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Immunopathology in Virus Disease [and Discussion]

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Immunopathology in virus disease

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Immunopathology contributes to almost all virus infections, and can be the cause of death. The formation of immune complexes in tissues induces inflammation. Circulating immune complexes are often harmless, but when deposited in tissues can lead to glomerulonephritis, arthritis and vasculitis. Classic examples are provided by certain persistent virus infections, in which antibody responses are of low affinity or directed against non-critical sites on the virus particles, and in which complexes are deposited over long periods.

Cytotoxic T cells show powerful effects *in vitro*, but have rarely been proved to cause serious tissue damage *in vivo*. Destruction of cells by antibody plus complement, by antibody and K cells or by NK cells plays an ill-defined role in viral pathology. Delayed hypersensitivity T cells are more obviously important in immunopathology, inducing inflammation, cell infiltration and macrophage-mediated damage.

Viral immunopathology could be of major importance in certain chronic diseases of unknown aetiology if damaging autoimmune responses were triggered by virus infection. Possible mechanisms are discussed.

Introduction

The expression of the immune response necessarily involves a certain amount of inflammation, cell infiltration, lymph node swelling, even tissue destruction. When the immune response is suppressed, viruses generally show increased replication and spread, but if in spite of this the disease is less severe than in the normal host it as assumed that immunopathology plays an important part. Immunopathological changes are sometimes so severe that they are lethal, as in adult mice infected intracerebrally with lymphocytic choriomeningitis (LCM) virus, whereas at other times they play a minimal part in pathogenesis. We still have an imperfect understanding of the mechanisms by which these immunopathological changes are brought about. Phenomena that are well characterized *in vitro* (e.g. antibody-dependent cellular cytotoxicity) or in experimental animals (e.g. the Arthus reaction) often turn out to be difficult to assess in the intact host suffering from a virus disease.

IgE-mediated reactions

IgE-mediated reactions are not known to be important in virus infections. When they take place at body surfaces they possibly play a part in the pathogenesis of upper respiratory virus infections or in the pathogenesis of certain viral exanthems. Infants infected with respiratory syncytial virus develop more severe disease and wheezing in association with detectable virus-specific IgE responses (Welliver *et al.* 1981). The degree of hypoxia and the histamine levels in secretions were maximal at the time of peak IgE titres.

Cytotoxic reactions

Cells infected with enveloped viruses and also with non-enveloped viruses, such as adenoviruses (Inada & Uetake 1978) and papovaviruses, display virus-coded antigens on the plasma membrane. This renders the cell vulnerable to immune recognition and destruction. The antigens often appear at an early stage in the virus growth cycle so that the cell can be destroyed before replication is completed. Cell destruction can be mediated by the following mechanisms. Each is fairly well defined *in vitro* and can generally be demonstrated when antibodies or reactive cells are taken from the infected host.

1. Antibody-mediated complement lysis.
2. Antibody-dependent cellular cytotoxicity (by 'K' cells). This generally requires fewer antibody molecules than mechanism 1. (Virus-infected cells can at times activate the alternative complement pathway, so that complement lysis takes place in the absence of antibody, or K cell lysis is mediated via C_3b rather than Fc receptors (Hirsch 1982).)
3. Cytotoxic T cells (Tc).
4. Natural killer (NK) cells.

Persistent viruses in particular often fail to damage or destroy the infected cell, so that the host is obliged to destroy intact cells if the infection is to be controlled and the effects of disease are to be minimized. Recent studies have shown how persistently infected but otherwise intact cells can nevertheless be functionally impaired. For instance, the production or reception of neurotransmitters is impaired in neural cells infected with LCM (Oldstone *et al.* 1977) or rabies virus (Tsiang 1982). There is interference with the production of growth hormone by posterior pituitary cells in mice infected with LCM (Oldstone *et al.* 1982), with the presentation of antigen by mouse macrophages infected with lactate dehydrogenase virus (Isakov *et al.* 1980), and the division rate of cells is impaired in the human embryo infected with rubella virus (Rawls & Melnick 1966).

