

European AIDS Treatment

NEWS

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STATEMENT OF PURPOSE

The **European AIDS Treatment News** is a bimonthly publication issued by the **European AIDS Treatment Group e.V. (EATG)**. The EATG is a group of activists from thirteen different European countries and a growing number of associates who participate in treatment activism, community-based research and treatment training programmes.

EATN reflects this by giving information on:

- * **basic medical knowledge**
- * **research results and issues**
- * **treatment news**
- * **treatment activism in Europe**

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IMPRESSUM

European AIDS Treatment News

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Editorial

We all know about the perfect tastes of the French Nouvelle Cuisine and appreciate the stimulation to our salivatory glands when opening a recipe book. Asking ARCAT-Sida, Paris, to have their perspectives on nutrition published in EATN was therefore an undertaking that risked loss of the visual and gustatory pleasures of preparing food.

Several more practical and stimulating recipe books were published by different AIDS-service organisations.

Please refer to EATG members or your local AIDS-service organisation for more information about preparing the most appetizing food and invigorating immune function.



Special

HIV & Nutrition

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HIV & Nutrition

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Mobilization	p. 2
Advice & support	p. 3
Life expectancy	p. 5
Pediatric	p. 5
Gustatory	p. 6
Drugs in wasting	p. 7
Nutritional status	p. 8
Trace Elements and vistamins	p. 10
Supplementation	p. 12

Mobilization

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HIV infection is a slowly progressive disease comprising an asymptomatic phase often spanning several years followed by clinical events that include the criteria for AIDS and

terminating in severe deterioration and death. Recent studies show that underlying this apparently erratic course is a permanent process of viral replication, infection of new cells, destruction of these infected cells by the immune system and cell renewal, in the body's attempt to maintain a balance in the face of the infection. This improved understanding of the pathophysiology of HIV infection, despite the many gaps that remain, has sharpened our appreciation of therapeutic intervention and its limitations. The ideal treatment should be initiated at the time of diagnosis ; even if it fails to destroy the virus, it should at least provide an effective and sustained blockade of viral replication and cell destruction. No such ideal treatment exists, the overall aim of current management being to delay the course of infection, prevent opportunistic complications and minimize the effects of those occur.

Despite the focussed yet authentic efficacy of some individual treatments, the overall status of intervention is palliative, in that it cannot reverse or even block, to any sustained extent, the march of the infection. This is the context in which we need to view the issue of nutrition ; we should neither delude ourselves that it is the panacea for the problems that remain unsolved nor dismissively consider it as an accessory which can do no harm but of course can do no good.

The main merit of the Cannes conference is to have given nutrition the status which it deserves in the management of HIV infection. By bringing together the leading groups in the field, together with a vast number of the dieticians who are working with HIV patients on a daily basis, it will have testified to the mobilization that already exists and laid the foundations for improved cooperation between partners in care. It is, however, a pity that there should be relatively few of the general physicians, whether family or hospital doctors, who manage HIV patients and need to be aware of the nutritional problems involved. Part of the reason is probably the lack of a consensus on key questions which could help inform therapeutic intervention : what kind of nutritional work-up is appropriate for a seropositive patient, and what are its indications in the overall management ? What results can be anticipated from long-term

nutritional support ? What are the indications for vitamin and trace element supplementation, what form should it take and how should it be given ? When and how should high-protein and high-calorie nutritional supplements be used ? When and how should enteral and parenteral nutrition be given and withdrawn ? Studies are beginning to provide answers to some of these questions, though as yet they vary in methodological status and the robustness of their results. Our efforts in this field have not only to be continued but amplified, and we must hope that the Cannes conference leads to the drafting of guidelines on these various issues so that appropriate intervention can be routinely initiated in combination with the other standard treatments now being prescribed.

Nutritional advice and support

Nathalie Chahine
Arcat-Sida, Le Journal du Sida

Nutritional management of HIV patients should be initiated early and tailored to the needs of the individual patient. It is essential to suggest rather than impose the nutritional adjustments required, and to support the patient as these are put into effect.

Reduced food intake and increased energy expenditure at rest - the main initial factors in weight loss - are early events in the natural history of HIV infection (1). Physicians, nutritionists and dieticians thus have an early advisory role to play with their patients. The modalities of nutritional management discussed in the various presentations can be broadly summarized under four headings : analysis of food intake, patient information on HIV-associated malnutrition, nutritional advice, and supervision of compliance with this advice comprising the surveillance of body weight, food tolerance and nutritional status.

