Immunosuppression in Viral Infections

Barry T. Rouse and David W. Horohov

From the Department of Microbiology, College of Veterinary Medicine, University of Tennessee, Knoxville, Tennessee; and the Division of Virology, Office of Biologics Research and Review, Center for Drugs and Biologics, Food and Drug Administration, Bethesda, Maryland

Viruses may cause immunosuppression by a variety of mechanisms. This review delineates four categories. First, immunosuppression can result from the direct effects of viral replication on lymphocyte functions. Either all classes of lymphocytes can be affected, as occurs in measles, or the effect can be restricted to a cell subtype, as is the case with human T cell-lymphotropic virus type III. Second, the activity of soluble factors of viral or host origin released from infected cells can affect immunosuppression. A third mechanism results from viral infection of macrophages and affects the function of these cells in natural and acquired immunity. Finally, immunosuppression may result from viral triggering of an imbalance in immune regulation, which culminates in the overactivity of suppressor cells. A detailed knowledge of the mechanisms by which viruses are involved in immunosuppression may help in the design of strategies to reverse the effect.

Since early in this century, viral infections have been associated with suppressed immunity. Starting, perhaps, with Sir William Osler in 1905, many astute physicians have linked viral infection with subsequent exacerbated disease caused by secondary infecting agents. In human medicine, the example currently catching the most attention is the acquired immunodeficiency syndrome (AIDS). Indeed, this apparently new disease represents an epidemiologic threat of unknown and perhaps alarming proportions. From observations in animals and in vitro models, a variety of mechanisms have been identified by which viruses can suppress immunity. In a few cases, a molecular explanation of how suppression is mediated appears to be at hand. Such information is required in all cases since molecular approaches may reveal ways of circumventing virus-induced immunosuppression. The purpose of this review is to discuss some common examples of virus-mediated immunosuppression and to categorize the mechanisms involved. In many instances, this categorization will be speculative since the exact mechanisms remain unknown and could be multi-

ple in nature. Emphasis will be directed at viruses as a cause of immunosuppression rather than at viral infections that result from primary or secondary immunodeficiency.

Viruses can cause immunosuppression by at least four different mechanisms. First, as a result of complete or abortive viral replication, they may lyse or functionally impair lymphocytes. Such direct effects may involve either all classes of lymphocytes—as seems to occur in measles and certain parvovirus infections—or only subsets of cells—as occurs in human T cell-lymphotropic virus type III (HTLV-III) infection, the cause of AIDS, and in Epstein-Barr virus-induced infectious mononucleosis. Lymphopenia and shifts in the representation of different lymphocyte types are frequent occurrences in several viral infections.

Second, immunosuppression may result from the activity of soluble factors of viral or host origin released from infected cells. A well-characterized example of the former is the P15(E) protein of feline leukemia virus. Included in the category of host-derived suppressor factors is the family of interferons. These cytokines express a wide range of immunoregulatory activities, of which suppression of lymphocyte function is but one. The early, temporary depression of immunity observed in several acute viral infections is probably the result of interferon induction.

A third mechanism of immunosuppression occurs when viruses infect and damage cells involved in phagocytosis, antigen presentation, and the non-

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Please address requests for reprints to Dr. Barry T. Rouse, Department of Microbiology, University of Tennessee, Walters Life Sciences Building, Knoxville, Tennessee 37996-0845.

specific effector aspects of cell-mediated immunity. Viruses that infect macrophages fall into this category. This mechanism may be a cause of immunosuppression in influenza and may contribute to the suppression observed during infections with herpesvirus, canine distemper virus, and several other viruses.

Finally, suppression of immunity may result from viral triggering of an imbalance in immune regulation, which culminates in the overactivity of suppressor T cells. This dysregulation could result from a variety of causes, such as viral replication in a lymphocyte subset, infection of macrophage subsets involved in immune induction, or generation of suppressor factors from cells. Obviously, this fourth category overlaps to some extent with the other three; however, it will be discussed separately because recent work has made it evident that the finely tuned immune system can easily become disrupted by agents and factors affecting only one component of the suppressor cell cascade.

Immunosuppression Resulting Mainly from Direct Effects on Lymphocyte Function

Many viruses are lymphotropic, and their replication in lymphocytes, which can be complete or abortive and can be accompanied or not accompanied by cell pathology, may result in loss of immune function. A few viruses replicate in all types of lymphocytes and can give rise to a profound lymphopenia and immunosuppression; a commoner outcome, however, is the preferential infection of certain lymphocyte subsets, resulting in more selective effects on immune function. In this section, individual viruses will be discussed.

Measles and Canine Distemper Viruses

Measles was the first viral disease in which immunosuppression was noted to be a feature. In 1908, von Pirquet noted a loss of skin reactivity to tuberculin following measles virus infection [1]. Patients also show impaired responsiveness to antigens other than tuberculin, such as those of *Candida*, diphtheria toxoid, and vaccinia virus [2]. Measles infection may also abrogate antibody production [3]. Likewise, anergic cutaneous reactions to antigens and impaired antibody responses are features of the related canine distemper virus infection of dogs, and susceptibility to low-grade secondary bacterial infec-

tions is a frequent outcome of distemper in dogs [4, 5]. The molecular mechanism of immunosuppression in measles remains ill defined, although the suppression appears to be the direct result of infection of all types of lymphocytes by infectious virus. As a result of the infection, lymphocytes show both diminished proliferative responses to antigen and non-specific mitogens [2, 6] and diminished natural killer (NK) cell activity [7]. In addition, the measles virus antigen(s) themselves suppress the in vitro mitogen responsiveness of normal lymphocytes [8]. The fact that no similar effect is observed with inactivated virus shows that no structure of the measles virus alone is responsible and that complete or incomplete replication is required. An assessment of the action of measles virus on T and B cells involved in antibody production in the mouse system revealed that this effect is confined to inhibition of helper-T cell function [8]. However, with human cells, measles virus replicates in and effects the function of B cells and of both major subsets of T cells [9], although some authors suggest that replication in helper cells is favored [10]. In all types of lymphocytes, measles virus replicates far more effectively following its activation by antigen or mitogens [7].

Recently, Rice et al. [7] and Casali et al. [11] have evolved an intriguing concept from their studies on measles virus [7, 11]. They have shown that whereas measles virus infection of lymphocytes is noncytotoxic and fails to affect the function of differentiated lymphocytes, infection of uncommitted cells stops differentiation [7, 11]. Both NK cell function and IgG synthesis are affected, but cells functionally able to mediate antibody-dependent cellular cytotoxicity, produce helper factors, or mediate cytotoxic-T lymphocyte activity are unaffected. The selective effect of measles virus on differentiated, or "luxury," functions may be a common outcome of other persistent viral infections, with immunosuppression being just one of many possible consequences of such infections. A molecular explanation of how infections such as measles can selectively disturb luxury functions and leave "housekeeping" functions intact is required.

Canine distemper virus infection in dogs results in immunosuppression, as indicated by several lines of in vitro and in vivo evidence [5, 12]. Dogs acutely and severely infected with this virus seldom develop antibody responses [13]. During acute fulminating infection, the virus spreads to all lymphoreticular tissues and can affect virtually all cell types within the

body. The affected animals usually die of neurologic involvement or secondary bacterial infection brought on by immunosuppression. In milder forms of the disease, animals survive and show transient *in vivo* and *in vitro* immunosuppression. This immunosuppression may be both subtle and selective, affecting, for example, antibody responses to envelope proteins but not core polypeptides [13]. As a consequence of direct viral infection of lymphoid cells and possibly macrophages [14], lymphocytes from canine distemper virus-infected dogs do not generate effective *in vitro* and *in vivo* immune responses; in addition, the lympholytic infection can suppress established immune responses. Immunosuppression, however, cannot be explained simply by a direct effect on lymphocytes since the effect may be prolonged, lasting long after virus is no longer detectable in lymphoreticular tissue [5]. Thus, phytohemagglutinin A and pokeweed mitogen responses may be diminished for months, and convalescent dogs respond poorly to immunization. There is mounting evidence that this prolonged immunosuppression is associated with a nonspecific suppressor-T cell response [14]. This aspect of immunosuppression is discussed further in a subsequent section.

Parvoviruses

Since these small, nonenveloped, single-stranded DNA viruses require certain cellular functions expressed during the S phase of the cell cycle [15], they have a predilection for rapidly dividing cells, including lymphocytes. Productive infections are generally lytic, giving rise to a profound lymphopenia during acute infection, as best exemplified by feline panleukopenia virus infection of cats and canine parvovirus infection of dogs [16]. In addition to lymphopenia, cats with feline panleukopenia have pronounced lesions in lymphoid tissue, suppressed immunity, and a range of clinical problems attributable to their immunosuppression [17]. *In vitro* studies of the function of lymphocytes from experimentally infected animals have demonstrated suppressed mitogen responses affecting mainly T cells. Such suppressed responses are transitory, and effects are minimal on functional aspects of cell-mediated immunity *in vivo*. The functional nature or extent of immune suppression in naturally infected cats has yet to receive close attention. It is noteworthy that specific pathogen-free cats do not die after experimental infection [18].

With murine parvovirus (minute virus of mice), an interesting variant has been isolated from a murine T lymphoma cell line that differs from the prototype virus in being selectively lytic to T cells *in vitro* [16]. B cells are unaffected since they lack receptors for the variant. The variant, but not the parent virus, interferes with several T lymphocyte functions *in vitro*, but immunosuppression *in vivo* has not been observed, perhaps because of a strong association between virus and erythrocytes, which also have receptors for the virus.

Immunosuppression is one of the many effects of persistent infection of mink with Aleutian disease virus [16]. The major features of this infection are progressive immune-complex disease, B cell proliferation, and hypergammaglobulinemia. Unlike minute virus of mice, Aleutian disease virus probably replicates mainly in B lymphocytes, and the immune aberrations that occur mainly affect B lymphocyte function. In addition, unlike the situation in other parvovirus infections, lympholysis is not a feature. The result of Aleutian disease virus infection is a channeling of humoral responses against viral antigens at the expense of responsiveness to other antigens, an effect that may reflect the fact that infection results in defective immune regulation.

Parvoviruses have been considered possible causative agents of AIDS [16], although, with the discovery of HTLV-III, they may now be considered only possible cofactors rather than primary causative agents.

Human Lymphotropic Viruses

The most topical example of virus-induced immunosuppression syndrome in humans is the recently identified acquired immunodeficiency syndrome. This syndrome results primarily from infection of a restricted subset of T lymphocytes [19–21]. Overwhelming evidence incriminates HTLV-III as the causative agent of AIDS [19], although several other agents, especially viruses, undoubtedly act as cofactors, contributing to the overall disease syndrome. The subject of AIDS has recently received many excellent reviews [19–23], so our discussion will be only cursory.

Numerous retroviruses cause immunosuppression in a variety of species [23–27], but only in the case of HTLV-III is there a definite tropism for a subset of T lymphocytes. The distantly related HTLV-I virus, the etiologic agent of an adult form of T cell

leukemia, also causes immunosuppression but seems to affect the function of all types of T cells, and immunosuppression is not the principal feature of the disease [23]. With HTLV-III, there is a clear tropism for a T subset that expresses the T4 (Leu 3) marker and, in particular, for those T4 cells responsible for mediating delayed-type hypersensitivity and the provision of help for other T cell responses [22]. The T4 antigen appears to act as the viral receptor, and monoclonal antibodies to T4 can block infection [28]. Activated T4 cells are more susceptible to infection *in vitro* and the same is probably true *in vivo* [28]. It is possible that only when sufficient T4 cells are activated *in vivo* by various cofactors does the extent of infection become significant. Infected T4 cells may be killed by the virus [28] or perhaps die as a result of some host response to the infected cells [29]. Ultimately, numbers of circulating T4 cells are diminished—a change that accounts for a major feature of AIDS: a decrease in the ratio of T4 to T8 cells [21]. This decrease can be of the order of eight- to 10-fold, with levels of circulating T8 cells, monocyte/macrophages, and B cells remaining normal. The result of T4 cell lymphopenia is a marked immunosuppression that permits life-threatening infections by opportunistic organisms and certain cutaneous neoplasms, of which the most notable is Kaposi's sarcoma [20] (an otherwise extremely uncommon neoplasm).

Patients with AIDS show cutaneous anergy to a battery of recall antigens and marked depression of *in vitro* lymphoproliferative and lymphokine synthesis responses [21]. Some of the *in vitro* responses can be restored by the administration of exogenous interleukin-2 (IL-2), a growth factor elaborated principally by T4 cells [30]. Such observations have given impetus to the launching of *in vivo* trials with IL-2 in patients with AIDS, a syndrome that to date is inevitably fatal.

Cellular defects in AIDS principally affect T4 cells, although other immunologic abnormalities occur, many of which could be the consequence of intercurrent infection with several opportunistic agents that seem characteristic of AIDS. Prevalent secondary infecting agents that suppress immunity are the herpesviruses, cytomegalovirus (CMV), and Epstein-Barr virus (EBV) [31]. Accordingly, AIDS patients have normal numbers of circulating B cells, but levels of all immunoglobulin classes may be raised [21, 22, 32]. Paradoxically, patients with AIDS show marked deficiencies in antibody production to spe-

cific antigens, and their B cells respond poorly *in vitro* to mitogen stimulation [33]. In fact, the B cells behave as if polyclonally activated and spontaneously produce high levels of nonspecific immunoglobulins. This effect most likely results from concurrent persistent infection with EBV.

Patients with AIDS also have diminished numbers of NK cells; in addition, despite normal numbers of circulating macrophages, the proportion of these cells that express MHC class 2 antigens may be reduced [22]. Both effects possibly represent an inadequate production of γ -interferon, and the administration of this lymphokine, at least *in vitro*, can overcome the defect [34].

Molecular virologists have recently shown that the HTLV-III genome codes for transacting regulatory factors that serve to activate viral genes and perhaps some cellular genes [35]. How these factors affect cell division and both the housekeeping and the luxury functions of cells requires clarification. One group has suggested that HTLV-III codes for an "exuberant" transacting factor, which may explain how the virus kills cells [28]. Rapid progress in understanding the biologic importance of transacting factors is expected.

