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Environmental factors, the immune system and the susceptibility to infection

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Individual susceptibility to infection, disease and death is influenced by various factors such as host genotype, age, psychological state, virulence of the infectious agent and also by ecological, socio-economical and cultural changes. The interplay between these internal and external factors is complex and their relationship to new or resurgent infections is often very poorly understood. It is known that environmental factors can impair the immune system. To what extent these immunological changes modify susceptibility to infection is more difficult to assess and is often speculative.

In this paper, the diversity of the immune response to infectious agents and the impact of external factors such as malnutrition and environmental 'modulators' on these responses are reviewed. As an illustrative example, susceptibility to infection with the human immune deficiency virus (HIV) will be discussed, as well as the way in which this virus, as a recently introduced 'environmental' factor itself, has affected the reappearance of other infectious diseases. HIV changes host susceptibility to tuberculosis, toxoplasmosis and herpes simplex but not to streptococcal infections or malaria. To explain this paradox, it is essential to understand the mechanism of protective immunity to these infectious agents and the nature of the immune defects caused by HIV itself.

The immune response to infectious agents

When an infectious agent invades the body, the immune system activates innate and acquired (adaptive) immune responses (Figure 6.1). Innate immune responses are not antigen-specific, do not 'mature' upon repeated exposure, and require no 'education'. They constitute the first line of immune defence and involve humoral

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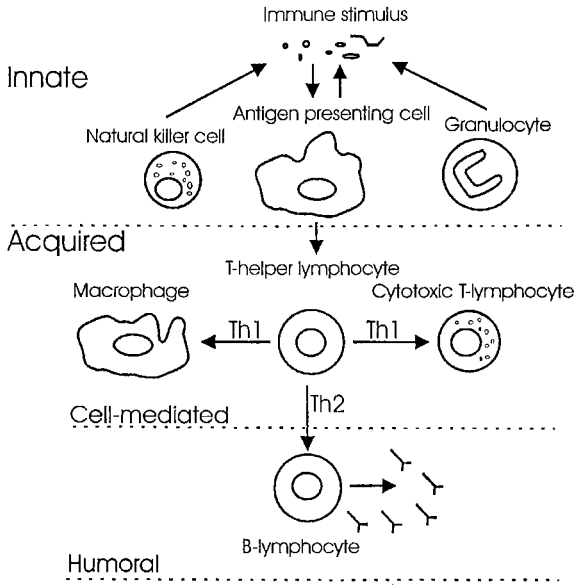

Figure 6.1 Immune responses to infectious agents comprise innate or non-specific responses and acquired or antigen-specific responses. The type of immune response is determined primarily by the nature of the infectious agent. Obligate intracellular viruses and parasites induce a cell-mediated immune response which is facilitated by cytokines which enhance cell-mediated immunity (Th-1 cytokines). Extracellular bacteria and parasites are neutralized mainly by a humoral immune response (antibodies, complement, etc.) which is driven by cytokines which enhance humoral immune responses (Th-2 cytokines)

components such as complement proteins, acute-phase proteins and other inflammatory mediators such as interferons and interleukins, as well as cellular components such as neutrophils, platelets, various tissue cells, mononuclear phagocytes and natural killer cells. On the other hand, adaptive immune responses are highly specific for a particular pathogen and improve with each re-exposure to the same pathogen. The adaptive immune response 'learns' and 'remembers' the infectious agent and can often prevent it from causing disease on a subsequent encounter. Cells which are central to adaptive immune responses are T-lymphocytes (T-cells) and B-lymphocytes (B-cells). B-cells produce antibodies whereas T-cells have another range of activities. Some subsets of T-cells are involved in helping B-cells to produce antibodies directed against extracellular pathogens (T-cell-dependent antibody production) whereas others interact with phagocytic and cytolytic cells and instruct them to destroy intracellular pathogens. Adaptive immune responses are generated in the context of the major histocompatibility complex (MHC) and are thus dependent on the genetic constitution of the host.

Mechanisms of protective immunity depend largely upon the nature of the infectious agents. Viruses are obligate intracellular organisms and require different immune responses than extracellular bacteria and parasites. As a rule, humoral immune responses are very efficient in neutralizing extracellular microbes whereas virus-infected cells and intracellular parasites can be destroyed only by cytolytic effector cells.