In practice, a strategy should be adopted as soon as a patient loses > 5 % of their normal body weight or reports loss of appetite for > 5 days. In the assessment of malnutrition, Dr

Claude Pichard, from the University Cantonal Hospital in Geneva, argued that body weight is not an adequate marker of incipient malnutrition (2). Other techniques, such as impedance analysis and muscle strength measurement, can be used to heighten diagnostic accuracy.

The prophylaxis of malnutrition has to contend with the multiplicity of factors involved. It should always be tailored not only to the individual patient's state of health and degree of weight loss, but also to his social circumstances and nutritional practices and beliefs. "Even if the causes of malnutrition are complex, it is often possible to modify eating behavior simply by giving dietary advice, achieving weight gain (5 % in the majority of patients", reported Dr Achim Schwenk (3), who heads the Nutrition and HIV Infection Study Group at the Cologne University medical clinic. "Nutritional advice involves an emotional message, encouraging what we term 'internal control'. The idea is to convince patients that they can influence the course of the nutritional process".

Nutritional management specialists are unanimous about the need to increase calorie and protein intake from the start of HIV infection, giving preference to high-fat milk products, fried rather than steamed foods, and adding egg yolk or chopped ham to purées and soups etc. Such advice sometimes runs counter to the nutritional convictions of patients committed to a particular diet. Specialists must learn how to accommodate such beliefs, at the same time as warning patients of the danger of the wholesale elimination of a particular food from their diet. "By proposing acceptable alternatives, such as emphasizing the value of fish and uncooked vegetable oils for those on macrobiotic diets, we can make patients aware, once they begin to regain weight, of the benefits of changing their diet and and to initiate it for themselves", reported Hazel Ross, dietician at the Chelsea and Westminster Hospital, London (4). The recommendations

EATN special

should be suggested and adapted, rather than imposed in their entirety. If they are too foreign to patients' nutritional habits, compliance will be partial or non-existent.

At any event, a normally constituted diet should be encouraged from the outset. Dr Claude Pichard emphasized that supplements are of little value outside a context of normal nutrition. In the absence of a supplementation consensus, Dr Isabelle Poizot-Martin, from the Paoli-Calmettes Institute in Marseille, only recommended their use after taking a dietary history (5). "As protein requirements are often covered - distaste for meat is rare - the use of high-protein substitutes is not always justified. On the other hand", said Dr Poizot-Martin, "high-calorie supplements may be useful for enriching a meal, e.g. in the form of cream puddings".

Solutions to the problems caused by the patient's state of health can be found on a case-by-case basis. "Anorexia, nausea and vomiting can often be overcome by fractionating meals into attractively presented small portions", explained Gisela Kremer, dietician at the University of Cologne medical clinic (6). "Snacking and liquid supplements should be encouraged, while strongly scented foods should be avoided together with high-fiber or high-fat dishes that rapidly induce satiety. Antiemetics taken half an hour before eating are useful for preventing nausea. Gustatory complaints require tackling on an individual basis, often by eliminating spices. Patients with dysphagia need practical advice about preparing liquid meals. They should also avoid anything which increases abdominal pain, such as strong spices, bitter or fizzy drinks, and very cold or very hot foods".

As for diarrhea, this is rarely caused or compounded by what patients eat (authentic lactose intolerance, which is rare, can be avoided by using fermented milk). If milk has to be avoided in such cases, patients should be advised, often in contrast to their normal practice, to increase their food intake to maintain their water and electrolyte balance.

Practical problems can also weigh heavily in malnutrition. Many patients do not know how to cook, "forget" to eat, have no idea about what constitutes a balanced diet and may live on just one or two foods only. The solutions are in principle fairly simple, provided they are initiated early enough. At the Chelsea and Westminster Hospital, London, nutritional information evening courses have been instituted. An Australian group presented a poster recommending cookery classes as a way of encouraging the participants to take meals together (7). This novel experiment was prompted by the observation that during their own illness or after the death of a partner HIV patients often have difficulty in preparing meals and / or eating on their own. It is a useful reminder that the treatment of malnutrition is not simply a matter of dispensing dietary and lifestyle advice, but that appetite also comes with preparing meals, chatting and in the eating process itself.

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Impact of malnutrition on life expectancy

Nathalie Chahine
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Degree and rate of weight loss are the determining prognostic indicators in seropositivity.

Malnutrition has a determining impact on the course of HIV infection. "There is a relationship between the degree of cell depletion, weight loss and life expectancy. Malnutrition is an important predictive factor of mortality, independently of the CD4 lymphocyte count", stated Dr Kotler from the St Lukes - Roosevelt Hospital Center, New York, when presenting his 1989 study (1). Other investigators in the United States - Chlebowsky et al and Guenter et al - had confirmed these data at the time.

