22

Conclusions and Prospects

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Previous chapters of this multiauthored volume have dealt with the interactions that individual viruses or groups of viruses establish with the host's immune system and with the functional consequences of these interactions. Rather than simply recapitulating data and concepts already developed, this chapter focuses on future goals of research in this area. The interest here is provocative thought. Thus, speculations are presented especially in regard to the clinical implications of the problem.

1. PHENOMENOLOGY

The amount of information available concerning the immunosuppressive activity of different viruses is uneven, but a great deal of phenomenology has been described. As a result of extensive investigation, we now know that (1) virtually no acute systemic viral infection is devoid of effects on the ability of the immune system to respond normally to heterologous immunogens. In addition to those covered extensively in this book, viruses for which there is very little information but that are known to be endowed with at least some immunomomodulatory activity include Norwalk agent,[1] canine, and murine parvoviruses,[2,3] African swine fever virus,[4] and others; (2) enhancement of selected immune responses is occasionally observed, but immunosuppressive changes are largely predominant (Table I); and (3) as dramatically exemplified by patients with the acquired immune deficiency syndrome (AIDS), but clearly evident in many other viral infections as well, this immune deficit can be

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TABLE I
Alterations of Immune Effector Functions, as Measured with Heterologous Stimuli, Observed in Virus-Infected Hosts

Parameter	Viruses inducing[a]	
	Enhancement	Depression
Antibody responsiveness	Few	Many
Immunoglobulin level in serum	Many	Some
Antibody-dependent hypersensitivity	—	Few
Antibody-dependent cellular cytotoxicity	—	Few
Circulating autoantibody	Several	Some
Lymphocyte circulation	Some	Several
Delayed hypersensitivity reactions	Several	—
Contact sensitivity	—	Several
T-cell-mediated cytotoxicity	—	Several
Skin allograft rejection	—	Several
Graft-versus-host reaction	—	Some
Immunologic maturation	—	Some
Autoimmune lesions	Some	Few
Tolerance induction	Few	Some
Clearance of foreign particles from blood	Some	Some
Lymphocyte trapping in spleen	Few	Few
Antigen trapping by spleen	Few	—
Interferon responsiveness to inducers	—	Several
Natural killer cell activity	Many	Some

[a]Reported differences may reflect the frequency with which various parameters have been examined.

paralleled by an increased susceptibility to superinfections that may have considerable clinical significance.

There still are, however, aspects that are in need of much scrutiny. Most experimental work on viral immunosuppression has been done by infecting otherwise immunologically normal hosts. For example, mouse models of infection have almost invariably employed genetically homogeneous otherwise healthy young adult animals often bred under specific pathogen-free conditions. This has the obvious advantage of minimizing compounding variables but can hardly reproduce the clinical setting, in which the extent and consequences of virus-induced immunomodulation might be quite diverse, depending on many disposing factors, such as genetic makeup, extreme ages, nutritional deficiencies or excesses, hormonal imbalances, and the concomitance of underlying pathology, including superimposed infections and neoplasia. Studies concerned with defining the genetic regulation of susceptibility to viral immunosuppression are few, but there are indications that the matter is quite complex. In mice, for example, the same H-2 haplotype can have markedly different effects on immunosuppression, depending on the infecting virus.[5] Individuals whose immune system is already not completely functional due to physiologic, pathologic, or iatrogenic reasons have an increased risk of devel-

oping more severe viral diseases. It seems logical to assume that in such individuals the impact of viral infections on residual immune competence is particularly severe.[6] Recent observations that cytomegalovirus (CMV) infection of immunosuppressed allograft recipients can result in chronic T-cell inversion[7] indicate that exploration of these aspects might be particularly rewarding. A multifactor hypothesis for the etiology of AIDS has been the subject of much speculation, but there are virtually no experimental data to support the contention.

Another aspect deserving further scrutiny is the effect of localized viral infections and, more generally, of primary viral replication during the early stages of systemic infections, on the functioning of immunologic effectors and anti-infective defenses operating locally at the site of infection and in its proximity. Judging from influenza, the only localized viral infection for which there is sufficiently detailed information (see Chapter 16), it seems likely that substantial changes of such effectors of immunity take place. These changes might contribute to the successful initiation of infection, its progression, or the facilitation of local superinfections. Investigation of this problem has been hampered by the limited knowledge of immune mechanisms that operate in infected tissues and organs and by the shortage of specific assays to assess their activity.