Host susceptibility or resistance to infection is determined, at least partially, by the type of immune response that the host develops. For instance, protective immune responses to intracellular viruses, bacteria and parasites such as cytomegalovirus, influenza virus, *Listeria monocytogenes, Mycobacterium leprae, M. tuberculosis, Leishmania* spp. and *Trypanosoma cruzi* are achieved predominantly through an adaptive cell-mediated immune response (Th1), whereas susceptibility to some of these agents is seen in individuals who mount a predominantly humoral immune (Th2) response.

Environmental factors can selectively interfere with either one or with both arms of the immune response and thus change the host susceptibility to infectious agents. Host factors which influence the immune response include genetic determinants and age. Environmental factors that can modulate the immune response include malnutrition, immunosuppressants, co-infections, mental stress, depression and exposure to pollutants and immunotoxins (Table 6.1).

Effect of the nutritional status on the immune response

Nutritional status is a well recognized determinant of immunocompetence. Nutritional disorders, affecting several hundred million people worldwide, can increase morbidity and mortality from many infections (Chandra and Newberne, 1977). Among the factors that determine nutritional status are food quality, food quantity and digestive efficiency. In addition, infection itself can deprive the body of nutrients and contribute to immunodeficiency, thus establishing a vicious circle (Storey, 1993). At one end of the spectrum of malnutrition are the gross changes seen in protein-energy malnutrition (PEM). More subtle changes are observed when specific nutrients like certain minerals and trace elements are selectively lacking.

Several components of the immune system are impaired in children who suffer from severe malnutrition. In PEM, the observed immunological defects are partially due to the effect of malnutrition on the lymphoid tissues, which are particularly susceptible as a result of their rapid rate of turnover and synthesis of immunomodulating proteins. Thymus, spleen, lymph nodes and Peyer's patches are altered in size and structure in children with severe PEM (Chandra, 1992).

Skin test responses to recall-antigens (delayed hypersensitivity skin responses), a useful *in vivo* measure of cell-mediated immunity, are reduced. Complete anergy (non-responsiveness) to a battery of different antigens is sometimes seen. A profound reduction of CD4+ T-helper cells is found in PEM, resulting in a

Table 6.1 Environmental factors which can affect the immune response

Environmental factor	Immunological impairment	Mechanism	Further reading
Malnutrition			
Protein energy malnutrition (PEM)	IFN-γ and IL-2 production, phagocytic activity, complement pathway, mucosal IgA response, DTH, T-LPR	Atrophy of lymphoid organs	Chandra, 1992; Chandra and Kumar, 1994 (overview)
Trace element deficiency			
Fe, Zn, Cu, Se	T-LPR (mitogens), NK, CTL, intracellular killing of bacteria by phagocytes, lymphokine production, neutrophil function	Reduced antioxidant function (metalloenzymes catalase (Fe), superoxide dismutase (Zn/Cu), glutathione peroxidase (Se))	Good and Lorenz, 1992; Bendich, 1993; Weiss *et al*, 1995; Harbige, 1996
Vitamin deficiency			
Vitamin A	CMI, T-cell-dependent antibody production, secretory IgA production	Unknown	Rumore, 1993
Vitamin B6 and B12	DTH, T-LPR, CTL	Thymic atrophy, B6 and B12 mediate DNA synthesis	Miller, 1992 (overview)
Vitamin C, Vitamin E	DTH, T-LPR, neutrophil bactericidal function, mucosal surface integrity	Antioxidant, co-factor in hydroxylation of proline and lysine (collagen synthesis)	Harbige, 1996; Chew, 1995
Neurological stress			
Mental stress	NK, CTL	(?) Neuropeptide receptors on immune cells	Cohen, 1995; Cohen and Herbert, 1996; Glaser *et al*, 1992; Irwin, 1988; Maes *et al*, 1991
Severe depression	NK, T-LPR		