In Cannes, more recent supplementary data were presented. Retrospective analysis of 22 patients dying in a specialist Canadian clinic indicated that the prime determinant of survival was the rate of weight loss ; the CD4 lymphocyte count was not a determining factor (2). Other Canadian work highlighted the impact of weight loss associated with *Pneumocystis carinii* pneumonia (PCP) on survival : a retrospective study based on the casenotes of 100 patients from 1983 to 1993 showed that weight loss > 7.5 kg before and, above all, during an episode of PCP was associated with significant reduction in survival at the end of 1 year (3). The importance of food intake in maintaining body weight is becoming increasingly clear, including in the presence of diarrhea : a prospective study in 115 patients with chronic diarrhea showed a correlation between degree of wasting, reduction in dietary intake, with particular regard to lipid and protein, and certain diarrhea characteristics (4). On the other hand, it is not yet known whether nutritional intervention has a significant impact on survival. Even though the clinical experience of major centers involved in the management of seropositive patients suggest that this is indeed the case, Dr Kotler emphasized that studies are required in populations maintained on different diets to reach a consensus on preventive and therapeutic strategy.

EATN special

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Pediatric HIV infection: Preempt the break in the growth curve

Nathalie Chahine, Arcat-Sida, Le Journal du Sida

Two studies on the effect of HIV-induced malnutrition on the growth curve. A specific feature of HIV-induced malnutrition in children is its rapid impact on the growth curve, with somatic repercussions that are more severe than in adults. Dr Olivier Goulet from the Necker Hospital for Sick Children, in Paris, presented a study in 89 children (seronegative : n = 37 ; seropositive : n = 52) of seropositive mothers, all of whom had been followed from birth (1). The two groups did not differ in weight / height ratio at birth. At 18 months, however, the HIV-infected children were 1 - 2 standard deviations (SD) below the normal height and weight ; they also exhibited growth retardation in fat and

muscle mass, unlike the seronegative children. The growth rate of 88.5 % of the HIV-infected children was (10 % slower than the normal value for their age group. Similar results were reported in a Canadian study (2) in which 18 / 31 HIV-infected children followed from 1988 to 1994 showed growth retardation, with particular respect to body weight, associated in all cases with the diagnosis of AIDS. The main risk factors in the 3 months preceding the break in the growth curve were superinfection, encephalopathy and death of the mother. All these factors were associated with a significant decrease in food intake.

Therapeutic response should be initiated as early as possible, stressed Dr Goulet, to preempt the break in the growth curve. At the first evidence of weight loss, a trial of oral supplementation should be instituted. If the child is uncooperative and body height below normal, nocturnal enteral nutrition - feasible from the age of 8 - 9 months - gives good results and can be continued over several years. Parenteral nutrition becomes mandatory when weight loss exceeds 20 % of the original body weight or in the presence of severe gastrointestinal complications.

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Gustatory disorders

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Sweet and salt perception thresholds are raised in seropositive subjects. Gustatory disorders are common in HIV-infected subjects. Despite their recognized relationship with anorexia in cancer patients, they had not previously been addressed in the context of HIV infection. A study of their nature and frequency was presented at Cannes (1). It showed that sweet and salt perception thresholds are significantly higher in seropositive vs seronegative subjects. Furthermore, gustatory disturbances increase as the disease progresses. These findings may help to guide some aspects of nutritional advice and to design nutritional supplements more suited to the special needs of patients with HIV infection. The study population comprised 82 seropositive patients (AIDS : n = 38 ; asymptomatic HIV : n = 44), and a control group from the hospital staff (n = 47).

The perception thresholds for four tastes - sweet, salt, sour, bitter - were measured by placing on the tongue one drop of a solution containing increasing concentrations of sucrose, salt, urea and hydrochloric acid, respectively. The mean salt perception threshold was 36 mM / l in the controls vs 70 mM / l in asymptomatic HIV patients and 86 mM / l in AIDS patients. The corresponding sweet values were 38, 44 and 65 mM / l, respectively. Bitter perception was only mildly affected in HIV infected subjects, and sour perception was virtually identical in all groups. The investigators concluded that gustatory disorders are clearly correlated with weight loss, but that they are not significantly related either to ongoing treatment or the presence of oral candidiasis.