A third important aspect that requires further phenomenologic analysis, both in the clinical setting and in experimental models, are the long-term consequences of persistent and latent viral infections on immunity. Although persistence of viruses such as lymphocytic choriomeningitis, lactic dehydrogenase, and chronic leukemia viruses has been associated with significant changes of immunocompetent cells and immunomodulation,[8–10] at this point it would appear that immunologic perturbations associated with chronic viral infection are far less dramatic than observed in most acute infections. However, many viruses that can linger more or less dormantly in lymphoreticular tissues might serve as a cause of cumulative injury to immunocompetent cells. This may result from bursting out of the virus from time to time or otherwise and may lead to clinically significant immunologic deficits as well as other immunopathology. Determination of the involvement of persistence in marginal or slowly progressing immune deficiencies remains as a promising avenue of research. Given the present pace of progress in virologic and immunologic technologies, many difficulties that still prevent a clear definition of these aspects might soon be overcome.

2. PATHOPHYSIOLOGY

Understanding the mechanisms whereby viruses immunosuppress their hosts remains a major challenge, because even in the infections most extensively investigated a precise definition of the cellular and subcellular pathways that culminate in the immunosuppressed state are not completely understood. Viruses are associated with pathology of the immune system much more frequently than are other infectious agents, be they bacterial, fungal, protozoan,

or metazoan. Even benign infections, such as a rhinoviral common cold, are associated with transient changes in the immunologic profile of patients.[11]

As frequently suggested in the preceding chapters, most often this seems to be related to the fact that viruses are strictly intracellular parasites and that viruses encounter immunocytes very early after entrance into the host. Apparently, both lymphocytes and macrophages are among the body's cells which produce abundant interferon (IFN), but this does not appear to be sufficient to protect them from infection. Several viruses selectively infect B cells, T cells, or macrophages, and many replicate in such cells as in others (Table II). The tropism of many viruses for macrophages and specific lymphocyte subsets, the range of interactions that viruses can establish with such cells, and their functional consequences have only just begun to be appreciated.

Virus-immunocompetent cell encounter may result in the virus being eliminated without apparent consequences or in serious damage to the cells, but most often results in a split victory, whereby the acute viral infection is kept under partial check and the cells remain overtly or latently infected, often for prolonged periods or forever. Lymphocytes and macrophages have often been likened to Trojan horses; because of their high mobility, they are supposed to convey viruses throughout the organism and protect them from immune surveillance. The reasons that viruses so frequently and easily lodge and persist in lymphoreticular tissues are not clear. Cellular activation is often a prerequisite for efficient viral replication in lymphoid and monocytic cells.[12–14] It seems possible that the virus itself causes an activation of lymphoreticular cells, by classic immunologic mechanisms or otherwise, and this allows for the continuous replenishment/recruitment of permissive cells. Numerous additional sophisticated explanations have been suggested, including the clonal distribution

TABLE II
A Summary of Viruses Known to Replicate within Macrophages and Lymphocytes

Virus	Monocytes/ macrophages	Lymphocytes[a]
Adenoviruses	–	L
Arenaviruses		
Lymphocytic choriomeningitis	+	B
Coronaviruses		
Mouse hepatitis virus	+	L
Enteroviruses		
Coxsackie B	–	L*
Echovirus	–	L*
Poliovirus	+	L*
Hepatitis B virus	–	B,T
Herpesviruses		
Bovine herpesvirus	+	N.D.
Cytomegalovirus		
Human	+	B

TABLE II (*Continued*)

Virus	Monocytes/ macrophages	Lymphocytes[a]
Mouse	+	L
Epstein–Barr	−	B
Equine herpesvirus	+	B,T
Guinea pig herpes-like virus	+	B,T
Herpes simplex	+	B*,T*
Herpesvirus sylvilagus	−	B,T
Human herpesvirus 6	+	B,T
Infectious laryngotracheitis	+	N.D.
Marek disease	−	B,T
Mouse thymic virus	−	T
Pseudorabies virus	+	L
Varicella–zoster	+	?
Influenza	+	L*
Papovaviruses		
BK virus	−	B,T
B lymphotropic papovavirus	−	B
Paramyxoviruses		
Measles	+	B,T*
Mumps	+	B*,T*
Parainfluenza	+	B,T
Respiratory syncytial virus	+	T*
Poxviruses		
Ectromelia	+	N.D.
Leporipoxviruses (fibroma/myxoma)	?	B,T
Vaccinia	+	L*
Variola	?	?
Reoviruses	+	T (newborn mice)
Retroviruses		
Avian	+	L
Bovine	−	B
Caprine/ovine	+*	N.D.
Equine	+	L
Feline	+	L
Human	+	B*,T*
Murine	+	B*,T*
Simian	?	T
Rhabdoviruses		
Vesicular stomatitis virus	+	T*
Togaviruses		
Dengue	+	B,T*
Rubella	+	T
Yellow fever	+	T