Immune suppressants			
Azathioprine	CMI and humoral immunity (blocks DNA synthesis)	Interferes with purine biosynthesis	Sigal and Dumont, 1993 (overview)
Steroids	CMI, IFN-γ-antagonist, anti-inflammatory molecule	Steroid receptor on immune cells	Lew *et al*, 1988
Cyclosporin, FK-506	CMI (blocks lymphocyte activation)	Blocks IL-2 gene transcription	Sigal and Dumont, 1992
Rapamycin	CMI (blocks lymphocyte activation)	Blocks intracellular signalling through IL-2-R?	Sigal and Dumont, 1992
Environmental pollution			
Pesticides			
PCDDs, PCBs, PCDFs	NK, T-LPR, DTH, MLR, primary antigen-specific responses	TCDD binding to a cytosolic protein, the aryl hydrocarbon (*Ah*-) receptor, resemblance to TCDDs	de Swart *et al*, 1994, 1995; Ross *et al*, 1995
Ultraviolet B radiation (stratospheric ozone depletion)	DTH responses in the skin	Impairs function of antigen-presenting cells of the skin (Langerhans cells)	Morison, 1989; Patz *et al*, 1996

CMI = cell-mediated immunity; NK = natural killer cells; CTL = cytotoxic T-lymphocytes; DTH = delayed type hypersensitivity; MLR = mixed lymphocyte reaction; T-LPR = T-lymphocyte proliferative responses; PCDDs = polychlorinated dibenzo-*p*-dioxins; TCDDs = 2,3,7,8-tetrachloro-dibenzo-*p*-dioxin; PCBs = polychlorinated biphenyls; PCDFs = polychlorinated dibenzofurans

significant reduction of T-helper (Th1) activity which explains, to a large extent, the alteration of cellular functions seen in children with PEM. Humoral (Th2) responses are less affected, as shown by near normal serum antibody responses after immunisation with common antigens. Nevertheless, mucosal IgA responses can be seriously depressed, enhancing the risk of mucosal infections (Chandra and Kumari, 1994), which, by resulting in diarrhoea, can further aggravate nutritional status and hence immune competence.

Some minerals, such as potassium, sodium, calcium, phosphorus and magnesium, are present in large amounts in the body. Others, such as selenium, zinc, iron and copper, are required only in small quantities, but nutritional deficiency of those trace elements can occur if available food lacks diversity. Enzyme and metabolic function may be significantly reduced by deficiencies in trace elements and vitamins. The most thoroughly studied trace element and vitamin deficiencies are those involving zinc, copper, iron, selenium, and vitamins A, B and E. Iron deficiency is the most common single nutrient deficiency, occurring in both developed and underdeveloped countries. It is characterized by reduced intracellular killing of bacteria by phagocytes, decreased T-cell numbers, reduced lymphocyte transformation to mitogens and by lowered lymphokine production (Weiss *et al*, 1995). The cellular basis of these various effects is reduced activity of ribonucleotidyl reductase (explaining the decreased proliferative responses depending on DNA and RNA synthesis) and decreased myeloperoxidase activity and hydroxyl radical production (explaining the deficient intracellular killing of bacteria by phagocytes). Zinc deficiency is associated with a depressed antibody production to heterologous antigens, reduced lymphocyte proliferative responses to mitogens, and depressed polymorphonuclear neutrophil, natural killer and cytotoxic T-cell function (Good and Lorenz, 1992). Selenium is necessary in sufficient amounts for protective immune responses to viruses. A critically low selenium level impairs T-cell functions and decreases natural killer cell activity (Harbige, 1996). Zinc, copper and iron are important in the antioxidant activity of some metallo-enzymes which neutralise intracellular free radicals. Free radicals and reactive oxygen species are produced by immune cells to destroy invading pathogens whereas the antioxidative system ensures that the formation of free radicals in living cells does not result in cellular damage (Bendich, 1993).

Deficiency of certain vitamins can also adversely affect immune functions. Vitamin A deficiency depresses cell-mediated immunity and T-cell-dependent antibody production, including secretory IgA production essential for the establishment of immunity to mucosal pathogens (Rumore, 1993). Vitamin E and C are naturally occurring antioxidant nutrients and enhance immunity, at least in part, by maintaining the functional and structural integrity of important immune cells (Chew, 1995; Harbige, 1996).