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Drug therapy of wasting syndrome : the breakthrough is yet to come

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Despite an increasing research focus on the drug therapy of anorexia and cachexia, there has been no breakthrough to date. In recent years various agents have been used to combat weight loss, anorexia and cachexia. They include anabolic steroids, glucocorticoids, progestagens, cyproheptadine, growth hormone, acetylcysteine and cannabis derivatives. Studies with three of these agents - testosterone, medroxyprogesterone and growth hormone - were presented at the Cannes conference.

Fraser et al from the U.K. reported their study of testosterone replacement therapy (1) prompted by the observation that hypogonadism is common in HIV infection (affecting approximately one half of seropositive men) and that its occurrence is correlated to weight loss. Seven patients with weight loss > 10 %, hypogonadism and CD4 counts in most cases < 38 / mm³ received intramuscular testosterone for 8 weeks. The initial dose - 1 ml - was subsequently adjusted to maintain normal circulating levels. At 8 weeks, there was a mean increase in body weight of 4 kg, comprising a 4.8 kg increase in lean mass and a - 0.8 kg decrease in fat mass. There were no direct side effects. There was one death and one patient developed AIDS. The CD4 count was unchanged and a quality of life questionnaire showed no improvement at 3 months. In summary, testosterone has benefits in terms of body weight and body composition.

The second study (2) was a placebo-controlled Italian trial of the progestagen appetite stimulant, medroxyprogesterone acetate, which has long been used in breast cancer therapy. The population comprised 151 patients with weight loss > 10 % receiving medroxyprogesterone acetate 1 g daily or placebo orally for 12 weeks. Mean end-of-study weight gain was 6 kg in the active treatment group vs 3.6 kg on placebo. However, the increase in weight was predominantly in fat mass, i.e. despite increased appetite during the treatment period, the effect was limited. More conclusive data are expected from an ongoing phase III study at Edouard Herriot Hospital in

Lyon, France, comparing two doses of medroxyprogesterone acetate (400 and 800 mg daily) vs placebo.

The third study was with recombinant human growth hormone (rHGH) (3). GH stimulates protein synthesis, and hence in principle promotes an increase in lean mass. Having been borne out in a phase I study in 7 patients, this hypothesis was tested in 178 cachectic patients who received a subcutaneous injection of rHGH 0.1 mg / kg or placebo daily for 12 weeks. End-of-study body weight was increased in the active treatment group (+ 1.6 kg, $p < 0.03$ vs placebo), comprising a mean increase in lean mass of + 3 kg vs - 0.1 kg on placebo ($p < 0.001$) and a mean decrease of - 1.7 kg in fat mass ($p < 0.001$ vs placebo). Clinical outcome and side effects were similar in both groups. All GH-related side effects reversed after treatment withdrawal. rHGH had no effect on viral replication measured by branched DNA. On the basis of these results, a study is being set up in France involving the rHGH manufacturer and the National Agency for AIDS Research [Agence Nationale de Recherche sur le Sida (ANRS)].

In summary, there is as yet no definitive evidence of benefit from any of these compounds justifying their use in routine practice. Further clinical evaluation is therefore required.

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Evaluation of nutritional status

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Arcat-Sida

The body weight curve, anthropometry and bioelectrical impedance analysis are the three key tools in determining nutritional status ; their use is all the more important in that metabolism is impaired from the onset of infection.

Nutritional status is not routinely determined in seropositive patients despite the fact that we can now time metabolic and somatic changes to the onset of HIV infection. All relevant studies to date have yielded the same conclusions : seropositivity is associated with increases in energy expenditure and, especially, in protein catabolism, resulting in a deficit in lean vs fat mass, from the onset of infection onwards, before any change in body weight. Boulier and Melchior, from Bichat-Claude Bernard Hospital, Paris, suggest that there is also a relative increase in the extracellular fluid compartment (1).

The absence of clearly defined standards of nutritional status have prompted a search in the arsenal of available techniques (anthropometry, biochemistry, immunology etc) for cheap, reliable and convenient indicators. Monitoring of body weight remains essential : weight loss > 10 % associated with fever and diarrhea constitutes the wasting syndrome which is one of the criteria of AIDS. Body weight is also a good predictor of life expectancy : Lindan has shown that a Quetelet index (W / H^2) ($21 \text{ kg} / \text{m}^2$) is associated with greater mortality. However, body weight is only a gross indicator of body changes. It is therefore essential to integrate the rate of weight loss into the interpretation of body weight deficit. The more rapid the weight loss, the more adverse its significance.

Durnin's four skinfold measures (biceps, triceps, subscapular and suprailiac) give an estimate of fat mass corrected for gender and age (see box),

and the method is recommended by the Bichat Hospital group. However, loss of cell mass may be masked by increase in the extracellular compartment (1).