Certainly at times the immune destruction of infected cells can be important in recovery from virus infections. Administration of cloned specifically reactive Tc, for instance, decreases susceptibility of mice to influenza virus and herpes simplex virus infection (Lin & Askonas 1980; Sethi *et al.* 1983). Nevertheless the contribution of Tc to immunopathology remains doubtful. Specific depletion or selective reconstitution with Tc cells has not yet been tried in most virus infections, and T-cell mediated delayed hypersensitivity reactions often complicate the picture. In assessing antibody-mediated lysis it must be remembered that antibodies have other immunopathological actions as well as the mediation of cell destruction. Finally, it has not yet been possible to show that NK or K cells have *in vivo* immunopathological action.

Infection of adult mice with LCM virus illustrates these difficulties, in spite of the fact that it is a classic in viral immunopathology. When virus in injected intracerebrally into adult mice it grows in the meninges, ependyma and choroid plexus epithelium, but the infected cells do not show the slightest sign of damage. After 7–10 days, however, the mouse develops severe meningitis and cerebral oedema (Doherty & Zinkernagel 1974) and dies. The illness is completely preventable by adequate immunosuppression (Buchmeier *et al.* 1980), and can be induced in infected immunosuppressed animals by transferring immune spleen T cells. The disease is attributable to the mouse's own cell-mediated immune reaction to the infected cells in the central nervous system, which bear LCM viral antigens on their surface. Tc cells that will kill LCM-infected target cells *in vitro* are present in the cerebrospinal fluid of infected mice

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(Zinkernagel & Doherty 1973), and could destroy infected cells, thereby generating inflammation and neurological disease. But tissue destruction is not a feature of this disease and no signs of cell damage were seen in careful electron microscopical studies (Walker *et al.* 1975). Vigorous delayed hypersensitivity responses are induced in infected mice and their magnitude in different strains of mice is proportional to the severity of the neurological disease (Tosolini & Mims 1971), so perhaps it is delayed hypersensitivity T cells (Td) that induce inflammation, oedema and cell infiltration, giving rise to the characteristic disease. It may be noted that the cell-mediated immune response, although lethal in the central nervous system, with its unique vulnerability to inflammation and oedema, is nevertheless an attempt to do the right thing. Immune T cells effectively inhibit virus growth in infected organs (Mims & Blanden 1972), but a response that is useful in most parts of the body turns out to be self-destructive when it takes place in the central nervous system.

Another tissue that is especially vulnerable to inflammation is the lung. Oedema fluid or infiltrating cells appear first in the space between alveolar capillaries and the alveolar wall, and interfere with respiration by decreasing the efficiency of gaseous exchange. There is good evidence that specific T cell responses to influenza virus infection not only contribute to antiviral defence (see above) but also, by mediating delayed hypersensitivity responses, enhance the severity of lung pathology (Leung & Ada 1981).

Immune complex reactions

(*a*) *In tissues*

Inflammation is induced when antibody combines with viral antigen in infected tissues, and is an inevitable expression of the immune response. When the reaction takes place in extravascular tissues it often leads to mild inflammation, as seen in the red zone round the corner of a smallpox vaccination site after 7–8 days. When it takes place experimentally in the wall of blood vessels it can give a classic Arthus response, but there are no good examples of this in virus infections. However, when viruses infect vascular endothelium, antibodies reacting locally with viral antigen can induce vasculitis and this is probably the basis for the exanthems in certain virus infections. Cell-mediated immune responses, however, can contribute to viral exanthems as shown by the absence of a measles rash in children with thymic aplasia, and the presence of a typical rash in those with agammaglobulinaemia. Virus infection of vascular endothelium is fraught with pathogenic possibilities and is a neglected field in virus research; it could now be studied in cultures derived from capillary beds (Folkman *et al.* 1979) as well as from large vessels (Friedman *et al.* 1981).

Antibody–antigen reactions probably account for much of the inflammation seen in virus-infected tissues, but in most cases this has not been dissociated from the inflammation caused by the reaction of Td cells with viral antigen (see below).

