Lymphocyte function and virus infections

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Lymphocytes in the blood and central lymphoid tissues participate in a variety of host defence mechanisms against virus infections. These include cell-mediated reactions against infected cells and particularly those involving cytotoxic T lymphocytes, co-operation in the induction of antibody responses, and the production of immune interferon. During the early stages of many virus infections the invading virus replicates in lymphoreticular cells, and this is of advantage to the host because of the increased efficiency with which the resulting immune responses are induced. Indeed, in many virus infections of man viral antigens can readily be detected in circulating blood lymphocytes. Nevertheless, this association with lymphocytes does not always benefit the host and may increase the virulence of the virus and enhance its persistence.

There are many examples of experimental virus infections in which this train of events has been observed. For example, in inbred mouse strains infected with lymphocytic choriomeningitis (LCM) virus, either by intracerebral injection at birth or congenital in-utero infection, virus can be detected in all the major subpopulations of mononuclear cells—namely, T lymphocytes, B lymphocytes, and cells of the monocyte-macrophage series (Doyle and Oldstone, 1978). This infection of mononuclear cells of the peripheral and central lymphoid system persists throughout the life of the animal. It has also been suggested that by infecting lymphocytes the virus may on occasion prevent the induction of an appropriate immune response to the infecting agent. This suppression may be more likely if the host is infected at a time of immunological immaturity determined by the age at which the animal is infected or by other factors that have a general immuno-suppressive effect. In other words, the virus may delete precisely that clone of reactive cells which is programmed to respond to the invading agent. Another undesirable consequence of lymphocyte infection is the dissemination of virus in association with cells. It has been proposed, for example, that canine distemper virus enters the central nervous system in this manner (Summers *et al.*, 1978). To demonstrate that similar considerations apply to

human infections by pathogenic viruses is obviously more difficult. However, the damage to the immune system that may accompany congenital rubella infection is a clear indication that the same principles apply. Moreover, transient immunosuppression accompanies many virus infections of man. There are now precise means of examining the interactions between different viruses and human lymphocytes, and the findings of such experiments are reviewed in this paper. The results are considered in two ways—firstly, the effects of virus infection on lymphocyte function and, secondly, the effects of residence in lymphocytes on the biological properties of viruses.

Effects of virus infection on lymphocyte function

The effects of virus infection on lymphocyte function are summarised in Fig. 1. In general terms different
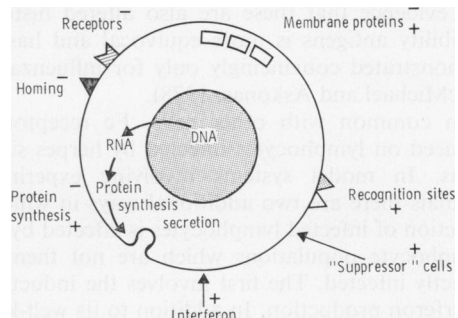

Fig. 1 *Effect of virus infection on lymphocyte function. Different viruses may suppress (−) or stimulate (+) the immunological and other functions of infected lymphocytes. Infection also stimulates uninfected cells in ways that may further suppress the immune responses of infected lymphocytes by generating cytotoxic T lymphocytes, 'suppressor' cells, and interferon production.*

viruses have varying effects. The infection may ablate various cellular functions and thereby induce immunosuppression. Conversely, some viruses stimulate various biosynthetic processes in the infected cells and indirectly in other lymphocytes that are not directly infected. Several functions of lymphocytes

are depressed as the result of infection with different viruses, and the most important of these are the synthesis of membrane protein, DNA and RNA synthesis, and protein synthesis. These effects have all been demonstrated with human lymphocytes. In the case of lymphocytes from experimental animals there is also good evidence that virus infection interferes with receptors for mitogens and specific antigens and that some viruses such as lactic dehydrogenase virus and myxoviruses also interfere with the normal circulation pattern and homing of blood lymphocytes. However, these effects have not been systematically analysed for human lymphocytes.

