Immune response during disease and recovery in the elderly

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The present article reviews immune ageing and its relationship with nutritional ageing, with a particular insight into the influences of disease on both ageing processes. Immune ageing can be described primarily as the progressive appearance of immune dysregulations, mainly acquired immunity (mature: immature, naive: memory T lymphocyte subset decreases) leading to gradual increases in T-helper 2: T-helper 1 cells. This change is due initially to decreased thymic function, and later to accumulative antigen pressure over the lifespan. In contrast, innate immunity (macrophage functions) is preserved during the ageing process and in the elderly this leads to macrophage–lymphocyte dysequilibrium, which is particularly critical during on-going disease. Indeed, any disease induces long-lasting acute-phase reactions in aged patients and leads to body nutritional reserve (mainly protein) losses. Episodes of disease in the aged patient progressively deplete body nutritional reserves and lead to protein–energy malnutrition, undernutrition-associated immunodeficiency, and finally cachexia. Undernutrition is a common symptom in the elderly; protein–energy malnutrition is found in more than 50 % of hospitalized elderly patients and in most elderly diseased subjects. In addition, micronutrient deficit or low levels are common in home-living self-sufficient apparently-healthy elderly subjects. All these nutritional deficits induce decreased immune responses, and micronutrient deficits are now thought to be partly responsible for the decreased immune responses (immune ageing?) observed in the apparently-healthy elderly. Indeed, several studies have shown that micronutrient supplements induce increased immune responses in the healthy elderly. The progression of infectious diseases depends on immune responses and on nutritional status before the onset of illness in aged subjects. In addition, recovery depends on the intensity of acute-phase responses in the undernourished elderly. In fact, chronic acute-phase responses, commonly associated with diseases in aged patients, lead to progressive lowering of metabolic responses in the undernourished elderly. This can be quantified by increased production of free radicals during treatment and these increases may explain the difficulty in successfully treating aged patients. Nutritive therapy in order to improve metabolic processes and also to maintain body reserves should be considered as a necessary adjuvant therapy in the treatment of elderly patients.

Immune response: Disease: Ageing: Elderly

One of the most important changes for man in the 20th century is a drastic increase in life expectancy. Life expectancy has almost doubled in the last 100 years (Haut Comité de la Santé Publique, 1994). As a consequence, the elderly population is rapidly increasing. In France, the elderly population (>60 years) has grown from 10 % in 1960 to 17 % in 1992, and will continue to increase to comprise one-third of the population by 2030 (Institut National de la Statistique et des Etudes Epidemiologiques, 1995). The present life expectancy at birth is 82·4 years for women and 73·8 years for men (Robine & Mormiche, 1993). This increase is due to major progress in health-related research in this century, the most important being hygiene, food supply and preservation, and knowledge of diseases and their treatment. It is important to note that the great majority of 70-year-olds are self-sufficient home-living individuals, in good health; only 5–7 % of the young elderly (<80 years) and less than 15 % of the older elderly (>80 years) live in institutions (nursing homes and/or long-term care facilities) (Commissariat du Plan, 1993). As the elderly population has increased, the cost of retirement pensions and health care has also increased, almost leading to bankruptcy of the social security system. Thus, ageing has become an important subject for research and in the last 20 years ageing has

Abbreviations: IFN γ, interferon γ; IL, interleukin; PEM, protein–energy malnutrition; PG, prostaglandin; RDA, recommended dietary allowance; TH, T-helper.

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been studied extensively. Ageing is now better understood, and most present research relates to the study of ageing *per se* rather than the study of pathological ageing, in order to establish the most important factors relating to ageing and which of these induce accelerated ageing. Environmental factors such as nutrition (Lesourd, 1990*a*; Feldman, 1993) and infectious diseases (Proust *et al.* 1985; Nafziger *et al.* 1993) appear to be major factors influencing immune ageing, which also depends on the genetic background of the individual (Proust *et al.* 1982; Yong-Xing *et al.* 1997).

Immune responses, mainly T lymphocyte function, have been shown to decline with ageing (Makinodan & Kay, 1980; Goodwin *et al.* 1982). Many factors have been shown to be involved in the decreased immune responses of the elderly, including decreased thymic function (Tosi *et al.* 1982; Utsuyama *et al.* 1997), changes in peripheral T lymphocyte subpopulations (Deviere *et al.* 1985; Brohee, 1987) and decreased capacity of peripheral T lymphocytes to be stimulated (Murasko *et al.* 1986; Hallgren *et al.* 1988). Environmental factors, particularly nutritional deficit, have also been shown to be involved in the age-related immune deficit, especially in aged patients (Chandra, 1988; Lesourd, 1990*b*; Feldman, 1993). It is only recently that nutritional deficiencies have been thought to have a role in the decreased immune responses of the apparently-healthy elderly. Several investigators have reported that home-living self-sufficient elderly subjects have low immune responses, probably in relation to low intakes of micronutrients (Payette *et al.* 1990; Penn *et al.* 1991; Monget *et al.* 1996), since supplementation with micronutrients improves immune responses (Talbott *et al.* 1987; Meydani *et al.* 1990; Bogden *et al.* 1994). Furthermore, it has been shown that micronutrient supplementation may lower infection rate in home-living self-sufficient elderly subjects (Chandra, 1992). These findings led Bendich (1990) to suggest that the requirements of the elderly for some micronutrients are higher than those of adults, and to propose that investigations should be carried out into whether immune function should be considered when determining the recommended dietary allowances (RDA) for those nutrients. Furthermore, studies in rodents have shown that the decrease in immune responses may be delayed in diet-restricted animals (Venkatraman *et al.* 1994; Fernandes *et al.* 1997). These studies have shown that free radical production due to overfeeding is a major phenomenon in age-related immune deficiency and that diets which lower free radical production delay immune ageing (Venkatraman & Fernandes, 1994; Fernandes *et al.* 1997). Finally, we have found that very-carefully-selected healthy elderly subjects, without any micronutrient deficit, do not show decreased immune responses, i.e. normal mitogen-induced T lymphocyte proliferation and/or interleukin (IL)-2 secretion (Lesourd & Meaume, 1994; Mazari & Lesourd, 1998). Since disease induces free radical production and, therefore, decreases immune responses, and as micronutrient deficiency (which is common even in healthy elderly subjects; Wahlquist, 1990; Haller *et al.* 1996; Lesourd *et al.* 1998) may lower protection against free radicals, it is obvious that nutritional factors play an important role in immune ageing.

