

Nutritional factors and immunological ageing

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Undernutrition profoundly affects immune responses, particularly at the extremities of life: in infants and in the elderly. The present review focuses on this interrelationship in the elderly. It describes three different stages of ageing: stage 1, healthy ageing, which is observed in very healthy elderly individuals who have no nutritional deficit; stage 2, common ageing, which is observed in most elderly individuals in whom various micronutrient deficits are found; stage 3, pathological ageing, which is observed in patients with protein–energy deficiency. Stage 1, primary immune ageing, is essentially characterized by changes in T-cell subsets but no change in T-cell function; T-cell function is reduced only in the very elderly (>90 years old). Stage 2, secondary immune ageing, is influenced by micronutrient deficits that may be corrected by providing nutritional supplements. Furthermore, immune responses may also be enhanced by supplementation of subjects who have no micronutrient deficits, indicating that the immune system of elderly individuals is highly susceptible to the influence of micronutrients. In stage 3, tertiary immune ageing, the immune responses are strongly related to the decreased nutritional status. In these patients decreased immune responses lead to long-lasting acute-phase responses, which induce greater use of nutritional reserves during disease and lead to increased frailty. As nutritional status has a marked effect on immune responses in elderly individuals, nutritional therapy should be given to elderly individuals who have nutrient deficits, and perhaps also to individuals who do not have nutrient deficits in order to promote healthy ageing and extend the lifespan.

Immune ageing: Nutritional ageing: Nutrition–immunity interactions

Ageing has been shown to induce decreases in the immune responses, mainly in cell-mediated immune (CMI) responses (Albright & Albright, 1984; Miller, 1992), and also changes in humoral immunity, with lower levels of specific antibodies (Arreaza *et al.* 1993). However, more recent studies that have quantified immune responses in well-selected healthy elderly individuals have indicated that the decreased CMI responses are less important than was previously suggested (Mazari & Lesourd, 1998; Ahluwalia *et al.* 2001). Indeed, very healthy elderly individuals aged 70–80 years who have been very carefully selected using defined protocols for healthiness (Lighthart *et al.* 1984; Lesourd & Mazari, 1999) have levels of lymphocyte proliferation and IL-2 release that are comparable with those of young controls aged 20–30 years (Lesourd & Mazari, 1999; Lesourd *et al.* 2002) and no changes in CD3+ cells (Pawelec *et al.* 1997). CMI responses appear to be lowered only in very elderly healthy individuals

(age \geq 90 years; Lesourd *et al.* 2002). These findings suggest that factors other than immune ageing have a major influence on the immune responses of elderly individuals and that different factors influence the ageing of the immune system.

Environmental factors, through antigen enhancement, permanently activate the immune system. There is consequently a state of permanent renewal within the immune system, with the daily production of millions of immune cells. Immune cell renewal is increased during all metabolic processes, not only during infections, but also during diseases such as cardiac diseases. As ageing is characterized by the presence of disease processes, it seems obvious that such processes, even at low levels that are not always clinically manifest, may influence immune ageing. In order to be efficient, permanent cell renewal needs appropriate nutrition. As a consequence all nutritional deficits can affect immune responses. Indeed, it has been shown that

Table 1. Functions of peripheral blood lymphocytes, stimulated *in vitro* with purified phytohaemagglutinin (PHA_p), in healthy young individuals and in healthy and frail young elderly and old elderly individuals‡
(Values are means and standard deviations)

	Young adults (25–34 years; n 54)		Young elderly (65–85 years; n 44)		Old elderly (>90 years; n 25)		Frail young elderly (70–85 years; n 50)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age (years)	28·7	3·1	79·8***	5·1	94·3***	3·4	79·6***	6·2
Albumin (g/l)	43·5	2·8	42·4	3·9	41·4	3·8	37·1***†	3·6
C-reactive protein (mg/l)	<6		<6		<6		13·4***†	
Lymphocyte proliferation with PHA _p (1 µg/10 ⁶ cells):								
[³ H]thymidine (cpm/10 ³ cells)	144	47	121	36	78·0**	31	71***††	35
Percentage CD25+ cells at 72 h	65·3	6·8	58·9	7·4	45·0***†	9·1	41·2††	11·4
<i>In vitro</i> cytokine release after 22–24 h								
IL-2 (ng/ml)	2·09	0·33	1·83	0·39	1·29***†	0·49	1·16***†	0·42
IL-6 (ng/ml)	1·38	0·15	1·74*	0·23	1·92***	0·35	1·41	0·41

cpm, counts per min.