Several other retroviruses cause various forms of immunodeficiency, anemia, and aplasia. These include the type C feline leukemia virus [25], several type C viruses in the mouse [24], and the type D simian leukemia viruses [27]. Recently, attention has been directed at the type D agent in rhesus monkeys since outbreaks have occurred in a number of colonies of these animals in the United States [36]. The syndrome resembles human AIDS, but the model is not an ideal one since the simian agents are not related antigenically to HTLV-III and affect a much broader spectrum of lymphocyte types. Very recently, it was demonstrated that wild African green monkeys are infected with viruses similar to HTLV-III; these agents are named STLV-III [37]. Such viruses, which probably represent the origin of HTLV-III affecting humans, appear not to be immunosuppressive in their native hosts [37].

Infection with feline leukemia virus in cats commonly causes a profound immunodeficiency [25]. The syndrome appears to result from the action of a viral protein, P15(E), and not from damage to lymphocytes due to viral replication. This mechanism of immunosuppression generated by feline leukemia virus, which also occurs with some murine leukemia viruses [26], is discussed in a later section.

Herpesviruses

Infection with a number of herpesviruses has been associated with immunosuppression, and although the actual mechanism is unclear, the direct effect on lymphocytes is not the result of lympholysis. Herpesviruses, in addition to acting as primary causes of immunosuppression, become far more significant pathogens in states of immunodeficiency for iatrogenic, secondary, or genetic reasons (reviewed in [38–40]). The two herpesviruses most commonly associated with immunosuppression in humans are EBV and CMV. CMV is the virus most frequently isolated from patients with AIDS and probably plays a major role in predisposing patients to superinfection with opportunistic bacteria, fungi, and protozoa [41]. Increased susceptibility to superinfection also occurs in infants with cytomegalic inclusion disease and in adults with CMV infectious mononucleosis [41]. Murine CMV increases the lethality of subsequent experimental infection with several bacterial species [42].

EBV acts as a secondary infecting agent in AIDS and as a primary agent in infectious mononucleosis [39]. The virus primarily infects B lymphocytes and has at least three functional effects on such cells (reviewed in [43]). The most prominent effect is a complex series of events that leads to transformation and “immortalization.” Cells express neoantigens, such as Epstein-Barr nuclear antigen and lymphocyte-defined membrane antigen, and undergo continual multiplication. These cells represent most of the early atypical lymphocytosis characteristic of infectious mononucleosis. Second, the virus causes polyclonal activation of B cells. This effect seems to occur with both transformed and nontransformed cells. The outcome is the production of antibody, including autoantibodies, which in turn may become involved in immunopathologic reactions. The third effect is the production of antibody to EBV antigens by specific B cells.

The early B cell lymphocytosis stimulates a later, atypical lymphocytosis consisting primarily of proliferating T cells, which belong mainly to the cytotoxic/suppressor subset [39]. Such cells do not contain the EBV genome. Some T cells recognize and lyse the lymphocyte-defined membrane antigen on infected B cells in a major histocompatibility complex-unrestricted manner [44, 45]. The action of such cells, together with NK cells and perhaps other sub-

sets of T cells [46], serves to remove the transformed B cells from the circulation. Consequently, 15%–20% of the B cells are positive for Epstein-Barr nuclear antigen early in the disease, whereas such cells later account for no more than 1%–2%. Included in the cell population reactive to the infected B cells are suppressor T cells and perhaps suppressor macrophages. It may be the overactivity of such cells that accounts for the anergy observed later on in some cases of infectious mononucleosis. Immunosuppression can be detected during the first week of illness and can include temporary depression of delayed hypersensitivity and depression of T cell responses to mitogens and antigens [43]. In the absence of the cytotoxic- and suppressor-T cell response—as, for example, in the primary genetic defect known as X-linked immunoproliferative syndrome—uncontrolled B cell proliferation occurs, with fatal results [47].

Infections caused by CMV have also been associated with immunosuppression and, as has been mentioned, frequently occur in AIDS. In fact, CMV infections in humans usually cause clinical problems only in situations where there is immune imbalance or immaturity [40, 48]. The commonest are congenital infections of the fetus and infections of immunocompromised individuals because of immunosuppressive disease or chemotherapy. In such individuals, CMV is assumed to contribute to immunosuppression, although the mechanism of such suppression remains unresolved. Primary CMV infection of normal young adults occasionally gives rise to mononucleosis [41]. Patients show a markedly increased susceptibility to infections with other agents and have hyporesponsive proliferative responses to a variety of mitogens and antigens [48]. Thus, concanavalin A and pokeweed mitogen responses are grossly impaired, whereas phytohemagglutinin responses are marginally affected. Antigen-induced proliferative responses and γ -interferon production are also diminished, with normalcy returning after recovery [41].

NK cells and antibody responses show no marked abnormalities, and so the major abnormalities in CMV mononucleosis appear to involve T lymphocyte function [41]. Characteristically, the ratio of helper-to-suppressor cells decreases [49]. However, unlike the situation in AIDS, the change in ratio reflects an increase in the suppressor cell-containing T8 subset, and numbers of T helper cells show little change [50]. The assumption that the increased

T8 cells act functionally as suppressor cells and mediate the general T cell immunosuppression observed in CMV mononucleosis remains to be proved. In fact, when the cell type responsible for suppression was analyzed by cell purification and mixing experiments, suppression was shown to be monocyte-mediated [51]. Whether or not suppressor monocytes provide the only explanation for immunosuppression in CMV infections remains uncertain. Thus, suppression could result from direct effects on lymphocytes, although the cell type that harbors virus is not known. The older literature contains occasional accounts of the isolation of CMV from leukocytes [52], but the identity of the affected cell type was not resolved. The question of which cell type harbors CMV was recently reinvestigated by Rice et al., with interesting results [53]. These authors showed that a minority of T and B lymphocytes, NK cells, and monocytes from the peripheral blood of healthy individuals could be infected with CMV. Moreover, using monoclonal antibodies to different viral polypeptides to examine infected cells, they demonstrated that expression was limited to immediate, early viral polypeptides. Even when such abortive infections were included, only a minority of cells were affected. Nevertheless, the cell populations showed diminished differentiated luxury functions, such as responses to mitogens.

Several species of animals develop CMV infections, but whether these infections are immunosuppressive has received little attention except in the mouse. In this animal, acute infection with CMV causes marked suppression, which primarily affects humoral immunity [54]. The viral infection appears to be confined to B cells. Such cells show more profoundly suppressed functional activity *in vitro* than do T cells, and the histopathologic changes in lymphoid tissues mainly involve the B cell areas [54, 55].

Although most information on the role of herpesviruses in immunosuppression pertains to EBV and CMV, other herpesviruses are also reported to suppress immunity. These include herpes simplex virus (HSV) and infectious bovine rhinotracheitis virus [56–59]. With respect to the latter, there is considerable interest in determining the mechanism of immunosuppression, since infectious bovine rhinotracheitis virus is considered one of the principal infecting agents that predispose cattle to shipping fever, a disease of considerable economic importance [56]. Preliminary evidence has indicated that the

mechanism of immunosuppression is complex and involves not only direct suppression of helper-lymphocyte function but also infection-mediated effects on macrophage and neutrophil function [56].

There are reports that HSV can suppress some aspects of immunity *in vivo* [59] and that the virus is inhibitory to mitogen- and antigen-induced blastogenesis *in vitro* [57]. The mechanism of immunosuppression has not been defined; it is well known, however, that HSV can replicate in all subsets of T cells, provided that they are activated with antigen or mitogens [60–62]. The virus fails to replicate in resting lymphocytes. Although HSV replicates in activated human T cells and may suppress immunity *in vitro*, it is unclear whether primary or recrudescent HSV infection gives rise to clinically significant immunosuppression. However, severe HSV infections are experienced by patients immunosuppressed for other reasons [38], and the infection of mice with HSV type 2 can result in immunosuppression, apparently because of infection of lymphoid tissue [58]. Moreover, with respect to HSV, there is a perplexing problem of latent infection and recrudescent disease. Recrudescence may well be the result of the development of regulatory suppressor cells. This aspect is discussed in a later section.

Other Viruses

Several other infections of domestic and laboratory animals also give rise to immunosuppression, apparently as a direct result of infection of some or all subsets of lymphocytes. These include togavirus infections of cattle and pigs (infections that are caused by bovine diarrhea virus and hog cholera virus, respectively [63]) and certain coronavirus infections of cats, mice, and chickens [64]. Chickens also become immunosuppressed following infection with lymphotropic influenza viruses [65] or with the reovirus infectious bursal agent. The latter virus has a marked tropism for B cells in the young chicken, especially B lymphocytes in the bursa of Fabricius [66]. The infection is apparently lytic for B cells and causes a marked reduction in the seeding of B cells to the circulation. Birds become highly susceptible to secondary infections and fail to generate an adequate antibody response upon vaccination with other viruses [67].

Table 1 summarizes the features of viruses caus-

ing immunosuppression by direct effects on lymphocytes.

Immunosuppression Mediated by Suppressor Molecules

Conceptually, two groups of immunosuppressive molecules can be recognized: those of viral origin and those derived from host cells. The best example of the former is the P15(E) protein of several retroviruses, whereas interferon is exemplary of a host-derived suppressive molecule.

Suppression by Viral Proteins

Infection with retroviruses often leads to immunosuppression, which may in turn be associated with

the subsequent generation of neoplasia (reviewed in [24, 26, 68, 69]). The immunosuppression may result from a direct infection of lymphocytes that leads to functional impairment or destruction, as already discussed for HTLV-III. Other retroviruses cause immunosuppression because one of their structural components acts as an immunosuppressive molecule. Feline leukemia virus infection in cats is a well-studied example (reviewed in [25, 70]).

Profound, long-lasting immunosuppression is one of the most significant effects that feline leukemia virus has on the infected cat. It is a prominent feature when cats are viremic and can occur during the acute productive preleukemic infection as well as during the productive leukemic phases of infection. Immunosuppression is not a feature of latent non-productive infection. During feline leukemia vi-

Table 1. Some viruses causing immunosuppression by direct effects on lymphocytes.

Virus	Affected species	Effects on functions of				Comments	Reference(s)
		T cells	B cells	NK cells*	Macrophages		
Measles	Human	+	+	+	...	"Luxury" functions not affected	2, 3, 6, 7
Canine distemper	Dog	+	+	...	+	Profound suppression	4, 5, 14, 16
Feline panleukopenia (parvovirus)	Cat	+	+	...	...	Marked lymphoid depletion	16
Aleutian disease (parvovirus)	Mink	...	+	...	...	Immune complex disease	16
Minute (parvovirus)	Mouse	...	...	...	...	In vitro effects only	16
HTLV-I†	Human	+	±	...	...	Mainly helper T cells	26
HTLV-III‡	Human	+	...	...	+	Profound helper-cell dysfunction	20-26
Simian type D retrovirus	Monkey	+	+	+	...	AIDS§-like syndromes	19, 25
Cytomegalovirus	Human	+	+	+	+	Usually a secondary agent	51, 53
Epstein-Barr	Mouse	...	+	...	...	Suppressed antibody	50
	Human	+	+	...	...	Mainly polyclonal B cell activation	39
Herpes simplex	Human	+	...	...	...	In vitro suppressors only	53, 55
Infectious bovine rhinotracheitis	Bovine	+	...	...	+	A factor in shipping fever	52
Infectious bursal agent	Chicken	...	+	...	...	Humoral suppression	66
Influenza	Chicken	+	+	...	...	Lymphoid cells destroyed	65
Bovine diarrhea	Bovine	+	...	...	...	Leukopenia	63

* Natural killer cells.

† Human T cell-lymphotropic virus type I.

‡ Human T cell-lymphotropic virus type III.

§ Acquired immunodeficiency syndrome.

rus-induced immunosuppression, which usually precedes neoplasia by months, there is paracortical lymphoid depletion in lymph nodes [71], a loss or reduction of responses to T cell mitogens [72], lymphopenia, delayed allograft rejection [73], and a marked susceptibility to a variety of intercurrent, often opportunistic, pathogens. Viremic cats frequently die of concurrent enteritis, gingivitis, pneumonia, sepsis of bacterial origin, infectious peritonitis of coronavirus origin, or diseases of hemotropic or multitropic parasitic origin [25]. Replication of the virus occurs principally in B lymphocytes, particularly in the early phases of infection [70]. The infection in B cells is noncytotoxic, and infected cells develop little or no functional impairment. Accordingly, naturally viremic cats respond normally to B cell mitogens and generate adequate IgM responses following immunization [25, 74]. In contrast, their IgG responses to T cell-dependent antigens may be inadequate and delayed [75]. Such observations could indicate that the major target cell for immunosuppression in feline leukemia virus infection is the helper T lymphocyte [74, 76]. Stiff and Olsen [76], however, found indirect evidence for a suppressor-T cell defect. They showed that the lymphoproliferative responses of cells from cats with persistent productive feline leukemia virus infection, unlike those of normal cat cells, do not increase in magnitude when the cells are briefly cultured *in vitro* before stimulation. Although the authors noted a good correlation between the appearance of spontaneous suppressor-cell activity and levels of virus production, direct evidence for changes in suppressor cell function is lacking.

There is substantial evidence that the abrogation of T cell immune responses for feline leukemia virus infection is mediated by the P15(E) structural protein of the retrovirus released from infected B cells [25]. That the viral antigen itself can be immunosuppressive became evident from observations that the simultaneous administration of killed virus with other antigens impairs antibody responses [25]. Injections of killed virus also enhance tumor engraftment and increase susceptibility to viremia [77]. Furthermore, the addition of inactivated feline leukemia virus to mitogen-stimulated lymphoid cells from normal cats impairs responsiveness but is not directly cytotoxic [72, 75]. P15(E) is the only component fraction of this virus that inhibits mitogen-induced blastogenesis [75]. In addition, the capacity of this protein to suppress IgG responses and to increase

susceptibility to disease is similar to that of inactivated virus [78]. Moreover, P15(E) of feline leukemia virus suppresses lymphocyte blastogenic responses of a wide range of species, including humans [79]. Other retroviruses have P15(E) proteins, although such proteins are not always immunosuppressive in their homologous hosts. In addition, certain tumors produce an immunosuppressive P15(E)-like protein that may serve to perpetuate tumor survival [26].

