Memoranda

Virus-associated immunopathology : animal models and implications for human disease*

1. Effects of viruses on the immune system, immune-complex diseases, and antibody-mediated immunologic injury

The tissue damage caused by virus infection has been traditionally explained by the ability of viruses to multiply in cells and thereby injure or destroy them. Recent evidence suggests, however, that lesions may also be caused by the host's immune response to viral antigens and that the immune system itself may be perturbed by some viruses. This memorandum reviews recent developments in viral immunopathology, with special reference to animal model systems, and indicates the possible relevance of the new concepts and techniques for certain diseases of man. Certain viruses, notably the leukaemia viruses and some of those causing persistent infections, depress the host's ability to mount an antibody response to antigens, while other viruses may enhance the antibody response. Cell-mediated immunity may also be depressed. Another immunopathological manifestation of virus infection is immune-complex disease. When viruses or their antigens persist in the circulation they combine with specific antibody, and the resulting complexes lodge in various sites, especially the kidney. Further combination with complement leads to the release of tissue-damaging substances. A third condition associated with virus infection is antibody-mediated immunologic injury. Both oncogenic and non-oncogenic viruses frequently induce new antigens on the surface of the cells they invade. When antibody attaches to these antigens in the presence of complement, the cells are destroyed.

The lesions associated with virus infections have traditionally been explained by the ability of viruses to replicate in cells and hence cause cell injury and even death. However, recent studies indicate that virus-associated tissue damage may be due in part to the immune response of the host to viral antigens. The properties of viruses are seemingly ideal for producing immunopathological damage. Viruses are foreign antigens and, being self-replicating, can continue to produce antigen for long periods of time. Certain viruses are also known to be able to induce new antigens on the surface of cells they infect. The host's immune system can respond to these antigens.

In view of these properties, immunopathological changes may be initiated by a number of different mechanisms in the course of virus infection:

(1) Certain viruses can infect the cells of the immune system and cause direct immunologic derangements. Many processes and parameters of immune function may be thus affected, including graft rejection, the induction of immunologic tolerance, antibody production, graft-versus-host reactions, lymphocyte transformation, immunoglobulin levels, phagocytosis, and delayed-type skin reactions.

(2) The host's immune response to viral antigens can lead to the formation of virus–antibody complexes capable of reacting with anti-immunoglobulins, rheumatoid factor, and the components of complement.

(3) New antigens produced by viruses on infected cell surfaces can interact with specific antiviral antibody plus complement, thus causing cell destruction.

(4) Recent findings suggest that sensitized lymphocytes can also react with virus-induced cell surface antigens and destroy the cell. Furthermore, cell-mediated (or antibody-mediated) immune responses to viruses may result in the release or activation of biological mediators causing immunopathological changes.

* This memorandum was prepared by the signatories listed on page 262.

(5) An autoimmune response may be produced if the virus (*a*) releases host-cell antigens, (*b*) alters host-cell antigens and act as a " helper determinant ", or (*c*) depresses the host genome, thus increasing the production of embryonic or other antigens.

In addition, the genetic makeup of the host, while not a mechanism of producing immunopathological damage, can influence the nature and severity of injury incurred during virus infection (Notkins et al., 1970).

In some infections, such as lymphocytic choriomeningitis, the immune response of the host may be the principal cause of the pathological manifestations while in other infections it may be of less importance. In most if not all virus infections, the host's immune response probably contributes somewhat to the pathological picture. It should be emphasized, however, that in the majority of cases the overall effect of the immune response is more likely to be beneficial than harmful.

Recent studies on virus-induced immunopathological reactions in domestic and experimental animals have led to the development of concepts and technical methods that may be useful in investigating certain viral diseases in man, including hepatitis. Progress in the field of viral immunopathology has been rapid, and it was felt that a summary and critical review of present knowledge would encourage its wider application to clinical problems. Only selected references have been included, since the breadth of the subject made a complete review of the literature impracticable. Suggestions for further lines of investigation in viral immunopathology in general and in viral hepatitis in particular will be offered in Part 2 of this Memorandum, to be published later.