(*b*) *In the circulation*

In recent years a great deal of attention has been given to circulating immune complexes and their role in disease processes. Certain persistent virus infections of animals provide classic examples of the pathogenic role of circulating immune complexes. Viral antigens are often present in the blood during infection, and when antibody enters the blood, immune complexes with antibody in excess are soon formed. These are rapidly removed by reticuloendothelial cells

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in the liver and spleen, which have receptors for the Fc portion of the antibody molecule. During the early stages of the antibody response, however, there is a transitional stage when complexes are formed in antigen excess. These are not rapidly removed from the circulation, and have the opportunity to localize in small blood vessels elsewhere in the body. These sites include the joints, eye, choroid plexus, small blood vessels in the skin, and especially the kidney glomeruli. The mechanisms of localization are not clear but the complexes are generally dissociated at a later stage, or disposed of by entering the urine or after uptake by mesangial cells in the glomeruli. As more sensitive techniques were used for detection of immune complexes, they were found in a variety of conditions but also in normal individuals, and during normal pregnancy (Masson *et al.* 1977). They are probably present at some stage in most virus infections, and are generally of little or no pathological importance.

TABLE 1. THE DEPOSITION OF CIRCULATING IMMUNE COMPLEXES IN PERSISTENT VIRUS INFECTIONS

virus	host	kidney deposits	glomerulonephritis	vascular deposits
mouse leukaemia	mouse	+	±	−
cat leukaemia	cat	+	±	−
lactic dehydrogenase virus (LDV)	mouse	+	±	−
LCM	mouse	++	+	±
Aleutian disease virus (ADV)	mink	++	+	++
equine infectious anaemia	horse	+	+	+
hepatitis B	man	+	−	+
rubella†	man	?	−	?

† Circulating immune complexes in chronic infection are associated with congenital rubella (Coyle *et al.* 1981) and progressive rubella panencephalitis (Coyle & Wolinsky 1981), but the pathogenic role is unknown.

However, under certain circumstances immune complexes continue to be formed over long periods, and their continued deposition may 'overload' disposal mechanisms, and generate pathological changes. This takes place in persistent virus infections, particularly when antibody responses are minimal, of low affinity, or directed at non-neutralizing (non-critical) sites on the virus. Examples are summarized in table 1. In the well studied examples, the severity of the resulting pathology has been shown to be determined by host genetic factors. When different strains of mice are persistently infected with LCM virus, circulating immune complexes are formed, but they develop differing degrees of glomerulonephritis ranging from almost zero in wild mice (Lehmann-Grube 1981) to severe disease and death with uraemia in many strains of laboratory mice. It is not certain to what extent this is due to differences in the formation of the pathogenic type of complexes, to differences in their disposal, or to differences in the pathological sequelae to deposition. Mice persistently infected with LDH virus develop little or no glomerulonephritis (table 1), and this appears to be associated with a decreased deposition of complexes in kidneys (Oldstone & Dixon 1971). In mink infected with Aleutian disease virus, very large amounts of antibody are formed of low neutralizing capacity. Circulating immune complexes are deposited in glomeruli and blood vessels over long periods, resulting in death due to glomerulonephritis or due to haemorrhage from affected arteries (Porter *et al.* 1980). Mink with the Aleutian coat colour gene show a striking susceptibility to this immunopathological virus disease.

Circulating immune complexes also generate fever, as do systemic cell-mediated immune reactions, and this is mediated by endogenous pyrogens liberated from polymorphs and

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macrophages. Perhaps the characteristic subjective sensations of illness and some of the 'toxic' features of virus diseases are caused by immune reactions. Endogenous interferon is another possible source of these symptoms, because purified human interferon is known to cause headache, myalgia and fever (Scott *et al.* 1981). Recent work with LCM virus strongly implicates interferon production by the infected mouse as a pathological force (Rivière *et al.* 1980; Jacobson *et al.* 1981). In so far as this may be immune interferon it could be regarded as immunopathology. It seems likely, however, that in adult mice, at least, interferon acts by restricting the extraneural replication of the virus so that a more intense focusing of the cell-mediated immune response occurs at the site of growth in the central nervous system.

Systemic immune complex reactions very occasionally give rise to a serious condition, disseminated intravascular coagulation, which is sometimes seen in yellow fever and other haemorrhagic virus diseases (Abildgaard *et al.* 1975). In this case immune reactions activate the enzymes of the coagulation cascade, leading to histamine release and increased vascular permeability. Fibrin is formed and deposited in organs, leading to multiple thromboses, infarcts and also haemorrhage. Haemorrhage is additionally caused because of a depletion of platelets, prothrombin, fibrinogen, etc. (Hamilton 1978). It was once thought to form the pathophysiological basis for dengue haemorrhagic fever, but this now seems rather to depend on antibody-mediated enhancement of infection of mononuclear cells (Halstead 1981; and see below).