The P15(E) of feline leukemia virus binds to all cells, but not all cells are functionally impaired. Thus, of the several cell types involved in mitogen-induced blastogenesis, T lymphocytes are the targets of the major suppressive effect of P15(E), which is exerted against the production of and response to IL-2 [80]. The P15(E) protein of feline leukemia virus appears not to affect the function of accessory cells involved in blastogenesis by human [77] or cat cells [25]. Furthermore, P15(E)-treated peritoneal macrophages respond normally to chemotactic stimuli. However, some contrasting observations have been made with the antigenically similar P15(E) of murine retrovirus and a P15(E)-like protein isolated from human malignant lymphomas [81]. For example, immunosuppressive effects mediated by murine retrovirus P15(E) appear to be directed mainly at macrophages. Thus, the accumulation of such cells at experimental inflammatory sites in mouse skin is inhibited by murine P15(E), although, curiously, not by viral extracts that contain the P15(E) of feline leukemia virus [82]. Murine retrovirus P15(E) also inhibits the response of human monocytes to chemotactic stimuli [81], an effect not reported for feline leukemia virus P15(E). Although antigenically related and functionally equivalent, P15(E) proteins appear to differ in their biologic activities. In fact, several retroviruses that have a P15(E) protein exert no immunosuppressive effects in the host. An example is visna virus of sheep (O. Narayan, personal communication).

It is important to determine how P15(E) proteins mediate their activity as well as to explain the apparent cell-restricted activity. Hypotheses favored for the mechanism of action include cell membrane changes that serve to block the triggering of CA^{+2} /calmodulin-dependent activation of adenyl cyclase, with disruption of microtubule and microfilament function because of insertion of P15(E) into the cell membrane [25]. This aspect of research requires further investigation.

Suppression By Host-Derived Proteins

Most viruses cause the production of interferons following infection. Around 30 years ago, these cellular proteins were shown to mediate antiviral effects *in vitro*, and in some instances the induced interferon (IFN) response served to control the viral infection *in vivo*. In recent years, especially through the work of Gresser and colleagues, the IFN family of proteins have been shown to mediate a wide range of biologic activities in addition to their antiviral effects (reviewed in [83, 84]). Upon measurement of the direct effect of various types of IFN on the metabolism of virus-infected and normal cells, numerous chemical changes have been observed. These include the induction of new enzymatic activities that regulate the function of different messenger RNA species [85], the inhibition of cell replication, and changes in cell metabolism [86]. Certain cells—for example, some tumor cells and cells of the immune system—are more affected by the anticellular activity than others. Immunosuppression is one consequence of IFN's anticellular activity. Indeed, several laboratories have shown that IFN can inhibit cell-mediated immunity as well as humoral responses both *in vitro* and *in vivo* [87, 88]. Antibody responses to both T cell-dependent and T cell-independent antigens are inhibited. *In vitro* mitogenic responses of both T and B cells are also inhibited by IFN. Various types of IFN have been investigated; IFN- γ is 10–100 times more suppressive than IFN- α or IFN- β [89].

Demonstration of immunosuppressive effects of IFN *in vivo* has required the administration of relatively large amounts of crude material, and it remains questionable whether IFN acts as an immunosuppressive moiety at concentrations produced during viral infections. In addition, the use of IFN in anticancer trials does not appear to depress antibody responses [90]. Nevertheless, recent evidence strongly indicates IFN as the mediator of at least temporary immunosuppression during viral infection [91]. For instance, lymphopenia is often a feature early during infection by several viruses. This phenomenon has been extensively studied in mice infected with Newcastle disease virus [92] and has been demonstrated to result from altered lymphocyte homing patterns brought on by viral neuraminidase. However, lymphopenia also occurs in infections caused by viruses lacking neuraminidase. Examples include canine distemper virus infection of dogs and vesic-

ular stomatitis virus infection of mice. In both situations, changes in homing patterns were suggested as a mechanism of lymphopenia and suppressed immunity [4, 93]. With respect to vesicular stomatitis virus (which does not replicate in mouse lymphocytes), the lymphopenia appeared to result from the inhibitory effects of IFN [91]. Accordingly, the effect could be mimicked by the administration of either IFN or IFN inducers such as polyriboinosinic-polyribocytidylic acid and was abrogated by antiserum to IFN. Since histologic evidence for lymphocyte destruction was lacking and the lymphopenia terminated rapidly as IFN disappeared, changes in homing patterns were proposed as the likely explanation for the IFN-induced lymphopenia.

More direct evidence for virus-induced IFN as a mediator of immunosuppression was recently provided by the work of Brenan and Zinkernagel [93]. They investigated the influence of one viral infection on the immune response to a subsequent primary infection with a second virus. Infection with viruses such as lymphocytic choriomeningitis virus or Newcastle disease virus, which induced high IFN levels some two to six days before infection with vaccinia virus, resulted in a diminished virus-specific, cytotoxic-T lymphocyte response to vaccinia. No interference with the antivaccinia response followed concurrent infection with lymphocytic choriomeningitis virus and vaccinia virus. Since the cytotoxic-T lymphocyte inhibition correlated in its extent with the levels of IFN induced, could be mimicked by administration of the IFN inducer polyriboinosinic-polyribocytidylic acid, and was preventable by anti-IFN administration, IFN was assumed to mediate the immunosuppression. It was not resolved whether IFN exerted this effect by preventing adequate antigen expression of the second virus or by directly affecting cells involved in immunologic defense mechanisms. Interferons cause a wide range of changes in cells of the immune system, and these changes may influence cellular interactions involved in immunoregulation. Such changes include alterations in membrane major phospholipids [94], enhanced expression of several cell surface antigens [95], increased membrane Fc receptor expression [96], alterations in membrane charge and ion transport [97], and changes in the complex series of events that constitute cell activation [98]. All could influence the function of cells involved in immunity. For instance, IFN, especially IFN- γ , can change the membrane expression of antigens intricately involved in accessory cell

function during immune induction [99]. This fact suggests that IFN induced during viral infection could change the functional activity of the various subpopulations of accessory cells involved in immune responses. For example, if accessory cells involved in suppressor cell induction were stimulated in activity, diminished immune responses could result. Alternatively, IFN could induce macrophages or T cells to mediate suppressor effects directly [100], although there is some evidence that the opposite (stimulatory) effect could also occur [101]. How IFN mediates immunosuppressive effects is still largely unknown.

Immunosuppression Resulting from Changes in Macrophage Function

Phagocytosis stands as the hallmark function of macrophages, but these cells also participate in numerous other activities that relate to defense and immune regulations (table 2). Their distribution throughout the body insures that macrophages are often the first leukocytes to encounter invading organisms. As such, they represent the first line of defense against microbial invaders such as viruses. In addition to phagocytosing virions, macrophages lyse virus-infected cells, mediate antibody-dependent cellular cytotoxicity, and exhibit both intrinsic and extrinsic antiviral activities [102–104]. Perhaps of even greater significance is the role of macrophages in the regulation of antiviral immune responses. Macrophages process and present viral antigens and secrete a variety of immunoregulatory molecules necessary for the induction of antiviral immune responses of both T and B cells as well as for the activation of suppressor cells that regulate antiviral immunity. These macrophage activities have been the subject of a voluminous literature and frequent reviews [105–110]; however, the influence of viruses on these functions has received little attention. Although table 2 lists numerous functions of macrophages, it is becoming evident that a single cell does not participate in all functions. Rather, it appears that functional and antigenically distinguishable subsets exist [111]. Evidence includes the differential microbicidal and cytotoxic activities of macrophages [102] and the involvement of antigenically distinct macrophage subsets that present antigen to different subclasses of lymphocytes [105]. The representation of different functional and antigenically distinct macrophage subsets at various sites in the body differs,

Table 2. Some functions of macrophages in immunity that could be affected by viruses, leading to immune dysfunction.

Phagocytosis of particles (e.g., bacteria, immune complexes)
Microbicidal activity and bacteriostasis
Uptake, localization, and processing of antigens
Degradation of antigens and particles
Antigen presentation to various lymphocyte subsets
Secretion of immunoregulatory molecules (e.g., interleukin-1 and interferon)
Secretion of inflammatory molecules involved in defense
Direct and indirect cytotoxic activity
Suppressor activity

and the susceptibility of different subsets to viral infection is expected to vary. However, the functional consequences of viral infection on selected macrophage function require evaluation.

There may be various consequences of viral infection of macrophages. The infection may be inapparent, persistent, or lytic; it may culminate in viral destruction, abortive replication, or complete replication [102]. The ability of macrophages to resist certain viral infections is dependent upon the genetic background and age of the host [112–115]. Accordingly, monocytes from newborn humans and mice are permissive for HSV infection, whereas cells from older individuals may be resistant [115]. This age-dependent permissiveness reflects a similar susceptibility of newborn mice and humans to lethal herpesvirus infections [115, 116]. The development stage of the macrophage also dictates susceptibility to infection. Mature cells are generally resistant to most viruses, but precursors in the bone marrow may be susceptible to infection [117]. Likewise, macrophages isolated from anatomically different sites exhibit variations in their susceptibility to viral effects [118]. Resistance to infection may be mediated by various mechanisms [102–104]. The absence of appropriate viral receptors precludes viral attachment and penetration. Even when the virus is able to penetrate the cell, the potent lysosomal vacuoles of macrophages may destroy the internalized virus before the genetic material is released into the cytosol. Other mechanisms appear to be operative even beyond this stage of viral replication since it is possible to demonstrate the transcription of some viral proteins during abortive replication cycles [119]. These various intrinsic mechanisms of antiviral activity contribute to the overall innate defense of the host to viral infection. However, even in the absence of replication, viral in-

teraction with macrophages can impair the function of these cells (see below).

Macrophages can be productively infected by some viruses [51, 114, 120, 121]. The consequences of this event are multiple. Because of the migratory nature of macrophages, infection may result in the dissemination of the virus beyond the initial infection site. Infection of the macrophages may also allow the virus to avoid detection and elimination by other effector cells. Some so-called slow viruses appear to evade the host's immune mechanism in this manner [122]. Finally, destruction of macrophages may occur as a result of the cytotoxic activity of the virus or as a result of the host's immune response to the viral antigens present on the surface of infected cells [123]. The latter mechanism may perhaps operate even when the virus has undergone abortive replication. In either event, the result is the loss of a cellular population essential for both innate and adaptive immunity.

Even in the absence of obvious virus-induced injury, macrophage functions may be severely impaired. Most of our knowledge of the influence of viruses on macrophages relates to viral effects on phagocytosis. Any one or all of the many phases of phagocytosis could be impaired by viral infection. The result of such impairment is a decrease in natural immunity and an increase in susceptibility to intercurrent and often opportunistic pathogens. We know little about the mechanisms and consequences of macrophage-virus interaction in terms of the role of macrophages as immune regulators and effectors of immunity.

Effects of Viruses on Natural Defense Functions of Macrophages

Viral infections of the respiratory tract are frequently complicated by bacterial superinfections [124]. Although several mechanisms may be responsible for the increased sensitivity to infection, it appears that in many instances increased sensitivity is the result of damage to the phagocytic activity of alveolar macrophages [102]. Virus-mediated dysfunction may occur at any stage of the phagocytic process, including microbicidal activity. Some examples are discussed below.

Suppression of chemotaxis frequently occurs in the absence of cytopathology caused by viral replication. Inhibition appears to be mediated only by certain viruses since infection and even replication

by other viruses do not alter chemotactic behavior [125]. Thus, macrophages infected with bovine diarrhoea virus, HSV, or influenza virus fail to respond to chemotactic stimuli, whereas cells infected with vaccinia virus, poliovirus, or reovirus respond normally [125, 126]. How chemotaxis is suppressed remains unknown. Presumably, since chemotaxis is mediated via specific surface receptors and involves cellular motility, any effect of viral infection on the expression of chemotactic factor receptors or on the biochemical processes necessary for microfilament function could inhibit chemotaxis. Likewise, chemotaxis is regulated by intracellular concentrations of cyclic AMP (cAMP) [127]. Thus, virus-induced production of E series prostaglandins and the subsequent increase in intracellular cAMP levels could inhibit chemotaxis. Presumably, treatments that lower the level of intracellular cAMP should reverse this inhibition. The biologic response modifier levamisole overcomes virus-mediated inhibition of chemotaxis, perhaps by way of its effect on cAMP levels [128]. Similarly, indomethacin, an inhibitor of the prostaglandin-forming cyclooxygenase, also restores chemotaxis [128]. In some instances, suppression of chemotaxis has been associated with a specific viral protein. The P15(E) structural protein of certain murine retroviruses stands as example [82]. Here, suppression may be the result of an alteration in membrane function caused by the viral protein [78].

Viruses may also suppress macrophage function by interfering with the attachment phase of phagocytosis [129, 130]. For attachment to occur, the electrostatic repulsion between the macrophage surface and the particle to be ingested must be neutralized. Opsonization with either antibody or complement components is one way to overcome this repulsion. Particles having bound antibody or complement proteins attach to macrophage Fc or C3b receptors. The Fc receptor is also responsible for mediating the attachment of macrophages to antibody-coated target cells, the result being the destruction of the target cell by antibody-dependent cellular cytotoxicity (ADCC).