The present paper considers immune responses in elderly patients. First immune responses in healthy elderly subjects will be discussed in order to understand the role of ageing *per se* in immune responses. Then immune responses will be described in elderly diseased subjects. The role of immune responses on nutritional status in the elderly and on patient outcome will be discussed. Finally, the results of studies on immune function during recovery will be presented to show that nutritional recovery is essential for immune recovery in elderly patients.

Immune responses in aged individuals

Ageing is associated with increased frequency of disease related to immune dysfunction, i.e. higher incidence of infections (Phair, 1988; Scrimshaw *et al.* 1988) and of mortality related to infection (Sprenger *et al.* 1991; McBean *et al.* 1993), higher levels of monoclonal immunoglobulins (Crawford *et al.* 1987; Ligthart *et al.* 1990) and a higher rate of monoclonal gammopathies (Crawford *et al.* 1987). Initially, ageing was thought to induce a global immunodeficiency (Makinodan & Kay, 1980; Goodwin *et al.* 1982). More recently, however, it was established that disease is only partly responsible for the age-related immunodeficiency observed, and a protocol was designed to study the influence of ageing on elderly subjects not affected by disease (Ligthart *et al.* 1984). In the last 10 years, most of the studies analysing age-related changes in immune responses have conformed to the Senieur (Ligthart *et al.* 1984) criteria. These findings will be summarized.

Lymphocytes are actively produced daily by bone marrow (billions of lymphocytes each day) and mature in the thymus. Both functions, the ability of stem cells to undergo clonal proliferation (Tyan, 1981) and thymic maturation (Hirokawa *et al.* 1994), decrease with age. Accordingly, T lymphocyte equilibrium in peripheral blood changes with age; elderly individuals characteristically show increased immature : mature (CD2 + CD3 − : CD3+) T-cells (Alés-Martinez *et al.* 1988; Lesourd & Meaume, 1994) and increased numbers of natural killer cells (CD57+; Ligthart *et al.* 1986), in relation to increased levels of immature T lymphocytes (Alés-Martinez *et al.* 1988; Lesourd & Meaume, 1994). It was even demonstrated in aged mice that a small percentage of peripheral-blood lymphocytes are generated in the liver (Abo, 1992; Nakayama *et al.* 1994), and the same probably occurs in man (Lesourd *et al.* 1994). Thus, decreased thymic maturation may be partly compensated by extra-thymic maturation in aged subjects. These changes are of borderline significance in very-carefully-selected healthy elderly (Lesourd *et al.* 1998; Mazari & Lesourd, 1998; Table 1) in whom immature T lymphocytes represent only 10–15 % of blood T lymphocytes. These changes are mainly related to lower numbers of CD8+ subset, while numbers of CD4+ subset remain virtually unchanged (Lesourd *et al.* 1994; Lesourd & Meaume, 1994), even in nonagenarians (Table 1). In addition to decreased numbers of CD8+, peripheral CD8+ have a lower cytotoxic capacity than CD8+ from young adults (Mbawuike *et al.* 1997). This indicates that age-related changes are due to changes in T-cell subset equilibrium, as well as to the capacities of those subsets, both phenomena

Table 1. Absolute counts of T-cell subsets‡ in peripheral blood of very healthy subjects§

	Young adults		Young elderly (65–85 years of age)		Old elderly (> 90 years of age)	
n . . .	46		30		16	
	Mean	SD	Mean	SD	Mean	SD
Age (years)	29·4	3·5	77·9	5·2	94·3	3·4
Lymphocytes (/mm^3)	2210	470	1980	620	1830*	680
CD2+ (/mm^3)	1980	310	1730**	410	1605**	470
CD3+ (/mm^3)	1850	280	1510***	320	1360**†	380
CD2+ CD3− (/mm^3)	130	130	220*	210	240*	250
CD57+ (/mm^3)	210	135	390***	180	430***	205
CD4+ (/mm^3)	1245	190	1115*	260	1084*	290
CD8+ (/mm^3)	670	145	460***	190	405***	220
CD45RA (/mm^3)	1230	340	560***	180	380***††	200
CD45RO (/mm^3)	760	235	1090***	420	1125***	470

CD45RA, naive T lymphocytes; CD45RO, memory T lymphocytes.
Mean values were significantly different from those for the young adults: *$P < 0{\cdot}05$, **$P < 0{\cdot}01$, ***$P < 0{\cdot}001$.
Mean values were significantly different from those for the young elderly: †$P < 0{\cdot}05$, ††$P < 0{\cdot}01$.
‡ Quantified on freshly drawn blood, as previously described (Lesourd *et al.* 1994).
§ Healthy young adults (25–34 years of age) and elderly of different ages were selected according to the SENIEUR protocol (Ligthart *et al.* 1984) and added criteria (Lesourd *et al.* 1994; Lesourd & Meaume, 1994).

contributing to the reported age-related defect in cell-mediated immunity.

The most drastic change in the peripheral-blood T-cell subset is the increase in memory (CD45RO) T lymphocytes which compensates for the parallel decrease in naive (CD45RA) T lymphocytes. This change in value from 2 to 0.25 for naive : memory T lymphocytes during the lifespan occurs mainly during childhood and early adulthood (Cossarizza *et al.* 1992), and reflects antigen exposure. However this change continues at a lower rate later in life (Cossarizza *et al.* 1992) and naive : memory T lymphocytes continues to decrease in later life (Table 1). The aged peripheral microenvironment was found to induce accelerated maturation of CD4 T lymphocytes from naive to memory cells in aged mice (Thoman, 1997).

The previously described changes have major consequences for lymphocyte functions. Lymphocytes from aged persons are poor IL-2 secretors (Rabinowich *et al.* 1985; Nagel *et al.* 1988; Lesourd, 1990*a*) and show decreased ability to proliferate (Murasko *et al.* 1987; Nagel *et al.* 1988; Lesourd, 1990*a*). Decreased lymphocyte proliferation in aged subjects has been linked to a higher percentage of immature T-cells (Alés-Martinez *et al.* 1988; Lesourd *et al.* 1992, 1994) and/or of memory T lymphocytes (Nagelkerken *et al.* 1991; Hobbs & Ernst, 1997), both subsets being poor IL-2 secretors. The decrease in lymphocyte proliferation is also due to intrinsic modification of peripheral lymphocytes (Lesourd, 1990*a*; Miller *et al.* 1997), e.g. the appearance of new receptors on lymphocyte cell walls after mitogen stimulation is delayed (Lesourd *et al.* 1992; Wakikawa *et al.* 1997). Whatever the major cause, T lymphocyte subsets and T lymphocyte functions have been reported to decrease with ageing. These changes lead to important modifications in cell-mediated immunity, including helper and suppressor functions, cytotoxicity, cytokine secretions, graft rejection and delayed-type hypersensitivity (see Lesourd, 1990*a*).