Some virus infections also stimulate protein synthesis in the infected cell, reflected in the increased synthesis of normal cytoplasmic or membrane components or in the appearance of 'luxury functions' that have no direct relevance to the normal function of lymphocytes. Lymphocytes infected by virus commonly display viral coded antigens on the cell surface which serve as recognition sites for the immune attack mediated by cytotoxic T lymphocyte or by antibody in combination with complement. The receptors for cytotoxic T lymphocytes in virus infections of experimental animals are found in close association with histocompatibility antigens (Doherty et al., 1976). While receptors for cytotoxic T lymphocytes have been clearly demonstrated on human lymphocytes infected by a variety of viruses, the evidence that these are also altered histocompatibility antigens is more equivocal and has been demonstrated convincingly only for influenza virus (McMichael and Askonas, 1978).

In common with other cells, Fc receptors are induced on lymphocytes infected by herpes simplex virus. In model systems involving experimental animals there are two additional ways in which the function of infected lymphocytes is affected by other lymphocyte populations which are not themselves directly infected. The first involves the induction of interferon production. In addition to its well-known effects on virus replication in the cells of infected hosts interferon also has an inhibitory effect on the immunological function of lymphocytes, including delayed hypersensitivity reactions and immunoglobulin synthesis. Human lymphocytes both produce interferon and induce its production by macrophages. But there is as yet little evidence that interferon has a similar regulatory role in the immune function of human lymphocytes measured either in experimental in-vitro systems or after natural in-vivo infections. Similarly some virus infections allegedly suppress immune responses under experimental conditions by inducing the proliferation of 'suppressor' cells. As yet, however, there is no evidence that immunosuppression accompanying virus infections in man is attributable to 'suppressor' cells (Lucas et al., 1978a).

Different virus infections in man produce these effects in variable degree. For example, whereas measles virus suppresses cell-mediated immune reactions Epstein-Barr virus induces the polyclonal proliferation of B lymphocytes. To some extent these differences are determined by the varying susceptibility of each lymphocyte subpopulation to infection by different viruses (Table 1). The susceptibility is determined partly by the availability of receptors on the cell surface and partly by the extent to which the virus can utilise the biosynthetic properties of different lymphocytes once these have been penetrated.

Most experiments designed to study these factors have involved stimulating lymphocytes in vitro with polyclonal mitogens such as phytohaemagglutinin or pokeweed mitogen. Such experiments are difficult to interpret because not only is lymphocyte activation more general than would be expected to occur in vivo but many such mitogens facilitate the direct spread of virus from the cells initially infected to other cells. Thus estimations of the nature and size of the population initially infected are often imprecise. Studies using more selective antigenic stimulation have often produced different results. Since DNA herpesviruses initiate life-long infections and one member of this group, EB virus, persists

Table 1   *Viral replication in blood mononuclear cells*

Virus	Population			Reference
	T lymphocytes	*B lymphocytes*	*Monocytes*	
Herpes simplex	+	+	−	Kirchner et al. (1977)
Cytomegalovirus	−	−	+	Rinaldo et al. (1978)
EB virus	−	+	−	Jondal and Klein (1973)
Measles	+	+	+	Lucas et al. (1978a, b)
Dengue	−	−	+	Theofilopoulos et al. (1976)
Influenza	±	±	±	Zisman and Denman (1973)

Note, + = growth; − = no growth; ± = incomplete replication.

exclusively in B lymphocytes, this group of viruses has received detailed attention. EB virus penetrates B lymphocytes because only these lymphocytes possess the necessary receptors. But even among B lymphocytes susceptibility is limited to a small proportion of these cells, not exceeding 0·05% even at the height of infectious mononucleosis (Rocchi *et al.*, 1977). While both specific and non-specific host immune factors limit the extent to which infected B lymphocytes proliferate *in vivo* and the subsequent fate of the infected populations they are probably unimportant in determining the size of the initial population which is infected.

Herpes simplex virus (HSV) has also attracted attention because, while it either produces no illness or at worst recurrent 'cold sores' in normal individuals, it has been implicated in neoplastic and demyelinating disorders. Several groups have examined the fate of HSV in different lymphocyte subpopulations. In the context of infection with HSV the difficulties in relating the results of *in-vitro* experimental systems to *in-vivo* reality are clearly illustrated. Using non-specific mitogens such as phytohaemagglutinin HSV appears to replicate primarily, and possibly exclusively, in T lymphocytes (Kirchner *et al.*, 1977). Indeed, most T lymphocytes in cultures stimulated by phytohaemagglutinin become infected (Westmoreland, 1978). HSV, however, grows to a limited extent only in lymphocytes stimulated by specific antigen (Pelton *et al.*, 1977). When human tonsil lymphocytes are stimulated with diphtheria toxoid this antigen induces a specific antibody response *in vitro* provided that the donors have been primed by diphtheria toxoid immunisation in childhood. The generation of a secondary antibody response *in vitro* is suppressed by HSV provided the responding cells are infected within 72 hours of antigen stimulation. Delayed infection has no effect on the antibody response. From this it can be deduced that helper T lymphocytes needed in the induction of the response were susceptible to HSV.