Following infection of macrophages with certain viruses, a reduction in both receptor-mediated phagocytosis and ADCC can occur [131-133]. For example, a decrease in the Fc receptor-mediated ingestion of erythrocytes occurred after infection of alveolar macrophages with Sendai virus [131]. It is interesting that mice were most susceptible to bac-

terial superinfection late in infection, when receptor dysfunction was maximal. Similarly, bovine alveolar macrophages infected with infectious bovine rhinotracheitis virus exhibited a decrease in Fc and C3b receptor-mediated phagocytosis and ADCC [132]. As with Sendai virus, the loss of activity occurred late in the infection and was associated with an increased susceptibility to bacterial infections, in particular with *Pasturella haemolytica* [134]. Alterations in receptor-mediated phagocytosis and ADCC are also observed following infection of rabbit alveolar macrophages with HSV [133]. In these instances, the mechanism of dysfunction of receptor-mediated phagocytosis is unknown since herpesviruses actually cause an enhancement of Fc-receptor expression [135].

Some examples of virus-induced impairment of receptor-mediated phagocytosis seem to result from inhibition of the Fc receptor by immune complexes; this mechanism requires that the host mount an antibody response to the virus before suppression occurs. This scenario has been reported for influenza and parainfluenza infection in mice [131, 136, 137]. A maximal suppression of phagocytosis was noted late in the infection, at a time when viral titers in the lung were actually decreasing and antibody was appearing. The phagocytic dysfunction could be induced in vitro by incubation of macrophages with viruses and antiviral antiserum, although not with viruses alone. Consequently, virus-containing immune complexes were assumed to be responsible for inhibiting macrophage function. In this instance, however, the inhibition was selective in that the phagocytosis of some agents, for example, *Candida krusei*, was not significantly affected [137], perhaps because *Candida* adheres to macrophages via a mannose-type receptor rather than the Fc receptor [138]. Conversely, murine CMV inhibited the non-specific attachment of *Staphylococcus aureus* to infected macrophages without affecting Fc receptor-mediated attachment [130].

No information is available concerning viral inhibition of the engulfment process. One would predict that any alteration in microfilament function or cellular energetics would impede the ingestion of attached particles. Likewise, disruption of cytoskeletal components would affect intracellular movement of the phagocytic vesicles [139].

Following phagocytosis, macrophages may kill and degrade ingested microbes. This process requires the fusion of lysosomes with the phagocytic vesicle.

Viruses that interfere with this aspect of macrophage function include Sendai and influenza [140–142]. After infection, a progressive inhibition of phagosome-lysosome fusion occurs, with concomitant prolongation of intracellular survival of phagocytosed bacteria and yeasts. Peak inhibition coincides with maximal suppression of the host's antibacterial response. How viruses inhibit phagosome-lysosome fusion is not clear, but disruption of cytoskeletal elements necessary for intracellular vesicle movement is a likely possibility.

Effect of Viruses on the Macrophage's Role in Acquired Immunity

As discussed previously, macrophages participate in several functions that influence the adaptive immune response (table 2). Virus-mediated inhibition of phagocytosis, killing events, and intracellular degradation could impair the antigen-processing and antigen-presenting activity of these cells. Most of our knowledge concerning the effect of viral infection on the accessory functions of macrophages comes from the study of T cell proliferative responses. Many examples of virus-induced suppression of mitogenic responses have been reported [121, 143–147]. The suppression of macrophage function is usually documented by the demonstration of restored responsiveness after the replacement of infected by uninfected macrophages (but not by other cell types) in the mitogen-stimulated cultures [144, 146]. The accessory cell activity of peripheral blood, but not that of alveolar macrophages is suppressed by influenza virus [127]. While the reason for this disparity has not been discovered, a possible explanation is that physiologic differences exist in the cell membranes of macrophages obtained from these two anatomic sites. Subsets of macrophages that perform an accessory cell function against different lymphocyte subclasses are known to exist and to be antigenically distinguishable [110, 111]. In addition, alveolar macrophages appear to be more activated than other cells and so could resist viral infection [148]. It is well known that quiescent macrophages (peripheral blood, resident peritoneal) nonspecifically activated by immunomodulators such as *Corynebacterium parvum* also exhibit augmented resistance to viral infection [102, 109]. How viral infection influences accessory cell function is not known. Possibilities include impairment of antigen processing and presentation as well as interference with the secretion

of immunoregulatory molecules such as IL-1. The latter topic has been investigated with influenza and feline leukemia viruses and in both cases there is no effect on IL-1 secretion [25, 121]. Infection with CMV, on the other hand, appears to inhibit IL-1 production by monocytes [149]. The loss of IL-1 production is not associated with viral replication but, rather, with the production of an inhibitor by the infected monocytes. Interference with the antigen-processing and antigen-presenting function of macrophages has been reported [147]. For example, macrophages infected with lactate dehydrogenase virus and Moloney murine leukemia virus are unable to process and present third-party antigens to responding lymphocytes [145, 147]. Arenavirus suppression of immune responses has also been associated with an inhibition of macrophage accessory cell function [150]. The mechanism in the latter example appears to involve viral inhibition of DNA synthesis.

Finally, as discussed previously, macrophages may play key roles in the induction and propagation of suppressor-T cell activity [105, 151] and also can directly suppress a variety of immune responses [106, 128, 152, 153]. How suppression is mediated is not clear, but the secretion of products such as IFN and prostaglandins and the export of oxygen radicals are possibilities [100, 126, 128, 154]. Macrophages may also produce macromolecular inhibitors of lymphocyte function [152, 154, 155]. Viral infection of mac-

rophages may result in the production of such soluble suppressor molecules. Thus, infection with poliovirus [156], vaccinia virus [157], or dengue virus [158] results in the induction of suppressor macrophages; in the case of dengue, these macrophages mediate suppression by the production of soluble factors. The factor produced by dengue virus-infected macrophages is a cytotoxic factor that affects T lymphocytes [158].

Virus-mediated inhibition of macrophage activity can thus result in both a decrease in the host's primary nonspecific immune response and a far more insidious debilitation of the host's ability to generate specific immunity. Many of the mechanisms responsible for macrophage dysfunction remain unresolved, and their elucidation will continue to elude us until a more thorough understanding of their immunobiology is at hand.

The effects of viral infection of macrophages are summarized in table 3.

Suppressor Cell Regulation and Immunosuppression

The immune response to an antigen is finely tuned and is regulated by interactions between various mediators and cells [107, 159]. Some of these cells are involved in the induction of the response, while others suppress it. The interplay between these inducer and suppressor cells (SC) determines the extent and nature of the immune response and, conse-

Table 3. Viral effects on macrophage function in natural and acquired immunity.

Virus	Affected species	Macrophage function								Reference(s)
		Chemo-taxis	Attach-ment	Inges-tion	Lysosome fusion	Accessory function	Effects on function	IL-I*	Suppressor activity	
Murine leukemia	Mouse	+	...	...	...	+	...	...	...	82, 147
Sendai	Mouse	...	+	+	+	+	...	...	...	131
Cytomegalovirus	Mouse	...	+	...	...	+	...	...	...	130
Influenza	Mouse	+	+	+	+	+	...	...	...	129, 136, 137
Lymphocytic chorio-meningitis	Mouse	...	...	...	...	+	...	...	...	150
Lactic dehydrogenase	Mouse	...	...	...	...	+	...	...	...	145
Poliovirus	Human	...	...	...	...	+	...	...	...	156
Cytomegalovirus	Human	...	...	...	...	+	...	+	+	51, 52, 149
Herpes simplex	Human	+	...	...	...	...	+	...	...	125, 133
Dengue	Human	...	...	...	...	...	...	...	+	158
Vaccinia	Human	...	...	...	...	...	...	...	+	158
Bovine diarrhea	Bovine	+	...	...	...	...	...	...	...	126
Infectious bovine rhinotracheitis	Bovine	...	+	+	...	...	+	...	...	132

* Interleukin-1.

quently, affects the status of immunity. Under normal circumstances, the predominance of induction or suppression depends upon considerations such as the physical state of the antigen, the route of administration, and the host's genetic background. Thus, antigens may contain distinct "suppressogenic" and immunogenic determinants that preferentially activate different cell types [160, 161]. Intravenous injection of immunogenic antigens often result in SC-mediated immunologic nonresponsiveness (tolerance) [162]. Finally, the responsiveness to certain antigens is genetically controlled such that nonresponder strains preferentially develop SC upon exposure to antigen [163, 164]. Infection by certain viruses can change the immunoregulatory balance, providing an SC dominance and a situation of suppressed immunity.

In 1970, the concept emerged that a lack of detectable immune response could be mediated by the direct action of SC, which in most systems studied turned out to be subpopulations of T cells [165]. SC have been described that modulate the induction and activity of B cells, helper T cells, delayed hypersensitivity and contact sensitivity, proliferating B and T cells, cytotoxic T lymphocytes, and NK cells (reviewed in [166]). The regulation may be either selective and antigen-specific or nonspecific, accounting, in some cases, for immunologic anergy [167, 168]. Immune responses to all types of antigens appear to be regulated by suppressor mechanisms involving a cascade of several interacting cell types (reviewed by Dorf and Benacerraf [169]). Most of our information on the topic of SC regulation comes from studies on noninfectious antigens and mitogens, but from our fragmentary knowledge of SC regulation of responses to viral antigens, the patterns of events appear similar [170]. It seems that SC influence the nature of the virus-host relationship and can account for examples of suppressed immunity not only to the infecting agent but also to unrelated antigens [171].

Virus-Specific Suppression

From work with simple antigens, numerous cell types have been implicated as involved in SC induction and control [169]. We can only suppose that similar SC circuits control responses to viral antigens, although variations could occur, reflecting, perhaps, the nature and form of the virus, the route of infection, and the possibility of either direct or indirect effects

of the virus on cells that participate in the SC circuit. The most reliable method for inducing an SC response in mice is exposure to antigen via the intravenous route, a procedure that results in split tolerance mediated by suppressor T cells [172–175]. With some viruses, exposure via the anterior chamber of the eye [175] or the oral route [176] also generates SC-mediated split tolerance. Virus-specific SC-mediated tolerance has been studied in murine models of HSV, influenza virus, Sendai virus, and reovirus infections [175–179].

Intravenous injection of HSV leads to tolerance of only the HSV-specific delayed-hypersensitivity response [177, 178]. This tolerance is mediated by SC, which act as either afferent or efferent suppressors, according to the nature of the viral preparation used for infection [172, 178]. Sonicated particles of virus induced Lyt-1⁺ afferent-acting SC, whereas virus-infected syngeneic cells induced Lyt-2⁺ efferent-acting SC. Both SC types were present in the spleens of mice four weeks after infection with either viral preparation. The afferent-acting cells prevented the generation of a de novo delayed-hypersensitivity response in mice that received the SC. This effect was confined to HSV type 1 and did not affect even the response to HSV type 2. The efferent-acting SC prevented the expression of delayed hypersensitivity by adoptive transfer of cells to naive mice. This suppression was also antigen-specific and affected only delayed hypersensitivity, not antibody production or cytotoxic-T lymphocyte (CTL) induction. The noteworthy observation that mice rendered tolerant to delayed-hypersensitivity were less able to clear virus indicates that the overactivity of SC may impair immunity. SC regulation of HSV-specific CTL induction has also been demonstrated [179]. Intraperitoneal injection of HSV does not result in detectable CTL activity in vivo, though it does prime the mice for CTL and lymphoproliferative responses. This lack of in vivo CTL induction could result from SC regulation since CTL induction does occur if putative suppressor mechanisms are removed by treatment with cyclophosphamide [180]. Recently, the role of suppression in regulating HSV-specific CTL induction in vitro has been closely examined [170, 179]. At least two T cell subsets and a macrophage subset that expressed a cell marker called IJ were shown to be involved in regulation, as were both nonspecific and specific suppressor factors. The latter factor appeared to express both IJ and antiidiotypic [181, 182] determinants, but the role the factor

played in the pathogenesis of HSV *in vivo* was not elucidated.

Results obtained in the influenza and Sendai virus systems differed from those with HSV. Exposure via the intravenous route to ultraviolet-inactivated influenza or Sendai viruses induced suppressor T cells that suppressed only virus-specific CTL induction. Neither delayed-hypersensitivity nor antibody responses were affected [174, 177]. Influenza-specific delayed-hypersensitivity responses, however, could be suppressed by the intranasal exposure of mice to infectious virus [174]. The suppression was mediated by an afferent-acting Lyt-1⁺ cell, which functioned to protect mice from an immunopathologic reaction [183] (discussed in succeeding section).

With reovirus, the oral route of exposure to ultraviolet-inactivated, but not infectious, virus favored SC-mediated tolerance induction [176]. In this instance, afferent-acting SC were also induced, and their activity was directed at the suppression of delayed-hypersensitivity responses. In the case of reovirus, some data indicate the existence of distinct suppressogenic and immunogenic determinants on the virus. The former was identified as a capsid protein [176]. It is possible that suppressogenic and immunogenic determinants are differentially sensitive to inactivating agents such as ultraviolet radiation.

Some viruses show distinct cell tropisms, and since cells involved in the induction and expression of suppression express surface markers that distinguish them from cell subsets involved in the positive aspects of immunity, viral infection of different subsets could disrupt the normal functioning of suppressor circuits. One outcome of this state of affairs could be the loss of SC control and the development of immunopathology and autoimmune disease. Several viruses have been associated with autoimmune diseases, but further direct evidence is required to prove such associations with SC. This topic will not be further discussed.

A documented example wherein experimental viral infection seemingly interferes with suppressor circuits is the effect of Newcastle disease virus on mice sensitized to the contactant chemical oxalozone [184]. Mice sensitized to oxalozone and infected with the virus failed to produce a nonspecific suppressor factor when the appropriate SC subsets were incubated with and antigen-presenting cells. The virus also impaired the function of presenting cells involved in induction of hapten-specific SC. The mechanism by which Newcastle disease virus dis-

rupted the SC circuit regulating contact sensitivity to oxalozone remains unknown, but the authors proposed that it was an alteration in membrane function. The implication of the model is that viral infection could affect responsiveness to irrelevant antigens, and this effect could result in either immunosuppression or hyperresponsiveness.