The recent progress in cytokine research has revealed separate helper functions for T-helper (TH) 1 and TH2 cells (Mosmann & Coffman, 1989; Openshaw *et al.* 1995). Both subsets are activated through different cytokines (Siveke & Hamann, 1998) and express different functions (Shearer, 1997). TH1 cells are helper cells for cytotoxic T-cells and secrete IL-2, IL-10 and interferon γ (IFNγ), while TH2 cells secrete IL-3, IL-4, IL-6, IL-12 and have helper functions for B lymphocytes. TH1 functions decrease with ageing (decreased IL-2 and IFNγ), while TH2 functions remain unchanged (comparable with IL-3, IL-4, IL-6; Kubo & Cinader, 1990; Ershler *et al.* 1993; Castle *et al.* 1997; Segal *et al.* 1997) or may be enhanced (Mbawuike *et al.* 1997; Table 2). Thus, ageing is now described as immune dysregulation (Weksler, 1995; Cakman *et al.* 1996) rather than immune deficiency, since some T-cell functions (TH2) remain unchanged or are even increased in aged subjects. However, IFNγ does not always show a decrease in aged subjects (Chen *et al.* 1987; Sindermann *et al.* 1993), indicating that TH1 functions may also be normal. Since IFNγ is also synthesized by memory T-cells (Sanders *et al.* 1988), which increase with age (Cossarizza *et al.* 1992), this does not contradict the principle of age-related decreases in TH1. More recently, it was reported that IL-2 secretion may also be normal in very-carefully-selected healthy elderly subjects (Gueldner *et al.* 1997; Mbawuike *et al.* 1997; Mazari & Lesourd, 1998), since a similar finding was reported in aged mice, probably in relation to genetic background (Kubo & Cinader, 1990). It appears, therefore, that immune ageing is mainly influenced by environmental factors, principally nutrition (Lesourd *et al.* 1998; Mysliwska *et al.* 1998) and antigenic exposure over the lifespan (Cakman *et al.* 1996).

Age-related changes in humoral immune responses (B lymphocyte functions) are altogether more subtle, in that immune responses to foreign antigens decline while responses to self antigen increase. Indeed, some B lymphocyte responses are increased in elderly subjects, i.e. levels of immunoglobulins G and A (Batory *et al.* 1984) and autoantibody levels (Hijmans *et al.* 1984; Manoussakis *et al.* 1987). Such increased responses may result from age-related B-cell subset changes (i.e. increases in CD5+ B lymphocytes; Weksler, 1995), and/or age-related decreases in TH1 : TH2 (Castle *et al.* 1997; Shearer, 1997; Lesourd

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Table 2. Monocyte cytokine releases in lipopolysaccharide-stimulated cultures‡ (Mean values and standard deviations)

n . . .	Young adults§ 36		Young elderly§ 24		Old elderly§ 11		PEM elderly§ 30	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age (years)	29·3	3·6	78·2	4·9	94·4	3·7	84·6	7·7
Albumin (g/l)	43·3	2·9	42·2†††	4·1	41·3†††	3·7	26·3***	4·7
C-reactive protein (mg/l)	< 6		< 6		< 6		18·4	5·9
Interleukin-1 (ng/ml):								
Spontaneous	ND		0·3	1·4	0·3†	1·1	2·3	3·4
Stimulated	2·6	2·3	2·5††	2·7	2·8††	3·0	0·9***	0·9
Interleukin-6 (ng/ml):								
Spontaneous	ND		ND		ND		0·18	0·09
Stimulated	1·25	0·3	1·65†††***	0·4	1·8†††***	0·4	0·80***	0·35

PEM, protein–energy malnutrition; ND, not detected.
Mean values were significantly different from those for young adults: ***$P < 0·001$.
Mean values were significantly different from those for PEM elderly: †$P < 0·05$, ††$P < 0·01$, †††$P < 0·001$.
‡ Procedures for lipopolysaccharide-stimulated cultures and quantification of supernatant fraction cytokine levels were as previously described (Lesourd *et al.* 1994).
§ Healthy young adults (25–34 years of age) and elderly of different ages were selected according to the SENIEUR protocol (Ligthart *et al.* 1984) and added criteria (Lesourd *et al.* 1994; Lesourd & Meaume, 1994).

et al. 1998; Mysliwska *et al.* 1998). In contrast, antibody responses to foreign antigens are decreased, mainly primary antibody responses which depend on naive T-cells, while booster responses depending on memory T-cells have been shown to be unchanged (Moulias *et al.* 1985*b*) or decreased in relation to memory (anti-idiotype) antibodies (Goidl *et al.* 1983; Arreaza *et al.* 1993). It appears, therefore, that B lymphocyte responses in elderly subjects are very dependent on T-cell function and environmental factors such as antigenic exposure over the lifespan, which induces decreases in TH1 : TH2 and/or increases in anti-idiotype antibodies. Indeed, once again, nutritional status at the time of antigenic exposure is a major factor influencing B lymphocyte responses (Chandra *et al.* 1984; Moulias *et al.* 1985*a*,*b*; Lesourd, 1990*a*,*b*). With regard to age-related changes in B lymphocyte responses, ageing also appears to induce a dysregulation of immune system.

In contrast to observations relating to lymphocytes, macrophage numbers and function are unchanged or even enhanced in aged animals and human subjects. Monocyte numbers progressively increase with age in mice (Barrat *et al.* 1997). Antigen-processing ability, as well as IL-1 secretion are comparable in old and young mice (Goldberg *et al.* 1991). Lipopolysaccharide-activated monocytes from healthy aged subjects release similar levels of IL-1 (Nafziger *et al.* 1993) and increased levels of IL-6 (Table 2) to those of monocytes from young subjects. Lysosomal activity as well as metabolic burst are maintained in aged subjects (Grigolo *et al.* 1994). Furthermore, monocyte prostaglandin (PG) E_2 secretion is increased in aged mice (Hayek *et al.* 1997). The unchanged and/or enhanced function of monocytes may contribute to the observed dysequilibrium of immune system with ageing. Indeed, lymphocytes from aged individuals are particularly sensitive to PGE_2 (Goodwin *et al.* 1982), which induces lower T-cell function. Increased PGE_2 secretion may be partly responsible for decreased T-cell proliferation and/or T-cell IL-2 release (Hayek *et al.* 1997). Furthermore, PGE_2 is also involved in TH cell function; high PGE_2 secretions induce responses in TH2 subset rather than TH1 (Beharka *et al.* 1997). Furthermore, it has been shown that decreased TH1 function in aged subjects, i.e. decreased CD8+ lymphocyte cytotoxic activity and decreased IFNγ secretion, are enhanced by recombinant human IL-12, a pivotal cytokine that stimulates TH1 subset (Mbawuike *et al.* 1997). Similar findings were observed in mice in which recombinant cytokine treatment is an effective way to reset the age-related TH1 : TH2 changes (Frasca & Doria, 1997). It appears, therefore, that some of the immune system changes related to ageing are linked to age-related changes in monocyte and/or macrophage functions.