Initially only 0·1% of tonsil cells stimulated by diphtheria toxoid are infected by HSV. The eventual figure does not exceed 10% of the cultured cells, which are exclusively T lymphocytes. In contrast, the percentage of tonsil cells infected after stimulation by phytohaemagglutinin eventually exceeds 60%. This discrepancy is accounted for by the non-specific effects of PHA. Thus the suppressive effect of HSV on antibody synthesis *in vitro* is accounted for by the initial infection of a small minority of specialised T lymphocytes. Moreover, the same effect is achieved when tonsil cultures are infected with temperature-sensitive mutants of HSV (Pelton *et al.*, 1978). At the temperature of the cell cultures (37°C) these mutants undergo an abortive cycle of replication and infective particles are not released by the lymphocytes. Temperature-sensitive mutants of HSV produce this immunosuppression by their effects on the small population of lymphocytes initially infected provided that the selected mutants block protein synthesis in the infected lymphocytes.

Nevertheless, there are experimental conditions under which HSV can be induced to replicate in T lymphocytes. Thus HSV grew to the same titre in human peripheral blood B lymphocytes separated by virtue of their surface Ig receptors as it did in T lymphocytes from the same donors (Rinaldo *et al.*, 1978). Similarly HSV replicated in separated populations of B lymphocytes that had been stimulated by the appropriate strain of EB virus—namely, B95-8 (Kirchner and Schröder, 1979). These contrasting results emphasise that while HSV replicates preferentially in the T cells of unseparated lymphocyte suspensions experimental conditions can be devised under which the virus also replicates in B lymphocytes. Such observations raise the possibility that HSV may penetrate B cells *in vivo* under certain circumstances.

There is some controversy about the ability of cytomegalovirus to replicate in human lymphocyte populations. This ubiquitous agent has assumed increasing importance because of the high incidence of cytomegalovirus infection in immunosuppressed patients receiving corticosteroids and cytotoxic drugs after renal transplantation or in patients with disorders of immunity. Moreover, there have been reports that cytomegalovirus is latent in B lymphocytes of mice persistently infected with this virus and that the virus can be reactivated by appropriate manoeuvres such as mixed lymphocyte reactions. Similarly it has been claimed that cytomegalovirus establishes a persistent infection in human lymphocytes with a different growth curve from the acute pattern of infection usually observed in permissive cells such as fibroblasts (St. Jeor and Weiser, 1977). This persistence, however, might equally well be explained by the survival of the input virus as by the synthesis of new virus. Others have not detected CMV replication in unstimulated or mitogen-stimulated cultures of human lymphocytes obtained from adult donors or from neonatal cord blood (Rinaldo *et al.*, 1978). Since CMV grows at best in a very small minority of blood lymphocytes the discrepancy may be accounted for by the limited sensitivity of the assays that were employed. It is still possible that CMV can indeed remain latent in a susceptible subpopulation of circulating lymphocytes *in vivo* and thereby serve as a reservoir for further infection.

There has also been widespread interest in the effect of measles virus infection on immune function because of the long-recognised depression of cell-

mediated immune responses that accompanies infection by this virus. Moreover, measles virus has a paradoxical role in different human diseases since it produces remission in disorders such as the nephrotic syndrome and juvenile chronic arthritis but has been implicated in the pathogenesis of degenerative diseases of the central nervous system—more particularly in that of subacute sclerosing pan-encephalitis. Since measles virus antigens have been repeatedly detected in circulating blood lymphocytes by immunofluorescence and infectious virus has been recovered from lymphocytes stimulated by phyto-haemagglutinin in vitro, it has been inferred that measles affects immune responses by infecting certain lymphocyte subpopulations. Measles virus replicates equally well in all major human mononuclear cell subpopulations—namely, T lymphocytes, B lymphocytes, and monocytes (Joseph et al., 1975). While unstimulated cells support virus growth with reasonable efficiency much higher titres are attained in mitogen-stimulated cultures. Moreover, both T and B lymphoblastic cell lines release infectious virus over a period of several weeks in culture.

