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EFFECT OF VIRUS INFECTIONS ON THE FUNCTION OF THE IMMUNE SYSTEM

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INTRODUCTION

Although there is a vast amount of information about the immune response of the host to infectious viruses, there is considerably less information about the effect that virus infections might have on the function of the immune system. It is surprising that this area has received so little attention since many viruses are known to replicate in cells of the lymphoreticular system. Viruses or virus-like particles have been found in the thymus, lymph node, spleen, bone marrow, bursa of Fabricius, stem cells, plasma cells, lymphocytes, macrophages, germinal centers, monocytes, polymorphonuclear leukocytes, and Kupffer cells (1–7). Since these cells are important constituents of the immune system, viruses or other agents which infect and alter these cells could influence the function of the immune system. The nature and extent of the immunological alterations would depend on the organ or cell type which becomes infected. One reason why so little is known about the effect of viruses on the immune system is that immune function tests are rarely performed in connection with virus infections; most studies have been concerned with overt clinical symptoms and gross pathology. By the usual clinical and laboratory methods of detection, viruses which subtly alter immune function would go unrecognized. Only by specifically measuring such alterations can the effect of viruses on the immune system be evaluated.

The purpose of this review is to summarize what is known about this newly emerging area of the effect of virus infections on immune function,

to consider the mechanisms by which viruses can alter immune function, and to discuss the effect that these virus-induced changes might have on disease processes.

Humoral Immunity

In 1963, Peterson et al (8) showed that a virus infection could depress the immune response of the host. They found that the ability of mice to make antibody to T2 bacteriophage was decreased if the mice were infected at birth with Gross leukemia virus. Similarly, Cremer et al (9) found that the ability of rats to make antibody to sheep red blood cells (SRBC) was decreased if the rats were infected at birth with Moloney leukemia virus. Subsequently, investigators from a number of laboratories (10–25) showed that infection of adult mice with Friend or Rauscher leukemia virus and infection of chickens with avian leukosis virus or the agent of Marek's disease (5, 26, 27) also resulted in immunodepression. As illustrated in Table 1 the leukemia viruses diminish host immune responses to a variety of antigens. In general, infection prior to the administration of the antigen resulted in immunodepression, whereas infection after administration of the antigen was less effective (11, 13, 14, 18, 19, 21, 25). The degree of immunodepression was related to the dose of the infecting virus (11, 21, 25) and depression of the immune response could be detected prior to the appearance of leukemia (8, 9, 11, 16, 20–23). In addition to the depression of circulating antibody, the plaque technique of Jerne showed that the number of cells producing antibody to certain antigens (SRBC) was decreased by as much as 99 percent (11–13, 19, 21, 23, 25). Depression of both the primary and secondary immune responses and 19S and 7S antibody have been reported (10, 11, 13, 14, 18–21, 23, 25, 28). There also is evidence that certain viruses can selectively affect different classes of immunoglobulins (9, 30–34).

Viruses which do not produce leukemia but infect lymphoid tissue also can decrease the immune response of the host. Mims & Wainwright (29) found that mice infected with lymphocytic choriomeningitis virus (LCM) made four- to eight-fold less antibody to SRBC and human serum albumin than did uninfected mice. Depression of the immune response was greatest in adults, temporary in neonatal mice, and absent in mice which were chronically infected with LCM. Padnos et al (35) showed that infection of mice with M-P virus depressed their immune response to SRBC and that the degree of immunodepression was related to the degree of lymphopenia produced by the virus. Parodi et al (36) found that infection of guinea pigs with Argentinian hemorrhagic fever virus (Junin) decreased both the primary and secondary immune response to human RBC. Investigators from several laboratories (37–39) have shown that the ability of mink to make antibody to *Brucella abortis*, keyhole limpet hemocyanin, and bovine gamma globulin was markedly depressed by infection with Aleutian Mink Disease Virus (AMDV). Maximum depression of the immune response oc-

