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Use of Viral Infections in Animal Models to Assess Changes in the Immune System

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Viral infections in animal models appear to be ideal systems for determining toxicity to the immune system by environmental substances. Since many viral infections that are utilized in animals produce systemic disease, these models provide an opportunity to evaluate the interaction between virus and components of host resistance. In these infections it is possible to delineate the role of antibody, interferon, cell-mediated immunity, neutrophils and macrophages in response to infection. A change in any of these components responsible for resistance to a particular virus may be correlated with an alteration of mortality and pathogenesis of the viral infection. Three experimental viral infections in mice that are potential candidates for use in determining immunotoxicity are discussed in terms of the response of individual components of resistance to infection and how changes in these components result in alterations of viral pathogenesis. The resistance to encephalomyocarditis virus infection in mice appears to be primarily mediated by antibody and interferon while with herpes simplex virus, infections are mainly controlled through cell-mediated immunity, macrophages, and possibly interferon. Cellular immunity also appears to be primarily responsible for resistance to cytomegalovirus infections. Therefore, it is important in the use of these systems for evaluating immunotoxicity to define the pathogenesis of the viral infection and the specific host responses to these infections and to be able to correlate a change in host resistance with an alteration of the viral infection.

Interactions between Viruses and Host Defenses

Viral infections are probably the most common cause of morbidity in man. We are continually being exposed to a variety of different viruses, often become infected, but generally recover without serious consequences. There are a number of viruses, however, that do have the capability of producing severe disease in man and in many cases result in mortality. There are many factors that may play a role in determining whether the infected host recovers or not; the two most important appear to be the virulence of the virus and its pathogenesis of infection and the ability of the host's defense mechanisms to control the viral infection. This is a very complex set of interactions that result in disease manifestations ranging from complete recovery to death.

Once the host becomes infected, dependent on the particular virus, there are a variety of possible patterns of pathogenesis of the viral infection that may occur in the host. There may be disease only at the local site of infection such as the upper respiratory tract. An example of this type of infection is caused by rhinoviruses or other viruses which produce a limited respiratory infection. After infection at a local site there may be direct spread of virus to other target organs such as the lower respiratory tract. Influenza virus, the parainfluenza viruses and respiratory syncytical virus can result in this type of pathogenesis. The virus may spread from an

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initial site of infection to other target organs such as the lungs, liver, spleen, brain, or skin by way of the blood stream or the lymphatic system. The virus may be free in the plasma, be carried within leukocytes, or in some cases may actually replicate in the leukocytes. Some of the viruses that are disseminated through the host in this manner include measles virus, mumps virus, hepatitis virus, poliovirus, and the arthropod-born togaviruses. Certain viruses such as herpes simplex virus and rabies virus have the capability of traveling from an initial site of infection to the central nervous system by way of direct neural spread. The nature of the interaction between the infecting virus and the host's immune system is going to be dependent on the pathogenesis of the viral infection. The more generalized the infection is, the greater may be the role of the host's defense in contributing to the control of the infection.

There are numerous components of host resistance, both humoral and cellular that may respond to viral infections. These include antibody produced by B-lymphocytes, interferon, cytotoxic T-cells, natural killer (NK) cells, neutrophils and macrophages. In addition to these there are also subsets of some of these, particularly the T-lymphocytes, that carry out different functions. Some subsets may act as helper cells, while others may actually suppress certain immune functions. In addition to these individual components of host resistance, there are multiple interactions between the components. It would appear unlikely that one component of the immune system is responsible for the recovery of the host from a viral infection but rather that host resistance is a complex interaction of many components. There is also selectivity in that some components appear to be more important in recovery to certain viral infections than in others.