(*c*) *Delayed cell-mediated reactions*

Delayed hypersensitivity T cells can cause immunopathology after reacting with viral antigens by liberating lymphokines, which induce inflammation and accumulation of lymphocytes and activated macrophages. Activated macrophages can cause damage to normal tissues, especially if antibody (otherwise non-cytotoxic) is present. For instance, when tuberculin-sensitized rats are injected into a dorsal nerve root with PPD, a typical delayed hypersensitivity reaction is produced, and local tissue destruction (demyelination) follows (Wisniewski & Bloom 1975). Activated macrophages also release potentially damaging enzymes, prostaglandins and other inflammatory mediators. Delayed hypersensitivity reactions are complex, involving a variety of lymphokines and monokines, and antibody-mediated or Jones–Mote (basophil) responses can contribute to the reaction.

Enhancing antibodies

Virus infection of macrophages can be enhanced rather than prevented by specific antibody. Enhancing antibodies act by taking virus into the susceptible cell via the latter's Fc receptors, and have been reported for dengue and other arboviruses, for LDH virus (Cafruny & Plageman 1981) and for murine cytomegalovirus (Inada *et al.* 1983). Studies with monoclonal antibodies show that the enhancing activity can be distinguished from neutralizing activity, but mechanisms are not clear (Peiris *et al.* 1982). Enhancing antibodies may greatly increase the infection of mononuclear cells *in vivo* (Halstead 1979) and this is thought to play a part in the pathogenesis of dengue haemorrhagic fever. It can therefore be regarded as a type of immunopathology.

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Autoimmune responses triggered by virus infections

If virus-induced immune responses are directed not only against the virus and infected cells but also against normal host components, then the stage is set for further immunopathological events, which are classed as autoimmune. In an acute infection this would merely lead to increased tissue damage, but if the infection became chronic, more extensive tissue damage would be possible. If the autoimmune phenomena continued over a longer period, after the disappearance of the virus that originally triggered it, it might be very difficult to show that a virus was responsible. The autoimmune responses could theoretically be induced in the following ways.

(*a*) If host antigens were present and were closely associated with viral antigens on the viral envelope and on the surface of the infected cell, then anti-host as well as antiviral responses might be induced. Generally in the viral envelope there is almost complete replacement of host-cell components by viral polypeptides. However, Lodish & Porter (1980) labelled the plasma-membrane polypeptides of susceptible cells with ^{125}I and then infected them with vesicular stomatitis virus. They detected 2% of the cell-surface label in highly purified virions. Evidence for this type of autoimmune response comes from experiments by Bromberg *et al.* (1982). They found that antibody responses to antigens on mouse thymus cells increased 30-fold when these cells were first infected with herpes simplex, vaccinia or Newcastle disease virus. The virus antigen perhaps acted as a helper determinant for a response to the host cell, or conceivably host antigen was displayed in a novel fashion when coupled to viral antigen.

(*b*) Damage to infected cells and the delivery of normal host-cell antigens to the immune system might result in anti-host responses. This assumes that the host antigens are not normally delivered in the same way to the immune system.

(*c*) There might be clones of lymphocytes that recognize determinants present on both viral and host antigens, so that cross-reactive immune responses were generated. Work with monoclonal antibodies will soon provide more definitive answers about this type of immunopathology. There are unconfirmed reports of monoclonal antibodies to herpes simplex virus glycoproteins that also react with neutral glycolipids from uninfected cells (Lane & Koprowski 1982). In an analogous situation, a monoclonal antibody has been obtained that reacts with *Trypanosoma cruzi* parasites and also with normal neurones and cardiac muscle cells, providing a mechanism for the degeneration of neurons and cardiac muscle cells seen in Chaga's disease (Wood *et al.* 1982). Findings such as this strengthen the possibility that certain genetically predisposed individuals can generate immune responses to viral antigens that cross-react with normal host tissues.

(*d*) If an autoimmune response occurs spontaneously, but is normally kept in check by specific suppressor mechanisms, the virus infection might interfere with this, perhaps by infecting suppressor cells. The immunoregulatory balance could be upset, allowing autoimmunity to become manifest (Patterson *et al.* 1981).