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TABLE 1. EFFECT OF VIRUSES ON IMMUNE FUNCTION

Immune Function	Infecting Virus	Immunizing Antigen	Animal	Reference
I. Humoral Immunity				
(a) Antibody Production				
Depressed	Gross leukemia	T_2 Phage	Mouse	8
Depressed	Friend leukemia	SRBC, Salmonella Lipopolysaccharide, Coxsackie A9, Influenza	Mouse	11–15, 18–21, 25 28, 43, 100
Depressed	Moloney leukemia	SRBC, BSA	Rat, Mouse	9, 21, 44
Depressed	Rauscher leukemia	BSA, SRBC, Diphtheria toxoid, Measles, Coxsackie, Influenza, Murine Sarcoma virus	Mouse	10, 14, 16–18, 22–24
Depressed	Avian leukosis	BSA, T_2 Phage	Chicken	5, 27
Depressed	Marek's disease	BSA	Chicken	27
Depressed	Lymphocytic choriomeningitis	HSA, SRBC, BSA, HGG	Mouse	29, 118
Depressed	M-P virus	SRBC	Mouse	35
Depressed	Junin	HRBC	Guinea pig	36
Depressed	Aleutian Mink disease	*B. abortis*, KLH, BGG	Mink	37–39
Depressed	Mouse cytomegalovirus	Newcastle disease	Mouse	40
Depressed	Newcastle disease	BSA	Rabbit (in vitro)	42
Enhanced	Lactic dehydrogenase	HGG, RGG	Mouse	50, 51, 63
Enhanced	Venezuelan Equine Encephalitis	HGG, BGG	Mouse, Guinea pig	52, 53
Enhanced	M-P virus	SRBC	Mouse	35

Abbreviations: SRBC, sheep red blood cells; BSA, bovine serum albumin; HSA, human serum albumin; HGG, human gamma globulin; HRBC, human red blood cells; KLH, keyhole limpet hemocyanin; BGG, bovine gamma globulin; RGG, rabbit gamma globulin.

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TABLE 1. (*Continued*)

Immune Function	Infecting Virus	Immunizing Antigen	Animal	Reference
(b) Anaphylaxis				
Depressed	Lymphocytic choriomeningitis	Ovalbumin	Mouse	29
Depressed	Leukemic agent	Rabbit Serum	Mouse	41
(c) Induction of tolerance				
Depressed	Lactic dehydrogenase, Venezuelan Equine Encephalitis	HGG	Mouse	53, 63
Depressed	Lymphocytic choriomeningitis	HGG, BGG	Mouse	64, 118
(d) Immunoglobulins				
Elevated	Lactic dehydrogenase, Venezuelan Equine Encephalitis, Rauscher leukemia		Mouse	17, 50, 53
Elevated	Aleutian Mink disease		Mink	39, 54, 57
Elevated	Equine infectious anemia		Horse	34
Elevated	Infectious mononucleosis, Hepatitis, Rubella		Human	34, 55, 56
Depressed	Moloney leukemia		Rat	9, 30, 31
Depressed	Rubella		Human	32, 33
II. Cellular Immunity				
(a) Host-vs-Graft				
Depressed	Lactic dehydrogenase, Gross leukemia	Histocompatibility antigens	Mouse	72, 73
Depressed	Marek's disease	Histocompatibility antigens	Chicken	27
(b) Graft-vs-Host				

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TABLE 1. (*Continued*)

Immune Function	Infecting Virus	Immunizing Antigen	Animal	Reference
Depressed	Lactic dehydrogenase	Histocompatibility antigens	Mouse	73
Enhanced	Marek's disease	Histocompatibility antigens	Chicken	27
(c) Delayed-type skin reaction				
Depressed	Measles, Influenza, Chickenpox, Polio	Tuberculin	Human	80–86
(d) Lymphocyte transformation				
Depressed	Rubella, Measles, Hepatitis, Infectious mononucleosis		Human	88–96, 121
III. Phagocytosis (RES)				
Depressed	Lactic dehydrogenase, Ectromelia, hepatitis, Lymphocytic choriomeningitis		Mouse	98, 99
Depressed	Dengue, Sandfly fever		Human	101
Enhanced	Venezuelan Equine Encephalitis, Friend leukemia, Moloney leukemia		Mouse	53, 98, 100