Several studies report the use of bioelectrical impedance in measuring extra- and intracellular water, over and above the determination of lean and fat mass. This gives a more accurate measure of the active cell mass, which directly reflects

Anthropometry

The skinfolds provide a measure of fat mass, given that the sites chosen are representative of the mean thickness of subcutaneous adipose tissue and that there is a correlation between the latter and perivisceral fat mass. Skinfold thickness is measured by a trained operator using a Harpenden caliper which maintains a constant pressure ($10 \text{ g} / \text{m}^2$) irrespective of the distance between its arms. The four standard skinfolds are the biceps, triceps, subscapular and suprailiac. The biceps skinfold is measured halfway between the elbow and shoulder on the anterior upper arm. The triceps skinfold is measured on the posterior surface of the upper arm. The subscapular skinfold is located inferolaterally to the tip of the shoulder blade. The suprailiac skinfold is halfway between the iliac crest and the last iliac rib. There is no consensus as to which side(s) the measurements should be taken (right, left or both). In practice the skin is taken between thumb and forefinger to the full thickness of the subcutaneous tissue ; the caliper is placed on the fold, the finger pressure released and the reading taken (to 0.1 mm). Durnin's nomogram is used to convert the sum of the four skinfold measurements to percentage body fat corrected for gender and age. Skinfold measurement has two limitations : it does not recognize acute changes (the skinfold is a slow indicator), and it cannot be used in the presence of edema.

Bioelectrical impedance analysis

This method, described by Thomasset, is based on the differences in the conductance of biological media depending on current frequencies : water and electrolytes enhance the passage of current, adipose tissue hinders the passage of current. Depending on frequency, impedance (the alternating current equivalent of direct current resistance) varies with body compartments. Thus high- and low-frequency impedance provide measures of total and extracellular body water volume, respectively. In practice, the technique involves the use of either tetrapolar surface electrodes on the hands and feet (Hoffer) or two subcutaneous needles (Thomasset). A 1 - 10 kHz alternating current is used for low frequencies and a 1 MHz current for high frequencies. A nomogram is used to convert the data in function of gender, age, body weight and height into the following parameters : total water, fat mass, lean mass and its three constituents (intra- and extracellular water and active cell mass). The method is only moderately uncomfortable for the patient when needles are used. Being relatively non painful, it is readily reproducible.

nutritional status (see box). However, according to a study from the Hôtel Dieu in Paris, lean mass may be slightly overestimated using impedance analysis (2). The method has several advantages, nonetheless : it is simple in practice, noninvasive and cheap.

The Bichat-Claude Bernard and Hôtel Dieu groups found no significant difference in results between anthropometry (skinfold) and impedance analysis ; the correlation was good with respect to lean mass, and rather less good with respect to fat mass, due to the degree of extracellular hydration which influences the anthropometric results. Paton et al, from King's

College Hospital, London, indicated that other methods were still more accurate, including deuterium dilution (measurement of total water) and dual energy X-ray absorptiometry (DEXA) scanning (3). Allard, from Canada, reported the use of a further parameter, assessment of neuronally stimulated muscle function (hand clenching), in which the relaxation phase is increased in malnourished patients (4). The advantage of this method is its simplicity, since it can be carried out at the bedside, even in an unconscious patient. Given that abnormal results are reversible, it can also be used to monitor the efficacy of nutritional intervention.

For routine purposes, body weight, skinfold measurement and impedance analysis are an effective array for clinicians in reaching a reasonably accurate assessment of their patients' nutritional status. Serial investigation can be used both to evaluate the efficacy of nutritional intervention, whether preventive or curative, and as a potential foundation for the standardization of future interventional strategy.

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Effects of trace elements and vitamins on immunity

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There is increasing understanding of the fundamental contribution of individual trace elements and vitamins to immune system function. There are also extensive data on the effects of oxidative stress.

Many studies have demonstrated the crucial contribution of vitamins and trace elements to the maintenance of normal immune function via their involvement in many metabolic pathways and basic cell functions. Isolated deficits of these compounds are extremely rare as they are usually associated with other nutritional deficiencies. However, whether reproduced in animals or in some cases described in humans, they have helped to document the fundamental contribution of trace elements to immune function.

Iron and susceptibility to infection

The growth of a wide variety of Gram-negative and -positive organisms is enhanced by the addition of iron *in vitro*. The human body has multiple protective mechanisms designed to deprive bacteria of iron. Fever, the inflammatory response and endotoxins are all associated with a rapid decrease in serum iron due in part to the release of lactoferrin from granulocytes and to a decrease in transferrin saturation. This mechanism is mediated by interleukin (IL)-1.