(*e*) When a virus causes polyclonal activation of B cells, auto-antibodies may be formed and could theoretically damage host tissues. EB virus infects B cells, and 5–6 days after initial infection IgG secretion is induced in 5–7% of infected cells (Sugden 1982). The polyclonal activation of B cells probably gives rise to heterophil antibodies and other auto-antibodies in this infection.

(*f*) The infected host can form antibody to the idiotype on antiviral antibodies. Although

antidiotype antibody may have immunoregulatory functions it could, if directed against antibody to viral surface components, also react with virus-specific receptors on normal, uninfected cells, thus providing a possible basis for autoimmune changes. Nepom *et al.* (1982) have shown that antibody to the idiotype on antibody to reovirus 3 haemagglutinin also reacts with non-immune lymphoid cells and with neural cells.

TABLE 2. EXAMPLES OF AUTOIMMUNE RESPONSES IN VIRUS INFECTIONS

virus	host	autoimmune response induced	references
EB	man	rheumatoid factor, antinuclear antibody, cold agglutinins	Wager *et al.* (1968)
CMV	man		
hepatitis B	man	antibody and cell-mediated destruction of hepatocytes†	Chisari & Edgington (1978)
CMV	mouse	anti-hepatocyte antibody	Bartholomaeus *et al.* (1983)
JHM (coronavirus)	rat	lymphocytes respond to myelin basic protein *in vitro* and cause changes in c.n.s. on transfer to uninfected rats	Weger *et al.* (1983)
vaccinia (neurotropic)	mouse	antibody to myelin and oligodendrocyte components	Steck (1981)
reovirus type 1	mouse	antibody reacts with gut mucosa, pancreas, anterior pituitary (and with glucagon, insulin, growth hormone)	Onodera *et al.* (1981), Haspel *et al.* (1983)

† So far this remains an interesting possibility for which the evidence is slight.

Possibilities (*b*), (*c*) and (*d*) have been particularly attractive in theories of the pathogenesis of chronic diseases such as multiple sclerosis and rheumatoid arthritis. In multiple sclerosis, for instance, it is possible that immune responses to host oligodendrocytes and myelin are triggered by virus infection.

Whatever the exact mechanisms, autoimmune responses are known to occur in virus infections (table 2). Although they would not necessarily lead to tissue damage, the possibility is an important one. The report of Steck (1981) (table 2) needs confirmation, but interestingly that group has previously shown that a core-associated protein kinase from vaccinia virus phosphorylates myelin basic protein, and this could be involved in the autoimmune response (Steck *et al.* 1976). The peripheral nerve lesions in chickens infected with Marek's disease virus are associated with immune responses to peripheral nerve components induced by the virus infection (Pepose *et al.* 1981). One possible mechanism would be (*b*) above.

Recent work with mouse hepatitis virus provides examples of autoimmune responses triggered by virus infection. Rats develop chronic demyelination after infection with the JHM strain of mouse hepatitis virus (Wege *et al.* 1983). Their lymphocytes respond specifically to myelin basic protein *in vitro*, and can then, on transfer to normal rats, induce mononuclear cell infiltrations in the spinal cord. This constitutes suggestive evidence for an autoimmune response to myelin induced by JHM virus infection.

ANTIBODY-INDUCED ANTIGENIC MODULATION

When antiviral antibodies react with viral polypeptides present on the plasma membrane of infected cells, the resulting immune complexes move laterally to one pole of the cell

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('capping') and the complexes are then either shed into extracellular fluids or internalized. Modulation of antigen continues as long as sufficient antiviral antibody is present. It takes place, moreover, with less viral antigen expressed on the cell surface than is needed for Tc lysis or lysis associated with antibody and complement. This ensures that the infected cells escape immune destruction. The phenomenon was carefully studied in HeLa cells infected with measles virus (Oldstone & Fujinami 1982). Little if any virus buds from the plasma membrane during modulation and nucleocapsids accumulate in the underlying cytoplasm. The expression of viral polypeptides found inside the cell is also altered. If the modulating antibody is removed from the infected cells, within a few hours measles virus antigens are soon re-expressed on the cell surface, but after incubation of infected cells with antibody for 5 days viral antigen does not re-emerge until nearly a week after the removal of antibody. These experiments make it difficult to avoid the conclusion that antibody induced antigenic modulation is involved in the persistence of measles virus in subacute sclerosing panencephalitis. This is a lethal disease, and can be said to be partly immunopathological in nature.