The interaction between the virus and host can result in one of a number of potential outcomes (*1*). These are summarized in Table 1. The first possibility is that the host is completely resistant and no infection is established. In this case other factors than just immune functions are undoubtedly involved. Secondly, the host may undergo a mild or subclinical infection with either a complete recovery or recovery with a persistent or latent infection. The third possibility is that the host will suffer from an acute disease. Depending upon the particular virus and the ability of the host's immune system to control the infection, the outcome can be death, complete recovery, or again recovery with a persistent or latent infection. Finally, the virus can produce a persistent infection which may be asymptomatic, may be characterized by periodic recurrences, or may continue as a long term persistent or chronic infection. The final determination as to whether most viral infections result in recovery, a chronic infection or death is probably mediated by the host's immune system. It is well documented that many of the severe or chronic infections occur in patients with compromised immune functions. The outcome of a particular viral infection, thus, reflects both the virulence of the virus and the immunocompetence of the host. Factors which compromise host defense mechanisms would be expected to alter the virus-host relationships, therefore, animal model infections may be utilized for evaluating immunotoxicity.

Table 1. Potential results of virus-host interactions.

Interaction	Result
Host is resistant	No infection established
Subclinical infection	Complete recovery
	Persistent or latent infection
Acute clinical disease	Death
	Complete recovery
	Recovery with persistent or latent infection
Chronic infection	Asymptomatic with latent virus
	Latent with recurrence
	Persistent-chronic infection
	Malignant transformation

If one is to use the immune system as a target organ for assessing the effect of environmental substances, it is necessary to understand how a change in the immune system might result in a change in the pathogenesis of the viral infection. A few examples of how an alteration in some of the components of host resistance might affect viral replication are shown in Table 2. A suppression in the synthesis or function of antibody, interferon, T-cells or macrophages would likely result in enhanced viral replication and dissemination which we would predict would result in more serious disease or enhanced mortality. On the other hand, if the substance happens to induce interferon or activate macrophages we would predict that in some infections viral replication would be decreased resulting in less serious disease and lower mortality. It is

Table 2. Predicted change in viral pathogenesis resulting from an alteration in components of host resistance.

Component	Change	Viral replication
Antibody	Depression	No change, increase
Interferon	Induction	Decrease
	Suppression	Increase
T-Cells	Suppression	Increase
Macrophage	Activation	Decrease
	Suppression or destruction	Increase

obvious from the vast information collected in both man and experimental animals that some components of the immune system can be modulated in either direction. Specific examples of how those changes can result in the alteration of viral infections in animals models will be considered subsequently.

Use of Animal Models to Assess Changes in Host Resistance to Viral Infections

In the development and use of viral infections in animal models for determining the toxicity of various environmental substances a number of concepts concerning the virus-host relationship need to be considered. Some of the "ideal" properties of viral infections in animal models are: the viral infection should simulate a relatively common human disease; whenever possible the animals should be infected by a natural route, preferably by the same manner in which man becomes infected; a low inoculum of virus should be utilized so that one does not overwhelm the host's immune system; human viruses or ones closely related should be utilized; the course and pathogenesis of infection should be similar to that seen in the corresponding disease in man; and the host used should have an immune response similar to that of man. It is probably not possible to fulfill all these criteria, however, we should strive to use as many of the properties as possible so that data collected in these models will be relatively predictive for what we would expect in man. Due to convenience and cost as well as viral susceptibility, most animal models have utilized mice. Although this host is a good one for immunological studies, its small size presents major problems for toxicological evaluation. Additionally, there may also be differences in metabolism, pharmacokinetics, etc., of the test substance.

The use of viral infections in animal models to determine changes in the immune system is ideal because an effect can be evaluated and correlated both in the viral infection and in the host's immune system. The most useful parameters that are used to determine changes in the viral infection are final mortality rates, mean survival times, viral replication in specific target organs, viral replication at local site of infection and mean lesion scores, time to healing, etc.