Mean values were significantly different from those of the healthy young adults: * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

Mean values were significantly different from those of the healthy young elderly: † $P < 0.05$, †† $P < 0.01$.

‡Healthy young adults and elderly of different ages and health status were selected according to the criteria for the SENIEUR protocol of Ligthart *et al.* (1984) with the additional criteria of Lesourd & Mazari (1999).

the immune system is particularly sensitive to undernutrition (Chandra, 1994; Lesourd, 1995, 1997; Bell & High, 1997). Undernutrition is a common situation in elderly populations, not only major undernutrition such as protein–energy malnutrition (PEM; Lesourd *et al.* 1996; Bell & High, 1997), but also micronutrient deficits (Tucker, 1995; Lesourd *et al.* 1998), which are far more common than PEM, even in apparently healthy elderly individuals.

The aim of the present review is to describe the influence of nutrition on immune responses in elderly individuals. Three different aspects of immune ageing will be described. The first is ‘primary immune ageing’, which can be observed in healthy elderly individuals carefully selected for having no nutritional deficit. This type of immune ageing corresponds to the now well-recognized ‘successful ageing’. The second is the influence of micronutrient deficit on the immune responses of apparently healthy elderly individuals, termed ‘secondary immune ageing’. This type of immune ageing is common in elderly populations and can therefore be termed ‘common ageing’. The third is the immune responses that are observed in PEM in the elderly, i.e. ‘tertiary immune ageing’, which becomes increasingly common with advancing age and is certainly of great importance in elderly populations. This type of immune ageing is observed in diseased individuals and may therefore be termed ‘pathological ageing’.

The present review attempts to provide a comprehensive overview of nutritional factors that influence immune ageing. Possible action to counteract common and pathological immune ageing will be suggested, as well as guidelines on measures to slow down immune ageing and extend the lifespan.

Primary immune ageing: successful ageing

In 1984 the EU Concerted Action Programme on Ageing (EURAGE) defined, for the first time, specific criteria for

participants in studies of immune ageing. The SENIEUR protocol (Ligthart *et al.* 1984) was defined to better characterize criteria of healthiness. In 1988 a nutritional criterion was added, such that only subjects who did not have PEM (serum albumin >35 g/l) would be eligible. As micronutrient deficits may influence the immune responses of elderly subjects, new criteria relating to micronutrient levels were subsequently added (Lesourd & Mazari, 1999). Currently, elderly subjects who fulfil the SENIEUR criteria should have a serum albumin level of ≥ 39 g/l and no deficit in Zn, Se, folic acid and vitamins C, E, B₆ and B₁₂ (all micronutrient known to influence immune responses) and, in addition, no major acute-phase response (serum C-reactive protein level of <30 mg/l).

When CMI responses were quantified in elderly (80 years old) individuals who met all the protocol criteria it was shown for the first time that lymphocyte proliferation and IL-2 release are comparable with those of young (20–30 years old) adults (Lesourd & Meaume, 1994). This finding has been confirmed in subsequent studies (Mazari & Lesourd, 1998; Lesourd & Mazari, 1999; Ahluwalia *et al.* 2001). Age-related changes in CMI are mostly characterized by T-cell subpopulation changes: decreases in CD3+ T-cells, partly replaced by an increase in the CD2+CD3– T-cell subset; a switch from CD45RA+ (naïve cells) to CD45RO+ (memory cells); a switch from T-helper (Th) 1 cells to Th2 subsets. These T-cell subset changes have little effect on T-cell functions (Table 1; Lesourd & Meaume, 1994; Lesourd *et al.* 1994; Mazari & Lesourd, 1998; Lesourd & Mazari, 1999; Ahluwalia *et al.* 2001). Some of these changes, such as the naïve–memory switch, occur early in life, mainly before 30 years of age, but continue to occur at a lower rate throughout life (Cossarizza *et al.* 1992). However, although peak lymphocyte proliferation is comparable for young and elderly individuals, peak responses are reached later in elderly individuals (3–4 d) when compared with their young counterparts (2–3 d; Mazari & Lesourd, 1998; Lesourd