[a]B, B lymphocytes; T, T lymphocytes; L, undefined lymphocyte population; *, replicate preferentially in activated cells; ?, replication reported but not confirmed; +, positive; −, negative information; N.D., no data.

of molecules expressed on the surface of lymphocytes and the fact that macrophages can be entered by viruses by means other than plasma membrane receptor binding (sometimes with the help of virus-specific antibodies or complement), but none has been proved with certainty,[15,16] leaving enormous matter for future research.

The events linking the invasion of immunocompetent cells to pathology of the immune system now are being addressed increasingly in molecular terms. Apparently, direct cytopathology is neither sufficient nor necessary. Even in AIDS, in which the only evidence of a cythopathic effect *in vivo* is the description of giant cells in the brain of infected individuals, it seems unlikely that the immunodeficiency is the result of direct progressive destruction of T4 cells, because *in situ* hybridization and other sensitive techniques indicate that less than 1 in 10,000 lymphocytes are replicating the virus at any given time, and *in vitro* studies support this view. Indeed, a number of alternative ingenious hypotheses are being envisaged to explain the T-lymphocyte depletion observed in this disease, for example, autoimmune destruction of viral receptor-expressing cells by anti-idiotypical antibody or by antiviral antibody following passive absorption of viral proteins produced in other cells.[14] In certain instances, some satisfactory answers have emerged. For example, virion proteins and glycoproteins mitogenic for B cells and that have other immunomodulatory activities are increasingly being described regarding infections due to several viruses, including human immune deficiency virus (HIV).[17,18] Analysis of the functionally active part of such molecules has also been initiated and at least in one case, the functional part has been synthesized.[19,20] Clearly, identifying the viral molecule(s) and fragment(s) thereof that are responsible for the immunosuppressive effects may lead not only to a better understanding of viral immunosuppression but may permit the delineation of rational therapeutic approaches, the development of better-designed (subunit) vaccines, and possibly provide new clinically useful immunosuppressive products as well. Interestingly, virus-related immunosuppressive products have been detected in certain tumors.[21] Molecular biology has now provided the necessary tools to address these important aspects.

Immune functions and antimicrobial defenses in general result from the coordinate collaboration of many cell types, classes, and subclasses, the interactions of which are mediated by physical contact and soluble factors and regulated by suppressor cell circuits that may be either specific or nonspecific in activity. While these avenues are explored, it should not be forgotten that in such a complex network, even minor virus-induced modifications of the cell surface or alterations in the synthesis and response to soluble mediators are bound to reflect on other cells, generating multiple cascade effects that can ultimately overwhelm physiologic check-and-balance mechanisms and lead to immune hyporeactivity and dysfunction. As discussed in previous chapters, the activation of suppressor cells is a frequent occurrence in viral infections. Moreover, in certain viral infections, profound involution of lymphoid organs has been noted in the absence of detectable viral replication in such organs, and the intervention of autoreactive phenomena has been invoked.[22] Further investigation of these aspects may be rewarding, as mechanisms that regulate immune

function are progressively better understood. This is particularly true of the suppressor lymphokines, which are at different stages of characterization.