Most commonly used—and, of course, the easiest parameter to use—is effect on mortality. Is the mortality rate enhanced or is the animal protected, and does the time period of survival change. Additional and often more important information can be gained by determining the effect on viral replication in specific target organs such as the lung, liver, spleen, brain or in the nasopharynx, genital tract, skin lesions, etc. These parameters are generally more sensitive in determining effects on the viral infection than is final mortality. There are numerous parameters which can be utilized to determine alterations of each component of the immune system. A partial list of immune functions that could be used are tabulated in Table 3. One approach would be to begin with two or three general tests, then proceed to the use of more specific functional assays. The major pitfall in the use of these *in vitro* tests is that they may not necessarily be predictive of the response in the intact animal. Additionally, it is difficult to evaluate noted changes in an isolated component when in the intact animal there is certainly interaction between the various components along with control mechanisms. If one is able to correlate changes in the immune system with an alteration in the pathogenesis of the viral infection, however, valuable information concerning the potential toxicity of environmental substances can be gained.

Table 3. Parameters used to determine alteration of host resistance: the immune system.

Immune function	Test system
Antibody response	Specific viral antigen
	Other antigens, SRBC, etc.
Interferon response	Viral infection
	Other inducers
Lymphocyte blastogenesis	Nonspecific mitogens
	Virus-infected cells
Lymphocyte cytotoxicity	
T-Cells	Virus-infected cells
NK Cells	Tumor cells
Macrophage function	Viral replication
	Phagocytosis, killing, etc.
	Cytotoxic for tumor cells
	Protect virus-infected cell
	Monolayer
Neutrophil function	*Chemotaxis, phagocytosis*
	Chemiluminescence

Potential Model Viral Infections for Evaluating Immunotoxicity

From the numerous experimental viral infections of animals available, I have selected three as examples of systems that might be used for determining effects on the immune system. These models were

Table 4. Potential model systemic viral infections.

Infection	Parameters
Encephalomyocarditis (EMC) virus infection of mice	Pathogenesis of disease Role of antibody Role of interferon
Herpes simplex virus (HSV) infection of mice	Pathogenesis Role of cellular immunity – immunosuppression Role of macrophage – suppression or activation Role of interferon
Murine cytomegalovirus (MCMV) infection of mice	Pathogenesis Role of cellular immunity – immunosuppression Alteration of host resistance by infection

selected not necessarily because they are the best but because there is a considerable amount of information available on the pathogenesis of the viral infections and on the role of the immune system in the control of these infections. The three viruses are relatively easy to work with and do not have a significant health hazard when used under reasonable laboratory conditions. These three model infections and some of the virological and host resistance parameters that have been evaluated in each system are shown in Table 4. For each of the model infections the pathogenesis and the role of some of the key components of host resistance in the control of the infection will be presented.

Encephalomyocarditis (EMC) Virus Infection of Mice

This experimental system is a model of human enterovirus infections caused by the Echo viruses, Coxsackie viruses, and polioviruses. After intraperitoneal (IP) or intranasal inoculation of mice with EMC virus, the pathogenesis of this infection is characterized by an initial viremia followed by replication of virus in the heart and then the brain (*2-4*). The animals generally die on days 6-8. Clearance of virus from the blood is associated with an early rise in interferon in the serum followed by antibody production. Therefore, both of these components of host resistance appeared to be involved in recovery from this infection. To determine the role of antibody, Murphy and Glasgow (*5*) x-irradiated mice prior to infection with a sublethal dose of EMC virus (Table 5). Either EMC virus infection or x-irradiation alone resulted in only a low mortality, whereas the combination of the two resulted in a 90% mortality, and no antibody could be detected in these animals. In contrast, however, when the x-irradiated animals infected with EMC virus were given passive antibody early in the course of the infection, most of the mice were then protected. These data indicate that the production of antibody by B-cells is certainly involved in recovery from this infection.