& Mazari, 1999). Decreased T-cell function is observed only in the very old healthy elderly (>90 years old), who require very careful selection for criteria of healthiness (Table 1). Thus, in healthy individuals the decline in CMI occurs far later than has been previously reported. Changes in immune response are related either to changes in the body that are associated with ageing (i.e. the decline in thymus function that occurs after puberty, which is associated with CD3+ decline), or to antigenic stress that occurs during the lifespan for the naïve–memory and Th1–Th2 switches (Lesourd & Mazari, 1999; Ahluwalia, 2004). The Th1–Th2 age-related switch may be of great importance. Indeed, Th1 responses induce activation of CD8+ cytotoxic T-cells and those of Th2 induce B-cells to secrete Ig. Cytotoxic T-cell numbers and function decline with age (Mbawuike *et al.* 1997) and this decline is probably of major importance in CMI function *in vivo*, since cytotoxic T-cells represent a very effective mechanism for killing infected body cells. The decrease in this population may explain the age-related increase in susceptibility to infection, even though the replication rate of T-cells is apparently 'normal'. The increase in Th2 function may explain why Ig levels do not decline with age (Moulias *et al.* 1995).

Similar changes have been reported for humoral immunity (B-cell function). Ageing induces a switch from CD5– B-cells, which produce a specific antibody to foreign antigens, to CD5+ B-cells, which secrete autoantibodies (Weksler, 1995). Other reports have shown that antibody affinity declines with age (Muller *et al.* 1986) and autoantibodies increase with age (Arreaza *et al.* 1993). Thus, even though antibody production is only slightly reduced in elderly individuals, the specificity and affinity of the antibody produced is reduced, leading to less-adapted antibody responses.

Non-specific immunity (macrophage and polymorphonuclear functions) seems to be preserved or even enhanced with ageing. IL-1 production is sustained in human subjects (Nafziger *et al.* 1993), while IL-6 production is actually increased (Ershler *et al.* 1993; Lesourd, 2004). This situation represents a dysequilibrium in the immune response of the elderly individual; the functions of accessory cells that induce immune response are maintained and the functions of T-cells, which are the active cells, are partially decreased. Thus, in order to produce an appropriate immune response after an antigenic challenge, macrophages must secrete more cytokines to enhance partially-defective lymphocytes, which leads to greater or long-lasting proinflammatory responses in elderly individuals. Indeed, stress-induced metabolic effects are prolonged in old animals compared with young animals (Sapolski *et al.* 1983). As proinflammatory cytokines have numerous metabolic activities, such as increases in muscle protein breakdown, the metabolic effects of acute-phase responses are increased in elderly individuals. These catabolized muscle proteins are not fully replaced after recovery in elderly individuals because protein synthesis rates are reduced (Welle *et al.* 1993; Yarasheski *et al.* 1993). Thus, any antigenic challenge induces a reduction in muscle protein in elderly individuals, leading to a more frail state. In addition, monocytes from elderly individuals

produce more prostaglandin E₂, a suppressive factor to lymphocytes (Hayek *et al.* 1997). Furthermore, lymphocytes from elderly individuals are more sensitive to prostaglandin E₂ activity (Goodwin, 1982). Thus, any monocyte activation, i.e. acute-phase response, induces partial decreases in lymphocyte function, explaining the need for greater secretion of proinflammatory cytokines to stimulate lymphocytes during an antigenic challenge in the elderly. This requirement for higher levels of proinflammatory cytokines may explain the higher IL-6 levels observed in the elderly individuals, even when they are apparently very healthy (Ershler *et al.* 1993).

Secondary immune ageing: common ageing

Immune responses are influenced by micronutrient deficits, which are quite common in the elderly population. Indeed, one-third to half the 75-year-old self-sufficient home-living elderly population have decreased intakes in at least one micronutrient (Lesourd *et al.* 1998). Since many micronutrients influence immune responses, this decreased micronutrient intake may induce decreases in CMI responses.