These observations show that measles virus interferes with immunological functions by infecting lymphocytes, but they do not explain the selective nature of the immunosuppression. However, the in-vitro analysis of immunosuppression by measles virus provides at least a partial explanation. Measles virus suppresses lymphocyte reactivity in vitro to stimulation by phytohaemagglutinin, pokeweed mitogen, tuberculin purified protein derivative (PPD), or allogeneic lymphocytes (Lucas et al., 1977). But this effect is obtained only if the cells are infected in the early stages of culture. It does not appear to be explained by any cytopathic effect of measles on the infected lymphocytes. Indeed, the immunosuppressive effects of measles virus on human lymphocytes do not reflect the cytopathic effect which may accompany viral replication but follow interference with protein synthesis at an early stage in the infection. The subsequent assembly and release of infectious particles is irrelevant to this immunosuppression (Lucas et al., 1977).

Measles virus in vivo also affects the immune properties of circulating T cells. Not only are the absolute numbers of these cells reduced but the surviving T cells appear to have a defect in antigen processing attributable to the direct effect of measles virus, although inhibitory serum factors are partly responsible (Whittle et al., 1978). These workers did not detect measles virus in association with circulating lymphocytes either by immunofluorescence or by direct culture unless the cells were first stimulated with phytohaemagglutinin. The demonstration that impairment of lymphocyte function in vivo results from non-cytopathic infection of a small minority of lymphocytes is supported by in-vivo observations that measles virus does not cause a generalised depletion of lymphoid cells even in patients succumbing to severe measles who show considerable impairment of delayed hypersensitivity reactions (White and Boyd, 1973).

Using suitably precise assays of human lymphocyte function it can be shown that measles virus affects the immune function of different subpopulations in a highly selective manner and that virus replicating in some subpopulations does not necessarily interfere with the function of that population. Moreover, the immunosuppressive effects of measles virus infection mediated through its effect on a critical subpopulation of lymphocytes is not reflected in any accompanying cytopathic changes in the cultured cells. Using specific antibody synthesis to diphtheria toxoid and the synthesis of Ig of different classes by human tonsil lymphocytes as measures of immune function it can be shown that measles virus suppresses antibody synthesis by more than 60% when added during the first 48 hours of culture. Immunosuppression of lesser extent is seen if infection is delayed for a further 24 hours (B. K. Pelton, unpublished). Moreover, infectious centre assays show that not more than 5% of the lymphocytes in the cultures are infected when immunosuppression is maximal. Antibody synthesis is not affected if infection is delayed for 72 hours or more after the cultures are established even though viral replication can easily be demonstrated in both T and B lymphocytes.

The effect on the synthesis of antibody by blood lymphocytes is similarly selective. In these experiments lymphocyte donors who have been immunised with diphtheria toxoid in childhood receive a booster injection of diphtheria toxoid three weeks before their blood lymphocytes are cultured and stimulated in vitro with this antigen. Measles virus suppresses antibody synthesis when added within 72 hours of antigen stimulation (Table 2) but not if infection is delayed. The results of such experiments show that measles virus, like herpes simplex virus, interferes with antibody synthesis by its selective effect on T helper lymphocytes during the early stages of the response. Thereafter the cultures resist viral immunosuppression even though the virus grows to equally high titres.

In keeping with this interpretation, measles virus has no effect on immunoglobulin synthesis by B lymphocytes which are already responding to antigenic stimuli. For example, B lymphocytes from the blood of patients with systemic lupus erythematosus continue to secret immunoglobulin spontaneously despite continuous infection with measles through-

Table 2 *Measles virus suppresses the induction of
antibody synthesis in cultures of human blood lymphocytes*

Antigen	Virus	Response		
		Antibody (antitoxin μ/ml)	IgM (μg/ml)	IgG (μg/ml)
−	−	0·44	< 0·1	0·45
+	−	1·51	6·0	0·50
+	+	0·6	< 0·1	< 0·1

Note. Lymphocytes from a normal donor receiving a booster injection of diphtheria toxoid three weeks beforehand were cultured *in vitro* (2·0 × 10⁶ cells/culture) and stimulated with diphtheria toxoid (modified from Pelton *et al.*, 1977). Virus-infected cultures received Edmonston strain virus at a multiplicity of infection (MOI) of 0·1 24 hours after antigen stimulation. The supernatants were assayed after seven days' culture.