In summary, ageing induces dysequilibriums within cells of the immune system. Cells responsible for innate immunity (i.e. monocytes and macrophages) do not age and are preserved in numbers and functions as long as individuals remain healthy. In contrast, cells responsible for acquired immunity (mainly T lymphocytes, but also to a lesser extent B lymphocytes) do age, and age-related changes induce dysequilibriums within subsets. These changes are dependent on several mechanisms: the decrease in thymic functions (which have almost disappeared at mid-life); environmental (antigenic and diseases) pressures which accumulate over the lifespan. The different ageing modes of the two (innate and acquired) immune systems account for the inability of aged individuals to meet an antigenic challenge.

Immune responses in aged patients

Immune responses are always decreased in elderly diseased patients. Hallgren *et al.* (1988) showed that immune variables known to decline with age (i.e. decreased lymphocyte proliferation and decreased mature CD3+ subset) are even lower in elderly diseased subjects. It was subsequently postulated that the decline in immune response in aged subjects is more a reflection of health status than of ageing *per se*. In our studies of the immune responses in elderly patients, we always found changes in T lymphocyte subsets, including decreased mature CD3+ T-cells, with parallel increases in immature CD2+CD3− T-cells and natural killer (CD57+) cells, and lower CD8+ and CD4+ T-cells in peripheral blood (Lesourd, 1990*b*; Lesourd *et al.* 1992). In addition, the patients always showed low levels of

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Table 3. Changes in CD4+ subset (CD4+) and of serum soluble interleukin-2 receptor (sIL2-R) in peripheral blood during the progression of lung infections in elderly hospitalized patients† (Mean values and standard deviations)

Stage of infection . . .	Before infection		During infection				During recovery			
Day of investigation . . .	−5 to −15		1		3		7		15	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
CD4+ (/mm^3)	540	125	280***	110	220***	90	330***	190	490	140
sIL2-R (U/ml)	125	140	375***	185	440***	250	390**	290	160	170

Mean values were significantly different from those before onset of infection: $^{**}P < 0{\cdot}01$, $^{***}P < 0{\cdot}001$.

† Elderly hospitalized patients in a convalescent geriatric unit had been monitored continuously for immune responses. Patients (n 14, 83·7 (SD 7·4) years of age) who showed pulmonary infections during their hospital stay were monitored continuously during infection and recovery for CD4+ (Lesourd *et al.* 1994) and sIL2-R (Gupta, 1986) following routine procedures.

lymphocyte proliferation and low levels of release of IL-2 in mitogen-stimulated cultures (Lesourd, 1990*a*,*b*; Lesourd *et al.* 1992). These immune changes are more pronounced during acute diseases such as infections, which induce decreased lymphocyte numbers in peripheral blood (Proust *et al.* 1985). These decreases are far less important in adults (10 %) than in elderly patients (50 %) during acute pulmonary infections (Proust *et al.* 1985). Consequently, many elderly subjects with pulmonary infections have lymphopenia (< 1000 lymphocytes/mm^3) during the acute phase of the disease. The intensity and the duration of lymphopenia have prognostic value (Proust *et al.* 1985). The lymphopenia is due to increased lymphocyte destruction at the infection site, and provides an explanation for CD4+ counts being generally lower than 400/mm^3 a few days after disease onset (Moulias *et al.* 1988; Table 3). The increased lymphocyte destruction may be quantified by measuring soluble IL-2 receptor in peripheral blood (Table 3), as shown in patients with acquired immune deficiency syndrome (Gupta, 1986). Elderly patients in whom more lymphocytes are destroyed, have higher serum soluble IL-2 receptor levels and a higher mortality rate (Rosenthal *et al.* 1997). The intensity of lymphopenia partly results from higher apoptosis of mature (Phelouzat *et al.* 1996) or immature naive CD45− T lymphocytes (Herndon *et al.* 1997; Mountz & Hsu, 1997). Indeed, new T lymphocytes are recruited to fight infection. If apoptosis is accelerated, as reported by Phelouzat *et al.* (1996) and Herndon *et al.* (1997), recruitment of T lymphocytes may be ineffective in elderly patients. In summary, infectious diseases induce lymphopenia in aged patients and therefore induce an immunodeficit or enhance a pre-existing immunodeficiency. The fact that prognosis of the occurrence of infection is related to nutritional status and to immune responses (CD4 counts and lymphocyte proliferation) before infection and at the peak of the infection (Moulias *et al.* 1993; Lesourd, 1995) indicates the important relationship between nutrition and immunology in aged patients.