In the first controlled supplementation study conducted in an elderly population with a micronutrient deficit (Talbot *et al.* 1987) the subjects were given a physiological dose of pyridoxine (500 mg), which it was shown may enhance lymphocyte proliferation, but only in subjects with low serum pyridoxal 5'-phosphate levels. Similar observations have been documented for patients with Zn deficiency who received physiological doses of Zn (Boubaika *et al.* 1993; Prasad *et al.* 1993). Prasad *et al.* (1993) have reported that Zn supplementation enhances serum thymulin and IL-1 secretions from monocytes; an effect that is related to increased plasma Zn levels and polymorphonuclear Zn contents. Furthermore, Zn supplementation is also associated with decreased serum Cu, which may explain why there is no effect on lymphocyte function. It has also been shown that Zn supplementation may be detrimental (Bogden *et al.* 1990).

A similar study has been conducted in which a folic acid supplement at physiological doses (2 × RDA) was given to apparently healthy elderly subjects carefully selected for the absence of PEM (BMI >23 kg/m², albumin >38 g/l; Lesourd, 2004). The selected subjects did not have a folic acid deficit, only low erythrocyte folic acid contents that were within the normal range (200–780 µg/l) but in the lower part of this range (200–450 µg/l). In the folic acid-supplemented groups lymphocyte proliferation and IL-2 release were enhanced (Table 2) and were related to increased erythrocyte folic acid. It is now well-proven that some micronutrient deficits may be associated with decreased immune responses in 'apparently' healthy elderly and that correction of such deficits enhances immune responses (Lesourd, 1995; Lesourd *et al.* 1998). Thus, some of the reported age-related decreases in CMI responses may be a result of immune ageing or decreased micronutrient levels. The fact that immune responses can be enhanced in elderly individuals who do not have a folic acid deficit but have low erythrocyte folate levels indicates

Table 2. Functions of peripheral blood lymphocytes, stimulated *in vitro* with purified phytohaemagglutinin (PHA_p), in apparently healthy elderly‡ with or without folic acid supplementation
(Values are means and standard deviations)

	Serum folates (µg/l)		IL-2 (ng/ml)		[³ H]thymidine (counts per min per 10 ³ cells)		Percentage of CD25+ cells after 48 h of culture	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Placebo group (n 26)								
Before supplementation	332	214	1·12	0·31	64	33	39·7	10·9
After supplementation	386**	241	1·19*	0·26	59**	23	37·8**	12·4
Treated group (n 26)								
Before supplementation	322	221	1·08	0·27	68	24	41·6	9·4
After supplementation	743††	236	1·54††	0·36	99††	21·3	67·2††	10·1

Mean values were significantly different within groups before and after supplementation: * $P < 0·05$, ** $P < 0·01$.

Mean values were significantly different between groups before and after supplementation: † $P < 0·05$, †† $P < 0·01$.

‡Apparently healthy elderly, aged 78·4 (SD 5·6) years, carefully selected for the absence of a folic acid deficit (serum haematic folates > 200 µg/l) were treated with 800 mg folic acid/d for 20 d.

that micronutrients may have an important effect on immune responses in elderly individuals. Furthermore, Meydani *et al.* (1990, 1997) have shown that vitamin E supplements enhance lymphocyte proliferation, delayed-type hypersensitivity and IL-2 release in elderly individuals with 'normal' vitamin E levels. These effects were shown to be associated with decreased free radical production (lipoperoxidation) and were achieved using pharmacological doses ($5\text{--}10 \times$ RDA) of vitamin E provided as a supplement.

Such findings raise three major questions: (1) are decreases in CMI responses a result only of insufficient micronutrient levels in elderly individuals; (2) are the micronutrient requirements of elderly individuals different from those of their younger counterparts, and if so, are the current RDA appropriate for them; (3) are these different requirements associated with increased free radical production in elderly individuals. It would appear that free radical production is an important factor in the immune responses of elderly subjects and that the requirements are different (Meydani *et al.* 1995). Indeed, in the most recent French RDA (Martin, 2000) those for Se, folates, vitamin C and mainly for vitamin E have been increased for elderly individuals.