curred at the stage of the disease characterized by rapid infiltration of plasma cells and hypergammaglobulinemia. Infection of mink with AMDV after immunization with known antigens resulted in a monoclonal hypergammaglobulinemia but did not lead to a rise in antibody against the antigens used. This suggests that AMDV does not indiscriminately stimulate the proliferation of pre-existing clones of antibody-producing plasma cells.

Viruses also can depress the immune response of the host to a second virus infection. Animals infected with mouse cytomegalovirus produced less antibody to Newcastle Disease Virus than uninfected animals (40). Similarly, antibody production to murine sarcoma virus was decreased by over 97 percent in animals infected with Rauscher leukemia virus (17). However, experiments involving two replicating agents are difficult to interpret in terms of their effect on the immune system because the first virus might be inhibitory to the replication of the second virus and thereby reduce the amount of immunizing antigen.

Another parameter of humoral immunity, anaphylaxis, was studied by Mims & Wainwright (29) and Stansly et al (41). These investigators found that infection of mice with LCM or one of the murine leukemia viruses inhibited systemic anaphylaxis to ovalbumin or rabbit serum. Although no direct measurements were made, the inhibition of anaphylaxis was thought to be due to depression of humoral antibody.

The only in vitro experiment pertaining to the effect of viruses on antibody synthesis was performed by Medzon & Vas (42). These workers showed that infection of rabbit spleen cells with Newcastle Disease Virus depressed the ability of these cells to produce antibody to bovine serum albumin in vitro. The depressed immune response was attributed to virus-induced cell damage.

Many hypotheses and variations on these hypotheses have been proposed to explain how viruses depress immune function (5, 8–12, 14, 15, 18, 19, 21–23, 25, 27, 29–31, 36, 37, 39, 40, 42–45). Viruses which infect cells of the immune system could depress antibody production by altering the uptake and processing of antigens, by depressing cellular protein (antibody) synthesis, and/or by destroying antibody-producing cells or their precursors. Other factors such as competition between the infecting virus and immunizing antigen for noncommitted antibody-producing cells or the release of endogenous adrenocortical hormones during the course of virus infections might impair immunological competence. In the case of leukemia viruses, transformation of antibody-precursor cells into neoplastic cells could decrease the total number of cells capable of producing antibody, the amount of antibody produced per cell, and/or the type of immunoglobulin produced. Which of these or other factors are primarily responsible for viral-induced depression of humoral immunity has not been resolved.

In newborns, viruses might exert their immunodepressive effect through the thymus (8–9). Destruction of the thymus is known to interfere with immunologic maturation (46). Since certain of the leukemia viruses infect

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the thymus, virus-induced thymic damage could result in immunodepression. Nonleukemia-producing viruses also can infect the thymus. Rowe & Capps (47) described an agent which produced necrosis of the thymus in newborn mice, and recently Hanaoka et al (48) showed that infection of mice with LCM resulted in destruction of the thymic-dependent areas of lymph nodes and spleen. Unfortunately, there is no information in either of these reports on immune function.

The hypotheses discussed above are concerned with factors which decrease immunoglobulin synthesis. The possibility that immunodepression could be the result of increased immunoglobulin catabolism was studied by Cure & Cremer (31). These workers found that while the rate of immunoglobulin synthesis was depressed in rats infected with Moloney leukemia virus, the rate of immunoglobulin catabolism was not altered. Rapid catabolism of immunoglobulins, however, is known to occur in certain hypergammaglobulinemic states (49). Porter et al (39) showed that the half-life of immunoglobulins was considerably shortened in the hypergammaglobulinemic phase of AMDV infection. To what extent rapid catabolism is actually responsible for the immunodepression (37–39) seen in AMDV-infected animals has not been established.