Chandra (1972, 1983, 1994) and Chandra *et al.* (1984) have shown that protein–energy malnutrition (PEM) decreases immune responses in children (Chandra, 1972, 1994) and also in aged subjects (Chandra, 1983, 1994; Chandra *et al.* 1984). The effect of PEM on immune responses of elderly patients is linked to the intensity of malnutrition (Lesourd *et al.* 1992). The same relationships between protein status (i.e. albumin level) and changes in immune T lymphocyte subsets have been observed in apparently-healthy elderly subjects (Lesourd *et al.* 1994; Lesourd & Meaume, 1994; Mazari & Lesourd, 1998); aged individuals with low protein status but otherwise apparently healthy have higher numbers of immature CD2+CD3− T lymphocytes and lower phytohaemagglutinin-induced proliferative responses (Lesourd *et al.* 1994; Lesourd & Meaume, 1994). Furthermore, they have lower numbers of CD4+ in peripheral blood, an age-related change that is only of borderline significance in healthy elderly subjects with 'normal' protein nutritional status (Lesourd, 1990*b*; Lesourd & Meaume, 1994; Mazari & Lesourd, 1998; Table 1). Age-related changes in lymphocyte subsets, as observed in very healthy elderly subjects (Mazari & Lesourd, 1998), are very similar to those observed in healthy elderly subjects showing small decreases in serum protein (Lesourd, 1990*a*; Lesourd & Meaume, 1994; Mazari & Lesourd, 1998), but these changes are more important in the latter group. Similar changes are also observed in elderly diseased subjects, but to a greater extent (Lesourd *et al.* 1994; Lesourd & Meaume, 1994). These studies have indicated that lower protein levels are associated with an increase in age-related changes, disease being linked to more important changes in protein levels. Moreover, we have found that decreased lymphocyte proliferation in very-carefully-selected healthy elderly subjects is associated with low folate (erythrocyte and serum) levels (Lesourd & Meaume, 1994). We reported that healthy elderly subjects without decreased nutritional status and young healthy controls have comparable lymphocyte proliferation (Lesourd & Meaume, 1994; Mazari & Lesourd, 1998) and *in vitro* IL-2 release (Mazari & Lesourd, 1998), indicating that age-related changes in immune responses may be linked to decreased nutritional status. Other studies have also suggested that immune responses of home-living self-sufficient elderly subjects are decreased in relation to low micronutrient levels (Bogden *et al.* 1987; Talbott *et al.* 1987). Several micronutrient deficiencies have been linked to decreased immune responses in healthy elderly subjects, including: antioxidant vitamins (A, E, C; Meydani *et al.* 1990; Payette *et al.* 1990; Penn *et al.* 1991): antioxidant trace elements (Zn, Se; Bogden *et al.* 1987; Monget, 1992; Boukaïba *et al.* 1993); vitamins playing a role in cell division (pyridoxine (Talbott *et al.* 1987); folate (Lesourd *et al.* 1994)). These findings have been supported by supplementation studies using one micronutrient (Talbott *et al.* 1987; Meydani *et al.* 1990; Boukaïba *et al.* 1993), several micronutrients (Payette *et al.* 1990; Penn *et al.* 1991; Monget, 1992) or multi-micronutrient supplementation (Bogden

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et al. 1990; Chandra, 1992; Pike & Chandra, 1995). In all these studies increased immune responses were observed after long-term supplementation (4–12 months), indicating that immune responses of healthy elderly subjects are lowered when nutritional status is low. Furthermore, one study has shown a reduction in the incidence of infection in home-living self-sufficient elderly subjects in response to multi-vitamin–mineral supplementation (Chandra, 1992). Similar findings have also been reported for institutionalized elderly subjects (Girodon *et al.* 1997*b*). From these studies it appears that micronutrient consumption may be too low in many apparently-healthy elderly subjects. We have proposed (Lesourd *et al.* 1998; Mazari & Lesourd, 1998), together with others (Mysliwska *et al.* 1998), that the ageing immune process is strongly influenced by nutritional and health status. Furthermore, it has been suggested that immune responses may be one criterion to be considered in determining RDA of aged subjects (Bendich, 1990).

If immune responses of aged healthy subjects are influenced by low intakes of several micronutrients, even at RDA levels, and/or by deficits of several micronutrients, the influence of nutrition on immune responses of elderly diseased subjects must be important. Indeed, nutritional deficits are common in aged diseased subjects; PEM, which is associated with decreased immune responses (Lesourd, 1990*b*; Lesourd *et al.* 1992), is present in 50 % of hospitalized elderly subjects (Rudman & Feller, 1987; Lesourd, 1994) and represents the major cause of decreased immune function in elderly subjects (Lesourd & Meaume, 1994; Lesourd, 1995). The onset of disease promotes both PEM and hospitalization in elderly subjects (Mowe *et al.* 1994), showing that disease and PEM are strongly correlated in aged subjects. In fact, half the elderly patients entering hospital suffer from PEM (Lesourd, 1994). PEM is always associated with many micronutrient deficits (Johnson, 1990; Wahlquist, 1990; Lesourd, 1994), many of them (e.g. Zn and pyridoxine) inducing immunodeficiency (Meydani *et al.* 1995) or decreased immune responses in healthy elderly subjects (see pp. 89–90 and Lesourd *et al.* 1998).

Immune responses are decreased markedly in elderly subjects with PEM; compared with healthy elderly subjects, aged patients with serum albumin lower than 30 g/l have less than half the number of CD4+ in peripheral blood ($< 400/mm^3$ on average) and release one-quarter to half the amount of IL-2 in mitogen-stimulated lymphocyte cultures (Lesourd *et al.* 1992; Lesourd, 1996; Lesourd & Mazari, 1997). With severe PEM, in addition to a profound T-cell defect, monocyte functions are also lowered (De la Fuente & Munoz, 1992; Munoz *et al.* 1994; Lesourd & Mazari, 1997; McMurray, 1998); the ability of monocytes to release cytokines (monokine) in lipopolysaccharide-stimulated *in vitro* cultures is decreased (De la Fuente & Munoz, 1992; Munoz *et al.* 1994; Lesourd & Mazari, 1997; Table 2). A similar finding has been reported for mouse monocytes (De la Fuente & Munoz, 1992). In contrast, tissue macrophages seem to be unchanged in animals with PEM (Filteau & Hall, 1991; McMurray, 1998), indicating that *in situ* responses are unchanged. In human subjects mild PEM, as observed in acute infectious diseases, is associated with normal monocyte cytokine release in elderly patients (Cederholm *et al.* 1997). We have reported that *in vitro* release of monokine is decreased in patients with PEM (Lesourd & Mazari, 1997; Tables 2 and 4) but serum cytokines are increased, indicating that *in vivo* secretion is normal in elderly patients with PEM. In spite of apparently-normal *in vivo* secretion of monokine, acute-phase responses induced by such secretions (Klasing, 1988; Lesourd, 1992) are lowered in patients with PEM (Curtis *et al.* 1995). A strong correlation was established in rats between the intensity of PEM and the magnitude of the acute-phase response (Jennings *et al.* 1992). The inefficiency of *in vivo* secretion of monokine has been related

Table 4. Changes in *in vivo* (serum) and *in vitro* (supernatant fraction) cytokines† in elderly subjects with protein–energy malnutrition during 2 months of refeeding‡
(Mean values and standard deviations)