Iron supplementation of deficient patients has been associated with an increase in the number of infections and deaths. It does not therefore appear desirable to increase the iron content in the diet of patients with acute infection or immunosuppression. Such a stance is borne out by the high incidence of septic complications in hemochromatosis (high rates of *Yersinia*

infection) and hemolytic anemia (high rates of systemic *Salmonella* poisoning). Similarly, parenteral iron supplementation in 2 month old infants in New Guinea was associated with an increase in *Plasmodium falciparum* parasitemia vs controls, though not with increased morbidity or mortality. However, clinically, the facts appear to indicate the reverse : neither iron deficiency nor its correction has any effect on the severity of infection.

Relationship between zinc and immunity

Barrier immunity

Breaks in skin integrity, degenerative lesions of enterocytes and microvilli, and impaired pulmonary function have all been described in zinc-deficient animals.

Humoral immunity

IL-1 stimulates both pre-B lymphocytes and cloning of the mature B lymphocytes responsible for antibody synthesis. At the same time, IL-1 shifts the distribution of zinc : it decreases serum levels while increasing levels in liver, bone marrow and thymus. Production of IL-1 and IL-2 and their membrane receptors is also zinc-dependent, as is that of interferon.

Cell-mediated immunity

Zinc deficiency induces involution of lymphoid tissue (thymus and spleen) and a decrease in the synthesis of the thymic hormone responsible for T cell maturation. The T lymphocyte response to mitogen stimulation is reduced in zinc deficiency. Impaired macrophage function and decreased neutrophil chemotaxis have also been demonstrated.

Zinc deficiency and immunity in humans

In humans, zinc deficiency has been associated with an increased frequency of infection in various situations. Infectious complications are common in acrodermatitis enteropathica, a genetic disorder of zinc metabolism. In children, protein-calorie malnutrition associated with zinc deficiency is responsible for abnormalities of cell-mediated immunity, all of which respond to

zinc supplementation. A relationship between zinc deficiency and immune dysfunction has been found in a variety of conditions including HIV infection, renal failure, alcoholic liver disease and cancer. It has also recently been suggested that zinc may play an important role in the activation and inactivation of immunoregulatory genes.

Selenium

Effects on B lymphocytes

As early as 1972, several investigators provided experimental evidence for an effect of selenium, either alone or in synergy with vitamin E, on the synthesis of specific IgG and IgM following vaccination with various antigens (sheep erythrocytes, leptospirchetes, tetanus toxin, hepatitis virus). The site of action, at particular doses, was splenic B cell differentiation.

Effects on T cells

Selenium augments the T lymphocyte response to mitogens [concanavalin A and phytohemagglutinin (PHA)]. Patients receiving total parenteral nutrition without selenium exhibit abnormal T lymphocyte function.

Effects on the functions of phagocytes (macrophages and neutrophils)

Selenium deficiency decreases the levels of cellular glutathione peroxidase (GSHpx), the enzyme free radical scavenger system (see below); macrophage function is impaired as a result. Polymorphonuclear neutrophil phagocyte function remains intact, but bactericidal activity is depressed. Reduced phagocytosis has been observed against *Staphylococcus aureus* in subjects with moderate deficiency, due to the following mechanism: during phagocytosis, non-mitochondrial respiration increases, resulting in the production of large quantities of the superoxide anion O₂⁻ and hydrogen peroxide (H₂O₂), which are potentially toxic to the cell. Protection against oxygen radicals is ensured by vitamin E, thiol radicals, superoxide dismutase (SOD), which reduces oxygen species production, and catalase and selenium-GSHpx which accelerate their metabolism.

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Baker and Cohen have shown that the phagocytic cells of selenium-deficient animals are less protected against free radicals than those of non-deficient animals and that this causes rapid loss of their phagocytic properties. Decreased phagocytosis has also been demonstrated in diabetics who are more susceptible to infection.

The contribution of selenium and GSHpx to immune function consists primarily in the control of excess peroxide production in immunocompetent cells and in other tissues. Selenium and GSHpx are found in a variety of cells.

Effects in infection

Surprisingly few studies have addressed this problem. However, all have shown a decreased resistance to infection in animals. Evidence of the effect on superoxide release has been provided by Deneke et al who demonstrated increased mortality in selenium-deficient rats exposed to 100 % oxygen.