References

Abildgaard, C., Harrison, J., Espana, C. *et al.* 1975 Simian hemorrhagic fever: studies of coagulation and pathology. *Am. J. trop. Med. Hyg.* **24**, 537–544.

Bartholomaeus, W. N., Shellam, G. R., Allan, J. E., Reed, W. D. & Joske, R. A. 1983 Autoantibodies to liver-specific lipoprotein following hepatitis induced by mouse cytomegalovirus. *Clin. exp. Immunol.* **52**, 89–97.

Bromberg, J. S., Lake, P. & Brunswick, M. 1982 Viral antigens act as helper determinants for antibody responses to cell surface antigens. *J. Immunol.* **129**, 683–688.

Buchmeier, M. J., Welsh, R. M., Dukto, F. J. & Oldstone, M. B. A. 1980 The virology and immunobiology of lymphocytic choriomeningitis virus infection. *Adv. Immunol.* **30**, 275–331.

Cafruny, W. A. & Plageman, P. G. W. 1981 Immune enhancement of macrophage infection with lactate dehydrogenese-elevating virus. *Fedn Proc. Fedn Am. Socs exp. biol.* **40**, 1120.

Chisari, F. V. & Edgington, T. S. 1978 An intregrating immunoregulatory hypothesis for the immunopathogenesis of liver disease associated with hepatitis B virus infection. In *Persistent viruses* (ed. J. G. Stevens *et al.*), pp. 499–520. New York: Academic Press.

Coyle, P. K. & Wolinsky, J. S. 1981 Characterization of immune complexes in progressive rubella panencephalitis. *Ann. Neurol.* **9**, 557–562.

Coyle, P. K., Wolinsky, J. S., Buimovici-Klein, E., Moncha, R. & Cooper, L. Z. 1981 Rubella-specific immune complexes following congenital infection and live virus vaccination. *Neurology* **31**, 126.

Doherty, P. C. & Zinkernagel, R. M. 1974 T cell mediated immunopathology in viral infections. *Transpl. Rev.* **19**, 89–120.

Folkman, J., Handenschild, C. C. & Zetter, B. R. 1979 Long-term culture of capillary endothelial cells. *Proc. natn. Acad. Sci. U.S.A.* **76**, 5217–5221.

Friedman, H. M., Macarak, E. J., MacGregor, R. R., Wolfe, J. & Kefalides, N. A. 1981 Virus infection of endothelial cells. *J. infect. Dis.* **143**, 266–273.

Halstead, S. B. 1979 In vivo enhancement of dengue virus infection of rhesus monkeys by passively transferred antibody. *J. infect. Dis.* **140**, 527–533.

Halstead, S. B. 1981 Viral hemorrhagic fevers. *J. infect. Dis.* **143**, 127–129.

Hamilton, P. J., Stalker, A. L. & Douglas, A. S. 1978 Disseminated intravascular coagulation: a review. *J. clin. Path.* **31**, 609–619.

Haspel, M. V., Onodera, T., Prabhakar, B. S., Horita, M., Suzuki, H. & Notkins, A. L. 1983 Virus-induced autoimmunity: monoclonal antibodies that react with endocrine tissues. *Science, Wash.* (In the press.)

Hirsch, R. L. 1982 The complement system: its importance in the host response to viral infection. *Microbiol. Rev.* **46**, 71–85.

Inada, T., Chong, K. T. & Mims, C. A. 1983 Enhancing antibodies in mouse cytomegalovirus infection. (In preparation.)

Inada, T. & Uetake, H. 1978 Cell-mediated immunity assayed by ^{51}Cr release test in mice infected with mouse adenovirus. *Infect. Immun.* **20**, 1–5.

Isakov, N., Feldman, M. & Segal, S. 1980 Effect of lactate dehydrogenase virus on macrophage function. Presented at IV Int. Congress on Immunology, Paris, abstract no. 11.2.09.

Jacobson, S., Friedman, R. M. & Pfau, C. J. 1981 Interferon induction by lymphocytic choriomeningitis virus correlates with maximum virulence. *J. gen. Virol.* **57**, 275–283.

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

Johnson, K. J. & Ward, P. A. 1982 New concepts in the pathogenesis of immune complex-induced tissue injury. *Lab. Invest.* **47**, 218–226.