Table 3 *Measles virus does not suppress Ig synthesis
by responding B lymphocytes*

Virus added	Response	
	IgM (μg/ml)	IgG (μg/ml)
−	3·11	40 0
+	2·02	40·0

Note. Lymphocytes from a patient with systemic lupus erythematosus and polyclonal hypergammaglobulinaemia (45 g/l) were cultured and infected under the conditions outlined in the footnote to Table 2 but without the addition of diphtheria toxoid.

out the period of culture (Table 3). The selective effects of measles infection of human lymphocyte subpopulations are summarised in Table 4.

The association of dengue virus infection with lymphocytes is of practical importance because of the possibility that these cells may be a site of viral persistence. It has been postulated that dengue virus enters many cells including blood leucocytes and replicates, and that viral antigens expressed on the cell surfaces thereby attract lysis by antibody in association with complement with resulting release of biologically active substances. Circulating lymphocytes displaying viral antigens are particularly likely to contribute to this release. Although dengue virus replicates more efficiently in blood macrophages than lymphocytes appropriately stimulated B lymphocytes also support its growth. In contrast, T lymphocytes have receptors for dengue virus but there is a block in viral replication at some unknown stage after absorption (Theofilopoulos *et al.*, 1976).

So far we have considered only viruses that go through a complete cycle of replication in lymphocyte subpopulations. Viruses which undergo an incomplete growth cycle may still affect the function of infected lymphocytes. Influenza virus is a good example. Influenza viruses of both A and B strains fail to produce infectious progeny that can be detected by even the most sensitive of plaque techniques. Influenza virus enters a small subpopulation of lymphocytes and for a time after infection can be detected by electron microscopy within cytoplasmic vacuoles (Hackemann *et al.*, 1974). Thereafter the virus is rapidly inactivated (Zisman and Denman, 1973). Nevertheless, some virus functions are expressed by the infected cells, including surface antigens which are recognised by cytotoxic T lymphocytes (McMichael and Askonas, 1978). Indeed, there is serological evidence that viral antigens are expressed *in vivo* on the lymphocytes of patients suffering from acute influenza virus infection (Wilson *et al.*, 1976).

Although only a small percentage of lymphocytes are non-productively infected, T and B lymphocytes appear equally susceptible (D. J. Appleford and S. Patterson, unpublished). It has long been recognised that *in-vivo* influenza infection transiently depresses the numbers of circulating T lymphocytes and also to some extent depresses the response of blood lymphocytes to non-specific mitogens. Therefore it might be predicted that influenza viruses would interfere with the 'helper' function of T lymphocytes in antibody synthesis in the same manner as herpes viruses and measles virus. In the event, influenza virus has a slight statistically insignificant effect on specific antibody synthesis by human tonsil lymphocytes *in vitro*, but reproducibly enhances IgG synthesis in the same cultures (Table 5).

There are two possible explanations for this enhancement. The first is that virus-infected cells act as an adjuvant for the increased production of antibody by cells which were already primed *in vivo*, and the second that influenza virus directly initiates the increased synthesis of immunoglobulin by the infected B lymphocytes. Such observations are of general interest because of the possibility that unexplained hypergammaglobulinaemia would be induced by similar mechanisms involving persistent non-productive infection of B lymphocytes. The

Table 4 *Human lymphocytes and measles infection—summary of interactions*

Population	Susceptibility	Survival	Function
T lymphocytes	Yes—mainly 'latent'	Decreased?	'Helper' function depressed
B lymphocytes	Yes	Normal	Not directly affected
Macrophages	Yes	Normal	Unaffected

Table 5   *Effect of influenza virus infection on antibody synthesis by human tonsil lymphocytes*

Antigen	Virus	Response		
		Antibody (antitoxin μ/ml)	IgM (μg/ml)	IgG (μg/ml)
−	−	0·45 (0·07)	54·0 (8·4)	12·5 (0·7)*
+	−	1·67 (0·03)	56·0 (5·6)	11·5 (4·8)
+	+	0·78 (0·17)	46·1 (4·1)	26·0 (2·8)*