Table 5. Effect of administration of anti-EMC antibody on mortality of x-irradiated, EMC virus-infected mice.[a]

Treatment	Mortality, %
EMC virus only	12
x-Irradiation only	5
EMC + x-irradiation	90
EMC + x-irradiation + antibody at	90
–24 hr	0
+24 hr	20
+48 hr	35
+72 hr	55
+96 hr	80

[a]Modified from Murphy and Glasgow (*5*).

To evaluate the role of interferon in the EMC virus infection, two types of experiments have been performed. In the first case mice were inoculated with EMC virus and then given either passive interferon or poly I:C, which is an inducer of interferon, to determine if enhancing the amount of circulating interferon might result in the protection of the infected animals. In the second case, mice inoculated with EMC virus were given anti-interferon antibody to determine if elimination of interferon would result in the enhancement of mortality. The effect of treatment with passive interferon or poly I:C on the mortality of mice inoculated with EMC virus is presented in Table 6. The untreated control mice had a final mortality of 83%, while those treated shortly after infection either with interferon or the inducer were protected. Protection of these animals was associated with a significant alteration in the pathogenesis of the infection. In treated animals there was no detectable viremia and no seeding of the heart or brain (*3,4*). The effect of anti-interferon antibody on EMC virus infection of mice is shown in Table 7. When mice were inocu-

Table 6. Effect of treatment with exogenous interferon or poly I:C on mortality of mice inoculated with EMC virus.

Treatment	Mortality		
	n/tot	%	*p* value
None	33/40	83	—
Exogenous interferon			
−1 hr	0/15	0	< 0.001
+1 hr	2/15	13	< 0.001
+24 hr	11/15	73	N.S.
Poly I:C			
−6 hr	1/25	4	< 0.001
+1 hr	1/24	4	< 0.001
+24 hr	10/25	40	< 0.01

Table 7. Effect of anti-interferon globulin on EMC virus infection of mice.[a]

Virus dilution	Treatment	Mortality, %
10^{-6}	None	100
	Normal globulin	100
	Anti-IFN globulin	100[b]
10^{-7}	None	0
	Normal globulin	15
	Anti-IFN globulin	100[b]
10^{-8}	None	0
	Normal globulin	0
	Anti-IFN globulin	80

[a]Modified from Gresser et al. (*6*).
[b]Mice treated with anti-interferon globulin died 3-5 days earlier than untreated mice.

lated with a concentration of virus that resulted in 100% mortality, the ones treated with antibody to interferon died 3-5 days earlier than untreated ones. If the virus inoculum was reduced to where no control animals died, the administration of anti-interferon antibody resulted in 100% mortality. Additionally, the enhanced mortality in antibody-treated mice was correlated with a dramatic increase in viral replication in critical target organs (*6*). These data strongly suggest that interferon is also involved in host resistant to this type of viral infection. Enhancement of interferon production results in protection of the animal, while inhibition of the interferon response results in a marked enhancement of the infection. In experimental EMC virus and other similar enterovirus infections both antibody and interferon appear to be primarily responsible for resistance. Cellular-mediated responses appear to be less important.

Herpes Simplex Virus (HSV) Infection of Mice

Herpes simplex virus is the causative agent of a variety of diseases in man including herpes labialis, herpes genitalis, encephalitis, and disseminated infection in the neonate. There are two major antigenic types. The type 1 strains are generally associated with infections of the mouth, face and the central nervous system in adults and the type 2 strains which generally are responsible for genital infections and disseminated disease in neonates. A model systemic infection may readily be established in adult mice by IP administration of most type 2 strains; however, they are considerably more resistant to type 1 strains. In most cases, immunosuppressive agents need to be used prior to IP challenge with type 1 strains. For localized infections of the orofacial or genital areas either types can be used. Since the role of the immune system in localized HSV infection remains poorly defined this discussion will be limited to the use of systemic infections in mice. When mice are inoculated with HSV-2, the pathogenesis of the infection can be variable depending on the age of the animal and the route of viral inoculation. When three-week-old female mice are inoculated IP, virus is first detected in the gut, liver and spleen, and later on in the lung, brain and spinal cord. Virus is sporadically recovered from the blood. If a more natural route of infection is used by inoculating mice intranasally with HSV-2, virus is first detectable in the lung, with subsequent spread of virus through the blood to the liver and spleen. Concomitantly, virus also spreads from the nasopharynx by way of trigeminal nerves to the brain (*7*). In both of these models there is a generalized infection involving multiple target organs, particularly those containing the cellular components of host resistance such as the liver and the spleen.