Within this context, it is worth recalling that IFN and other substances released by virus-infected cells not only have direct immunoregulatory effects but may also induce cells, which normally do not, to express immunoregulatory relevant molecules such as class I[23] and class II[24] major histocompatibility complex antigens. Increased numbers of Ia-like-positive cells have been detected in patients infected with viruses as diverse as mumps[25] and HTLV-I.[26] Lymphocytes have also been noted to change surface phenotype as a consequence of viral infection.[27] Lymphocytotoxic substances are frequently found in the serum of patients during the acute phase of viral infections, but nothing is known about their genesis and function. They may be either cytotoxic or cytostatic, depending on their concentration and the nature of the target cells. Furthermore, lymphotoxic, IFN-inhibitory, and more generally immunomodulatory substances have been detected in several virus-infected cell cultures and hosts.[28–31] However, the full extent to which this increasingly wide range of soluble mediators contributes to immunosuppression remains to be established. Also to be defined is the role that the formation of immune complexes and the consequent activation of complement may have in the genesis of immunosuppression. These are presumably physiologic events in antigen clearance but, when occurring on a large scale due to the self-replicating nature of viral antigens and in proximity to immunocompetent cells, might provoke significant perturbation of immune homeostasis.[32]

As a final comment on pathophysiology, we would like to mention again that present knowledge of mechanisms of immunosuppression derives mainly from studying animals, especially rodents, experimentally infected with very large doses of laboratory passaged viruses, usually by routes that do not necessarily reflect the natural disease process. Recent studies show that viral variants and the passage history of the virus can affect the ability of a virus to immunosuppress.[33] Future experimental studies should examine whether the mechanisms of immunosuppression vary depending not only on the infecting virus but on the many variables that influence infections as well. At the single-cell level, this possibility is exemplified by repeated observations showing that *in vitro* virus–host lymphocyte balance is sensitive both to external influences and to the physiologic state of these cells. Recently added examples are observations showing that herpes simplex virus (HSV) and HIV replication are enhanced by interleukin-2 (IL-2)[13] and prostaglandin E_2 (PGE_2).[34] At the organism level, it is suggested by recent findings that in irradiated reconstituted mice retroviruses immunosuppress by mechanisms at least partially different from those in normal mice.[35]

3. BIOLOGIC SIGNIFICANCE

There is no factual basis for an attempt to guess the significance of viral immunosuppression in the biologic cycle of viruses. We wish nevertheless to touch briefly on a couple of points. In order to be able to be perpetuated in

nature, a virus must rapidly adapt to each new situation in the evolutionary continuum as the host undergoes a modification that can impede the biologic cycle of the virus. Indeed, the close evolutive parallelism that exists between viruses and their hosts finds increasing supportive evidence as light is shed on the mechanisms of viral replication and infection. It also seems likely that the ability possessed by many viruses to dodge the host's immune system is a result of this evolutive adherence. Although this important instrument of defense has been shaped over millions of years to increase resistance against infectious agents, viruses are able to avoid or resist its action effectively, for the time needed to replicate and diffuse to new hosts, and often for much longer periods. The strategies used by different viruses to avoid the action of the immune system seems to be quite varied, and each virus seems to employ those more suited to its general properties and to the characteristics of infection.[15] The only characteristic that appears to be common to most, if not all, viruses is the ability to immunosuppress. This suggests that viral immunosuppression is an essential element in the economy of viral infections, possibly a prerequisite for other, more sophisticated, mechanisms of escape from the host's defenses to engage in action. A possible example of obligatory mutualism between a virus and a host mediated by the ability of the former to abate the host's defense mechanisms has been described in an insect.[36] Viral immunosuppression has also been suggested to be important in the collaboration between helper and defective viruses *in vivo*.[37]

Teleologically, one might argue that the transient nature of viral immunosuppression, as observed in most cases, is in the best interest of the virus, since this permits both survival of the virus and survival of the host. The tendency of viruses to reach an equilibrium with the host is proved by the high frequency of persistent viral infection, wherein the host becomes a potential reservoir for the spread of the virus. Regardless of the argument taken, it is apparent that there is a balance to be achieved between the ability of the virus to depress host defenses and the ability of the host to generate a response to the virus capable of leading to recovery. Fortunately, in most instances, the balance favors the host, but far too often it favors the virus, with severe or fatal consequences for the host. Achieving an understanding of the circumstances under which the virus is favored and developing methods to tip the balance in favor of the host are major goals of this field of study.