It is clear that with viral antigens SC regulate the type of immune response generated and ultimately affect the outcome of infection. It is also clear that the nature of the viral antigen and the route of administration influence whether suppression occurs. However, it remains to be shown why certain routes of infection favor SC induction and why the targets of the effect of SC are often limited. One explanation could be that subsets of macrophages involved in antigen presentation to SC are better represented at certain locations—for instance, the lamina propria [185]. Alternatively, SC induction could be associated with the ability of the SC to bind antigen directly, an event that is more likely to occur when virus is administered by routes such as the intravenous route. Since many viral infections are characterized by viremia, it will be of interest to establish whether such blood-borne antigens also result in the suppression of some components of immunity.

Suppressor Cell Activity in Humans

Most of our information regarding SC has resulted from studies in the murine model. SC activity in humans is usually assessed in one of two ways: either by documentation of SC activity *in vitro* or by determination of the ratio of SC to helper T cells in the circulation. SC activity is measured *in vitro* with a model originally developed in the murine system. This model involves the activation of T cells with either mitogens [186] or antigens [187, 188] to induce SC that inhibit a variety of immunologic responses. Alternatively, *in vivo*-activated SC may be demonstrated by the addition of fresh peripheral-blood leukocytes to a mixed lymphocyte reaction and observation of the suppressed proliferative response. The cells responsible for suppression in these two models appear to be T cells [189–191], although other cells, including monocytes, may exhibit suppressor activity [154, 192].

In both humans and mice, subsets of T cells with different functions express unique cell-surface antigens [159, 193]. Recently, monoclonal antibodies that react with the different T lymphocyte subsets of hu-

mans have been developed. By use of such reagents, along with cell sorting by cytofluorography, the numbers of different cell types in lymphoid populations can be rapidly defined and isolated.

In human medicine, the determination of the ratio of helper cells to SC has become a useful and rapid criterion by which changes in immune competence can be gauged. In normal individuals, the ratio of circulating helper lymphocytes (T4) to suppressor lymphocytes (T8) is approximately 3:1 [193]. A decrease in the ratio is often associated with viral infections. This alteration can be due to either a decrease in the number of circulating T4 cells, as characteristically occurs in HTLV-III infections [21], or an increase in the number of circulating T8 cells, as happens in EBV and CMV infections [50, 194]. A decrease in the T4-to-T8 ratio is often associated with diminished mitogen responsiveness *in vitro* and increased susceptibility to infectious disease [194].

In most instances, decreases in T4-to-T8 ratios are transient, reflecting a particular stage in the virus-host relationship. The clinical significance of these transient alterations depends upon the particular infection. In some HSV infections, a decrease in the ratio may signal the onset of recrudescence [195]. During EBV infection, a decrease in the ratio actually indicates a recovery, possibly because both suppressor and cytotoxic cells in humans are OKT8⁺ and recovery is mediated in large part by CTL [39]. The fact that in humans SC and CTL share the same OKT type can therefore pose a problem in the interpretation of T4-to-T8 ratios. However, it is possible to distinguish the two populations on the basis of another cell-surface antigen, 9.3 [196]: cytotoxic cells are 9.3⁺, whereas suppressor cells are 9.3⁻. Likewise, the OKT4 subset contains not only helper cells but also suppressor-inducer cells. However, helper-inducer cells are OKT4⁺ 4B4⁺, and suppressor-inducer cells are OKT4⁺ 2H4⁺ [197]. The variation in the relative frequencies of these subpopulations during viral infections requires investigation.

Suppressor Cells and Immunopathology

The possible biologic significance of the induction of tolerance to viral antigens was recently demonstrated during attempts to determine the role of delayed-type hypersensitivity-mediating Lyt-1⁺ cells (T_D) in influenza virus infections [183]. *In vitro*-expanded T_D were adoptively transferred into recipient mice that had received an intranasal challenge of influenza virus. Instead of conferring protection,

the adoptively transferred T_D cells exacerbated the infection, causing increased mortality. The recipient mice exhibited extensive lung consolidation similar to that in influenza pneumonitis in humans. If the T_D cells were instead suppressed by incubation *in vitro* with SC from intranasally immunized mice, the pathologic effect of the adoptive transfer was negated and the recipients recovered. Thus, with influenza, SC-mediated depression of the delayed-hypersensitivity response prevents immunopathologic reactions. Since natural infection with influenza in humans involves the respiratory tract, the induction of SC could represent a means by which the host avoids immunopathologic disorders.

A parallel study in which immunization to favor SC induction resulted in the modulation of an immunopathologic delayed-hypersensitivity response was recently reported in a model of HSV infection in mice [198]. In this model, viral infection in the pinna led to demyelination and ear paralysis, situations seemingly resulting from a virus-specific delayed-hypersensitivity response. Support for the role of T_D came from the demonstration that mice given virus intravenously as well as in the pinna were rendered tolerant to delayed hypersensitivity and failed to develop demyelination or ear paralysis. In addition, in adoptive transfer experiments, cells from such mice prevented (to some extent) demyelination in naive infected mice. Unfortunately, however, mice protected from demyelination often developed lethal encephalitis and were more susceptible to recurrent disease.

A protective role for SC has been demonstrated in other infections characterized by adverse delayed-hypersensitivity responses leading to immunopathogenesis [199, 200]. Furthermore, the lack of induction of an appropriate SC response may be the reason for some instances of vaccine failure. For example, administration of inactivated vaccines for measles and respiratory syncytial viruses resulted in an exacerbation of disease upon subsequent natural infection [201, 202]. The pathology of the lesions resembled an immunopathologic response to the virus. Although the reason for these adverse reactions was not determined, it is possible that the inactivated vaccines sensitized for delayed hypersensitivity but failed to stimulate a protective SC response.

Veto Cells As an Explanation for Immunosuppression

Veto cells are not truly SC but do play a role in damping an immune response. The Veto cell concept, first

introduced by Miller [203] and extended by Fink et al. [204, 205], holds that these cells, upon specific recognition by a particular lymphocyte, serve to inhibit any differentiation of that lymphocyte. Thus, unlike SC, which recognize their target antigens and then exert their regulating activity, Veto cells are recognized by the cell, which is then subject to Veto cell regulation (figure 1). The Veto cells themselves are considered to be of CTL lineage and in fact may function as normal CTL when they recognize appropriate target cells by means of their major histocompatibility complex-restricted antigen recognition receptors. How Veto activity is mediated remains to be shown. The possible mechanism of action of Veto cells was illustrated by an experiment recently reported by Fink et al. [204, 205]. These authors developed CTL clones (H-2^b) reactive with a specific histocompatibility antigen (anti-H-2^d). When such cells were injected into an allogeneic animal (H-2^k), the recipient animal failed to generate an anti-H-2^b CTL response, as would normally occur after immunization with splenocytes from H-2^b donors. The anti-H-2^b CTL response was thought not to occur because the H-2^b antigen was on a

Figure 1. The Veto cell concept. The Veto cell is the Lyt-2⁺ cell and is shown with its antigen receptor (<) as well as viral antigen (□) and self marker (○). The cell that recognizes the Veto cell and receives the "off" signal is the cytotoxic T lymphocyte precursor (CTL-P). It has a receptor for viral antigen plus self (⌢). If it binds antigen on a macrophage (MØ), it differentiates into a cytotoxic T lymphocyte (CTL).

CTL that acted as a Veto cell. These Veto cells served to prevent the differentiation of anti-H-2^b CTL precursors into CTL. Had the CTL precursors recognized H-2^b as presented by an antigen-presenting cell, they would have differentiated into CTL.

The activity of a Veto cell system could provide an explanation for the split tolerance and immunosuppression observed in lymphocytic choriomeningitis infection of mice as well as in other persistent viral infections. Lymphocytic choriomeningitis produces diverse disease syndromes, depending upon the strain of virus, the route and dose of infection, and the age and strain of mouse [206]. Infection of newborn mice results in viral persistence characterized by the production of antiviral antibodies but no virus-specific CTL activity. Adult mice infected with low doses of lymphocytic choriomeningitis virus generate a vigorous virus-specific CTL response. The failure of the persistently infected mice to generate CTL specific to this virus has remained an immunologic anomaly. Various mechanisms have been proposed, including the deletion of responding cells [207], mutual destruction by virus-infected CTL [206], SC induction [208], and the production of viral variants [209]. What is known is that high doses of virus, or injections of virus-infected splenocytes, can induce tolerance in adult animals, especially those immunosuppressed with cyclophosphamide.

The lymphocytic choriomeningitis virus-specific "tolerization" of CTL activity may result from the induction of Veto cells in the spleens and thymuses of the infected mice. Since lymphocytic choriomeningitis virus is lymphotropic, T cells, including CTL specific for the whole repertoire of antigens, become infected. Such infected T cells then express viral antigen at their cell surface (in the context of their MHC class I antigens). Because of the viral antigen (plus MHC) expression, the CTL (Veto cells) can be recognized by lymphocytic choriomeningitis-specific CTL precursors. Since the infected CTL act as Veto cells, they now serve to prevent functional differentiation of anti-lymphocytic choriomeningitis virus CTL precursors into specific CTL. It would be of interest to ascertain whether similar mechanisms of immunoregulation occur in other viral infections.

Conclusions

We hope that this review has served to demonstrate that viral infection can lead to immunosuppression by a variety of mechanisms. Often, the outcome in

the host is susceptibility to intercurrent infections with opportunistic pathogens. At times, these infections become life-threatening, a situation best exemplified by infections due to HTLV-III in humans and feline leukemia virus in cats. A detailed knowledge of mechanisms by which viruses cause immunosuppression at the molecular level is still lacking in most instances, yet such information is mandatory if successful strategies are to be devised for the avoidance and reversal of immunosuppression. For instance, in the case of feline leukemia virus infection, a profound cause of immunosuppression is seemingly mediated by a structural protein, P15(E). Early vaccines consisting of inactivated whole-virus preparations contained P15(E). Thus, instead of imparting protective immunity, vaccination rendered cats more susceptible to tumor engraftment and to disease upon subsequent challenge with infectious virus [25]. Inactivated vaccines also caused interference with lymphocyte function *in vitro*. Nevertheless, once P15(E)—the molecular component of feline leukemia virus responsible for immunosuppression—was identified, it became possible to devise subunit vaccines that contained none of the immunosuppressive form of this protein. Such vaccines effectively induce protective immunity without undesirable immunosuppression [210].

Our detailed knowledge of cellular and molecular requirements for immune induction and suppression is likely to be clinically valuable. For instance, with simple antigens such as lysozyme, simple determinants have been recognized that induce immunity, whereas others induce suppression [211]. Obviously, as subunit vaccines against viruses become more popular, we must be aware of the possible existence of such immunogenic and suppressogenic determinants. Moreover, since viruses are frequently a cause of immunopathologic disorders, we need to redirect the immune system to engender suppression in some instances. The identification and use of suppressogenic determinants in vaccines, or the use of adjuvants or routes of administration and doses that generate controlled levels of suppression, could prove vitally important.

Should suppressor manipulation be desirable, necessary information must be accumulated about factors that mediate suppression and act either directly or indirectly and either specifically or nonspecifically (discussed in [212]). It is conceivable that suppression could be modulated by the injection of appropriate suppressor factors or by the ad-

ministration of molecules that change the activity of SC. Substances known to influence the activity of SC include α -fetoproteins [213], prostaglandins [214], thymic hormones [215], cyclic nucleotides [216], antihistamines [217], and levamisole [218, 219]. In addition, since the T cells involved in suppressor activity and the antigen-presenting cells for SC induction may express cell-surface markers different from those involved in other types of immunity [159], it is possible that the outcome could be modulated by the administration of appropriate antisera.

Finally since, a common outcome of virus-induced immunosuppression is increased susceptibility to secondary infections, a useful strategy may be to reverse the suppression with nonspecific immunopotentiators. Although such substances have been advocated for more than 50 years, only recently has the use of immunopotential been studied seriously by immunopharmacologists. For example, the chemically defined immunopotentiators levamisole and isoprinosine prove useful at augmenting T cell responses both *in vivo* and *in vitro* [218]. In addition, immunity may be enhanced following the injection of cytokines such as IFN, IL-2, and (perhaps) transfer factor [84, 220–222]. Doubtless, as more becomes known about the mechanisms of action and interaction of physiologic cytokines and synthetic chemicals that influence immunoregulation, we should be better able to deal effectively with any consequence of virus-induced immunosuppression.