Period of refeeding (d)	Albumin (g/l)		C-reactive protein (CRP) (mg/l)		IL-2 Supernatant fraction (μg/ml)		IL-2 Serum (μg/ml)		IL-6 Supernatant fraction (ng/ml)		IL-6 Serum (pg/ml)		IL-1 Supernatant fraction (ng/ml)		IL-1 Serum (μg/ml)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Subjects with low acute-phase responses (CRP < 30 mg/l; *n* 14)§																
0	26·4	5·5	15·3	7·2	0·90	0·24	nd		0·75	0·39	nd		0·81	0·74	nd	
21	29·3*	4·7	13·6	3·6	1·16**	0·22	nd		1·03**	0·25	nd		1·59**	1·20	nd	
56	31·5	4·4	11·4*	3·3	1·51	0·23	nd		1·19	0·26	nd		2·71	1·27	nd	
Subjects with acute-phase responses (CRP < 30 mg/l; *n* 29)§																
0	23·5	5·5	70·7	33·7	1·07	0·61	125	122	0·91	0·38	70	31	0·83	0·61	nd	
21	24·0	7·3	40·8***	21·2	0·73*	0·35	63*	53	0·59	0·74	42**	30	0·87	0·52	nd	
56	28·3**	4·1	15·9	13·8	1·25	0·62	40	36	1·10	0·51	7	18	1·83***	1·18	nd	

nd, not determined.
Mean values were significantly different from those at day 0: $^*P < 0·05$, $^{**}P < 0·01$, $P < 0·001$.
† Serum and supernatant fraction (from phytohaemagglutinin-stimulated mononuclear and lipopolysaccharide-stimulated monocyte cultures) were quantified as previously described (Lesourd & Mazari, 1997; Mazari & Lesourd, 1998).
‡ Intakes at 3 weeks (period required to reach maximal intakes): group with CRP < 30 mg/l 160·7 (SD 33·9) kJ (38·4 (SD 8·1) kcal)/kg per d, group with CRP > 30 mg/l 200 (SD 25·5) kJ (47·8 (SD 6·1) kcal)/kg per d.
§ The two groups (patients with undernutrition in relation to previous undernutrition and patients with undernutrition associated with high acute-phase responses related to on-going disease) were classified according to acute-phase protein levels (Lesourd & Mazari, 1997).

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to increases in IL-1 receptor antagonist in serum from rats with PEM (Jennings *et al.* 1992). It may be also related to a T-cell defect in aged patients, since lymphocytes from aged individuals show a reduced reaction to stress signals such as heat-shock proteins (Jurivich *et al.* 1997). The fact that acute-phase responses are restored in CD2-*fas* transgenic aged mice (Mountz & Hsu, 1997) further suggests that a T-cell defect is responsible for the inefficiency of *in vivo* secretion of monokine. Thus, it appears that the dysequilibrium between monocyte and lymphocyte is of major importance in elderly diseased subjects. Indeed, to stimulate T lymphocytes with decreased functions at an efficient level macrophages must increase their *in vivo* release of cytokines. However, monokines are not only a major activator of T lymphocytes, but also play a central role in adjusting body metabolism (Klasing, 1988; Lesourd, 1992) in order to fight disease. IL-1, IL-6 and tumour necrosis factor β, three major monokines, are directly and/or indirectly (through induced hormonal responses; Carlson & Little, 1992) responsible for body metabolic changes found in hypermetabolic states. These monokines induce catabolism of body reserves (muscle proteolysis, lipolysis, insulin hyposecretion and bone accretion) in order to provide sufficient macronutrients and Ca to activate lymphocytes (Lesourd, 1996). In addition, monokines are also responsible for changes in hepatic protein synthesis, including decreases in transport proteins (e.g. albumin) and increases in the synthesis of acute-phase proteins (e.g. C-reactive protein). Monocytes, therefore, exert opposing effects on lymphocytes in PEM, i.e. a boosting effect through direct IL-1 lymphocyte activation and a depressive effect through an IL-1-induced decrease in albumin level to which lymphocytes of aged subjects are especially sensitive. The lower efficacy of monocyte secretions in elderly subjects with PEM, whatever the causes, leads to prolonged monokine secretion and, therefore, to prolonged use of body nutritional reserves. The nutritional effect of prolonged cytokine secretion could have major consequences in the elderly (Cederholm *et al.* 1997). Ageing is characterized by increased muscle protein catabolism (Fereday *et al.* 1997) and lower protein synthesis (Welle *et al.* 1993; Yarasheski *et al.* 1993), not only at the whole-body level (Young, 1990; Fereday *et al.* 1997), but also at the cellular level (Welle *et al.* 1993; Yarasheski *et al.* 1993). As a consequence, prolonged monokine secretion in aged patients could induce more loss of muscle during on-going disease and less muscle rebuilding during recovery (Lesourd, 1996; Lesourd & Mazari, 1997). The monocyte–T-cell dysequilibrium which leads to prolonged monokine secretion during on-going disease in the elderly is certainly of importance in the increased sarcopenia observed in aged patients (Roche, 1994; Dutta & Hadley, 1995).

Immune responses during recovery

Recently the effects of age and undernutrition on immune responses have been extensively studied, but the changes in immune responses during disease and/or recovery from PEM in aged patients require investigation. Indeed, only a few studies have been carried out in aged patients during long-term or severe illness and during recovery.