4. EFFECTS ON THE EVOLUTION OF THE INDUCING INFECTION

Evidence concerning the effects of immune suppression on the evolution of the inducing infection is limited. In virus-immunosuppressed hosts, responses against heterologous antigens are usually scarcely impaired if antigen is given at the outset of infection. Since exposure to antigens of the infecting virus occurs before the immunosuppressed state is fully established, this has been interpreted as evidence that virus-specific responses might be affected

only marginally if at all. In most viral infections, antiviral antibody and effectors of cell-mediated immunity are readily demonstrable. Stimulation by viral antigens continues, however, for the duration of infection and responses to different viral epitopes become detectable at different times, making it quite possible that overall immunity mounted against the infecting virus is lower than it would be in the absence of viral immunosuppression. In fact, we cannot know what the antiviral response would be like if the viral infection was not accompanied by immunomodulatory effects. Further investigation of these aspects is clearly warranted. In these studies, attention should again be paid to passage history of the virus and other variables that, as recently suggested,[33] might affect the ability to suppress immune responses to homologous antigens.

All things considered, the infected organism does not appear to cope very effectively with viral infections. Complete elimination of the infecting virus is infrequent. Theoretically, viral immunosuppression may influence the course of the inducing infection in several ways. For example, it might (1) limit the host's ability to block viral spread from the primary site(s) of replication to target organs; (2) lengthen the duration of the acute unchecked phase of viral growth; (3) be a prerequisite for the development of virus-specific T-suppressor (Ts) cells and more generally for specific unresponsiveness known to occur in several viral infections; and (4) facilitate the establishment of viral persistence. Although currently available data neither prove nor disprove such possibilities, a correlation between these parameters of infection and viral immunosuppression has often been suggested. For example, a common feature of heart transplant patients with primary or secondary CMV infections is a large increase of Ts cells and an inversion of the T-helper/Ts ratio that lasts up to 3 years. In a recent study, chronic excretion of the virus was found to correlate with persistence of such changes.[38]

5. EFFECTS ON PATHOGENESIS BY THE INDUCING VIRUS

Theoretically, the overall impact of viral immunosuppression on the severity and extent of pathogenesis caused by the inducing virus may be either detrimental or beneficial to the host, depending on the mechanisms whereby the disease induced by the infecting virus is generated (Table III). When the disease is sustained mainly by direct viral damage to cells and tissues (e.g., due to cytolysis), viral immunosuppression could lead to an aggravation of damage by affecting the host's ability to mount protective immunity against the virus, thereby enhancing its replication and hampering or delaying its clearance. Interestingly, in recent studies, lymphocytes from patients susceptible to frequent recurrences of HSV-induced lesions proved most susceptible to inhibition of proliferative responsiveness by exposure to HSV *in vitro* and were less efficiently restored by exogenous IL-2 than were cells from patients subject to infrequent recurrences.[39] The same seems to be true for viral diseases sustained by the proliferation of cells bearing antigens readily recognized by the

TABLE III
Clinical Implications of Viral Immunosuppression

	Human infections with		Animal models
	HIV	Other viruses	
For disease			
Facilitates spread of infecting virus	?	?	Possibly
Prolongs infection	?	?	?
Enhances virus-induced damage	?	?	Possibly
Decreases virus-induced immunopathology	?	?	Possibly
Facilitates secondary infections	Yes	Yes	Yes
Facilitates tumor development/progression	Yes	?	Yes
Causes long-term sequelae			
Growth retardation	Possibly	?	Yes
Apparently idiopathic immune deficiencies	Yes	Possibly	?
Autoimmunity	Possibly	?	Possibly
Others	?	?	?
For treatment			
Justifies use of immunopotentiating drugs	No[a]	No	No

[a]Except for full-blown AIDS.

host's immune system, such as in virus-induced hyperplastic or neoplastic growth. Indeed, a correlation between viral immunosuppression and progression of virus-induced tumors has been noted. Examples are tumors caused by Aleutian disease virus of mink[40] and leukemias caused by oncogenic retroviruses of mammals and birds.[10] It is clear, however, that documented information in this area is extremely sketchy.

Immunopathology appears to play a key role in the pathogenesis of many viral infections.[41] In viral infections in which immunopathogenetic mechanisms are essential determinants of disease, turning down of immune responses might have an adaptive value because it might interfere with the mechanisms whereby cell and tissue damage is generated. Although the possibility that viral immunosuppression is beneficial to the host remains essentially speculative, indirect support comes from clinical observations that the nephrotic syndrome, a disease that frequently responds to immunosuppressive therapy, and allergic manifestations can undergo remission in the course of measles.[42] Supportive evidence comes also from findings showing that the administration of immunopotentiating drugs can exacerbate virus-induced pathology in certain animal models of infection.