Single supplements and multi-supplements that combine antioxidants or other micronutrients may influence immune responses in elderly subjects. A combination of antioxidant vitamins has been reported to enhance CMI responses after 28 d in hospitalized patients (Penn *et al.* 1991). Similarly, the MIN.VIT.AOX study (Galan *et al.* 1997), which used combinations of physiological doses of antioxidant vitamins and/or trace elements, has shown that non-specific immunity (IL-1 production) is enhanced in the institutionalized elderly. This effect has been reported to be associated only with the antioxidant vitamin supplements and to be correlated with decreased free radical production (Girodon *et al.* 1997). In contrast, these supplements may enhance antibody titres after treatment with an influenza vaccine, but this effect is only correlated with the antioxidant trace element supplement (Girodon *et al.* 1999). This latter effect has also been shown to be associated with a reduced incidence of infection over a 2-year study period (Girodon *et al.* 1999). Other studies that have used

commercial 'cocktails' of various combinations of multivitamins and multimineral at physiological doses ($0·3\text{--}1 \times$ RDA) have also shown that such supplements may enhance immune responses in elderly subjects (Chandra, 1993, 2002; Bogden *et al.* 1994; Pike & Chandra, 1995). These effects have been observed in both institutionalized (Penn *et al.* 1991; Girodon *et al.* 1997, 1999) and self-sufficient home-living elderly subjects (Chandra, 1993, 2002; Bogden *et al.* 1994; Pike & Chandra, 1995; Lesourd, 2004). Three studies have also shown that such multivitamin-multimineral supplements may reduce the period of infection (d) in supplemented individuals over 1 year (Chandra, 1993, 2002; Girodon *et al.* 1999). This effect is associated with enhanced CMI responses (numbers of CD3+ cells, lymphocyte proliferation and IL-2 release) and is correlated with enhanced blood levels of vitamins and trace elements (Chandra, 1993), but the clinical effect is not observed when the same supplement is used for a shorter period (Pike & Chandra, 1995).

All these reports confirm that immune responses may be enhanced in elderly individuals by the use of micronutrient supplements. This outcome is associated with correction of micronutrient deficits in most cases but has also been observed, in a few studies, in individuals with 'normal' micronutrient levels (Meydani *et al.* 1990, 1997). The effect has also been found to be associated with clinical efficacy (i.e. a reduction in infection rate or length) in three of the studies (Chandra, 1993, 2002; Girodon *et al.* 1999) and with reduction in the consequences of free radicals in other studies (Meydani *et al.* 1990, 1995, 1997; Galan *et al.* 1997; Girodon *et al.* 1997), indicating that part of the effect is associated with the antioxidant action of the micronutrients used.

Tertiary immune ageing: pathological ageing related to undernutrition

Major undernutrition, PEM, is a common disease in elderly populations. It has been reported that PEM is present in 2–4% of home-living self-sufficient elderly subjects (Lesourd, 1994) and in $\leq 50\%$ of institutionalized elderly subjects (Alix *et al.* 1992). In home-living subjects PEM is