We have monitored immune responses in aged patients with lung infections in order to determine which factors may be important for recovery from CD4+ lymphopenia. At the onset of disease patients show a profound immunodeficit, i.e. decreased mature CD3+ T-cells, mostly due to decreased CD4+ in relation to peripheral CD4+ destruction (Moulias *et al.* 1988; Lesourd, 1990*a*; Table 3). The decreases in CD3+ are partly balanced by an increase in immature CD2+CD3– T-cells, mostly due to increases in very immature CD2+CD4–CD8– T-cells (Lesourd, 1993). The increases in this very immature T-cell subset confirmed that T-cells destroyed at the periphery are being replaced, but at insufficient levels, since the patient becomes lymphopenic for 3–8 d (Proust *et al.* 1985; Moulias *et al.* 1988, 1993). At day 3 after the onset of disease, while CD4+ lymphopenia (Table 3) and immature CD2+CD4–CD8–CD3– T-cells are at their highest levels (Proust *et al.* 1985; Moulias *et al.* 1988, 1993; Lesourd, 1993), a CD2+CD4+CD8+ double positive population develops (Lesourd, 1993). The appearance of the double-positive CD4+CD8+ subset occurs when blood cortisol levels start to decrease (B Lesourd, P Chretien, C Laisney and M Mazari, unpublished results). It is possible that this is related to glucocorticoid responses to lower T-cell replacement in infected aged subjects, since CD4+CD8+ double-positive thymocytes are very sensitive to glucocorticoid-induced apoptosis (Le *et al.* 1995). Simultaneously, IL-1 production is decreased at the onset of infection (Nafziger *et al.* 1993), and this decrease may stimulate thymocytes to be more sensitive to glucocorticoid-induced apoptosis (McConkney *et al.* 1990). The aged-related decrease in the level of thymic hormones (Lewis *et al.* 1978) may also contribute to the higher sensitivity of thymocytes to glucocorticoid-induced apoptosis (Baumann *et al.* 1995). The requirement for production of new T lymphocytes is high in elderly subjects with infection (important peripheral destruction), but bone marrow cell maturation (Yu *et al.* 1997) and thymus functions (Utsuyama *et al.* 1997) are decreased (which leads to lower T-cell regeneration; Mackall & Gress, 1997), and thymocyte and naive lymphocyte sensitivity to apoptosis are increased (Herndon *et al.* 1997; Mountz & Hsu, 1997). These findings indicate that lymphopenia is far more intense in elderly subjects with infection (Proust *et al.* 1985) and may contribute to the higher detectable changes in T-cell subsets observed. These changes are probably not seen in younger adult subjects with infection, since the need for T-cell replacement is far lower due to lower peripheral lymphocyte destruction, and lymphocyte maturation is greater. Recovery depends on the intensity of lymphopenia at the peak of infection. Not only does mortality depend on the intensity of lymphopenia (Proust *et al.* 1985; Moulias *et al.* 1993; Lesourd, 1995) but also on the length of the hospital stay (Moulias *et al.* 1993) and of lymphopenia recovery (Table 3). Thus the aged-related decrease in the ability to compensate for peripheral lymphocyte destruction is of major clinical significance. This has been shown in patients with acquired immune deficiency syndrome; the faster progression of human immunodeficiency virus infection in aged patients (Volberding, 1996) does not

Table 5. Serum malondialdehyde levels in healthy elderly subjects and in elderly patients with protein–energy malnutrition during refeeding (Mean values and standard deviations for thirteen subjects per group)

	Healthy elderly (84·3 (SD 5·2) years)		Undernourished elderly (88·4 (SD 5·7) years)					
			Day 0 (on admission)		Day 21		Day 42	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Energy intake: kJ/kg per d			78·3	18·0	135·6	39·3	148·1	17·6
kcal/kg per d			18·7	4·3	32·4	9·4	35·4	4·2
Body wt (kg)	54·7	10·4	44·6**	9·2	44·8	9·7	46·8	9·3
Albumin (g/l)	42·4	2·1	29·8***	5·7	31·7	6·4	34·7†	5·1
C-reactive protein (mg/l)	< 6		29	31	11†	17	7††	4
Malondialdehyde‡ (mmol/l)	0·59	0·43	1·28***	0·40	1·70††	0·45	1·65†	0·48

Mean values were significantly different from those for the healthy elderly: ** $P<0·01$, *** $P<0·0001$.
Mean values were significantly different from those for Day 0: † $P<0·05$, †† $P<0·02$.
‡ Peroxidation measured as serum malondialdehyde levels (Monget, 1992; Monget *et al.* 1996).

appear to be due to greater destruction of lymphocytes, but rather to an inability of older individuals to replace destroyed functional T-cells (Adler *et al.* 1997). We had shown that adjuvant treatment of infections with an immunomodulator drug may hasten recovery (Lesourd *et al.* 1987). In a double-blind placebo controlled study, treatment with Imuthiol® (Merieux Institute, Lyon, France) leads to a faster decrease in fever, in clinical signs and in lymphopenia recovery. This drug is known to facilitate thymocyte maturation (Pompidou *et al.* 1985). In our study lymphopenia and neutropenia recoveries were strongly correlated with decreases in the clinical signs. Consequently, we believe that the ability to replace destroyed lymphocytes is one of the major factors influencing recovery from infection in aged patients, and this depends on the effect of age on lymphocyte maturation.

Nutrition does exert a major influence on immune responses in aged subjects (see pp. 89–90). We have tried to measure the influence of nutrition on the recovery of aged patients with PEM treated for undernutrition. However, both nutrition and disease influence the observed effects. We investigated two different types of undernourished elderly subjects during nutritive therapy: patients with undernutrition in relation to previous undernourishment; patients with undernutrition associated with high acute-phase responses related to on-going disease. The classification of the two groups was based on acute-phase protein levels, i.e. C-reactive protein (> or < 30 mg/l) and α-1-glycoprotein acid (> 1.4 g/l or < 1.0 g/l); Lesourd & Mazari, 1997). The two groups were followed for 3 weeks, the period required to reach maximal intakes in our experiment, and then for a further 5 weeks to quantify the effects of refeeding on immune responses. Refeeding improved the immune responses of undernourished elderly subjects, but in a different manner with regard to the levels of acute-phase responses (Table 4). In undernourished patients with low acute-phase responses, we were unable to detect any cytokines in the serum. Refeeding induced improved secretion of cytokine in *in vitro* cultures, not only in phytohaemagglutinin-activated lymphocyte cultures (IL-2) but also in lipopolysaccharide-activated monocyte cultures (IL-1 and IL-6; Table 4). This effect was highly correlated with increases in serum albumin. In contrast, the immune effect of refeeding required longer-term nutritive therapy to be quantifiable in aged patients with high acute-phase responses. In these patients *in vivo* activation of the immune system was evident, since serum cytokines could be quantified at the onset of treatment. Furthermore, supernatant fractions from cell cultures had lower cytokine contents after 3 weeks of nutritive therapy (Table 4). At this stage, serum albumin was unchanged even though there was a decrease in serum acute-phase proteins, which were still at high levels (CRP > 30 mg/l, on average). Subsequently, when acute-phase responses had further decreased (CRP < 30 mg/l for approximately all subjects), serum albumin levels and the release of cytokine from cell cultures were increased. This finding indicates that immune responses only increase in undernourished elderly subjects when nutritive therapy is effective, as assessed by serum albumin levels. Furthermore, the number of patients who died during the study was low (data not shown). In those who died neither serum albumin nor *in vitro* cytokine from cultures of the supernatant fraction increased but, in contrast, they decreased. Moreover, *in vivo* serum cytokines also decreased, indicating that patients were no longer able to fight on-going disease or to boost their immune system *in vivo*. The fact that acute-phase responses remained unchanged and/or decreased in dying patients indicates that they had reached a state where they had exhausted their metabolic capacities.