Thus, although limited, available information clearly indicates that generalizations on these issues are not possible. Each viral infection should be examined and evaluated separately with regard to the detrimental or beneficial effects of immune suppression.

6. EFFECTS ON RESISTANCE TO OTHER INFECTIONS

Acquired immune-deficiency syndrome is the prototype example of a viral infection that predisposes to secondary opportunistic infections. However, long before AIDS was recognized, clinical practice had shown that patients with, or convalescent from, viral infections presented an increased susceptibility to superinfections and to the reactivation of latent infections. For example, following measles there may be an increased susceptibility to bacteria and viruses for periods of 1 year or more.[43] It is generally accepted that in patients with influenza, the diminution of resistance is usually short-lived and is most evident locally as enhanced incidence and gravity of bacterial pneumonia. It is recognized that CMV infection predisposes graft recipients to superinfections that may represent a serious threat to life.[44] Furthermore, patients hospitalized with specific infectious diseases in an area of Japan in which HTLV-1 is endemic were found to have an almost threefold incidence of antibody to that virus than did the general population,[45] suggesting that HTLV-1-induced immunosuppression may have considerable public health significance. Natural viral infections of animals known to predispose their hosts to secondary infections include feline leukemia virus, canine parvovirus, and bovine herpesviruses.[46] In many such infections, the viral attack would cause minor symptoms and lesions and then resolve within a short period, if secondary bacterial, fungal, or protozoal infection did not occur.

While there seems to be little doubt that the enhanced susceptibility to superinfections associated with viral infections is due to the underlying virus-induced immunosuppression, much remains to be learned on the relative importance of the various immunologic dysfunctions caused by the virus in determining such increased susceptibility. Thus, for example, the relative contribution of damage to the adaptive and natural effectors of antimicrobial defenses remains to be established. The recognition that HIV replicates very effectively in cells of the monocyte–macrophage series[47,48] and in altered B lymphocytes[49] has led to a proposal that pathogenesis leading to AIDS requires persistant infection in macrophages followed by subsequent infection of lymphocytes and neural cells.

In conclusion, the study of viral immunosuppression in animal models should always be completed by the assessment of resistance to challenge with a battery of superinfecting agents known to take advantage of defects in different branches of immunity. This would not only prove the significance of the observed changes in immunologic parameters but would possibly lead to a better correlation between such changes and increased susceptibility to selected agents as well.

7. EFFECTS ON RESISTANCE TO TUMORS

One of the hallmarks of progressive HIV infection is the development of Kaposi sarcomas and other neoplasms that are usually very rare and less virulent in the normal population. Many such tumors have a suspected viral

etiology; it is therefore possible that their enhanced incidence is another aspect of the reduced resistance to superimposed infections discussed earlier. Apart from anecdotal evidence, there are no indications that other viral infections of humans are related to subsequent neoplasia.

The few experimental studies in animals have been performed with retroviruses and indicate that both virus-induced and transplanted tumor growth is facilitated.[10] Clearly, it is an important area worth further investigation.

8. IMPLICATIONS FOR THERAPY OF VIRAL DISEASES

This aspect has been extensively covered in Chapter 21. Here, we wish to emphasize the need for great prudence in suggesting the use of immunopotentiating and immunorestorative agents for the treatment of viral infections. The low number of efficient antiviral drugs available has led to consideration of substances that nonspecifically stimulate the immune system as potentially useful therapeutic tools (in certain instances rushing them into clinical use). Superficially, the immunosuppressed state so often associated with viral infection might be considered a further rationale for this kind of treatment. However, the information available is far from encouraging in this direction. The reasons are manifold, but three are stressed here.

1. The limited knowledge we still have of the contribution of immunopathology to viral diseases, especially of humans:[41] Our understanding of viral pathogenesis is insufficient to predict the effects immunopotentiating treatments can have on specific viral diseases and their sequelae. In properly controlled experimental systems, immunopotentiation has given contradictory results. For example, while a thymic hormone increased the survival rate of mice infected with mengovirus,[50] the administration of immunopotentiating agents to mice infected with a similarly cytolytic virus, coxsackievirus B_3, resulted in exacerbation of cardiac damage.[51]
2. The fact that *in vitro* many viruses replicate more efficiently in stimulated than in resting lymphocytes and macrophages and most immunopotentiating agents are mitogenic for lymphocytes and/or activate macrophages. Thus, an unwanted result of immunopotentiating treatment might be more extensive replication of the virus within the lymphoreticular tissue. This might, for example, facilitate the establishment of viral persistence.
3. The possibility of paradoxical effects on the functioning of the immune system: Interestingly, immunopotentiating agents were found to enhance the lymphoid depletion caused by coxsackievirus B_3 infection of mice.[22]