Not all viruses depress the functional capacity of the immune system. In mice, lactic dehydrogenase virus (LDV) acted as an adjuvant (50, 51) by enhancing the animals' capacity to make antibody to human gamma globulin. Infection with LDV shortened the induction period, raised the maximum antibody titer, increased the number of mice that showed an immune response and raised the level of gamma globulin. Although the greatest enhancement of the immune response was produced by infecting mice shortly before administering the antigen, enhancement of the immune response also occurred in chronically infected mice. Immunoenhancement was not detected, however, in mice which had been infected with LDV two or more days after administering the antigen. Similarly, mice and guinea pigs infected with Venezuelan equine encephalitis virus (VEE) made more antibody to bovine and human gamma globulin than uninfected animals (52, 53). The greatest degree of immunoenhancement was observed in acutely infected animals. Infection of mice with M-P virus (35) also resulted in augmentation of the immune response if the antigen (SRBC) was given 48 hr after injection of the virus. Immunization at other times resulted in no change or a depression of antibody production. Infection of mink with AMDV greatly depressed the primary immune response to keyhole limpet hemocyanin, but Lodmell et al (38) found that the anamnestic response was seven-fold greater in infected mink than uninfected mink. In addition, a number of viruses raise the level of immunoglobulins in the circulation (17, 34, 50, 53–56) and in at least one case (AMDV), a monoclonal hypergammaglobulinemia was produced (39, 57).

Several hypotheses have been proposed to account for the adjuvant effect of these viruses. First, virus infections might increase the number of

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antibody-producing cells (50). It has been shown that animals infected with LDV, VEE, and AMDV have a larger number of germinal centers and plasma cells than do uninfected animals (50, 53, 58, 59). Second, since oligonucleotides can act as an immunologic adjuvant (60), the release of oligonucleotides from virus-infected cells might stimulate antibody formation. Third, as the virus particle enters the macrophage or lymphocyte it might passively facilitate the entrance of circulating antigens or alter in some other way the uptake and processing of antigens. In other situations, host cell antigens which had become attached to or incorporated into the virion might, during the viremic phase of infection, reach the cells of the immune system. In this connection Lindenmann & Klein (61) suggested that the incorporation of tumor cell antigens into the envelope of the virion might be responsible for the enhanced immune response to Ehrlich's ascites tumor following infection with influenza virus.

Infection with certain viruses can influence the development of immunological tolerance. Dresser (62) showed that adult mice could be made tolerant to a foreign protein by prior injection of that protein in an "aggregate-free" form. Studies on virus-infected animals showed that infection of adult mice with LDV or VEE one day prior to injecting "aggregate-free" human gamma globulin prevented the development of immunological tolerance to human gamma globulin (53, 63). The development of immunological tolerance was not prevented if the mice had been infected with LDV 10 days prior to injecting the "aggregate-free" globulin (63). Pincus et al (64) showed that infection of neonatal mice with LCM prevented the development of immunological tolerance to bovine gamma globulin when these animals were tested at six weeks of age. The demonstration that viruses can prevent the development of immunologic tolerance suggests that the difficulty reported by some (65, 66) but not all investigators (67, 68) in making NZB mice tolerant to "aggregate-free" proteins might, in part, be due to the presence of a chronic virus infection (69–71). The mechanism by which viruses prevent the development of immunologic tolerance is not known, but some of the factors described above in connection with the adjuvant effect of viruses may be involved.