Effect on arachidonic acid metabolism

Selenium or its enzymes have indirect local effects on the circulation via modulation of the synthesis of thromboxane, prostaglandins and platelet activating factor and inhibition of lipooxygenase pathways (decreased leukotriene production).

Copper

Copper deficiency is associated with an impaired immune response. Decreases in reticulo-endothelial system function and macrophage bactericidal activity have been described in animals, based on the involvement of copper in two enzyme systems, SOD and cytochrome C oxidase. Antibody synthesis is also reduced in the presence of antigen.

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Thiamine (vitamin B6)

Vitamin B6 deficiency is associated with decreases in the following : lymphocyte stimulation by mitogens, post-vaccination antibody synthesis, thymus volume, thymulin activity, and T lymphocyte cytotoxicity.

Folic acid

In animals, folic acid deficiency induces high mortality in the presence of experimental infection. The T cell response to mitogens is reduced. In humans, neutrophil dysfunction has been described by Youinou et al : folic acid supplementation restores phagocytosis but not bactericidal activity.

Ascorbic acid (vitamin C)

Vitamin C is required for neutrophil and monocyte chemotaxis. In vitamin C-deficient animals, there are decreases in antibody synthesis, lymphocyte response to mitogens, and macrophage phagocytosis. Ascorbic acid is also an antioxidant.

Retinol (vitamin A)

Much the same applies to vitamin A as to iron. Vitamin A deficiency induces lymphoid tissue involution. In rats on a low vitamin A diet, thymus and spleen volumes are reduced. The lymphocyte response to PHA is lower than in non-deficient animals. Vitamin A also stimulates NK cell activity.

Tocopherol (vitamin E)

Vitamin E deficiency decreases both antibody synthesis in the presence of antigen and the T cell response to mitogens. Its action is often indistinguishable from that of selenium.

Oxidative stress

Oxidative reactions form part of the body's natural defences against aggression and can be triggered by radiation, chemicals (chemotherapy) and infectious agents (viruses, bacteria, yeasts). Oxygen derived radicals (superoxide anion, hydrogen peroxide, hydroxyl radical) help to destroy the cell membranes of infectious agents. Under certain conditions, the amount of such products exceeds requirements for infection control, with the result that free radicals pursue their main function elsewhere, causing irreversible cell membrane destruction in a variety of healthy organs.

The body has buffer systems designed to regulate radical activity, largely made up of enzyme systems that are heavily dependent on vitamins and trace elements : intracellular glutathione and plasma or cellular GSHpx, which are selenium-dependent ; SOD, which is copper-, zinc- and manganese-dependent ; and catalase, which is iron-dependent. Alongside these enzyme systems, there are non-enzymatic compounds which are vitamin A- or E-dependent. Thus excessive oxidative reactions may occur under conditions of excess free radical production and impaired physiological defence, due to trace element and / or vitamin deficiency, whether from a reduction in intake, an increase in elimination or an imbalance between intake and elimination.

Management of trace element and vitamin supplementation

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Though trace element and vitamin deficiencies are common in HIV infection, they are usually part of a cumulative deficit, making it difficult to determine specific individual impacts on the course of the infection. Documented deficits should be corrected, but excessive supplementation may prove deleterious.

In advanced HIV infection, malnutrition is a compounding morbidity and mortality factor. However, in early disease, despite the absence of weight loss, changes are already present, both in body compartments (loss of lean fat and increase in extracellular water) and metabolism, together with trace element and vitamins deficiencies despite a generally normal nutritional intake. The relationships between malnutrition and immune deficiency have been known for many years (1). Trace element and vitamin deficiencies are of prime importance as they account in part for the increased prevalence of infectious complications (2).

What deficiencies are observed ?

Isolated trace element and vitamin deficiencies are extremely rare in HIV infection. In the great majority of cases, they are combined with other deficits which may be either the cause or the result of the deficiency. Thus deficiencies of antioxidants (selenium and vitamins A, E and C) can induce specific immunological changes and lower natural killer activity (3). A steady decrease in the zinc pool occurs in the course of HIV infection and induces a parallel decrease in the serum levels of the active fraction of the thymic hormone that plays a fundamental role in cell-mediated immunity (T lymphocyte development and maturation) (4). Mononuclear cell proliferation is increased in zinc-deficient HIV-positive subjects (3) and zinc has a demonstrated impact on CD4 proliferation and immune function.