Since most people who have recurrent HSV infections of the oral or genital regions also have high levels of circulating antibody, this component of immunity is probably not a major factor in host resistance to this virus. However, it has been demonstrated that the presence of antibody can prevent reinfection or result in less severe disease. Members of the herpesvirus group, including HSV, cytomegalovirus and varicella-zoster virus, frequently cause severe disease in immunocompromised patients, suggesting that cell-mediated immune functions may be the most important part of host resistance to these viruses. As mentioned previously, adult mice are highly resistant to infections with HSV-1. In the animal model, the use of immunosuppressive agents such as cyclophosphamide or anti-lymphocyte serum which destroys T-lymphocytes dramatically increase the susceptibility of animals to HSV (*8,9*). One representative experiment in which susceptibility of mice to HSV-1 given either orally or IP is shown in Table 8. Increased mortality was associated with enhanced viral replication in target organs

Table 8. Effect of cyclophosphamide (CPA) immunosuppression on mortality of herpes simplex virus (HSV) type 1 infection in adult mice.[a]

Treatment	Mortality	
	n/tot	%
HSV (IP) control	19/40	48
HSV (IP) + CPA	29/30	97
HSV (oral) control	1/30	3
HSV (oral) + CPA	13/30	43

[a]From Rajcani et al. (*10*).

(*10*). From the data available it seems certain that T-cells are involved in resistance to HSV.

Another component that appears to be an important determinant in resistance to HSV is the macrophage. These cells appear to be of major importance in the development of age-related resistance in that it has been shown that HSV will replicate in macrophages from susceptible newborn animals, but not in macrophages from resistant adult mice (*11,12*). Two general types of experiments further document the role of the macrophage in resistance to HSV. Agents such as silica which transiently destroy macrophages can result in enhanced susceptibility. The effect of silica treatment on the mortality of mice subsequently inoculated IP with HSV-2 is shown in Table 9. In two experiments with two different silica preparations, mortality was enhanced significantly compared to control animals. The increase in mortality was correlated with a change in the pathogenesis of the HSV-2 infection. In control mice, low levels of virus were found sporadically in the visceral organs, and virus was not detected in the brain until late in the course of infection. In contrast, in silica-treated mice, virus was present in high titers in target organs 2 days after infection, and virus was detected in the brain on day 4 (*13*). The second concept that can be used to implicate the macrophage as a primary component of host resistance to HSV comes from the fact

Table 9. Effect of silica treatment on systemic HSV-2 infection.[a]

	Log LD_{50}	
	Normal mice	Silica-treated mice
Experiment 1		
Sargeant-Welch Silica	2.7	3.7
Dorentruper Silica	2.7	3.7
Experiment 2		
Dorentruper Silica	2.7	3.7

[a]From Morahan et al. (*15*).

Table 10. Effect of immunopotentiators on resistance to HSV-2 infection in adult mice.

Treatment	Mortality		*p* value
	n/tot	%	
PBS	15/15	100	
C. acnes	3/15	20	< 0.05
C. parvum	4/14	29	< 0.05
Pyran	7/15	47	< 0.05

that immunomodulators such as BCG, *C. parvum* and pyran which have been shown to activate macrophages or increase their function result in increased resistance to HSV infection (*13-15*). An example of the use of these substances to increase resistance to HSV-2 is shown in Table 10. To be effective in increasing resistance the substances must be given 5-14 days prior to infection. In these experiments the enhanced protection also correlated with the absence of virus in the target organs, and with the activation of macrophages by these agents. Therefore, resistance to HSV infection can be modulated by manipulation of the macrophage population. Destruction or suppression of macrophages results in increased susceptibility, while enhancement of macrophage activity results in increased resistance.