References

1. von Pirquet C. Das Verhalten der Kutanen Tuberkulinreaktion während der Masern. *Deutsch Med Wochensh* 1908;**34**:1297–300
2. Fireman P, Friday G, Kumata J. Effect of measles vaccine on immunologic responsiveness. *Pediatrics* 1969;**43**: 264–72
3. Whittle HC, Bradley-Moore A, Fleming A, Greenwood BM. Effects of measles on the immune response of Nigerian children. *Arch Dis Child* 1973;**48**:753–6
4. Appel MJG, Gillespie JH. Canine distemper virus. In: *Virology monographs*. New York: Springer-Verlag, 1972:8
5. Krakowka S, Cockerell G, Koestner A. Effects of canine distemper virus infection on lymphoid function *in vitro* and *in vivo*. *Infect Immun* 1975;**11**:1069–78
6. Starr S, Berkovich S. Effect of measles, gamma-globulin-modified measles and vaccine measles on the tuberculin test. *N Engl J Med* 1964;**270**:386–91
7. Rice GPA, Schrier RD, Southern PJ, Nelson J, Casali P, Oldstone MBA. Cytomegalovirus and measles virus: *in vitro* models of virus-mediated immunosuppression. *J Leukocyte Biol* 1985;**37**:15–28

8. McFarland HF. The effect of measles virus infection on T and B lymphocytes in the mouse. I. Suppression of helper cell activity. *J Immunol* 1974;**113**:1978-83
9. Huddleston JR, Lampert PW, Oldstone MBA. Virus-lymphocyte interactions: infection of T_G and T_M subsets by measles virus. *Clin Immunol Immunopathol* 1980;**15**:502-9
10. Jacobson S, McFarland HF. Measles virus infection of human peripheral blood lymphocytes: importance of the OKT4⁺ T cell subset. In: Compans RW, Bishop DHL, eds. *Nonsegmented negative strand viruses*. Orlando, Fla: Academic Press, 1984:435-42
11. Casali P, Rice GPA, Oldstone MBA. Viruses disrupt functions of human lymphocytes. Effects of measles virus and influenza virus on lymphocyte-mediated killing and antibody production. *J Exp Med* 1984;**159**:1322-37
12. Krakowka S, Higgins RJ, Koestner A. Canine distemper virus: review of structural and functional modulations in lymphoid tissue. *Am J Vet Res* 1980;**41**:284-92
13. Miele JA, Krakowka S. Antibody responses to virion polypeptides in gnotobiotic dogs infected with canine distemper virus. *Infect Immun* 1983;**41**:869-71
14. Krakowka S. Mechanisms of in vitro immunosuppression in canine distemper virus infection. *J Clin Lab Immunol* 1982;**8**:187-96
15. Rose JA. Parovirus reproduction. In: Fraenkel-Conrat H, Wagner PR, eds. *Comprehensive virology*. Vol 3. New York: Plenum, 1974:1-61
16. Bloom ME. Parvovirus infections; features reminiscent of AIDS. *Ann NY Acad Sci* 1984;**437**:110-20
17. Schultz RD, Mendel H, Scott FW. Effect of feline panleukopenia virus infection on development of humoral and cellular immunity. *Cornell Vet* 1976;**66**:324-32
18. Rohovsky MW, Griesemer RA. Experimental feline infectious enteritis in the germ free cat. *Pathologia Veterinaria* 1967;**4**:391-410
19. Broder S, Gallo RC. A pathogenic retrovirus (HTLV-III) linked to AIDS. *N Engl J Med* 1984;**311**:1292-7
20. Lane HC, Fauci AS. Immunologic abnormalities in the acquired immunodeficiency syndrome. *Annual Review of Immunology* 1985;**3**:477-500
21. Fauci AS, Macher AM, Longo DL, Lane HC, Rook AH, Masur H, Gelman EP. Acquired immunodeficiency syndrome: epidemiologic, clinical, immunologic, and therapeutic considerations. *Ann Intern Med* 1984;**100**:92-106
22. Weiss A, Hollander H, Stobo J. Acquired immunodeficiency syndrome: epidemiology, virology, and immunology. *Annu Rev Med* 1985;**36**:545-62
23. Markham PD, Salahuddin SZ, Popovic M, Sarngadharan MG, Gallo RC. Retrovirus infections in man: human T cell leukemia (lymphotropic) viruses. *Progress in Leukocyte Biology* 1985;**1**:49-75
24. Dent PB. Immunodepression by oncogenic viruses. *Prog Med Virol* 1972;**14**:1-35
25. Rojko JL, Olson RG. The immunobiology of the feline leukemia virus. *Vet Immunol Immunopathol* 1984;**6**:107-65
26. Synderman R, Cianciolo GJ. Immunosuppressive activity of the retroviral envelope protein P15E and its possible relationship to neoplasia. *Immunology Today* 1984;**5**:240-3
27. Fine D, Schochetman G. Type D primate retroviruses: a review. *Cancer Res* 1978;**38**:3123-39
28. Wong-Staal F, Gallo RC. Human T-lymphotropic retroviruses. *Nature* 1985;**317**:395-403
29. Montagnier L. Lymphadenopathy-associated virus: from molecular biology to pathogenicity. *Ann Intern Med* 1985;**103**:689-93
30. Ciobanu N, Welte K, Kruger G, Venuta S, Gold J, Feldman SP, Wang CY, Koziner B, Moore MAS, Safai B, Mertelsmann R. Defective T-cell response to PHA and mitogenic monoclonal antibodies in male homosexuals with acquired immunodeficiency syndrome and its in vitro correction by interleukin 2. *J Clin Immunol* 1983;**3**:332-40
31. Sonnabend J, Witkin SS, Purtilo DT. Acquired immunodeficiency syndrome, opportunistic infections and malignancies in male homosexuals. A hypothesis of etiologic factors in pathogenesis. *JAMA* 1983;**249**:2370-4
32. Schroff RW, Gottlieb MS, Prince HE, Chai LL, Fahey JL. Immunological studies of homosexual men with immunodeficiency and Kaposi's sarcoma. *Clin Immunol Immunopathol* 1983;**27**:300-14
33. Lane HC, Masur H, Edgar LC, Whalen G, Rook AH, Fauci AS. Abnormalities of B-cell activation and immunoregulation in patients with the acquired immunodeficiency syndrome. *N Engl J Med* 1983;**309**:453-8
34. Murray HW, Rubin BY, Masur M, Roberts RB. Impaired production of lymphokines and immune (gamma) interferon in the acquired immunodeficiency syndrome. *N Engl J Med* 1984;**310**:883-9
35. Sodroski J, Rosen C, Wong-Staal F, Salahuddin SZ, Popovic M, Arya S, Gallo RC, Haseltine WA. *Trans*-acting transcriptional regulation of human T-cell leukemia virus type III longer terminal repeat. *Science* 1985;**227**:171-3
36. Weiss R. Retroviruses linked with AIDS. *Nature* 1984;**309**:12-3
37. Kanki PJ, Alroy J, Essex M. Isolation of T-lymphotropic retrovirus related to HTLV-III/LAV from wild-caught African green monkeys. *Science* 1985;**230**:951-4
38. Shore SL, Nahmias AJ. Immunology of herpes simplex virus. In: Nahmias A, O'Reilly R, eds. *Immunology of human infection*. New York: Plenum, 1982:21-72
39. Epstein MA, Morgan AJ. Clinical consequences of Epstein-Barr virus infection and possible control by an anti-viral vaccine. *Clin Exp Immunol* 1983;**53**:257-71
40. Kirchner H. Immunobiology of infection with human cytomegalovirus. *Adv Cancer Res* 1983;**40**:31-105
41. Schooley RT, Hirsch MS, Colvin RB, Cosimi AB, Tolkoff-Rubin NE, McCluskey RT, Burton RC, Russell PS, Herin JT, Delmonico FL, Giorgi JV, Henle W, Rubin RH. Association of herpesvirus infections with T-lymphocyte-subset alterations, glomerulopathy, and opportunistic infections after renal transplantation. *N Engl J Med* 1983;**308**:307-13
42. Hamilton JR, Overall JC Jr. Synergistic infection with murine cytomegalovirus *Pseudomonas aeruginosa* in mice. *J Infect Dis* 1978;**137**:775-82
43. Evans AS, Neiderman JC. Epstein-Barr virus. In: Evans AS, ed. *Viral infections of humans: epidemiology and control*. New York: Plenum, 1982:253-81
44. Seeley J, Svedmyr E, Weiland O, Klein G, Moller E, Eriksson E, Andersson K, Van Der Waal L. Epstein-Barr virus selective T cells in infectious mononucleosis are not restricted to HLA-A and B antigens. *J Immunol* 1981;**127**:293-300

45. Rickinson AB, Moss DJ, Pope JH, Ahlberg N. Long-term T-cell-mediated immunity to Epstein-Barr virus in man. IV. Development of T-cell memory in convalescent infectious mononucleosis patients. *Int J Cancer* 1980;**25**: 59-65
46. Tosato G, Magrath I, Koski I, Dooley N, Blaese M. Activation of suppressor T cells during Epstein-Barr-virus-induced infectious mononucleosis. *N Engl J Med* 1979;**301**:1133-7
47. Purtilo DT. Epstein-Barr virus induced oncogenesis in immune-deficient individuals. *Lancet* 1980;**1**:300-3
48. Adler SP. Transfusion associated cytomegalovirus infections. *Rev Infect Dis* 1983;**5**:977-93
49. Rubin RH, Carney WP, Schooley RT, Colvin RB, Burton RC, Hoffman RA, Hansen WP, Cosimi AB, Russell PS, Hirsch MS. The effect of infection of T lymphocyte subpopulations. *Int J Immunopharmacol* 1981;**3**:307-12
50. Carney WP, Rubin RH, Hoffman RA, Hansen WP, Healey K, Hirsch MS. Analysis of T lymphocyte subsets in cytomegalovirus mononucleosis. *J Immunol* 1981;**126**: 2114-6
51. Carney WP, Hirsch MS. Mechanisms of immunosuppression in cytomegalovirus mononucleosis. II. Virus-monocyte interactions. *J Infect Dis* 1981;**144**:47-54
52. Rinaldo CR Jr, Black PH, Hirsch MS. Interaction of cytomegalovirus with leukocytes from patients with mononucleosis due to cytomegalovirus. *J Infect Dis* 1977;**136**:667-78
53. Rice GPA, Schrier RD, Oldstone MBA. Cytomegalovirus infects human lymphocytes and monocytes: virus expression is restricted to immediate-early gene products. *Proc Natl Acad Sci USA* 1984;**81**:6134-8
54. Howard RJ, Najarian JS. Cytomegalovirus-induced immune suppression: humoral immunity. *Clin Exp Immunol* 1974;**18**:109-18
55. Selgrade MK, Ahmed A, Sell KW, Gershwin ME, Steinberg AD. Effect of murine cytomegalovirus on the in vitro response of T and B cells to mitogens. *J Immunol* 1976;**116**: 1459-65
56. Babiuk LA, Ohmann HB. Bovine herpesvirus-1 (BHV-1) infection in cattle as a model for viral induced immunosuppression. *Progress in Leukocyte Biology* 1985;**1**:99-114
57. Plaeger-Marshall S, Smith JW. Inhibition of mitogen- and antigen-induced lymphocyte blastogenesis by herpes simplex virus. *J Infect Dis* 1978;**138**:506-11
58. Martin JR, Reed EV, Striegl LC. Acute thymic atrophy in severe herpes simplex virus type 2 infection. *Progress in Leukocyte Biology* 1985;**1**:185-90
59. Pelton BK, Duncan IB, Denman AM. Herpes simplex virus depresses antibody production by affecting T-cell function. *Nature* 1980;**284**:176-7
60. Hammer SM, Carney WP, Iacoviello VR, Lowe BR, Hirsch MS. Herpes simplex virus infection of human T-cell subpopulations. *Infect Immun* 1982;**38**:795-7
61. Hammer SM, Gillis JM. Herpes simplex virus replication in interleukin-2-stimulated human T cells. *J Infect Dis* 1985;**151**:544-8
62. Plaeger-Marshall S, Smith JW. Experimental infection of subpopulations of human peripheral blood leukocytes by herpes simplex virus. *Proc Soc Exp Biol Med* 1978;**158**: 263-8
63. Blood DC, Radostits OM, Henderson JA. *Veterinary medicine*. 6th ed. London: Balliere-Tyndall, 1983
64. Lamontague L, Dupuy CD, Leroy D, Chausseau JP, Dupuy JM. Coronavirus-induced immunosuppression: role of mouse hepatitis virus 3-lymphocyte interaction. *Progress in Leukocyte Biology* 1985;**1**:29-42
65. Narayan O, Lang G, Rouse BT. A new influenza A virus infection in turkeys. IV. Experimental susceptibility of domestic birds to virus strain Turkey/Ontario 7732/1966. *Arch Ges Virusforschung* 1969;**26**:149-65
66. Fadly AM, Nazerian K. Pathogenesis of infectious bursal disease in chickens infected with virus of various ages. *Avian Dis* 1983;**27**:714-23
67. Meulemans G, Halen P, Vindevogel H, Gouffaux M. The immunodepressive effect of infectious bursal agent on vaccination against Newcastle disease. *Res Vet Sci* 1977;**22**:222-4
68. Butler RC, Friedman H. Leukemia virus-induced immunosuppression: reversal in subcellular factors. *Ann NY Acad Sci* 1979;**332**:446-50
69. Cerney J, Essex M. Mechanisms of immunosuppression by oncogenic RNA viruses. In: Neubauer R, ed. *Naturally occurring biological immunosuppressive factors and their relationship to disease*. Boca Raton, Fla: CRC Press, 1978
70. Essex M. Horizontally and vertically transmitted oncornaviruses of cats. *Adv Cancer Res* 1975;**21**:175-248
71. Hoover EA, Olsen RG, Hardy WD Jr, Schaller JP, Mathes LE. Feline leukemia virus infection: age-related variation in response of cats to experimental infection. *Journal of National Cancer Institute* 1976;**57**:365-9
72. Cockerell GL, Hoover EA, Krakowka S, Olsen RG, Yohn DS. Lymphocyte mitogen reactivity and enumeration of circulating B- and T-cells during feline leukemia virus infection in the cat. *Journal of the National Cancer Institute* 1976;**57**:1095-9
73. Perryman LE, Hoover EA, Yohn DS. Immunologic reactivity of the cat: immunosuppression in experimental feline leukemia. *Journal of the National Cancer Institute*. 1972;**49**:1357-65
74. Trainin Z, Wernicke D, Ungar-Waron H, Essex M. Suppression of the humoral antibody response in natural retrovirus infections. *Science* 1983;**220**:858-9
75. Mathes LE, Olsen RG. *Immunobiology of feline leukemia virus disease in feline leukemia*. Boca Raton, Fla: CRC Press 1981:77-88
76. Stiff MI, Olsen RG. Effects of retrovirus protein on the feline one-way mixed leukocyte reaction. *J Gen Virol* 1983;**64**:957-9
77. Schaller JP, Hoover EA, Olsen RG. Active and passive immunization of cats with inactivated feline oncornaviruses. *Journal of the National Cancer Institute* 1977;**59**:1441-50
78. Mathes LE, Olsen RG, Hebebrand LC, Hoover EA, Schaller JP. Abrogation of lymphocyte blastogenesis by a feline leukaemia virus protein. *Nature* 1978;**274**:687-9
79. Hebebrand LC, Olsen RG, Mathes LE, Nichols WS. Inhibition of human lymphocyte mitogen and antigen response by a 15,000-dalton protein from feline leukemia virus. *Cancer Res* 1979;**39**:443-7
80. Copelan EA, Rinehart JJ, Lewis M, Mathes L, Olsen R, Sagone A. The mechanism of retrovirus suppression of human T cell proliferation in vitro. *J Immunol* 1983;**131**: 2017-20