Lane, D. & Koprowski, H. 1982 Molecular recognition and the future of monoclonal antibodies. *Nature, Lond.* **296**, 200–202.

Lehmann-Grube, F. 1981 Infection of mice with lymphocytic choriomeningitis virus. In *The mouse in biomedical research* (ed. H. L. Foster, J. D. Small & J. G. Fox), p. 255. New York: Academic Press.

Leung, K.-N. & Ada, G. L. 1980 Cells mediating delayed hypersensitivity in the lungs of mice infected with an influenza A virus. *Scand. J. Immunol.* **12**, 393–400.

Lin, Y. L. & Askonas, B. A. 1980 Cross reactivity for different type A influenza viruses of a cloned T-killer cell line. *Nature, Lond.* **288**, 164.

Lodish, H. F. & Porter, M. 1980 Specific incorporation of host cell surface proteins into budding vesicular stomatitis virus particles. *Cell* **19**, 161–169.

Masson, P. L., Delire, M. & Cambiaso, C. 1977 Circulating immune complexes in normal human pregnancy. *Nature, Lond.* **266**, 542–543.

Mims, C. A. & Blanden, R. V. 1972 Antiviral activity of immune lymphocytes in lymphocytic choriomeningitis virus infection of mice. *Infect. Immun.* **6**, 695–698.

Nepom, J. T., Weiner, H. L., Dichter, M. A., Tardieu, M., Spriggs, D. R., Gramm, C. F., Powers, M. L., Fields, B. N. & Greene, M. I. 1982 Identification of a hemagglutinin-specific idiotype associated with reovirus recognition shared by lymphoid and neural cells. *J. exp. Med.* **155**, 155–167.

Oldstone, M. B. A. & Dixon, F. J. 1971 Immune complex disease in chronic viral infections. *J. exp. Med.* **134**, 32s–40s.

Oldstone, M. B. A. & Fujinami, R. S. 1982 Virus persistence and avoidance of immune surveillance: how measles viruses can be induced to persist in cells, escape immune assault and injure tissues. In *Virus persistence* (33rd Symposium of the Society for General Microbiology) (ed. B. W. J. Mahy, A. C. Minson & G. K. Darby), pp. 185–202. Cambridge University Press.

Oldstone, M. B. A., Holmstoen, J. & Welsh, R. M. 1977 Alteration of acetylcholine enzymes in neuroblastoma cells persistently infected with lymphocytic choriomeningitis virus. *J. cell. Physiol.* **91**, 459–472.

Oldstone, M. B. A., Sinha, Y. M., Blount, P., Tishon, A., Rodriguez, M., von Wedel, R. & Lampert, P. W. 1982 Virus-induced alterations in homeostasis leading to disease: alterations in differentiated but not vital functions of infected cells *in vivo*. *Science, Wash.* **218**, 1125–1127.

Onodera, T., Toniolo, T., Ray, U. R., Jenson, A. B., Knazek, R. A. & Notkins, A. L. 1981 Virus-induced diabetes mellitus. XX. Polyendocrinopathy and autoimmunity. *J. exp. Med.* **153**, 1457–1473.

Patterson, P. Y., Day, E. D. & Whitacre, C. C. 1981 Neuroimmunologic disease: effector cell responses and immunoregulatory mechanisms. *Immunol. Rev.* **55**, 89–120.

Peiris, J. S. M., Porterfield, J. S. & Roehrig, J. T. 1982 Monoclonal antibodies against the flavivirus West Nile. *J. gen. Virol.* **58**, 283–289.

Pepose, J. S., Stevens, J. G., Cook, M. L. & Lampert, P. W. 1981 Marek's disease as a model for the Landry–Guillain–Barre syndrome; latent viral infection in non-neuronal cells accompanied by specific immune responses to peripheral nerve and myelin. *Am. J. Path.* **103**, 309–320.

Porter, D. D., Larsen, A. E. & Porter, H. G. 1980 Aleutian disease of mink. *Adv. Immunol.* **29**, 261–286.

Rawls, W. E. & Melnick, J. L. 1966 Rubella virus carrier cultures derived from congenitally infected infants. *J. exp. Med.* **123**, 795–816.