EFFECTS OF VIRUSES ON THE IMMUNE SYSTEM

It has long been known that certain virus infections can alter the morphology of lymphoid organs. Electron microscopy studies have demonstrated the presence of virus particles in cells of the lymphoreticular system, such as macrophages, lymphocytes, neutrophils, thymocytes, Kupffer cells, and stem cells. More recent investigations have shown that certain viruses are able to replicate in macrophages (e.g., arboviruses, murine hepatitis virus, lactate dehydrogenase virus [LDV], and herpes simplex virus [HSV]) while others can replicate in lymphocytes (e.g., lymphocytic choriomeningitis virus [LCMV], leukaemia viruses, and Epstein-Barr virus [EBV]). Several viruses appear to replicate only in lymphocytes that have undergone blast transformation following exposure to specific antigen or phytohaemagglutinin. Not all infections of the immune system, however, result in cell destruction; some lead to a persistent infection. For example, infection with EBV can result in the establishment of a continuous lymphoid cell line *in vitro*, while infection with the leukaemia viruses may be followed by malignant transformation.

Recent studies indicate that certain virus infections can affect the function of the immune system. These investigations have utilized the immune response to a variety of antigens unrelated to the infecting virus in order to evaluate immunologic function. Murine leukaemia viruses have received the most attention. These viruses usually depress the immune system, under certain circumstances to a significant extent (Dent, 1972). For example, the number of antibody-producing cells as determined by the haemolytic plaque test (Jerne) may reportedly be depressed by as much as 99%. In general, infection prior to the injection of antigen was found to result in immunodepression, whereas infection after antigen administration had considerably less effect. The degree of immunodepression was dependent on the dose of virus and on the nature and concentration of the particular antigen. Moreover, some evidence has been adduced that the leukaemia viruses (particularly Friend virus) can exert " selectively " depressive effects, i.e. that they produce a greater depression of the 7S than of the 19S immune response. Selective effects also have been described in connexion with other viruses. Infection with Aleutian disease virus (ADV) can result in the appearance in the serum of an excess of monoclonal immunoglobulin. It also has been claimed that LDV and LCMV can produce an acute and " selective " depression of T cells, but these results need to be confirmed and extended. Several non-oncogenic viruses (e.g., ADV, LCMV, and Junin virus) are also able to depress the humoral immune response. In addition, certain viruses, such as LDV, LCMV, and Venezuelan equine encephalitis virus (VEEV), can prevent the development of experimentally-induced immunologic tolerance.

Although most studies of viral effects have been concerned with the humoral immune response, recent investigations of cell-mediated immunity and reticuloendothelial function demonstrate that these too can be depressed. For example, allograft rejection is profoundly depressed in animals infected with Gross leukaemia virus and mildly depressed in animals in-

fected with LDV. A number of viruses, including the Rauscher and Friend viruses and those causing measles and rubella, have been shown to inhibit blast transformation of lymphocytes (Dent, 1972).

Not all viruses exert depressant effects on the immune system. Several, such as LDV and VEEV, can act as adjuvants and potentiate the immune response to certain antigens.

A number of mechanisms have been postulated to explain the immunodepressive effect of certain virus infections (Allison, 1972; Notkins et al., 1970). These include (1) virus-induced changes in the uptake and processing of antigens, possibly by alteration of cell surfaces; (2) depression of nucleic acid and protein (antibody) synthesis; (3) destruction of antibody-producing cells or their precursors; (4) alteration of thymic function; (5) acceleration of immunoglobulin catabolism; (6) antigenic competition; and (7) lymphocytolysis as a result of increased adrenocortical secretion. Possible explanations of the immunologic enhancement associated with virus infections include (1) altered uptake and processing of antigens; (2) increase in the number of antibody-producing cells or their precursors; and (3) enhanced metabolism of antibody-producing cells.

The effects of virus infections on immune function may have several important pathological repercussions. Virus-induced immunodepression might allow certain infections to persist, thereby adding to the antigenic load and increasing the likelihood of immunopathological consequences (e.g.. immune-complex disease). Moreover, depression of the immune response might trigger or enhance the growth of certain tumours. Virus-induced potentiation of immune response might also have immunopathological consequences, such as the development of autoimmune disorders (WHO Scientific Group on Factors Regulating the Immune Response, 1970).

Recommendations

(1) A systematic evaluation of the effects of viruses on immune function should be undertaken. A number of viruses should be studied and a standard set of immune function tests should be employed. Among the factors that deserve special investigation are antigen types (e.g., thymus-dependent versus non-thymus-dependent), antigen dose, and the time relationship between infection and antigen administration.