*Significant difference.
Note. Tonsil cell cultures were stimulated with diphtheria toxoid (Pelton *et al.*, 1977), infected with influenza B virus (A/OKUDA strain) 24 hours later at a MOI of 0·1, and the supernatants were assayed after seven days' culture. Figures are mean (± SD) of triplicate cultures.

polyclonal stimulation of B lymphocytes to produce IgM *in vitro* has clearly been demonstrated with respect to EB virus infection (Slaughter *et al.*, 1978). The same authors have shown that peripheral blood lymphocytes from patients with rheumatoid arthritis already programmed to synthesise rheumatoid factor produce increased amounts of this autoantibody after *in-vitro* infection by this virus. EB virus also enables human lymphocytes to respond *in vitro* to primary antigenic stimulation (Steinitz *et al.*, 1977)—a response which is difficult to achieve in the absence of this virus.

Effect on viruses of residence in lymphocytes (Fig. 2)

In-vitro and *in-vivo* experiments have clearly established that the outcome of virus infection in different cell types and experimental conditions is variable. In general terms an infection may lead to the production of new infectious virus particles whose properties are identical with the input virus.
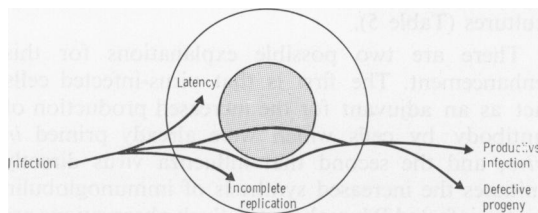

Fig. 2   *Effect of lymphocyte residence on viral function. Viral infection of lymphocytes may be non-productive resulting in latent infection or incomplete replication or production, in which event the progeny may have different physical or antigenic properties from those of the input virus.*

The newly synthesised virus, however, may have different properties, which may be detected by antigenic differences or by the production of temperature-sensitive mutants that will grow only at restricted temperatures. Virus growth may also be incomplete so that infectious particles are not produced and only certain viral functions are expressed. Incomplete growth is not invariably associated with the appearance of virus-coded antigens on the cell surface and the virus may remain latent in the infected cell and be demonstrable only by treating the cells with inductive agents or by 'rescuing' infectious virus by superinfecting the cells with a virus which complements the defective functions of the resident virus.

Persistent infection of lymphocytes by defective, non-productive virus strains may be of considerable importance in the pathogenesis of chronic disease. For example, if complete virions are not released from the infected cell and if these cells do not display antigens which can be recognised by the host the resulting immune response may be incomplete. The fate of measles virus in both freshly isolated lymphocytes and in lymphoblastoid cell lines has attracted particular interest in this context. Lymphocytes infected *in vitro* with measles virus in the absence of a lymphocyte-stimulating agent do not express surface antigens in any obvious manner, few of the cells are productively infected, and, indeed, virus particles are not detectable by electronmicroscopy. Nevertheless, these infected cells are subsequently unable to respond to phytohaemagglutinin, as judged by incorporation of tritiated thymidine, but measles virus is activated in the majority of cells (Lucas *et al.*, 1978b).

The interpretation of these findings is that measles virus establishes a latent infection in lymphocytes thereby depressing their function, but productive infection can subsequently be induced by exposing the cells to phytohaemagglutinin. These events are also reflected in natural measles infection. Although B lymphocyte function is severely depressed measles antigen can be detected in, or virus recovered from, the affected cell only after exposure to phytohaemagglutinin (Whittle *et al.*, 1978).

The fate of measles virus in lymphoblastoid cell lines has attracted considerable interest. Cell lines infected with measles virus produce a very heterogenous population of temperature-sensitive mutants

of the virus with differing physical and antigenic properties (Ju *et al.*, 1978). The implication of these observations is that in susceptible individuals measles infection may be followed by the persistent production and release of virus particles that have mutated from the original strain and against which the initial specific immune response would be ineffective. Non-specific host immunity may also be subverted since temperature-sensitive mutants of measles virus, for example, do not induce interferon production (McKimm and Rapp, 1977). The evasion of host defences by mutations of this nature is a well-recognised strategy for the survival of other human parasitic infections.