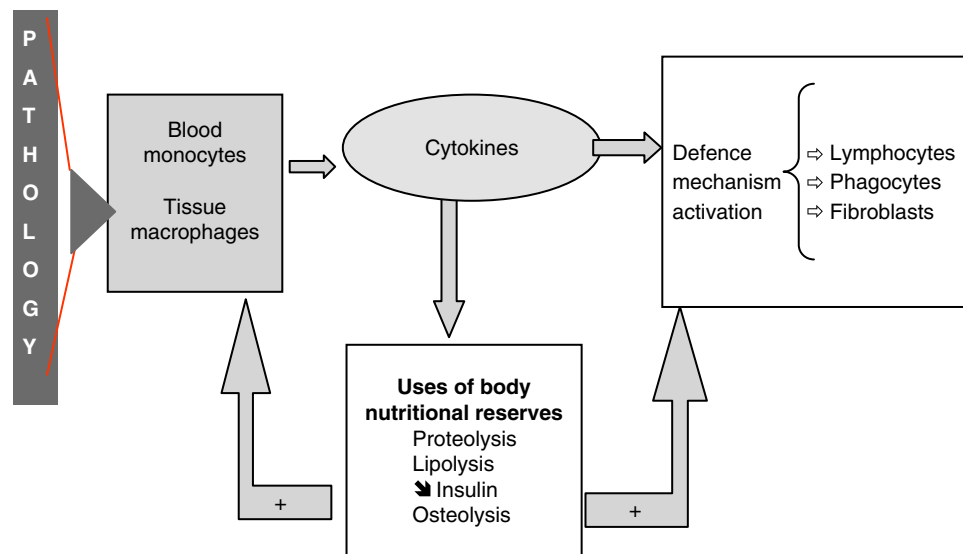


Fig. 1. Nutrition and disease. The body’s response to stress and the relationship with body nutrient reserves. +, Body reserves are used to enhance defence mechanisms and macrophage metabolism; ↘, insulin secretion decreases.

Table 3. Nutritional impact of disease in elderly subjects

Low nutritional reserves leading to osteoporosis and sarcopenia
Metabolic changes lead to incomplete replacement of the catabolized muscle
Macrophage–lymphocyte dysequilibrium leads to long-lasting acute-phase responses

often associated with chronically low intakes, while in nursing homes and hospitals PEM is often associated with on-going diseases (Lesourd, 1994). Immunodeficiency is strongly correlated with the severity of PEM (Lesourd, 1999; Lesourd *et al.* 2002) and is associated with increased complication rates (Sullivan *et al.* 1990; Sullivan & Walls, 1995), mainly infections (Sullivan *et al.* 1990; Sullivan & Walls, 1995), and with death rates (Cederholm *et al.* 1995; Sullivan *et al.* 1995). It is now well-known that under-nutrition leads to a more frail state in the elderly (Lesourd, 1996, 2001). The ability of refeeding therapy to restore immune responses depends on the presence or absence of acute-phase responses. Refeeding therapy has a rapid effect in patients with low acute-phase responses, but when acute-phase responses are more intense (i.e. C-reactive protein >30 mg/l) such therapies need to be given for a longer period to be effective (Lesourd & Mazari, 1997; Lesourd, 1999). This finding confirms the interrelationship between nutritional status and immune responses in elderly patients.

The stress response is a key for nutritional efficacy in elderly patients. Whatever the cause of stress, the body reacts with acute-phase responses associated with pro-inflammatory cytokine release from monocyte–macrophages, i.e. IL-1, TNF, IL-6 (Fig. 1). The cytokines enhance cells acting on body defences and, in parallel, induce the use of nutritional reserves, which is particularly harmful in the elderly for several reasons (Table 3): (1) body reserves are

already decreased in elderly individuals who exhibit osteoporosis and often sarcopenia; (2) acute-phase responses are long lasting in elderly animals and human subjects (Sapolski *et al.* 1983), so that more body reserves are used; (3) nutritional reserves are never fully replaced in elderly individuals during recovery, since protein anabolism is decreased (Welle *et al.* 1993; Yarasheski *et al.* 1993); (4) each acute-phase response in the elderly can therefore lead to lower nutritional reserves, mainly muscle protein reserves, which can increase frailty. In conclusion, in the elderly repeated bouts of disease can lead to a progressive loss of body reserves, a progressively lower nutritional status and increased frailty. In parallel, the lowered nutritional status induces lower immune responses, leading to increased susceptibility to disease complications such as infections, which in turn contributes to increased frailty. Thus, not only are decreased immune responses an important part of increased frailty in elderly individuals, but they are also partly responsible for increased frailty when a disease occurs.

Conclusions

Immune responses and nutritional status are closely inter-related in elderly individuals. Deficits of any nutrient (micronutrients and/or macronutrients) that affects the immune response induce decreased responses in elderly individuals. The decreased immune responses lead to increased susceptibility to disease, and disease induces further decreases in nutritional status and, as a consequence, in immune responses. Maintaining optimal nutritional status could therefore be a way of ensuring healthy ageing and extending the lifespan. Do elderly individuals have higher nutritional requirements than their younger counterparts? The question still remains to be answered, but the answer may be of importance for healthy ageing.

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