(2) The effects of virus infection on different cell types (e.g., macrophages, T and B lymphocytes) should be studied in greater detail, with morphologic changes perhaps serving as an indication of functional alterations. Since differences in terminology often make it difficult to assess reports of pathological changes in lymphoid tissue, all modifications of the lymphoid organs should be described according to standardized criteria. Efforts at standardization are currently being supported by the World Health Organization.

(3) An attempt should be made to ascertain whether viruses can in fact exert selective effects on immune function, e.g., by depressing 7S versus 19S antibody, or by affecting T cell function as opposed to B cell function (Allison et al., 1971). The possibility should also be looked into that the immune response to the virus may itself be impaired if the infecting virus damages more or less selectively the cells responding to the viral antigens. If this proves to be the case, virus-induced immunodepression might conceivably be highly instrumental in prolonging certain virus infections, such as murine leukaemia, hepatitis, subacute sclerosing panencephalitis, or infections caused by LDV, LCMV, or ADV.

IMMUNE-COMPLEX DISEASES

It is well known that the persistence of antigen–antibody complexes in the circulating blood can lead to serum sickness, as manifested by glomerulonephritis, polyarteritis, urticaria, arthralgia, and arthritis. Recently, it has been shown in animals that viruses can persist in the bloodstream in the form of virus–antibody complexes, and that the deposition of these complexes in the kidney can produce an immune-complex type of glomerulonephritis.

Infectious virus–antibody complexes have been detected in the blood of animals with murine leukaemias and those infected with LDV, ADV, and LCMV (Mellors et al., 1969; Oldstone & Dixon, 1969; Notkins et al., 1966; Porter et al., 1969; Oldstone & Dixon, 1971b, respectively). Preliminary evidence suggests that infectious complexes also exist in the bloodstream of horses infected with equine infectious anaemia virus (EIAV) (McGuire et al., 1971). Immunopathological studies have revealed the presence of viral antigens, specific antiviral antibody, and complement in the kidneys of these animals (Oldstone & Dixon, 1971b).

Severe glomerulonephritis has been found in LCMV carrier mice (Hotchin & Collins, 1964; Oldstone & Dixon, 1969, 1971b). The severity of the disease appears to be related to the strain of

the mouse, the amount of LCMV, and the amount of antiviral antibody (Oldstone & Dixon, 1969). Aleutian disease of mink also is characterized by severe glomerulonephritis (Porter et al., 1969). All mink appear to be susceptible to infection by ADV, but those homozygous for the Aleutian gene develop a more severe form of the disease, characterized by heavy deposition of virus, antibody, and complement in the glomeruli. However, relatively mild glomerular lesions are seen in mice infected with LDV. In humans, circulating Australia antigen can exist in the form of antigen–antibody complexes (Zuckerman, 1971). One case of immune-complex nephritis with deposition of Australia antigen, IgG, and complement in the glomeruli has been reported, and in 4 cases of hepatitis autopsy disclosed the presence of Australia antigen, IgG, IgM, and complement in glomerular capillaries.

There is generally little evidence that vasculitis can be caused by virus–antibody complexes, but vascular lesions suggestive of polyarteritis nodosa and containing immunoglobulins have been reported late in the course of infection with ADV and EIAV. Recently, polyarteritis nodosa has been described in patients with circulating Australia antigen (Gocke et al., 1971); in one such case, Australia antigen, immunoglobulin, and complement were detected in the arterial wall (Gocke et al., *op. cit.*). In 5 cases of fatal hepatitis, Australia antigen, immunoglobulin, and complement were found in the intima of arterioles exhibiting changes typical of periarteritis. It has also been suggested that immune complexes may be causally involved in the urticaria and arthritis (Alpert et al., 1971) sometimes associated with hepatitis.

Although deposition of circulating immune complexes appears to be the most likely explanation of these findings, the possibility has not been excluded that viral antibody might attach to viral antigens released locally from infected cells or to virus-induced antigens on the surface of infected cells (see section entitled " Antibody-mediated immunopathological injury "). In several autopsy studies of patients with various forms of hepatitis, intracellular and extracellular deposits of Australia antigen, immunoglobulins and complement were reportedly found in liver parenchymal and Kupffer cells (Nowoslawski et al., 1972). In these cases, immunoglobulins directed specifically against Australia antigen were eluted from the liver with 2.5 M thiocyanate. At present, however, there is very little information available to pinpoint the factors responsible for producing virus-induced immune-complex disease. Whether the causal factor is the size of the complex, the nature of the viral antigen, the amount or type of antibody, the attachment of accessory factors such as complement (Winchester et al., 1971) or rheumatoid factor (Notkins, 1971; Winchester et al., 1971; Ziegenfuss et al., 1971), or the rate at which the antigen and antibody turn over (in the glomerular lesions) remains to be determined.