Rivière, Y., Gresser, I., Guillon, J. C., Bandu, M. T., Ronco, P., Morel-Maroger, L. & Verroust, P. 1980 Severity of lymphocytic choriomeningitis virus disease in different strains of suckling mice correlates with increasing amounts of endogenous interferon. *J. exp. Med.* **152**, 633–640.

Scott, G. M., Secher, D. S., Flowers, D., Bate, J., Cantell, K. & Tyrrell, D. A. 1981 Toxicity of interferon. *Br. med. J.* **282**, 1345–1348.

Sethi, K. K., Omata, Y. & Schneweis, K. E. 1983 Protection of mice from fatal herpes simplex virus Type 1 infection by adoptive transfer of cloned virus-specific and H_2-restricted cytotoxic T lymphocytes. *J. gen. virol.* **64**, 443–447.

Steck, A. J., Siegrist, P. & Herschkowitz, N. 1976 Phosphorylation of myelin basic protein by vaccinia virus cores. *Nature, Lond.* **263**, 436–438.

Steck, A. J., Tschannen, R. & Schaefer, R. 1981 Induction of antimyelin and antioligodendrocyte antibodies by vaccinia virus. *J. Neuroimmunol.* **1**, 117–124.

Sugden, B. 1982 Epstein–Barr virus: a human pathogen inducing lymphoproliferation in vivo and in vitro. *Rev. infect. Dis.* **4**, 1048–1061.

Tosolini, F. A. & Mims, C. A. 1971 Effect of murine strain and viral strain on the pathogenesis of lymphocytic choriomeningitis virus infection and a study of footpad responses. *J. infect. Dis.* **123**, 134–144.

Tsiang, H. 1982 Neuronal function impairment in rabies-infected rat brain. *J. gen. Virol.* **61**, 277–281.

Wager, O., Rasanen, J. A., Hagman, A. & Klemola, E. 1968 Mixed cryoimmunoglobúlinemia in infectious mononucleosis and cytomegalovirus mononucleosis. *Int. Arch. Allerg.* **34**, 345–361.

Walker, D. H., Murphy, F. A., Whitfield, S. S. & Bauer, S. P. 1975 Lymphocytic choriomeningitis ultrastructural pathology. *Expl molec. Path.* **23**, 245–265.

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

Wege, H., Watanabe, R. & ter Meulen, V. 1983 Murine coronavirus infection of the central nervous system in rats. In *Viruses and demyelinating diseases* (ed. C. A. Mims, L. Cuzner & R. E. Kelly). London: Academic Press. (In the press.)

Welliver, R. C., Wong, D. T., Sun, M., Middleton, E., Vaughan, R. S. & Ogra, P. L. 1981 The development of respiratory syncytial virus-specific IgE and the release of histamine in nasopharyngeal secretions after infection. *New Engl. J. Med.* **305**, 841–846.

Wisniewski, H. M. & Bloom, B. R. 1975 Primary demyelination as a non-specific consequence of a cell-mediated immune reaction. *J. exp. Med.* **141**, 346–359.

Wood, J. N., Hudson, L., Jessell, T. M. & Yamamoto, M. 1982 A monoclonal antibody defining antigenic determinants on subpopulations of mammalian neurones and *Trypanosoma cruzi* parasites. *Nature, Lond.* **296**, 34–38.

Zinkernagel, R. M. & Doherty, P. C. 1973 Cytotoxic thymus-derived lymphocytes in cerebrospinal fluid of mice with lymphocytic choriomeningitis. *J. exp. Med.* **138**, 1266–1269.

Discussion

D. A. J. Tyrrell, F.R.S. (*M.R.C. Common Cold Unit, Salisbury, U.K.*). I would suggest that we need to be careful as to how we define immunopathology. I have a strong clinical impression that patients undergoing severe immune responses, such as drug reactions, are particularly prone to reactivations of a cytomegalovirus infection, which may then contribute to the clinical picture. Presumably the virus replicates in immunologically activated cells, but is that immunopathology? Then in mycoplasma infection of the lung in mice and hamsters Dr Geraldine Taylor has shown that the characteristic cellular infiltration is essential for the removal of the organism, so that what the pathologist sees as a histological lesion is part of the recovery process, and if you immunosuppress the animal you see no pathological lesion but the organism is replicating more freely than before, and that is probably the real pathological situation!

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