81. Cianciolo G, Hunter J, Silva J, Haskill JS, Snyderman R. Inhibitors of monocyte responses to chemotaxins are present in human cancerous effusions and react with monoclonal antibodies to the P15(E) structural protein of retroviruses. *J Clin Invest* 1981;**68**:831-44
82. Cianciolo GJ, Matthews TJ, Bolognesi DP, Snyderman R. Macrophage accumulation in mice is inhibited by low molecular weight products from murine leukemia viruses. *J Immunol* 1980;**124**:2900-5
83. Gresser I. On the varied biologic effects of interferon. *Cell Immunol* 1977;**34**:406-15
84. Toy JL. The interferons. *Clin Exp Immunol* 1983;**54**:1-13
85. Epstein DA, Torrence PF, Friedman RM. Double-stranded RNA inhibits a phosphoprotein phosphatase present in interferon-treated cells. *Proc Natl Acad Sci USA* 1980;**77**:107-11
86. Lengyel P. Biochemistry of interferons and their actions. *Annu Rev Biochem* 1982;**51**:251-82
87. De Maeyer E, De Maeyer-Guignard J, Vandeputte M. Inhibition by interferon of delayed-type hypersensitivity sensitivity in the mouse. *Proc Natl Acad Sci USA* 1975;**72**:1753-7
88. Johnson HM, Smith BS, Baron S. Inhibition of the primary in vitro antibody response by interferon preparations. *J Immunol* 1975;**114**:403-9
89. Sonnenfeld G, Mandel AD, Merigan TC. The immunosuppressive effect of type II mouse interferon preparations on antibody production. *Cell Immunol* 1977;**34**:193-206
90. Bloom BR. Interferons and the immune system. *Nature (Lond)* 1980;**284**:593-5
91. Schattner A, Meshorer A, Wallach D. Involvement of interferon in virus-induced lymphopenia. *Cell Immunol* 1983;**79**:11-25
92. Woodruff JJ, Woodruff JF. Virus-induced alterations of lymphoid tissues. IV. The effect of Newcastle disease virus on the fate of transfused thoracic duct lymphocytes. *Cell Immunol* 1974;**10**:78-85
93. Brennan M, Zingernagel RM. Influence of one virus infection on a second concurrent primary in vivo antiviral cytotoxic T-cell response. *Infect Immun* 1983;**41**:470-5
94. Chandrabose K, Cuatrecasas P, Pottathil R. Changes in fatty acyl chains of phospholipids induced by interferon in mouse sarcoma S-180 cells. *Biochem Biophys Res Commun* 1981;**98**:661-8
95. Lindahl P, Leary P, Gresser I. Enhancement of the expression of histocompatibility antigens of mouse lymphoid cells by interferon in vitro. *Eur J Immunol* 1974;**4**:779-84
96. Itoh K, Inoue M, Kataoka S, Kumagai K. Differential effect of interferon expression of IgG- and IgM-Fc receptors of human lymphocytes. *J Immunol* 1980;**124**:2589-95
97. Grollman EF, Lee G, Ramos S, Lazo PS, Kaback HR, Friedman RM, Kohn LD. Relationships of the structure and function of the interferon receptor to hormone receptors and establishment of the antiviral state. *Cancer Res* 1978;**38**:4172-85
98. Leanderson T, Hillorn V, Holmberg D, Larsson E-L, Lundgren E. Selective effects of interferon on distinct sites of the T lymphocyte triggering process. *J Immunol* 1982;**129**:490-4
99. Steeg PS, Moore RN, Oppenheim JJ. Regulation of murine macrophage Ia-antigen expression by products of activated spleen cells. *J Exp Med* 1980;**152**:1734-44
100. Aune TM, Pierce CW. Activation of a suppressor T-cell pathway by interferon. *Proc Natl Acad Sci USA* 1982;**79**:3808-12
101. Boraschi D, Neiderhuber JE. Regulation of macrophage suppression and cytotoxicity by interferon: role of Ia-bearing macrophages. *J Immunol* 1982;**129**:1854-8
102. Mogensen SC. Viral interference with the function of phagocytic cells. In: G. Falcone, ed. *Bacterial and viral inhibition and modulation of host defenses*. London: Academic Press, 1984: 89-107
103. Morahan PS, Morse SS, McGeorge MB. Macrophage extrinsic antiviral activity during herpes simplex virus infection. *J Gen Virol* 1980;**46**:291-300
104. Bonina L, Nash AA, Arena A, Leung KN, Wildy P. T cell-macrophage interactions in arginase mediated resistance to herpes simplex virus. *Virus Research* 1984;**1**:501-5
105. Ptak W, Zembala M, Gershon RK. Intermediary role of macrophages in the passage of suppressor signals between T-cell subsets. *J Exp Med* 1978;**148**:424-34
106. Ptak W, Zembala M, Asherson GL, Marcinkiewicz J. Inhibition of contact sensitivity by macrophages. *Int Arch Allergy Appl Immunol* 1981;**65**:121-8
107. Unanue ER. The regulatory role of macrophages in antigenic stimulation. Part Two: Symbiotic relationship between lymphocytes and macrophages. *Adv Immunol* 1981;**31**:1-136
108. Unanue ER. Antigen-presenting function of the macrophage. *Annual Review of Immunology* 1984;**2**:395-428
109. Morahan PS. Interactions of herpesviruses with mononuclear phagocytes. In: Rouse BT, Lopez C, eds. *Immunobiology of herpes simplex virus infection*. Boca Raton, Fla: CRC Press, 1984:71-90
110. Granstein RD, Green MI. Splenic I-J-bearing antigen-presenting cells in activation of suppression: further characterization. *Cell Immunol* 1985;**91**:12-20
111. Usui M, Aoki I, Sunshine GH, Dorf ME. Requirements for suppressor T cell activation. *J Immunol* 1984;**133**:1137-41
112. Lopez C. Genetics of natural resistance to herpesvirus infections in mice. *Nature* 1975;**258**:152-3
113. Meyer T, Horisberger MA. Combined action of mouse alpha and beta interferons in influenza virus-infected macrophages carrying the resistance gene Mx. *J Virol* 1984;**49**:709-16
114. Knobler RL, Tunsion LA, Oldstone MBA. Host genetic control of mouse hepatitis virus type 4 (JHM strain) replication. I. Restriction of virus amplification and spread in macrophages from resistant mice. *J Gen Virol* 1984;**65**:1543-8
115. Johnson RT. The pathogenesis of herpes virus encephalitis. II. A cellular basis for the development of resistance with age. *J Exp Med* 1964;**120**:359-74
116. Daniels CA, Kleinerman ES, Snyderman R. Abortive and productive infections of human mononuclear phagocytes by type 1 herpes simplex virus. *Am J Pathol* 1978;**91**:119-29
117. Leary K, Connor JR, Morahan PS. Comparison of herpes simplex virus type 1 DNA replication and virus production in murine bone marrow-derived and resident peritoneal macrophages. *J Gen Virol* 1985;**66**:1123-9
118. Jennings ST, Etensohn DB, Roberts NJ Jr. Influenza virus infection of human alveolar and peripheral blood-derived

- macrophages. Production of factors that alter fibroblast production. *Am Rev Respir Dis* 1984;130:98-102
119. deMarchi JM. Nature of the block in the expression of some early virus genes in cells abortively infected with human cytomegalovirus. *Virology* 1983;129:287-97
 120. Gollins SW, Porterfield JS. Flavivirus infection enhancement in macrophages: radioactive and biological studies on the effect of antibody on viral fate. *J Gen Virol* 1984;65:1261-72
 121. Ettensohn DB, Roberts NJ Jr. Influenza virus infection of human alveolar and blood-derived macrophages: differences in accessory cell function and interferon production. *J Infect Dis* 1984;149:942-9
 122. Narayan O, Wolinsky JS, Clements JE, Strandberg JD, Griffin DE, Cork LC. Slow virus replication: the role of macrophages in the persistence and expression of visna viruses of sheep and goats. *J Gen Virol* 1982;59:345-56
 123. Murphy FA, Buchmeier MJ, Rawls WE. The reticuloendothelium as a target in a virus infection. Pichinde virus pathogenesis in two strains of hamsters. *Lab Invest* 1977;37:502-15
 124. Mills EL. Viral infections predisposing to bacterial infections. *Annu Rev Med* 1984;35:469-79
 125. Kleinerman ES, Snyderman R, Daniels CA. Depression of human monocyte chemotaxis by herpes simplex and influenza viruses. *J Immunol* 1974;113:1562-7
 126. Ketelsen AT, Johnson DW, Muscoplat CC. Depression of bovine monocyte chemotactic responses by bovine viral diarrhea virus. *Infect Immun* 1979;25:565-8
 127. Stenson WF, Parker CW. Prostaglandins, macrophages and immunity. *J Immunol* 1980;125:1-5
 128. Metzger Z, Hoffeld JT, Oppenheim JJ. Macrophage-mediated suppression. I. Evidence for participation of both hydrogen peroxide and prostaglandins in suppression of murine lymphocyte proliferation. *J Immunol* 1980;124:983-8
 129. Jakab GJ, Warr GA, Sannes PL. Alveolar macrophage ingestion and phagosome-lysosome fusion defect associated with virus pneumonia. *Infect Immun* 1980;27:960-8
 130. Pesanti EL, Shanley JD. Murine cytomegalovirus-induced macrophage dysfunction. *J Leukocyte Biol* 1984;36:133-41
 131. Warr GA, Jakab GJ, Hearst JE. Alterations in lung macrophage immune receptor(s) activity associated with viral pneumonia. *J Reticuloendothel Soc* 1979;26:357-66
 132. Forman AJ, Babiuk LA. Effect of infectious bovine rhinotracheitis virus infection on bovine alveolar macrophage function. *Infect Immun* 1982;35:1041-7
 133. Plaeger-Marshall S, Wilson LA, Smith JW. Alteration of rabbit alveolar and peritoneal macrophage function by herpes simplex virus. *Infect Immun* 1983;41:1376-9
 134. Carter GR. Pasteurella infections as sequelae to respiratory viral infections. *J Am Vet Med Assoc* 1973;163:863-4
 135. Westmoreland D, St. Jeor S, Rapp F. The development by cytomegalovirus-infected cells of binding affinity for normal human immunoglobulin. *J Immunol* 1976;116:1566-70
 136. Jakab GJ, Warr GA. Immune-enhanced phagocytic dysfunction in pulmonary macrophages infected with parainfluenza 1 (Sendai) virus. *Am Rev Respir Dis* 1981;124:575-81
 137. Astry CL, Jakab GJ. Influenza virus-induced immune complexes suppress alveolar macrophage phagocytosis. *J Virol* 1984;50:287-92
 138. Warr GA. A macrophage receptor for (mannose/glucosamine)-glycoproteins of potential importance in phagocytic activity. *Biochem Biophys Res Commun* 1980;93:737-45
 139. Davies P, Allison AC. Effects of cytochalasin B on endocytosis and exocytosis. In: Tanenbaum SW, ed. *Cytochalasins - biochemical and cell biological aspects*. New York: Elsevier/North-Holland, 1978:143-60
 140. Jakab GJ, Green GM. Defect in intracellular killing of *Staphylococcus aureus* within alveolar macrophages in Sendai virus-infected murine lungs. *J Clin Invest* 1976;57:1533-9
 141. Warshawer D, Goldstein E, Akers T, Lippert W, Kim M. Effect of influenza viral infection on the ingestion and killing of bacteria by alveolar macrophages. *Am Rev Respir Dis* 1977;115:269-77
 142. Silverberg BA, Jakab GJ, Thomson RG, Warr GA, Boo KS. Ultrastructural alteration in phagocytic functions of alveolar macrophages after parainfluenza virus infection. *J Reticuloendothel Soc* 1979;25:405-16
 143. Finkel A, Dent PB. Abnormalities in lymphocyte proliferation in classical and atypical measles infection. *Cell Immunol* 1973;6:41-8
 144. Roberts NJ Jr, Steigbigel RT. Effect of in vitro virus infection on response of human monocytes and lymphocytes to mitogen stimulation. *J Immunol* 1978;121:1052-8
 145. Isakov N, Feldman M, Segal S. Acute infection of mice with lactic dehydrogenase virus (LDV) impairs the antigen-presenting capacity of their macrophages. *Cell Immunol* 1982;66:317-22
 146. Roberts NJ Jr. Different effects of influenza virus, respiratory syncytial virus, and Sendai on human lymphocytes and macrophages. *Infect Immun* 1982;35:1142-6
 147. Biasi G, Collavo D, Chieco-Bianchi L. Selective failure of accessory cell function in Moloney murine leukemia virus-tolerant mice. *J Immunol* 1983;131:16-8
 148. Hearst JE, Warr GA, Jakab GJ. Characterization of murine lung and peritoneal macrophages. *J Reticuloendothel Soc* 1980;27:443-54
 149. Rodgers BC, Scott DM, Munding J, Patrick Sissons JG. Monocyte-derived inhibitor of interleukin 1 induced by human cytomegalovirus. *J Virol* 1985;55:527-32
 150. Friedlander AM, Jahrling PB, Merrill P, Tobery S. Inhibition of mouse peritoneal macrophage DNA synthesis by infection with the arenavirus Pichinde. *Infect Immun* 1984;43:283-8
 151. Nakamura RM, Tanaka H, Tokunaga T. In vitro induction of suppressor T-cells in delayed-type hypersensitivity to BCG and an essential role of I-J-positive accessory cells. *Immunol Lett* 1982;4:295-9
 152. Calderon J, Williams RT, Unanue ER. An inhibitor of cell proliferation released by cultures of macrophages. *Proc Natl Acad Sci USA* 1974;71:4273-7
 153. Oehler JR, Herberman RB, Campbell DA Jr, Djeu JY. Inhibition of rat mixed lymphocyte cultures by suppressor macrophages. *Cell Immunol* 1977;29:238-50
 154. Wilkins JA, Sigurdson SL, Rutherford WJ, Jordan Y, Warrington RJ. The production of immunoregulatory factors by a human macrophage-like cell line. I. Characterization of an inhibitor of lymphocyte DNA synthesis. *Cell Immunol* 1983;75:328-36
 155. Chen PC, Gaetjens E, Broome JD. Macromolecular inhibitory factor for lymphoid cells produced by mouse macrophages. *Immunology* 1977;33:391-8

