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Nutrition and ageing

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Abstract

The reviewed literature indicates that, even in industrialised countries, the nutrition of mature and aged subjects is often inadequate (because of deficiency or excess), which may lead to premature or pathological senescence.

Recent nutritional research on ageing laboratory animals shows that dietary restriction may be the most effective procedure to achieve a long and disease-free life span, probably owing to a better protection against mitochondria-linked oxygen stress. Likewise, the experimental and clinical work from many laboratories, including our own, indicates that age-dependent changes in the cardiovascular and immune systems are linked to oxygen stress and that an adequate intake of dietary antioxidants may protect those systems against chronic degenerative syndromes in the physiopathology of which reactive oxygen species (ROS) play a key role.

The extant data indicate that the antioxidant vitamins C and E are centrally involved in defending the above two systems against ROS attack. Moreover, recent research suggests that the glutathione-related thiolic antioxidants, thiazolidine carboxylic acid (thioproline) and *N*-acetylcysteine, as well as the phenolic liposoluble 'co-antioxidants' of *Curcuma longa*, may have a significant protective effect against age-related atherogenesis and immune dysfunction.

Key messages from this paper are the following. (1) It is generally accepted that oxygen free radicals released in metabolic reactions play a key role in the physiopathology of 'normal ageing' and of many age-related degenerative diseases. (2) Consumption of adequate levels of antioxidants in the diet is essential in order to preserve health in old age. (3) A certain degree of protection against atherogenesis and immune dysfunction may be achieved by preventing vitamin E deficiency and an excessive oxidation of the glutathione-supported thiol pool.

Keywords
Ageing
Senescence
Free radicals
Oxygen stress
Antioxidants
Vitamin E
Glutathione
Immunosenescence
Atherogenesis

It is generally agreed that the intimate relationships between ageing and nutrition do not receive the attention they deserve from both nutrition experts and gerontologists. Moreover, it is felt that although many parameters have been proposed to detect malnutrition in the aged, only a few provide meaningful measurements. As noted by Rosenthal *et al.*[1], malnutrition is a common medical problem in elderly subjects that is associated with increased morbidity and mortality. The diagnosis of malnutrition is usually achieved through anthropometric measurements (body mass index, skinfold measurements), dietary assessment (calorie counts) and laboratory data. Serum albumin is the most commonly used laboratory parameter; total lymphocyte count and cholesterol are also often used. Other less frequently used determinations are prealbumin, transferrin, haemoglobin/haematocrit, retinol-binding protein, insulin-like growth factor I and nitrogen balance. According to Rosenthal *et al.*[1], serum albumin levels can predict the need for institutionalisation whereas body mass index (BMI) cannot, although both are indicators of nutritional status. This leads these authors to postulate that inflammation influences serum albumin level in some patients and therefore the abnormal findings of the nutritional tests reflect an inflammatory process rather than malnutrition.

As pointed out by Roebothan and Kuman[2], some controversy still exists over what is 'normal' for the aged. In their opinion, although normal standards for young adults are used to interpret tests performed on elderly subjects, it is becoming obvious that the aged community is a unique group that should be dealt with as such. These authors further comment that the nutritional problems of the aged generally arise from reduced intake and impaired absorption and metabolism of nutrients, but that an increased requirement of the body for certain nutrients is also involved. They conclude that, in view of the great heterogeneity of the elderly, future nutritional geriatric research should concentrate on specific aspects of the overall problem and on 'how targeted interventions might reduce illness and improve the quality of life for the elderly'.

In agreement with the above, we shall focus on some

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issues related to the main research interest of our laboratory. These are the role of reactive oxygen species (ROS; *oxygen stress*) and antioxidants on the normal ageing of laboratory animals and human subjects[3,4] and on senescence-related degenerative diseases[5,6], with emphasis on the effects of antioxidants on atherogenesis and immune dysfunction.

Rationale for an adequate antioxidant intake by mature and elderly individuals

Role of oxygen free radicals in ageing, according to Harman and Gerschman

These two authors, working independently in the University of California in Berkeley, published a series of articles implying oxygen free radicals in the pathogenesis of ageing. In 1956 Harman[5] suggested that free radicals could cause not only ageing but also other degenerative processes such as cancer, arteriosclerosis and immunodeficiency. More recently Harman[7] pointed out that these syndromes are the result of the deleterious reactions of free radicals that take place continuously in the cells and tissues. He also noted that these reactions were selected to play a role in metabolism and ensure evolution by causing mutations and death. This opinion is similar to that of Gerschman[8], derived from her studies on the *oxygen effect*, i.e. from the fact that the injurious effects of ionising radiation increase in the presence of oxygen while its lack has a protective action on the irradiated cells. There was no reasonable explanation for this fact until Gerschman published a general theory of *oxygen poisoning*, according to which the damage caused by this gas is linked to an increase in the intracellular concentration of free radicals, as happens in irradiated cells. This led her to extrapolate that oxygen toxicity also causes ageing, owing to the fact that the antioxidant defences of the organism do not exactly match the oxidative attack.

The oxygen stress–mitochondrial injury theory of ageing

Our research on the insect *Drosophila melanogaster* showed that experimentally induced change in its oxygen consumption determines its life span, that is inversely proportional to the rate of mitochondrial respiration and therefore to the rate of formation of injurious oxygen radicals per gram of *Drosophila* tissue *in vivo*[3]. This observation, and our finding that a progressive loss of mitochondria (with concomitant accumulation of age pigment from mitochondrial debris) is the *common denominator* of cell ageing[3], provided the basis for an oxygen stress theory[3,4] that views senescence as a *side effect* of the high levels of mitochondrial respiration in the differentiated cells and lack of the regenerating power of frequent mitoses in this cell type. This would lead to oxidative damage to the membranes and genome of the mitochondria with concomitant loss of mitochondrial function and bioenergetic and physiological decline. This theoretical concept is supported by a rapidly increasing amount of data on age-related mitochondrial changes and on the anti-ageing effects of mitochondria-protecting caloric restriction[9] and diet supplementation with antioxidants[10–12].