To investigate the role of interferon in host resistance to HSV, similar experiments to those performed in the EMC virus infection have been carried out. Exogenous interferon or interferon inducers have been used to enhance resistance, and anti-interferon antibody to determine if resistance is depressed. In a representative experiment shown in Table 11 mice were inoculated with HSV-2 by the IP route and then treated with either exogenous interferon or poly I:C at various times after infection. In the PBS-treated control animals, 95% of the animals died; in those treated with either interferon or the inducer, significant protection was observed when therapy was initiated as late as 48 hr post infection (*16*). In another model infection utilizing newborn mice inoculated by the intranasal route with HSV-2, treatment with poly I:C completely inhibited viral replication in lung, liver and spleen but not brain. In general, the control of HSV replication in target organs correlated with the induction of interferon in those tissues (*17*). From these and other data in the literature it is apparent that interferon or interferon inducers can protect animals against HSV infection and suggest that interferon is involved in resistance to and recovery from HSV infection. Data which more directly indicate that interferon is involved in resistance to HSV comes from the experiments of Gresser et al. (*18*), who used anti-interferon antibody to abolish

Table 11. Effect of treatment with interferon or poly I:C on mortality of mice inoculated IP with HSV type 2.

Treatment	Mortality		
	n/tot	%	*p* value
PBS	24/25	96	–
Interferon			
+ 1 hr	7/14	50	< 0.01
+24 hr	4/14	29	< 0.001
+48 hr	4/15	27	< 0.001
Poly I:C			
+ 1 hr	15/25	60	< 0.01
+24 hr	8/25	32	< 0.001
+48 hr	8/15	53	< 0.01

Table 12. Effect of anti-interferon globulin on HSV type 1 infection of mice.[a]

Virus dilution	Treatment	Mortality, %
10^{-2}	Normal globulin	50
	Anti-IFN globulin	100[b]
10^{-3}	Normal globulin	60
	Anti-IFN globulin	100[b]
10^{-4}	Normal globulin	0
	Anti-IFN globulin	100

[a]Modified from Gresser et al. (*18*).
[b]Mice treated with anti-interferon globulin died 3-5 days earlier than control mice

the interferon response in mice infected with HSV-1 (Table 12). In these animals the mortality rate was increased and viral replication in target organs was enhanced (*18*). These results in mice infected with HSV, also demonstrate that resistance can be altered in both directions by either increasing the amount of interferon produced or by inhibiting the endogenous response.

Murine Cytomegalovirus (MCMV) Infection of Mice

Cytomegalovirus infection of humans can result in a variety of diseases, including congenital infection of the fetus, a mononucleosis-like syndrome in patients receiving transplants or blood transfusions, a chronic infection involving numerous target organs and an asymptomatic infection of children or adults. Since the cytomegaloviruses exhibit strict species specificity, it is necessary to use closely related animal strains in experimental infections. When mice are inoculated IP with MCMV, the virus replicates to high titers in the liver, spleen, kidney and lung (*19*). This is a generalized infection involving all the major target organs and there should be maximum interaction between the viral infection and the immune system allowing one to identify numerous potential alterations of the immune response. Antibody has not been identified as a critical component of host resistance to CMV, although there is evidence that immunization may be effective in prevention of infection. The use of interferon or interferon inducers in animal or human studies have not resulted in significant protection against infection. Cytomegalovirus infections are a particular problem in the immunocompromised patient, and there are numerous studies in man and experimental animals which indicate that cell-mediated immunity is the primary component responsible for resistance to these infections. The effect of immunosuppression by cyclophosphamide, prednisolone or anti-lymphocyte serum on the immune response and mortality of mice infected with MCMV are summarized in Table 13. In immunosuppressed animals the mortality rate and reactivation of latent virus were both increased. The cell-mediated immune response to MCMV antigen, and the response to three mitogens were all suppressed. The development of humoral immunity did not appear to be altered (*20,21*). Similar data supporting the importance of cell-mediated immunity to infections by the herpesvirus group in humans have also been reported.