Immunosuppressants and susceptibility to infection

Immunosuppressants can increase the risk of infection significantly. Immunosuppressive agents can be grouped into several categories. Traditional immunosuppressives interfere with cellular metabolism and have a significant toxic effect. Examples of such antiproliferative agents are cyclophosphamide, methotrexate and azathioprine. They can cause non-specific suppression of both humoral and cell-mediated immune responses. Glucocorticosteroids suppress immune and inflammatory responses by inhibiting the expression of inflammatory mediators such as arachidonic acid metabolites and IL-1 (Lew *et al*, 1988). Another large group of agents inhibit signal transduction events at the cell surface or within the cell, resulting in non-specific immunosuppression and increased susceptibility to infection, although this is less drastic than that caused by the antiproliferative agents. Well known examples include cyclosporin A, FK-506 and rapamycin. They act as inhibitors of T-cell activation and interfere with the regulation of IL-2 gene transcription (CsA, FK506) or IL-2 receptor signal transduction (rapamycin) (Sigal and Dumont, 1992).

Mental stress, clinical depression and the immune system

Many studies have examined the relationship between mental stress, clinical depression and immunity (Cohen and Herbert, 1996). Emotional stress is often followed by increased susceptibility to bacterial and viral infections, at least for the less serious infectious diseases such as colds, influenza and herpes virus infection (Kiecolt-Glaser and Glaser, 1991; Cohen, 1995). The ability of mental stress to influence an immune response to a primary antigen has been well illustrated in a study of a group of students who were given a recombinant hepatitis B vaccine during a three-day academic examination period (Glaser *et al*, 1992). Those students who seroconverted after the first injection were significantly less stressed and anxious at the time of vaccination than those who did not seroconvert. Stress-associated reductions of important immunological anti-viral responses, such as those involving cytotoxic T-lymphocytes and natural killer cells, have also been observed in asymptomatic HIV-infected subjects (Evans *et al*, 1995). Similar observations were made in patients with severe depression (Irwin, 1988; Maes *et al*, 1991). Apparently, the immune system can be affected directly by innervation or by a neuro-endocrine cascade and vice versa. This bidirectional communication between the immune system and the central nervous system is achieved by means of common receptors and biologically active substances such as cytokines and neuropeptides (Savino and Dardenne, 1995).

Effect of environmental pollutants on the immune system

Because of the wide use of pesticides for domestic and industrial purposes, their potential immunotoxic effects are a matter of major concern for public health. Evidence that pesticides can severely impair immune functions in humans is scarce. Contact hypersensitivity is a well defined, although rare, consequence of exposure to pesticides, but immunologically mediated systemic reactions have been described only as debatable case reports (Vial *et al*, 1996). Studies in laboratory animals have shown that the mammalian immune system can be affected adversely by a variety of chemical agents (Vos and Luster, 1989; Saboori and Newcombe, 1992; Luster and Rosenthal, 1993; Lai *et al*, 1994) but, in most cases, these studies focused on acute immunotoxicity caused by relatively high levels of exposure. Potentially immunotoxic chemicals such as polychlorinated biphenyls (PCBs) and polychlorinated dibenzo-*p*-dioxins (PCDDs), dibenzofurans (PCDFs), hexachlorobenzene (HCB), dieldrin, β-hexachloro-cyclohexane (β-HCH) and dichlorodiphenyl trichloro-ethane (DDT) are present in abundance in the marine environment. Top predators are known to accumulate high levels of some of these xenobiotics. When morbillivirus infections led to massive mortalities among harbour seals in Europe in the early 1990s, it was speculated that this was caused by the adverse effect of environmental chemicals on the immune system of these animals. In a recent study carried out by de Swart *et al* (1995), statistically significant changes in cellular immune responses were detected in harbour seals that were fed on environmentally contaminated herring from the Baltic Sea. Whether induced immunological changes were the major determinant that promoted the virus infection and caused mass mortalities among seals is difficult to prove.