To date, virus-induced immune-complex disease has been attributed to the deposition of virus–antibody complexes during persistent virus infections (Oldstone & Dixon, 1971b). Conceivably, immune-complex disease also could occur from the repeated deposition of such complexes during various acute and recurrent virus infections. It should be emphasized that, in addition to virion–antibody complexes, antibody bound to virus-induced membrane antigens, soluble viral antigens, and viral nucleoproteins might contribute to the pool of circulating immune complexes.

The mechanism of tissue injury associated with deposition of virus–antibody complexes is presumably similar to that involved in the deposition of nonviral antigen–antibody complexes. It is known that activation of the complement sequence by immune complexes can effect the release of substances that have the capacity to increase vascular permeability, contract smooth muscle, and attract polymorphonuclear and mononuclear leucocytes. These factors would seem to play a role in the tissue injury associated with immune-complex disease. In addition, it has been postulated that immune complexes might activate components of the clotting system and thereby cause the deposition of fibrin.

Recommendations

(1) The presence of immune complexes in the kidney, arterial walls, or other tissues should be confirmed by demonstrating viral antigens, specific antiviral antibody, and complement in the lesions by immunofluorescence. If, however, the antigen cannot be detected because antigenic sites have been saturated by antiviral antibody, the antibody should if possible be dissociated by standard techniques (e.g., acid buffer, pH 2.0–3.0). The eluted antigen or antibody may be characterized by immunodiffusion, complement fixation, virus neutralization, or other techniques.

(2) Attempts should be made to recover and identify infectious virus from the kidney, extrarenal

tissue, and circulating blood by standard virus isolation techniques. To determine whether the isolated virus exists in the form of an infectious virus–antibody complex, the anti-immunoglobulin neutralization technique should be used.

(3) Efforts should also be made to detect non-infectious virus–antibody complexes in the circulation. Upon incubation with the C1q component of complement or rheumatoid factor (Winchester et al., 1971), these complexes may precipitate out demonstrably. Conversely, incubation in an acid buffer may dissociate the complexes and permit the viral antigens and specific antiviral antibody to be identified as described in (1) above.

(4) If virus cannot be recovered by any of the above techniques, the animals should be immunized with isolated complexes and their sera tested for antibodies to a variety of viruses.

(5) When DNA–anti-DNA complexes are present in the glomeruli, an endeavour should be made to distinguish between viral nucleic acids and nucleic acids of nonviral origin.

(6) Since glomerulonephritis of differing degrees of severity can be produced in the same host by different viruses (e.g., LCMV versus LDV), attention should be focused on the factors involved in the initiation and production of immune-complex disease. It would be desirable to develop models to study the clearance of virus–antibody complexes from the bloodstream and the rate at which these complexes deposit and turn over in the kidney.

(7) Animals with infections characterized by persistent or recurrent viraemia (e.g., feline leukaemia, African swine fever, hog cholera, and avian lymphomatosis) should be examined for antiviral antibody circulating virus–antibody complexes, and immune-complex nephritis.

(8) A major effort should be made to elucidate the role of immune complexes in the pathogenesis of viral hepatitis in man.

ANTIBODY-MEDIATED IMMUNOLOGIC INJURY

In the last decade it has been shown that the transformation of cells by oncogenic viruses results in the appearance of new antigens on the cell surface and that immune responses to these antigens may be involved in tumour rejection. Non-oncogenic viruses can also produce new antigens on the surfaces of infected cells, but the biological significance of these antigens has received relatively little attention. Evidence is now beginning to emerge, however, suggesting that the interaction of specific antiviral antibody and complement with surface antigens induced by non-oncogenic viruses can lead to cell destruction and may contribute to the pathogenesis of the lesions associated with certain virus infections.