Folate and vitamin B12 deficiencies are common ; they may be consecutive to decreased intake, malabsorption, ongoing infection, gastrointestinal cancer or therapy (5, 6, 7). Antigastric intrinsic factor antibodies were found in 9 % of patients in one study (5), in which there was also an increase in gastrin, a hormone which lowers vitamin B12 absorption. Vitamin B6 deficiency is frequent in early disease. A relationship between immunity and the vitamin B6 pool has long been recognized in non HIV-infected populations (8). Baum et al reported a relationship in seropositive subjects between the vitamin B6 pool and various immune parameters, e.g. the lymphocyte proliferative response to mitogen (9). Copper (10), iron (11) and selenium are decreased in HIV infection and may have an impact on immunity.

Relationship between individual deficiencies and course of infection

The relationships between trace element and vitamin deficiencies and the course of HIV infection have not yet been elucidated. In advanced disease, in the presence of obvious malnutrition, a number of clinical and laboratory features have been identified as due to micronutrient deficiencies and have been corrected by appropriate supplementation. Thus we conducted a study in patients with CDC class III disease [ex AIDS-related complex (ARC)] with no obvious sign of malnutrition (no weight loss) and no opportunistic infection. However, their intra-erythrocyte zinc pool was significantly lower than in a seronegative control group. Both groups received supplementation with zinc gluconate 135 mg daily for 2 weeks followed by 45 mg daily for 1 week. Immunological testing was performed before, during and at the end of treatment (CD4 and CD8 counts, lymphocyte transformation in the presence of mitogen, polynuclear neutrophil function). At the end of the study, there were no changes in the CD4 and CD8 counts ; however, lymphocyte responses were significantly enhanced in the seropositive group. Neutrophil chemotaxis also improved (though the groups did not differ significantly in this respect), indicating enhanced neutrophil function. Lymphocyte function was decreased in seronegative subjects. This finding is evidence of the immunological risks associated with supplementation in non-deficient healthy subjects and confirms the results of an early study by Chandra in healthy volunteers receiving a diet containing 10-fold the recommended dietary allowance (RDA) (1).

In a 1987 study, our group evaluated selenium therapy for cardiomyopathy in Intensive Care Unit patients with advanced AIDS. Nonobstructive cardiomyopathy is frequent in AIDS (though also observed in other non AIDS deficiency states) and is due to an imbalance between oxidants and selenium-based antioxidant systems. Supplementation reversed

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the cardiovascular abnormality in 7 / 10 AIDS patients (one non responder had combined vitamin B1 deficiency, the two others were non selenium-deficient).

How useful is systematic supplementation ?

Due to the descriptions of deficiencies widely circulated in the literature, many HIV-positive patients - and a number of their physicians - believed that early high-dose supplementation could have a positive effect on the course of the illness. Indeed, there is substantial evidence for a beneficial effect on some biological imbalances, particularly in terms of immunomodulation and restoration of a normal oxidant / antioxidant ratio. The increase in free radical production which has been described in AIDS may facilitate the appearance of viral or opportunistic infections. Oxidative stress is associated with HIV infection : peroxides stimulate viral antigen expression, alter the regulation of the genes controlling tumor promotion and have an immunosuppressant effect (T cell inactivation). In AIDS, antioxidants (mainly and indirectly of micronutrient origin) are decreased (13). However, no study to date has provided conclusive proof of the utility of systematic supplementation, despite much apparent *in vitro* evidence in its favor. In early infection, self-medication with megadoses of micronutrients does not necessarily have a systematically beneficial effect, as suggested in the study by Tang et al (14). Vitamin A at doses 2-4-fold the RDA, high-dose vitamin B3 (> 61 mg daily), vitamin C at 12-fold the RDA are associated with delay in the course of HIV infection. On the other hand, a zinc intake 1.3-fold the RDA accelerates progression to AIDS.

Other studies are required to confirm or invalidate these conclusions. However, they are difficult to conduct due to the vogue among HIV-positive patients for systematic supplementation, often to gross excess. A 1991 study from Houston in seropositive subjects

found trace element and vitamin supplementation rates greatly in excess of RDAs : 15-fold, in the case of vitamin C, 23-fold in the case of vitamin E, 3-fold in the case of iron. On the other hand, dietary selenium intake was only one third of the RDA, while the zinc intake only approximated to the RDA. In summary, such supplementation levels have no scientific justification : on the one hand, they do not always reverse preexisting deficiency (zinc, selenium), while on the other hand, the effects may be the reverse of those anticipated. Thus in the long run it is not impossible that excessive supplementation could trigger some cancers (vitamin C), neurological disturbances (selenium) and further immunological impairment (zinc).

In practice rule n° 1 is to correct documented deficiencies. Rule n° 2 is not to exceed a reasonable level of supplementation.

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