The mechanism of immune suppression induced by the most extensively studied group of immunotoxic chemicals, TCDD and related compounds including PCDDs, PCDFs and PCBs, is thought to be mediated by binding to a cytosolic protein, the aryl hydrocarbon receptor (Holsapple *et al*, 1991). The toxicity of these chemicals is largely dependent on their stereochemical resemblance to TCDD, the chemical with the highest affinity for this receptor. Through their interaction with this receptor, they can activate key protein kinases that are involved in the growth factor signal-transduction pathway (Matsumura, 1995).

Climatic factors can influence susceptibility to infectious diseases as well. Ultraviolet radiation is a possible factor involved in climate-related immune dysfunction. Ultraviolet B radiation induces selective biological alterations in the skin, including suppression of normal immune responses, probably through its effect on Langerhans cells, the most important antigen-presenting cells of the skin (Morison, 1989). The pathogenic consequences of UVB radiation can be observed in the exacerbation of infectious diseases and development of skin cancer (Vermeer and Hurks, 1994). UV-mediated immune suppression may become more important in the future as a consequence of an increased flux of ultraviolet radiation (Patz *et al*, 1996).

Susceptibility to HIV and the effect of HIV on the immune system

Cellular immune responses to HIV and disease progression

Human immune deficiency virus (HIV) is characterized by its dramatic effect on the immune system. It infects and kills CD4+ T-helper lymphocytes, which play a pivotal role in the generation of an immune response (Figure 6.1). Once an individual becomes infected with HIV, the host reacts with a vigorous immune response against the virus. HIV-specific cytotoxic T-cells are generated, killing infected cells, and neutralizing antibodies are produced which limit the spread of cell-free virus. Nevertheless, the virus escapes from these vigorous but apparently inadequate immune responses, resulting in a chronically overactivated immune system which finally collapses and leaves the host in a state of severe acquired immune deficiency (AIDS). Lymph nodes are the main reservoir for HIV, and even during the asymptomatic stage of the infection billions of virus particles are produced every day and millions of CD4+ T-cells are destroyed (Fauci *et al*, 1993; Ho *et al*, 1995; Wei *et al*, 1995).

CD8+ T-cells are thought to play an important role in the immune defence against HIV. Large numbers of activated cytotoxic CD8+ T-cells (CTL) are generated early after infection and may slow down disease progression (reviewed by Autran *et al*, 1996). Nevertheless, the persistence of virus replication indicates the inability of CTL to eradicate HIV. Moreover, during the asymptomatic stage of the infection, vigorous polyclonal CTL responses directed against HIV are associated with the generation of a large number of virus variants (Ho *et al*, 1995; Wei *et al*, 1995) which are no longer recognised by CTL (Phillips *et al*, 1991; Haas *et al*, 1996) and which ultimately result in disease progression.

CD8+ T-cells are also able to control HIV replication without killing infected cells. This antiviral activity appears to be mediated by soluble factors such as chemokines (Cocchi *et al*, 1995) and CD8+ T-cell antiviral factor (CAF) (reviewed by Levy *et al*, 1996). CD8+ T-cells from asymptomatic HIV-infected subjects produce high levels of these suppressor factors and it has been suggested that they are important in preventing progression to clinical disease (Levy *et al*, 1996).

CD8+ T-cells are activated by Th1-like cytokines (IL-2, IFN-γ, TNF-α) whereas Th2-like cytokines (IL-4, IL-5, IL-6, IL-10, IL-13) tend to suppress cell-mediated immune responses. Studies have suggested that HIV disease progression is associated with a profound shift from a 'protective' cell-mediated (Th1) to a 'non-protective' humoral (Th2) immune response (Clerici and Shearer, 1993) but this hypothesis has generated a great deal of controversy due to discordant findings from different laboratories and is not accepted universally.

Susceptibility or resistance to infection with HIV

During the past five years, it has become clear that (i) a small group of HIV-seropositive individuals who have been infected for at least 10 years have

not progressed to AIDS (so-called long-term non-progressors or LTNP) and (ii) there exists a small group of HIV-seronegative individuals who have been exposed to the virus many times and yet have not seroconverted or become infected.