156. Van Loon AM, van der Logt JTM, van der Veen J. Poliovirus-induced suppression of lymphocyte stimulation: a macrophage-mediated effect. *Immunology* 1979;37:135-43
157. Ferrante A, O'Keefe DE, Thong YH. Induction of suppressor cells in mice following Vaccinia virus infection. *Med Microbiol Immunol (Berl)* 1980;168:227-33
158. Gulati L, Chaturvedi UC, Mathur A. Dengue virus-induced cytotoxic factor induces macrophages to produce a cytotoxin. *Immunology* 1983;49:121-30
159. Cantor H, Boyse EA. Regulation of cellular and humoral immune responses by T-cell subclasses. *Cold Spring Harbor Symp Quant Biol* 1977;41:23-32
160. Naor D. Coexistence of immunogenic and suppressogenic epitopes in tumor cells and various types of macromolecules. *Cancer Immunol Immunother* 1983;16:1-10
161. Kölsch E. Interaction of suppressor and helper antigenic determinants in the dominance of either tolerance or immunity [editorial]. *Scand J Immunol* 1984;19:387-93
162. Parks DE. Tolerance: facts and views - 1983. *Surv Immunol Res* 1984;3:190-4
163. Kapp JA, Sorensen CM, Pierce CW. Antigen-specific suppressor T cell interactions. II. Characterization of two different types of suppressor T cell factors specific for L-glutamic acid⁵⁰-L-tyrosine⁹⁰(GT) and L-glutamic acid⁶⁰-L-alanine³⁰-L-tyrosine¹⁰(GAT). *J Exp Med* 1983;158:1962-78
164. Ikezawa Z, Nonaka M, Abe R, Tada T, Nagy ZA, Klein J. Induction of T cell responses in nonresponder mice by abolishing suppression with monoclonal antibodies recognizing a region-controlled, T cell-specific determinants. *J Immunol* 1983;131:1646-9
165. Gershon RK, Kondo K. Cell interactions in the induction of tolerance: the role of thymic lymphocytes. *Immunology* 1970;18:723-37
166. Schaff-Lafontaine N, Degiovanni G. Suppressor T cells. *Pathol Res Pract* 1981;171:159-72
167. Mehra V, Convit J, Rubinstein A, Bloom BR. Activated suppressor T cells in leprosy. *J Immunol* 1982;129:1946-51
168. Scott PA, Farrell JP. Experimental cutaneous leishmaniasis. I. Nonspecific immunodepression in BALB/c mice infected with *Leishmania tropica*. *J Immunol* 1981;127:2395-400
169. Dorf ME, Benacerraf B. Suppressor cells in immunoregulation. *Annual Review of Immunology* 1984;2:127-58
170. Horohov DW, Moore RN, Rouse BT. Regulation of herpes simplex virus-specific lymphoproliferation by suppressor cells. *J Virol* 1985;56:1-6
171. Iwasaka T, Sheridan JF, Aurelian L. Immunity to herpes simplex virus type 2: recurrent lesions are associated with the induction of suppressor cells and soluble suppressor factors. *Infect Immun* 1983;42:955-64
172. Nash AA. Tolerance and suppression in virus disease. *Br Med Bull* 1985;41:41-5
173. Leung K, Ashman RB, Ertl HCG, Ada GL. Selective suppression of the cytotoxic T cell response to influenza virus in mice. *Eur J Immunol* 1980;10:803-10
174. Liew FY, Russell SM. Delayed-type hypersensitivity to influenza virus. Induction of antigen-specific suppressor T cells for delayed-type hypersensitivity to hemagglutinin during influenza virus infection in mice. *J Exp Med* 1980;151:799-814
175. Whittum JA, Niederkorn JV, McCulley JP, Streilein JW. Role of suppressor T cells in herpes simplex virus-induced immune deviation. *J Virol* 1984;51:556-8
176. Rubin D, Weiner HL, Fields BN, Greene MI. Immunologic tolerance after oral administration of reovirus: requirement for two viral gene products for tolerance induction. *J Immunol* 1981;127:1697-701
177. Ada GL, Leung K-N, Ertl H. An analysis of effector T cell generation and function in mice exposed to influenza A or Sendai virus. *Immunol Rev* 1981;58:5-24
178. Schrier RD, Pizer LI, Moorhead JW. Tolerance and suppression of immunity to herpes simplex virus: different presentations of antigens induce different types of suppressor cells. *Infect Immun* 1983;40:514-22
179. Horohov DW, Moore RN, Rouse BT. The regulation of herpes simplex virus-specific cytotoxic T lymphocyte induction by suppressor cells. *Viral Immunology* 1986 (in press)
180. Lawman MP, Rouse BT, Courtney RJ, Walker RD. Cell-mediated immunity against herpes simplex induction of cytotoxic T lymphocytes. *Infect Immun* 1980;27:133-9
181. Horohov DW, Moore RN, Rouse BT. Production of soluble suppressor factors by herpes simplex virus-stimulated splenocytes from herpes simplex virus-immune mice. *J Virol* 1985;54:798-803
182. Horohov DW, Wyckoff JH, Moore RN, Rouse BT. The regulation of herpes simplex virus-specific cell-mediated immunity by a specific suppressor factor. *J Virol* 1986;58:331-8
183. Liew FY, Russell SM. Inhibition of pathogenic effect of effector T cells by specific suppressor T cells during influenza virus infection in mice. *Nature (Lond)* 1983;304:541-3
184. Salerno A, Romano GC, Dieli F, Colizzi V. Analysis of the T suppressor cell circuit which regulates contact sensitivity in mice infected with the virus of Newcastle disease. *Immunology* 1984;51:305-11
185. Green DR, Gold J, St. Martin S, Gershon R, Gershon RK. Microenvironmental immunoregulation: possible role of contrasuppressor cells in maintaining immune responses in gut-associated lymphoid tissues. *Proc Natl Acad Sci USA* 1982;79:889-92
186. Shou L, Schwartz SA, Good RA. Suppressor cell activity after concanavalin A treatment of lymphocytes from normal donors. *J Exp Med* 1976;143:1100-10
187. Shore A, Dosch H-M, Gelfand EW. Induction and separation of antigen-dependent T helper and T suppressor cells in man. *Nature* 1978;274:586-7
188. Smith JB, Knowlton RP. Activation of suppressor T cells in human autologous mixed lymphocyte culture. *J Immunol* 1979;123:419-22
189. Sakane T, Green I. Human suppressor T cells induced by concanavalin A: suppressor T cells belong to distinctive T cell subclasses. *J Immunol* 1977;119:1169-78
190. Fabio G, Scorza-Smeraldi R, Bonara P, Sabbadini MG, Vanoli M, Calabi F, Zanussi C. MLR-specific suppressor T lymphocytes in man. II. Functional and membrane characteristics of a specific MLR suppressor subpopulation. *J Immunol* 1982;129:2458-62
191. Tsokos GC, Christian CB, Balow JE. Concanavalin-induced suppressor cells: characterization on the basis of corticosteroid and radiation sensitivity. *Immunology* 1982;47:85-90
192. Lichtenstein A, Murahata R, Terpenning M, Cantrell J,

- Zigheboim J. Activation and mechanism of action of suppressor macrophages. *Cell Immunol* 1981;**64**:150-61
193. Reinherz EL, Schlossman SF. The characterization and function of human immunoregulatory T lymphocyte subsets. *Immunology Today* 1981;**2**:69-75
 194. Reinherz EL, O'Brien C, Rosenthal P, Schlossman SF. The cellular basis for viral-induced immunodeficiency: analysis by monoclonal antibodies. *J Immunol* 1980;**125**:1269-74
 195. Sheridan JF, Aurelian L. Immunity to herpes simplex virus type 2. V. Risk of recurrent disease following primary infection: modulation of T-cell subsets and lymphokine (LIF) production. *Diagn Immunol* 1983;**1**:245-56
 196. Damle NK, Mohagheghpour N, Engleman EG. Soluble antigen-primed inducer T cells activate antigen-specific suppressor T cells in the absence of antigen-pulsed accessory cells: phenotypic definition of suppressor-inducer and suppressor-effector cells. *J Immunol* 1984;**132**:644-50
 197. Morimoto C, Letvin NL, Boyd AW, Hagan M, Brown HM, Kornacki MM, Schlossman SF. The isolation and characterization of the human helper inducer T cell subset. *J Immunol* 1985;**134**:3762-9
 198. Altmann DM, Blyth WA. Protection from herpes simplex virus-induced neuropathology in mice showing delayed hypersensitivity tolerance. *J Gen Virol* 1985;**66**:1297-303
 199. Doughty BL, Phillips SM. Delayed hypersensitivity granuloma formation and modulation around *Schistosoma mansoni* eggs in vitro. II. Regulatory T cell subsets. *J Immunol* 1982;**128**:37-42
 200. Mathur A, Rawat S, Chaturvedi UC. Suppressor T cells for delayed-type hypersensitivity to Japanese encephalitis virus. *Immunology* 1984;**52**:395-402
 201. Fulginiti VA, Eller JJ, Downie AW, Kempe CH. Altered reactivity to measles virus. Atypical measles in children previously immunized with inactivated measles virus vaccine. *JAMA* 1967;**202**:1075-80
 202. Chanock RM, Kapikian AZ, Mills J, Kim HW, Parrott RH. Influence of immunological factors in respiratory syncytial virus disease. *Arch Environ Health* 1970;**21**:347-55
 203. Miller RG. An immunological suppressor cell inactivating cytotoxic T-lymphocyte precursor cells recognizing it. *Nature* 1980;**287**:544-6
 204. Fink PJ, Rammensee H-G, Benedetto JD, Staerz UD, Lefrancois L, Bevan MJ. Studies on the mechanism of suppression of primary cytotoxic responses by cloned cytotoxic T lymphocytes. *J Immunol* 1984;**133**:1769-74
 205. Fink PJ, Rammensee H-G, Bevan MJ. Cloned cytolytic T-cells can suppress primary cytotoxic responses directed against them. *J Immunol* 1984;**133**:1775-81
 206. Dunlop MBC, Blanden RV. Mechanism of suppression of cytotoxic T-cell responses in murine lymphocytic choriomeningitis virus infection. *J Exp Med* 1977;**145**:1131-43
 207. Burnet EM, Fenner F. The production of antibodies. Monograph of the Walter and Eliza Hall Institute. South Melbourne: MacMillan Company of Australia, 1949
 208. Hotchin J. Persistent and slow virus infections. In: Monographs in Virology. Vol 3. Basel: S. Karger, 1971
 209. Ahmed R, Salmi A, Butler LD, Chiller JM, Oldstone MBA. Selection of genetic variants of lymphocytic choriomeningitis virus in spleens of persistently infected mice. Role in suppression of cytotoxic T lymphocyte response and viral persistence. *J Exp Med* 1978;**160**:521-40
 210. Olsen R, Lewis M, Mastro J, Sharpee R, Tarr M, Mathes L. Feline retrovirus vaccines. In: Dale RP, Golde DW, eds. Leukemia: recent advances in biology and treatment. New York: A. R. Liss, 1985:239-48
 211. Adorini L, Harvey MA, Miller A, Sercarz EE. Fine specificity of regulatory T cells. II. Suppressor and helper T cells are induced by different regions of hen egg-white lysozyme in a genetically nonresponder mouse strain. *J Exp Med* 1979;**150**:293-306
 212. Gainer JH. Suppressor factors and their potential for immunotherapy and chemical influences on interferons. *J Am Vet Med Assoc* 1982;**181**:1107-10
 213. Murgita RA, Tomasi TB Jr. Suppression of the immune response by α -fetoprotein. I. The effect of mouse α -fetoprotein on the primary and secondary antibody response. *J Exp Med* 1975;**141**:269-86
 214. Webb DR, Nowowiejski I. Mitogen-induced changes in lymphocyte prostaglandin levels: a signal for the induction of suppressor cell activity. *Cell Immunol* 1978;**41**:72-85
 215. Serrou B, Rosenfeld C, Caraux J, Thierry C, Cupissol D, Goldstein A. Thymosin modulation of suppressor function in mice and man. *Ann NY Acad Sci* 1979;**332**:95-100
 216. Hadden JW, Coffey RG, Ananthakrishnan R, Hadden EM. Cyclic nucleotides and calcium in lymphocyte regulation and activation. *Ann NY Acad Sci* 1979;**332**:241-54
 217. Weinstein Y, Melmon KL. Control of immune responses by cyclic AMP and lymphocytes that adhere to histamine columns. *Immunol Commun* 1976;**5**:401-16
 218. Hadden JW, Lopez C, O'Reilly RJ, Hadden EM. Levamisole and inosiplex: antiviral agents with immunopotentiating action. *Ann NY Acad Sci* 1977;**284**:139-52
 219. Pike MC, Daniels CA, Synderman R. Influenza-induced depression of monocyte chemotaxis: reversal by levamisole. *Cell Immunol* 1977;**32**:234-8
 220. Rouse BT, Miller LS, Turtinen L, Moore RN. Augmentation of immunity to herpes simplex virus in vivo administration of interleukin 2. *J Immunol* 1985;**134**:926-30
 221. Klesius PH, Fudenberg HH, Smith CL. Comparative studies on dialyzable leukocyte extracts containing transfer factor—a review. *Comp Immunol Microbiol Infect Dis* 1980;**3**:247-60
 222. Viza D, Vich JM, Phillips J, Rosenfeld F. Orally administered specific transfer factor for the treatment of herpes infections. *Lymphokine Res* 1985;**4**:27-30