Cellular Immunity

In addition to their effect on humoral immunity, viruses also can affect cellular immunity. Dent et al (72) showed that infection of newborn mice with Gross leukemia virus prevented homograft rejection when grafting was done across a weak non-H-2 histocompatability barrier. Infection of adult mice with LDV, a nonleukemia-producing virus, resulted in slight but significant prolongation (two–three days) of graft survival across the stronger H-2 barrier (73). Other experiments showed that the graft-versus-host reaction was markedly inhibited in mice infected with LDV (73). Recently, Purchase et al (27) reported that chickens with Marek's disease showed enhanced graft-versus-host reactions but delayed homograft rejec-

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tion. This apparent discrepancy remains to be resolved. In addition, there are a number of viruses (lactic dehydrogenase, Friend leukemia, Rauscher leukemia, Moloney leukemia, Guaroa, and adeno) which can promote the growth of tumors (17, 74–78) and enhance the pathology produced by a second virus (29, 79), but it is not known whether this is due to depression of cellular immunity, humoral immunity, phagocytosis, interferon production, the presence of a "helper" virus, or other factors.

Another parameter of cellular immunity is the delayed hypersensitivity reaction. For years it has been known that infection of man with measles can result in depression of delayed hypersensitivity as measured by skin reactivity to tuberculin (80–83). Diminished reactivity to tuberculin also has been reported in humans infected with influenza, chickenpox, and polio viruses (84–86). Recently it was suggested that the capacity to engage in delayed hypersensitive reactivity could be correlated with the degree of in vitro lymphocyte blast transformation produced by phytohemagglutinin (87). With this system, Olson et al (88, 89) showed that lymphocytes from infants with congenital rubella were markedly depressed in their ability to undergo blast transformation. Other workers showed that lymphocytes from patients with infectious mononucleosis and infectious hepatitis also were depressed in their ability to undergo blast transformation (90–93). Recent studies from several laboratories (92, 94–96) showed that direct addition to human lymphocyte cultures of measles, rubella, Newcastle Disease, polio, ECHO, reo, vesicular stomatitis, mumps, influenza A, Sendai, adeno, herpes simplex, vaccinia, and human wart viruses depressed lymphocyte transformation. In part the depressed lymphocyte response was attributed to virus-induced cytotoxicity. Whether these viruses actually depress in vivo cell-mediated immunity remains to be determined. In this connection Olson et al (89) showed that infants with congenital rubella developed delayed hypersensitivity reactions to 2,4-dinitrofluorobenzene or *Candida* despite the hyporesponsiveness of their lymphocytes to phytohemagglutinin. Thus, caution is required in equating in vitro lymphocyte transformation with in vivo delayed hypersensitivity.

Many of the same factors discussed earlier in connection with the depression of humoral immunity may be involved in the depression of cellular immunity. The effect of viruses on the thymus or thymic-dependent lymphocytes would seem to be particularly important. Two additional factors should be mentioned. First, virus-induced changes on the surface of macrophages and lymphocytes could affect the ability of these cells to interact with phytohemagglutinin or antigens. Second, if cytophilic antibody plays a role in cellular immunity (97), then the effect of viruses on the production or fixation, or both, of cytophilic antibody could influence cell-mediated immune responses.

Reticuloendothelial System and Phagocytosis

The cells of the reticuloendothelial system (RES) are thought to play a

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role in the immune response, especially in the uptake and processing of antigens. Several viruses have been shown to alter the function of the RES as measured by the clearance of carbon particles or aggregated albumin. Infection of mice with LDV, ectromelia, hepatitis, and LCM depressed carbon clearance (98, 99), whereas infection of mice with VEE, Friend leukemia, and Moloney leukemia augmented carbon clearance (53, 98, 100). Wagner et al (101) found that the clearance of aggregated albumin was depressed in patients with dengue or sandfly fever and Kantoch et al (102) showed that the phagocytic activity of polymorphonuclear leukocytes from patients with viral hepatitis was depressed. Infection in vitro of polymorphonuclear leukocytes with mumps, influenza, and Coxsackie virus (103–106) decreased the ability of these cells to engulf bacteria. Additional experiments are needed to evaluate the effect of viruses on phagocytic activity and the relationship between altered phagocytic activity and immune function.