The majority of LTNP have high levels of HIV-specific CTL in their peripheral blood and in their lymph nodes (Pantaleo *et al*, 1995) and their CD8+ T-lymphocytes produce large quantities of HIV suppressor factor (Levy *et al*, 1996) responses that are thought to play an important role in preventing HIV disease progression in LTNP.

Interestingly, HIV-specific cellular immune responses have been detected in HIV-seronegative individuals who have been exposed to the virus many times without being infected, suggesting that innate and/or naturally acquired immune responses to HIV may be protective in rare individuals (reviewed by Shearer and Clerici, 1996). Peripheral blood mononuclear cells obtained from different individuals are not equally permissive to HIV, and CD4+ T-cells taken from apparently HIV-'resistant' subjects produce more chemokines (RANTES, MIP-1 and MIP-1β) than do CD4+ T-cells obtained from HIV-susceptible individuals (Paxton *et al*, 1996). Although it had already been shown that these chemokines could prevent infection of monocytes by monocytotropic HIV strains (Cocchi *et al*, 1995), the precise mechanism remained unknown until the discovery of the HIV co-receptors. The CD4 molecule, which is expressed at the cell surface of helper T-cells and monocytes, was identified as the primary cell receptor for HIV many years ago and, although HIV binds tightly to CD4, expression of CD4 was found to be insufficient to allow HIV entry into non-human cells (Maddon *et al*, 1986). The discovery that the chemokine receptor CCR5 acts as a co-receptor for HIV (Alkhatib *et al*, 1996) explains why and how certain chemokines can block HIV infection. They interfere with HIV infection by binding to and blocking receptor availability to HIV. Another member of the chemokine-receptor family, CXCR4 (fusin), had already been identified earlier as a co-receptor for lymphotropic HIV variants (Feng *et al*, 1996).

Shortly after the discovery of the two co-receptors for HIV, Samson *et al* (1996), Dean *et al* (1996) and Liu *et al* (1996) described a polymorphism in the gene coding for CCR5. The presence of a mutation in this gene, a 32 base pair deletion, confers resistance or partial resistance to HIV infection. The gene product results in a non-functional receptor that does not support membrane fusion of HIV with its target cell. Population studies indicate that the homozygous defect is found in 1–2% of Caucasians, and the heterozygous defect in 13–16% of this population (Samson *et al*, 1996; Huang *et al*, 1996). So far, no HIV-infected Caucasians, homozygous for the mutation, have been found. Whether heterozygotes are also less susceptible to HIV infection is still controversial (Samson *et al*, 1996; Huang *et al*, 1996). This protective allele appears to be absent in black populations from Western and Central Africa and from populations in Japan (Samson *et al*, 1996; Huang *et al*, 1996). Since apparent resistance to HIV has also been observed in

these populations (Fowke *et al*, 1996), factors other than defective co-receptors must also be involved.

Environmental factors can affect susceptibility to HIV infection

Successful replication of HIV in CD4+ T-lymphocytes is determined by the state of activation of HIV-infected cells. Only activated cells produce large amounts of infectious virus particles. Therefore, concurrent infections, which stimulate the immune system, may enhance HIV replication in infected cells and accelerate HIV disease progression. In addition, infections may activate the immune system of HIV-seronegative subjects and render them more susceptible to infection with HIV. As a consequence, one might expect to find a higher susceptibility to HIV in areas where many other infectious diseases are prevalent, such as most developing countries. The rapid spread of HIV in developing countries may, in part, be accounted for by this phenomenon. Infections, such as tuberculosis (TB), that chronically activate the immune system could be especially damaging (Vanham *et al*, 1996). *Mycobacterium tuberculosis* (MTB) can activate the expression of HIV in latently infected monocytic cell lines, and monocytes obtained from TB patients support HIV replication better than monocytes from control persons (Toossi *et al*, 1993; Lederman *et al*, 1994). MTB increases HIV replication in peripheral blood mononuclear cells and this is correlated with the level of cellular activation which is a predominant characteristic of HIV-infected subjects (Kestens *et al*, 1992; 1994; Goletti *et al*, 1996). HIV replication was found to increase 5- to 160-fold during the acute phase of MTB disease (Goletti *et al*, 1996). These observations provide the underlying explanation for the clinical finding that infection with MTB can accelerate the clinical course of HIV (Whalen *et al*, 1995).

