortunate and reduces the impact of the book on the medical AIDS community.

From his preface, the editor shows a bias in favor of nutritional methods as potentially therapeutic if not curative: "Nutritional support could help maintain health in the HIV+ patient by repleting lost nutrients, compensating for nutritional damage done by the retrovirus-induced immunodeficiency, and stimulating the remaining immune system and cells for better host defenses. . . . The goal of this book is to define recent advances in understanding the nutritional deficiencies of AIDS and HIV+ patients and to explore the scientific knowledge of how nutritional and dietary changes and herbal medicines benefit or harm them. . . . The overall goal is to provide the most current, concise scientific appraisal of the status of nutrients, foods, and herbal (alternative) medicines in preventing or treating AIDS and its symptoms for improved quality of life." Despite this goal, there is almost no information on herbal medicine in AIDS, and the drug-oriented treatment philosophy of the editor is reflected in the mainstream medical-school-faculty composition of the contributors. Nonetheless, the book and its 1011 references can serve as a starting point for interested scholars and curious students.

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PII S0899-9007(99)00260-9