In vivo, the best experimental evidence that antibody can play such a pathogenetic role comes from the demonstration that the passive administration of specific antiviral antibody to animals infected with LCMV (Oldstone & Dixon, 1970), ADV, or Japanese B encephalitis virus produces or intensifies the characteristic lesions associated with these infections. In addition, it has been speculated that the interaction of specific antiviral antibody and complement with antigens induced by the respiratory syncytial, measles, hepatitis, dengue, and equine infectious arteritis viruses may be partly responsible for the pathological picture seen in these infections. Another suggestion has been that the passive attachment of virus, antiviral antibody, and complement to the surface of platelets or erythrocytes may result in cell injury and might give rise to some of the haematologic abnormalities associated with virus infections, such as dengue shock syndrome (Russell, 1971)—the most severe form of dengue haemorrhagic fever—and equine infectious anaemia.

The strongest evidence that antiviral antibody and complement can injure virus-infected cells has been produced by *in vitro* experiments. It has been shown that the infection of cells with viruses that do not produce cytologic injury (rabies (Wiktor et al., 1968), LCMV) (Oldstone & Dixon, 1971a), or with viruses that ultimately do cause cell damage (HSV, vacciniavirus, influenzavirus, Newcastle disease virus [NDV] (Brier et al., 1970) is followed by the appearance of new antigens on the surface of the infected cells and that the interaction of specific antiviral antibody and complement with these antigens can produce immunologic injury. In the absence of either specific antiviral antibody or complement, such injury does not occur. The degree of injury may depend on a number of factors (Brier et al., 1970), including (1) the density of viral antigens on the infected cell surfaces; (2) the inherent susceptibility of the cells to lysis by complement; (3) the nature and concentration of the antiviral antibody; (4) the ratio of complement-fixing to non-complement-fixing antibody in the particular serum; and (5) the presence of inhibitors, such as

anti-immunoglobulins or rheumatoid factor, that might block complement-fixing sites on the antiviral antibody. The appearance of viral antigens might in turn be related to other factors, such as the phase of the cell cycle or coinfection with a second virus. If a particular virus produces few or no new antigenic sites on the surface of cells or if these antigenic sites are far apart, complement-mediated cell destruction may not occur. If, however, the density of virus-specific antigens on the cell surface should rise during the course of an infection, this would increase the likelihood of complement-mediated cell destruction. Fluctuations in the density of viral antigens on the infected cell surface might contribute heavily to the pathogenesis of lesions associated with " slow virus " infections (Porter, 1971).

Implications

The attachment of antiviral antibody in sublytic concentrations to the surface of infected cells may conceivably be instrumental in deciding the fate of the cell. On the one hand, the attachment of antiviral antibody might accelerate phagocytosis of the infected cell by activated macrophages. On the other hand, antiviral antibody might prevent sensitized lymphocytes from recognizing or reacting with the viral antigens and thereby inhibit the cell-mediated immune response. In virus infections, this might prove to be the counterpart of " blocking " or " enhancing " antibody.

Under certain circumstances the destruction of virus-infected cells by antiviral antibody and complement may be more beneficial than harmful to the host. Antibody-mediated cell destruction may be one of the mechanisms by which the host combats those viruses that tend to elude neutralization by spreading directly from cell to cell. Moreover, the destruction of cells that are actively producing virus would slow down viral replication and release or expose the infectious virus within the cell to neutralizing antibody. Thus, in virus infections, antibody-mediated cell destruction may fulfil many of the functions that have been postulated for cell-mediated immunity and may serve as a complementary or supplementary defence mechanism. In addition, *in vitro* experiments suggest that the release of one or more chemotactic-generating factors (Brier et al., 1970) from infected cells and/or the interaction between antiviral antibody and viral antigens can activate the complement sequence and cause the release of mediators able to attract polymorphonuclear and mononuclear leucocytes.

Recommendations

(1) Although many investigators have speculated that immunologic injury may contribute to the pathological picture in certain virus infections, it has been difficult to isolate and evaluate this phenomenon *in vivo*. The release of ^{51}Cr from virus-infected cells by antiviral antibody and complement provides a simple, objective, and quantitative technique for studying immunologic injury *in vitro*. With this technique it should be possible to (*a*) investigate a variety of viruses; (*b*) evaluate virus-induced immunologic injury in different types of cell; (*c*) compare the roles of cytolytic and non-cytolytic antibody in the serum of patients during the course of various virus infections; (*d*) determine whether biological mediators are released or activated as a result of the interaction of antiviral antibody and complement with viral antigens; and (*e*) investigate the relationship between antibody-mediated and cell-mediated destruction of infected cells.