The factors that determine the expression of EB virus in infected lymphocytes may largely decide the outcome of the *in-vivo* infection. It has long been recognised that the vast majority of lymphoblastoid cell lines established from peripheral blood or other lymphoid tissues carry the EB virus. The virus is variably expressed in these cells in that some cell lines carry the EB viral genome integrated in the DNA but express no other virus functions, whereas other cell lines produce complete infectious EB virus virions. There is a widely differing pattern of expression of virus-coded proteins between these two extremes. Since EB virus infection in man may be clinically silent, may induce infectious mononucleosis, or may even be implicated in the pathogenesis of neoplasms such as Burkitt's lymphoma and nasopharyngeal carcinoma the factors which determine the consequences of infection by this virus have been intensively investigated.

While the factors that may affect the host response to the virus have received particular attention we now know that variations in the strain of infecting virus may account for some of the different disease patterns. Two strains of EB virus designated B95-8 and P3HR-1 have been isolated from different human lymphoblastoid cell lines (Steinitz *et al.*, 1978). These two strains have differing effects on normal human lymphocytes with respect to their ability to transform normal lymphocytes, induce nuclear or surface antigens, and block the response of B lymphocytes to mitogens. The P3HR-1 strain is unusual in that it induces the characteristic nuclear antigen (EBNA) in human cord blood lymphocytes but, unlike other strains, does not transform these cells (Yamamoto and Hinuma, 1978).

Furthermore, there is good evidence that different strains of EB virus complement each other so that defective viral genomes of one strain can become activated by superinfection with a second strain (Fresen *et al.*, 1978). The manipulations involving recombination of different EB virus strains within lymphoid cells have been performed exclusively *in vitro* using lymphoblastoid cell lines. Nevertheless, these results suggest not only that EB virus could become reactivated *in vivo* as the result of superinfection by a different EB virus strain or by a closely related agent but also that the behaviour of the infected cell would change radically as the result of such recombinations.

The realisation that defence against EB virus infections is mediated by T lymphocytes and perhaps by other host mechanisms has prompted considerable investigation of patients with unusually severe manifestations of infection by this virus. In some instances an atypical disease course can be attributed to a specific immune defect. A 5-year-old girl with a fatal disease characterised by polyclonal hypergammaglobulinaemia developed this disorder because of her inability to produce immune interferon in response to a primary EB virus infection (Virelizier *et al.*, 1978). Illustrating the consequences of a different defect in cell-mediated immunity, a patient with primary EB virus infection who developed a severe disease characterised by autoimmune haemolytic anaemia and prolonged fever was unable to mount a cytotoxic attack against EB virus-infected cells reflected morphologically in the almost complete absence of atypical mononuclear cells in her blood (Smith and Denman, 1978). Nevertheless, there are indications that familial sensitivity to EB virus infections leading to prolonged lymphoproliferative disorders and lymphomas may result from a more fundamental X-linked defect. This abnormality may involve the expression of the virus in the initially infected cells and not be dependent upon any recognisable defect in the immune response (Purtilo *et al.*, 1977).

Conclusions

Virus infections can alter the immune response in a variety of ways, some taking the form of depressed immune responses and others leading to increased immune responsiveness. So far the evidence indicates that these defects result from the direct effect of virus on lymphocyte function and, at least where human lymphoid cells are concerned, indirect factors such as 'suppressor cells' or infection of macrophages do not appear to be involved. The varying effects of virus infections or immune responses result from the extreme selectivity displayed by viruses not only for different lymphocyte subpopulations but also for a small number of lymphocytes within these populations. The resulting immunological defects are amplified by as yet undetermined mechanisms. Furthermore, although some viruses undergo a complete cycle of productive infection in lymphocytes incomplete replication with only partial

expression of virus functions may have pronounced effects on the function of the infected lymphocytes.

Lymphocytes carry latent virus infections for long periods and this has deleterious consequences on the host response by two mechanisms. Firstly, in defective virus infections the infected cells may not display the surface antigens needed to attract an effective immune response, and, secondly, the biological properties of the virus may change as a result of residence in lymphocyte populations. These mechanisms enable the agent to escape elimination by the host response in a manner analogous to that displayed by other parasitic infections.

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