Both ulcerative and non-ulcerative sexually transmitted diseases (STDs) are known to increase susceptibility to HIV (Laga *et al*, 1993; Torian *et al*, 1995). Ulcerative STDs probably facilitate HIV entry through mucosal lesions, rather than by their effect on the immune system. The precise role of non-ulcerative STDs, such as gonorrhoeal, chlamydial and trichomonal infections, needs further elucidation.

Infections such as those caused by *Schistosoma mansoni* infection may drive the immune response towards a Th2-like profile and increase susceptibility to HIV infection. In mice infected with *S. mansoni*, suppression of Th1 reactivity by a dominant Th2 response has been shown to result in failure of virus-specific CD8+ T-cell responses to vaccinia virus (Actor *et al*, 1993). This suggests that helminth infections can influence immune responses to concurrent viral infections (Kullberg *et al*, 1992). Bentwich *et al* (1996) have shown a very high prevalence of helminthic and other infections associated with extreme immune dysregulation as well as a high prevalence of HIV-1 in Ethiopian immigrants to Israel. Although one of the striking characteristics of the AIDS epidemic in Africa is the way the

disease differs from the pattern seen in other areas, the reasons for this are not clear. It has been suggested that changes in the host immune response caused by endemic infections and mostly helminth infections could account for at least a part of this pattern (Bentwich *et al*, 1995).

Immunisation of HIV-seropositive patients with recall antigens temporarily enhances HIV replication in infected subjects (Stanley *et al*, 1996), raising the question of the advisability of vaccinations in HIV-infected subjects. However, the protection afforded in most cases by vaccination outweighs the potential risks from a transient increase in immune activation.

HIV changes the susceptibility to other infectious diseases

HIV induces progressive and selective immune defects in infected humans. Cell-mediated immune responses of the Th1 type which are required to confer protective immunity against pathogens are particularly compromised. Epidemiological data have demonstrated that HIV-infected individuals are more susceptible to MTB and that the HIV epidemic has a central role in the worldwide resurgence of this infection (Barnes *et al*, 1991). A study conducted by Burwen *et al* (1995) estimated that HIV-induced immunosuppression accounts for a minimum of 30% of the excess TB cases during the period 1985–1990 in the US. In Côte d'Ivoire, the incidence of tuberculosis was 1104 per 100 000 among HIV-infected persons in 1991 but only 96 per 100 000 in HIV-seronegative persons, a figure which is lower than the overall incidence measured in 1981 (155 per 100 000) (Richards *et al*, 1995). HIV affects not only the incidence of MTB but also its clinical presentation. Reactivation of pulmonary TB may occur early in HIV infection whereas extrapulmonary or atypical disease is seen in patients with profound HIV-induced immunodeficiency (Lucas and Nelson, 1994).

Visceral leishmaniasis (*Leishmania donovani*) is another opportunistic infection seen with increased frequency in patients infected with HIV who live in areas endemic for Leishmania. As a result of HIV, visceral leishmaniasis is becoming more important in non-endemic areas as well (Albrecht *et al*, 1996).

Toxoplasmosis, *Pneumocystis carinii* and *Herpes simplex* are classical examples of latent infections which can be reactivated by HIV. In contrast, leprosy (*M. leprae*), malaria (*Plasmodium falciparum*) and amoebiasis (*Entamoeba histolytica*), which are at least partially controlled by cell-mediated immunity and which should theoretically be more frequent in HIV-positive people than in HIV-negatives, do not appear to be more frequent or more aggressive in HIV-infected subjects. The reasons for this are unclear.

Conclusion

It is clear that a variety of environmental factors can disturb the integrity of the immune system in a direct or indirect manner. They can change the susceptibility

of the host to infection and they may have a role in the spread of new or resurgent infectious diseases. Numerous publications have demonstrated that many of these factors induce measurable changes in cellular and humoral immunity. The relative increase in susceptibility to infection depends on the nature of the infectious agent and on the type and degree of immune perturbation.

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