(2) *In vivo* studies should be extended and experimental models developed. Additional studies should be conducted to evaluate the results of the passive administration of cytolytic antiviral antibody to infected animals with normal and depleted levels of complement. Efforts should be made to demonstrate the presence of antiviral antibody and complement on the surface of injured cells at the site of the lesion. Further thought should be given to the potential beneficial or harmful effects of passive protection with immunoglobulins containing cytolytic antiviral antibody or with vaccines (e.g., rabies vaccine) that might induce cytolytic antibody.

(3) Attempts should be made to compare the *in vitro* and *in vivo* effects of antibody and complement on the lysis of virus-infected cells. Whether the attachment of nonlytic antibody to infected cells can inhibit the cell-mediated immune response should be investigated.

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RÉSUMÉ

ÉTATS IMMUNOPATHOLOGIQUES INDUITS PAR LES VIRUS: MODÈLES ANIMAUX ET RELATIONS AVEC LES MALADIES HUMAINES: 1. EFFETS DES VIRUS SUR LE SYSTÈME IMMUNITAIRE, MALADIES DUES À DES IMMUNCOMPLEXES ET LÉSIONS IMMUNOLOGIQUES PROVOQUÉES PAR L'INTERMÉDIAIRE DES ANTICORPS

On sait depuis longtemps que les virus produisent des lésions en endommageant et parfois en détruisant les cellules à l'intérieur desquelles ils se multiplient. Plus récemment, on a découvert que des altérations tissulaires peuvent aussi résulter d'interactions entre le virus et le système immunitaire de l'hôte. L'étude de diverses maladies des animaux a permis de déceler un certain nombre de mécanismes immunopathologiques responsables des lésions provoquées par des infections virales. Ces mécanismes — ainsi que les concepts et les techniques issus de ces recherches — sont décrits dans la 1re et dans la 2e partie du présent mémorandum. Leurs conséquences éventuelles au regard des maladies humaines sont examinées et plusieurs de leurs applications sont envisagées.

Un premier type de lésion immunologique est dû aux effets directs exercés par certains virus sur le système immunitaire. Des virus, notamment les virus des leucémies et des virus responsables d'infections de longue durée, diminuent la capacité de production des anticorps chez l'hôte; d'autres agissent en renforçant la réponse immunitaire à divers antigènes. Dans certains cas, il est manifeste que les virus inhibent également l'immunité à support cellulaire. Cette action des virus sur la fonction immunitaire pourrait avoir de nombreuses et importantes conséquences du point de vue clinique; c'est ainsi que l'affaiblissement de l'immunité serait susceptible de favoriser le développement de tumeurs.

Les maladies dues à des immuncomplexes représentent une autre forme de lésion immunopathologique provoquée par des virus. Dans les infections virales persistantes, les anticorps spécifiques se combinent parfois aux virus ou aux antigènes viraux pour former des immuncomplexes qui sont ensuite déposés dans divers endroits de l'organisme, et en particulier dans le rein. Dans cette dernière éventualité, on peut voir apparaître ultérieurement une glomérule-néphrite causée par la combinaison des immuncomplexes et du complément entraînant la libération de substances qui lèsent les tissus. Les dépôts d'immuncomplexes dans la paroi des petites artères peuvent provoquer des lésions vasculaires rappelant celles de la périartérite noueuse.

Enfin, un troisième type de lésion immunologique est celui réalisé à l'intervention des anticorps. Il s'agit de la réaction produite lors de la fixation des anticorps spécifiques sur les antigènes cellulaires de surface induits par les virus. Le complément, normalement présent, peut alors léser les cellules et même provoquer leur lyse. On connaît un certain nombre de virus, en dehors des virus oncogènes, qui produisent des antigènes à la surface des cellules dans lesquelles ils ont pénétré. L'expérimentation *in vitro* montre qu'en l'absence d'anticorps spécifiques ou de complément il ne se produit aucune lésion immunologique. Dans certaines conditions, la destruction des cellules infectées par le virus se révèle, en dépit du dommage causé, favorable pour l'hôte en ralentissant ou en arrêtant la multiplication du virus. Dans d'autres cas, et notamment lorsqu'un grand nombre de cellules d'un organe vital sont atteintes, la lésion peut avoir des conséquences graves et même fatales.

D'autres formes d'interaction entre les virus et le système immunitaire entraînant également des lésions sont décrites dans la 2e partie du mémorandum.

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