Evidence has been presented which suggests that experimental viral infections in animals provide ideal models for evaluating the potential immunotoxicity of substances to which humans may be exposed. It is important to note, however, that viral infections by themselves may result in alterations of immune responses in the infected host. These effects of the virus, therefore, must also be defined in any animal model utilized for toxicity studies. The MCMV infection of mice is an excellent example of how a viral infection can enhance or suppress individual components of host resistance (*22-26*). (Table 14). It appears from these data that

Table 13. Effect of immunosuppression on humoral and cellular immunity to murine cytomegalovirus infection in mice.[a]

Component tested	Result
CF antibody	Not altered
CMI to MCMV antigen	Suppressed
Mitogen response	
PHA	Suppressed
Con A	Suppressed
LPS	Suppressed
Mortality	Increased
Reactivation of latent virus	Increased

[a]Compiled from Howard et al. (*20*) and Mayo et al. (*21*).

Table 14. Alteration of host resistance by murine cytomegalovirus infection.

Component tested	Result
Antibody response, MCMV Ag	Not altered
Antibody response, other Ags	Suppressed
CMI to MCMV Ag	Not altered
Mitogen response – PHA	Suppressed
Mitogen response – Con A	Suppressed
Mitogen response – LPS	Suppressed
T-cell cytotoxicity	Not altered
NK cell cytotoxicity	Enhanced
Interferon response to MCMV	Not altered
Interferon response to other inducers	Suppressed
Macrophage function	Enhanced

[a]Compiled from data of Howard et al. (*24*), Kelsey et al. (*22*), Quinnan et al. (*23*), Stringfellow et al. (*25*) and Schleupner et al. (*26*).

Table 15. Potential effects of viral infections on the immune system.

Effect
Suppression of antibody response
Suppression of interferon production
Suppression of lymphocyte response
Nonspecific mitogen response
Specific antigen response
Suppression of macrophage function
Potentiation of macrophage function

specific responses to the virus, that is the antibody response to MCMV antigen, CMI to MCMV antigen, T-cell cytotoxicity to virus-infected cells, NK cell cytotoxicity, the interferon response to MCMV and macrophage function are either enhanced or not altered during acute MCMV infection. Certain other responses, however, such as antibody production to other antigens, lymphocyte response to mitogens, and the interferon response to other inducers are generally suppressed. This would indicate that there is specificity and regulation in the humoral and cellular response to viral infections. Immunosuppression of certain immune responses has also been documented in other viral infections such as influenza and measles (Table 15). In determining the effect of environmental substances on the immune system during a model viral infection, the components of host resistance for evaluation will have to be selected carefully such that an effect induced by a foreign substance can be distinguished from those caused by the viral infection.

Experimental viral infections in animals appear to be ideal models for assessing changes in the immune system. The virus-host interaction, however, is extremely complex, involving numerous components of host resistance. In any particular viral infection there is no one component responsible for resistance, instead there are multiple interactions among the various components. This concept is supported by the relationship of macrophages and B-cells in the production of antibody, the activation of macrophages by interferon, and the regulatory activity of helper and suppressor cells and lymphokines. One of the limitations in the use of these models is that the viral infection may also alter host responses. It should be stressed that the animal model cannot be utilized effectively by just treating the animal with a particular substance, infecting with virus and then haphazardly determining effects on components of host resistance. To provide optimal information it is important that one first understand the pathogenesis of that particular viral infection being used and the specific and nonspecific host responses to that infection.

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