In another study, we quantified malondialdehyde, a product of lipid peroxidation, in patients with PEM receiving nutritive therapy. Malondialdehyde levels were increased in elderly subjects with PEM as compared with healthy aged controls (Table 5). During refeeding treatment which provided 1- to 2-fold RDA for each antioxidant micronutrient (vitamins A, C and E, Zn and Se) for 40 d, malondialdehyde levels increased and remained high compared with initial levels. Refeeding therefore induced increased free radical production in elderly subjects with PEM. This increase was limited before nutritive therapy in patients with PEM, probably in relation to a PEM-induced decrease in metabolic capacity. When refeeding provided enough nutrients to boost metabolism processes, then metabolism and consequently free radical production increased. Providing antioxidants at RDA levels is inadequate to protect against the increased free radical production due to the boost in metabolism in elderly subjects with

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PEM, while RDA levels are sufficient in children (Khaled *et al.* 1995). In elderly patients hospitalized in long-stay units, it has been shown that providing antioxidant micronutrients at a similar level (1- to 3-fold RDA) leads to an increase in plasma micronutrient levels (Monget, 1992; Galan *et al.* 1994; Girodon *et al.* 1997*a*) and to lower malondialdehyde levels (Monget, 1992; Galan *et al.* 1994; Girodon *et al.* 1997*a*), but this treatment needs to be of longer duration (at least 6 months; Monget, 1992) and does not induce increased immune responses (Girodon *et al.* 1997*a*). The increased sensitivity to free radicals of elderly subjects with PEM and/or disease may be one of the factors limiting successful treatment. Free radicals induce decreased immune responses (Kehrer & Smith, 1994; Harman, 1995). This may be the key factor in explaining why immune responses in elderly subjects with PEM and inflammation improve slowly.

Ageing is partly due to free radical damage accumulated over the lifespan (Lang *et al.* 1992; Harman, 1995; Meydani *et al.* 1995). Any disease induces increases in metabolic processes and therefore increases free radical production (Kehrer & Smith, 1994; Scarfiotti *et al.* 1997) leading to cell damage. Diseases represent a form of accelerated ageing termed pathological ageing. Repeated episodes of infectious diseases, which occur in acquired immune deficiency syndrome (Allard *et al.* 1998), have a similar effect, and promote accelerated ageing of the immune system (Scarfiotti *et al.* 1997), as shown by changes in TH1 : TH2 (Lucey *et al.* 1996). Such changes were observed in acquired immune deficiency syndrome (Clerici & Shearer, 1994; Lee *et al.* 1998) and in Down's syndrome (Cosarrizza *et al.* 1991), two forms of accelerated ageing of the immune system (Cosarrizza *et al.* 1991; Clerici & Shearer, 1994). In both cases a change in helper immune responses from TH1 to TH2 was observed, a similar phenomenon to that observed in immune ageing (Shearer, 1997). The difference we observed during an episode of disease was the greater sensitivity of elderly subjects to free radical damage, which reveals an apparent inability to protect themselves from exposure to free radicals. It may be considered necessary to treat elderly diseased subjects with high levels of antioxidant micronutrients in order to protect cells from free radical damage. Higher levels than the present RDA have been proposed (Bendich, 1990) to prevent 'normal' ageing. This type of treatment may be of long duration, since stress responses are of long duration in aged patients (Hayek *et al.* 1997; Jurivich *et al.* 1997). The macrophage is now thought to be a key cell in immune ageing in relation to free radical production. It was recently shown that macrophage PG contributes to the age-associated decrease in T-cell function (Hayek *et al.* 1997). This effect is important in aged subjects due to high levels of macrophage PGE_2 production and the increased sensitivity to PGE_2 of lymphocytes from aged subjects (Goodwin *et al.* 1982). Antioxidant treatment with high vitamin E intakes reverses high PGE_2 production and partly restores immune functions (Beharka *et al.* 1997), and further points to the importance of macrophages and free radicals in immune ageing. Furthermore, in rodent models energy restriction, which decreases free radical production (Venkatraman & Fernandes, 1994), inhibits the age-related dysregulation in cytokine production (Spaulding *et al.* 1997).

Conclusion

Ageing of the immune system is characterized by the appearance of progressive dysregulation between different functions of the immune system. With ageing there are gradual increases in immature : mature, memory : naive, T lymphocyte TH1 : TH2 and B lymphocyte CD5+ : CD5–. These changes are induced by two main factors, i.e. decreased thymic function, and antigenic pressures over the lifespan. These changes are important during early life (up to 30–40 years of age in human subjects), a period which is important in acquiring adapted immune responses against foreign antigens. Nevertheless, similar changes in immune responses continue with age, but at a lower rate. Ageing is also characterized (mainly in the second half of life) by a progressive dysregulation between monocyte function (which is unchanged) and lymphocyte function (which decreases). It appears that acquired immunity weakens with age, probably because its adaptive capacity is limited by its own regulation, while innate immunity, a more primitive system, is unchanged.

Ageing is well-known to be associated with lower adaptive capacities. This is true for acquired immunity, not only in facing antigenic challenges but also in relation to metabolic changes such as those resulting from underfeeding and/or nutritional responses to disease (hypercatabolism syndrome). Aged subjects are particularly sensitive to nutritional influences, and any nutritional deficit (i.e. energy, protein or even micronutrient) may lower the immune responses of the elderly. As nutritional deficits are frequent in diseased subjects, many, if not all, elderly diseased subjects exhibit decreased immune response and a lower capacity to fight disease. Furthermore, micronutrient deficits are also frequent in the elderly, and some of the age-related change in immune response may be due to lower nutritional status. The declines in nutritional status and in immune response with age are interrelated. The lower capacity of the elderly to fight disease partly results from the dysregulation of the immune system, i.e. from the dysequilibrium between macrophage function (innate immunity) and lymphocyte function (acquired immunity). This dysequilibrium forces macrophages to play a more intense role in defence mechanisms of the elderly, i.e. to secrete more cytokines. Consequently, acute-phase responses are more intense and/or of longer duration in the elderly, leading to greater use of body nutritional reserves. Furthermore, the age-related decrease in metabolism is responsible for incomplete rebuilding of nutritional reserves during recovery. In the absence of nutritional treatment (which is necessary to help the elderly respond to the nutritional consequences of diseases) after recovery, the elderly have lower body reserves and lower immune responses. As a result of successive bouts of disease, the elderly progressively become frail. Nutritional therapy must be given to all elderly patients for both the duration of the disease and throughout the recovery period (which is of longer duration in aged patients). In addition, it may be necessary to consider higher micronutrient intakes in apparently-healthy elderly subjects, either to boost immune responses or to prevent a decline in immune response.

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