Glutathione deficiency in the ageing tissues

As previously reviewed[13,14], ageing is accompanied by a decrease in antioxidant competence and, more specifically, by a progressive oxidation of glutathione (GSH) and other thiolic compounds in many tissues of old animals, including the liver, kidney, blood and brain. In our opinion this justifies the attempts to decrease the rate of ageing by dietary administration of thiolic antioxidants that have been shown to prevent an excessive oxidation of the sulphur pool[13]. This has resulted in moderate life extension and protection against age-related biochemical and functional changes in insects and mammals[10–14]. As regards the prospects for clinical application of thiolic antioxidants, it is very interesting that low levels of GSH are found in various chronic diseases[15]. Therefore, according to Chen *et al.*[14], 'there is considerable merit in therapeutic intervention strategies to correct the GSH deficiencies in such situations'. Since GSH does not enter cells easily, its administration is not a suitable procedure to increase tissue thiol levels[16]. On the other hand, precursors of GSH or cysteine, such as GSH esters or thiazolidine-4-carboxylic acids, enter cells more readily and thus are quite effective in raising tissue thiolic antioxidant levels[17]. As will be discussed below, these precursor compounds are very effective in counteracting age-related changes in immune function. Further, a related thiolic antioxidant, namely *N*-acetylcysteine, has shown a protective effect against the age-related decline of oxidative phosphorylation in the liver mitochondria of laboratory mice[11]. On the other hand, recent data from our laboratory – summarised below – suggest that the thiol-protecting vitamin E and related liposoluble antioxidants may exert a significant anti-atherogenic action.

Antioxidants and atherogenesis

As reviewed by Meydani[18], several studies have shown an inverse relation between the consumption of (antioxidant-rich) fruit and vegetables and risk of morbidity and mortality from cardiovascular diseases. In Meydani's words: 'The totality of evidence from several epidemiological studies and clinical trials indicates that intake of vitamins E and C above the recommended dietary allowances may reduce the risk of cardiovascular disease'. According to Meydani, this may be due to the lowering effects of these vitamins against free radical formation, low-density lipoproteins (LDL) oxidation, platelet aggregation, and excessive synthesis of pro-inflammatory

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cytokines. In addition, dietary antioxidants may also decrease the activation of immune and endothelial cells of the vessel walls that triggers the production of cytokines such as IL-8 and monocyte chemoatracttant protein (MCP)-1, thus contributing to the atherogenesis-related inflammatory process in the arterial wall.

Recent data suggest that blood lipid peroxidation, which increases with age[19], plays a fundamental role in the formation of atheroma. This supports the above views on the anti-atherogenic role of the antioxidant vitamins as well as of liposoluble phenolic compounds that, owing to their 'co-antioxidant' action, have a vitamin-E-sparing effect. Accordingly, we have shown that the 'co-antioxidants' present in a hydro-alcoholic extract of the plant *Curcuma longa* protect against an excessive lipid peroxidation in the blood of ageing volunteers[20].

Antioxidants and the immune system

As reviewed by Mazari and Lesourd[21], recent research has led to the concept of age-associated immune dysregulation that is more compatible with current and emerging data than previous concepts of a system-wide decrease in immune response. According to these authors, this new concept of immunosenescence is in agreement with numerous data, including the fact that IL-2 decreases whereas IL-6 increases with age in both mice and humans, which suggests senescent changes in the TH1/TH2 ratio rather than a general age-related decrease in interleukin production.

As noted above, a deficient nutritional state may be superimposed on the age-related 'intrinsic' dysregulation in order to cause immune decline. Therefore an adequate supply of micronutrients, including antioxidants, seems essential for an optimal immune response and concomitant health preservation in later years. In this regard it is very important that ageing results in an increased accumulation of H_2O_2 in neutrophils of healthy aged volunteers[22]. These results provide evidence of an age-related impairment in the antioxidant defence mechanisms in immune cells and justify present attempts to gain more information on the key role that dietary antioxidants play in immune function preservation.

In agreement with the above, Meydani[18] concludes that dietary antioxidants increase several immunological parameters, including neutrophil mobility, delayed-type hypersensitivity response, and stimulated lymphocyte proliferation. Conversely, an insufficient level of vitamin E causes immune cell membrane alteration and increases the production of immuno-suppressors, such as prostaglandins. According to Meydani, since improvement of immune response both with short- and long-term dietary vitamin supplementation has been shown in aged humans, 'there is compelling evidence that intervention with dietary antioxidants such as vitamin E enhances immune response in the elderly and may reduce infection, thus improving the quality of life'.

The effects of antioxidants on the immune system have been also reviewed by De la Fuente[23], who states: 'The greater production of ROS and the age related oxidative stress occur at a time in life when malnutrition often occurs and there is a decrease in antioxidant defence. Therefore, it seems evident that antioxidant supplementation might have a favourable effect, neutralising oxygen stress and normalising the lost antioxidant/oxidant balance'. In agreement with this view, De la Fuente's research has shown a favourable effect of vitamin and thiolic antioxidants on immune cells, both *in vitro* and *in vivo*, including an enhancement of leukocyte functions in normally aged mice supplemented with thiazolidine carboxylic acid (thioproline)[12], as well as of macrophage functions in a model of premature mouse ageing[24]. Further, De la Fuente *et al.*[25] showed that the immune function of elderly women is improved by ingestion of supplements of vitamins C and E, which has important clinical implications.

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