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Implications

Although relatively few viruses have been studied in detail, it is clear from the data summarized above that virus infections can profoundly affect the functional capacity of the immune system. Many other parameters of the immune system ("natural antibody," secretory antibody, allergic reactions, autoimmune diseases, complement-dependent functions, and chemotaxis) remain to be studied. Detailed information can best be obtained by employing a systematic approach in which a number of immune function tests are performed following infection with different viruses. Such an approach with LDV showed that this virus affected humoral immunity, cellular immunity, and phagocytosis as measured by circulating antibody, immunoglobulin levels, germinal center formation, induction of tolerance, graft rejection, graft-versus-host reaction and RES function (50, 63, 73, 99). In addition, these studies suggest that cellular and humoral immunity can be affected independently. LDV depressed cellular immunity but augmented humoral immunity (50, 63, 73). VEE did not affect cellular immunity but augmented humoral immunity (52, 53). Gross leukemia virus, on the other hand, depressed both cellular and humoral immunity (8, 72). These observations suggest that the effect of viruses on immune function might aid in dissecting the immune system and could prove to be a valuable tool if the alteration in immune function could be related specifically to the site of virus replication. In addition, immune function tests might prove useful in detecting heretofore unrecognized transmissible agents which grow in the cells of the immune system.

The effect of viruses on immune function could produce important secondary biological effects (107). Depression of humoral immunity could make the host more susceptible to other infectious agents. Depression of cell-mediated immunity could make the host less able to reject malignant cells and this could initiate or potentiate the growth of tumors. Although the viral etiology of human lymphoreticular malignancies has not yet been

established, it is known that patients with tumors of the lymphoid system show an increased susceptibility to infections and that their ability to make antibody is often depressed (108–111). In addition, virus-induced depression of cell-mediated immunity could make the host less able to reject virus-infected cells, and this might account in part for the chronic nature of certain virus infections (112) and the persistence in the circulation of infectious virus-antibody complexes (113). Circulating virus-antibody complexes are thought to play an important role in the pathogenesis of chronic glomerulonephritis in animals infected with LCM, AMDV, and murine leukemia (114–116).

The effect of viruses on the enhancement of humoral immunity and the prevention of immunological tolerance might be important factors in the etiology of autoimmune diseases. While under ordinary circumstances animals do not make antibody to their own tissues, the immunoenhancing effects of viruses might stimulate the production of autoantibody. In addition, host antigens which are released from infected cells and host antigens which are incorporated into the envelope of the virion might reach the cells of the immune system and lead to the production of antibody against host antigens (117). Such a situation might in part be responsible for the "autoimmune" disease of NZB mice. In this connection, Oldstone (114, 118) found that infection of NZB mice with LCM, LDV, and polyoma virus accelerated the time of appearance of NZB "autoimmune" disease by as much as three months. The similarity between NZB disease and lupus erythematosus makes these observations particularly intriguing. Virus-like particles have recently been found in association with both diseases (69–71, 119, 120).

In conclusion, a systematic examination of different parameters of immunological competence following infection with known animal viruses is beginning to provide much new information about this important but still poorly explored virus-host relationship. In humans, in contrast to animals, even less is known about the effect of viruses on immune function. A number of human diseases of undetermined etiology (i.e., multiple myeloma, chronic lymphatic leukemia, Hodgkin's disease, sarcoidosis, primary acquired agammaglobulinemia, Chediak-Higashi syndrome, lupus erythematosus, etc.) are characterized by or are associated with alterations in immune function. The possibility that certain of these disorders of immune function might have a viral etiology should be seriously considered.

Summary

Until recently very little was known about the effect of virus infections on the function of the immune system. A survey of the literature reveals that viruses can influence many parameters of immune function including antibody production, immunoglobulin levels, induction of immunological tolerance, graft rejection, graft-versus-host reaction, delayed-type skin reaction, lymphocyte transformation, and phagocytosis. Information emerging

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from this new area of investigation suggests that viruses should be considered in the etiology of disorders of the immune system and that the effect of virus infections on immune competence may be a factor in tumorigenesis, the chronic nature of certain infections, and the pathogenesis of "autoimmune" disease.

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