In conclusion, far more experimental knowledge of the immunobiology and immunopathology of each viral infection is needed before immunostimulants can be safely used for the treatment or prevention of viral diseases. Empirical use of such substances is justified only for the patient whose prognosis is very poor. It should be mentioned in this context that, so far, the use of immunostimulants in patients with AIDS has given unsatisfactory results and that concern has often been raised that treating patients with minor symptoms of HIV infection with IL-2, IFN, or other drugs with lymphocyte stimulatory activity in the absence of a specific antiviral therapy might be hazardous because it could facilitate progression of the disease. Treatment of full-blown AIDS with leukocyte transfusions or bone marrow grafts has proved unsuccessful because grafted cells were rapidly overwhelmed by infection.[52]

9. POSSIBLE ROLE OF VIRUSES IN THE GENESIS OF IDIOPATHIC IMMUNE DEFICIENCIES

A viral etiology has repeatedly been proposed for some persistent immune deficiences of unknown origin. Cases of congenital hypogammaglobulinemia have, for example, been tentatively considered sequelae of congenital rubella or other intrauterine infections.[53] The importance that persistent viral infections might have in the genesis of such syndromes has attracted little experimental attention, however. Viral persistence often involves low-level viral replication in lymphoid tissues and, on a chronic basis even subtle changes might lead to alterations no longer compensated by balance mechanisms. Moreover, it has recently been emphasized that viruses can produce disorders of specialized cells and systems also in the absence of the familiar footprints of viral replication.[54] The effects of viral persistence on the functioning of the immune system have been little explored even in animal models. A role for viral immunosuppression in the genesis of the runting syndromes associated with congenital or perinatal viral infections of animals has, however, often been postulated. Recently, a similar failure to thrive was described in children congenitally infected with HIV.[55] In humans, the existence of a chronic paucisymptomatic pathology associated with immunologic disorders and due to Epstein–Barr virus (EBV) infection is slowly emerging.[56] Furthermore, a number of viruses, including EBV, hepatitis B, and human parvovirus, have been linked to bone marrow aplasia.[57]

Often immune-deficient hosts show altered functions of the existing immune apparatus as well as a lack of certain immunologic effector mechanisms. In idiopathic immune deficiencies, the incidence of allergic, autoimmune, and collagen diseases is high, suggesting that impaired and disordered functioning of the immune system is strongly intermingled. It has often been thought that viruses may trigger autoimmune diseases, a suggestion that is finding some interesting experimental basis.[16,58] Some among the most immunosuppressive viruses of animals and humans also cause polyclonal activation of B

cells;[18] such stimulation of B cells could potentially lead to autoimmune phenomena if tolerance is broken. It is also possible that viral infections act synergistically with other pathologic or physiologic causes of reduced immune responsiveness. In mice persistently infected with parainfluenza or CMV, the long-term effects on immunity were dependent on cofactors, such as the animal's age and diet.[59,60] Viewed from this standpoint, viral immunosuppression might also be considered as a possible factor in immune senescence.

Transient immunosuppression is difficult to evaluate immunologically. Nevertheless, it is everyday experience in clinical practice that most persons in certain periods of their life become more susceptible to infections. For example, they become more apt to be affected by minor respiratory illness and tend to recover slowly from such infections. For these elusive maladies, a viral origin seems a likely possibility. Examples of such infections include Kawasaki disease and chronic fatigue syndrome. The recent discovery of HIV encourages the search for novel immunosuppressive viruses that might be implicated in the genesis of such illnesses. Most interestingly, in recent experiments, serial transfer of lymphocytes pre-exposed to allogeneic cells resulted in the establishment of an infectious form of immune deficiency that appeared to involve a viruslike agent.[61]

In conclusion, although there is little more than educated guessing in the study of virus-induced immunosuppression, a rich harvest of research is to be expected, that can only be achieved through an active cooperation between biologists and clinicians. It is ironic that a lentivirus (HIV) is responsible for the acceleration of activity in this discipline.

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