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Pathogenetic Mechanisms Responsible for the Production of Secondary Immunodeficiency

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Summary

Abnormalities of the immune response can be secondary to old age, to several pathologic conditions (i.e. diabetes mellitus, renal failure, solid and lymphohematologic neoplasias, leukopenia, malnutrition, autoimmune diseases, AIDS), to surgical stress or to burns, and to immunosuppressive therapies, both medical (corticosteroids, cytotoxic agents, antilymphocytic globulins) and surgical (splenectomy) as well as radiant (extensive radiotherapy).

Old age can affect both humoral (reduced antibody synthesis) and cell-mediated (thymus involution, diminished ratio Th/Ts, depression of both delayed hypersensitivity reactions and cytotoxic activity of K cells) immune response. Hyponutrition, often observed in the elderly, adds a reduced production of secretory IgA, lysozyme and interferon, diminished complementary activity, phagocytosis defects, and vitamin deficits. Furthermore, in some chronic diseases we can observe reduced primary antibody response or depression of delayed hypersensitivity reactions (renal failure, neoplasias), changes in leukocyte functions (diabetes mellitus, leukemias and lymphomas) and, in particular in solid neoplasias, increased activity of Ts lymphocytes and the presence of circulating immunocomplexes. Changes in phagocytosis, opsonization and chemotaxis are typically seen in burns, whereas surgical stress can cause some inhibition of cell-mediated immunity. Finally, after splenectomy it is possible to observe an increased synthesis of IgA and IgG and, on the contrary, reduced production of IgM and properdin.

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INTRODUCTION

The term "secondary immunodeficiency" or acquired immunodeficiency brings immediately to mind subjects tied to AIDS. But in reality AIDS represents only the tip of the iceberg if one considers that significant alterations in the host immune response are caused by a whole series of physiological and pathological conditions (summarized in *Tables 1-3*), some of which (such as old age, malnutrition, surgical stress, diabetes mellitus, cancer) appear to be

TABLE 1 - *Causes of secondary immunodeficiency.*

- Diseases with diminished immune response
- Pharmacological or radiation immunodepressive therapy
- Extremely young or old age
- Surgery, trauma, burns
- Malnutrition
- Splenectomy

TABLE 2 - *Secondary immunodeficiency: diseases with diminished immune response.*

- Diabetes mellitus
- Renal insufficiency
- Malignant neoplasia or hemolymphopathy (leukemia, lymphoma, myeloma)
- Diseases causing leukopenia
- Autoimmune diseases: LES, rheumatoid arthritis
- AIDS, bacterial or viral infections

TABLE 3 - *Therapies which cause decreased immune response.*

- Extensive radiotherapy
- Use of corticosteroid or cytotoxic drugs (cyclophosphamide, azathioprin, methotrexate and others)
- Use of antilymphocytic globulin
- Splenectomy

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much more frequent than AIDS. The primary clinical consequences of immunodeficiency in a patient are a greater propensity not only to infections (*Table 4*) but also to cancer, autoimmune and allergic diseases.

TABLE 4 - *Pathogens most often responsible for infection.*

Bacteria
- Gram-negative aerobic bacilli (Enterobacteriaceae, Pseudomonadaceae)
- Staphylococci
- *Mycobacterium tuberculosis* and atypical mycobacteria
- *Listeria monocytogenes*
- *Legionella pneumophila*
- *Legionella micdadei* (agent of Pittsburgh pneumonia)
- *Nocardia asteroides*

Virus
- *Herpes simplex*
- *Varicella zoster*
- Cytomegalovirus
- Epstein-Barr virus
- Papova (papilloma) virus

Protozoa
- *Pneumocystis carinii*
- *Toxoplasma gondii*

Helminths
- *Strongyloides stercoralis*

Yeasts
- *Candida albicans*
- *Cryptococcus neoformans*
- *Histoplasma capsulatum*
- *Coccidioides immitis*
- *Blastomyces*
- *Aspergillus*

We will discuss the main alterations in the host immune system caused by the following:
- extreme young or old age
- malnutrition: *hypernutrition or hyponutrition*
- bacterial or viral infections
- immunosuppressive therapy: *corticosteroids, cytotoxic agents, radiation therapy*
- solid and hemolymphoproliferative neoplasias
- trauma: *surgical stress, burns*
- miscellaneous: *diabetes mellitus, chronic renal insufficiency, splenectomy, liver cirrhosis, autoimmune disease.*

It is evident that often more than one of the above factors appears simultaneously in the same patient (for example, an older patient with malnutrition or diabetes or a cancer patient undergoing cytostatic or radiation therapy, etc.), with the consequent negative effects.

EXTREME YOUNG OR OLD AGE

In this situation significant physiological variations of the immune functions are often observed.

Neonates, for example, have diminished capacity for polymorphonuclear (PMN) migration, while a reduction in their phagocytic or bactericidal activity is present only under certain limiting *in vitro* or *in vivo* conditions. Controversy exists over the possibility of qualitative and quantitative alterations in T lymphocytes, while notable reductions in serum opsonizing activity, production of chemotactic factors and of some components of the complementary system, particularly C3 have been observed[1]. Furthermore, the IgM IgG antibody response has been shown to be slower [2].

In older patients reduced function of T lymphocytes tied to thymic involution and demonstrated principally in diminished proliferative response to mitogens such as phytohemagglutinin (PHA) and concanavalin A (Con-A) and in depression of delayed hypersensitivity reactions was observed [3,4]. Reduced production of interleukin-2 is often encountered while interleukin-1 seems to remain unaltered [3].

Less frequent are alterations dependent on humoral immunity, even if the elderly are more frequent victims of infections caused by encapsulated bacteria [3]: serum IgG tends to increase and IgM to remain constant or diminish slightly [5]. Qualitative alterations in humoral immunity which are sometimes noticed are ascribed to some defects in B cells, others to increased suppressor T lymphocyte activity and/or to reduced helper T lymphocyte activity with consequent depression of especially the primary antibody response [3,4]. Reduced presence of secretory IgA, especially in the nasal mucus of healthy elderly and those with respiratory tract infections, has been observed [6]. Finally, altered PMN functions, particularly in chemotaxis and bactericidal activity, even if generally not associated with higher incidence of bacterial infections, can occur [7].