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SPECIAL ARTICLE

The status of CMV as a human pathogen

Cytomegalovirus (CMV) is a common infectious agent which is well adapted to its host. Following primary infection, which is almost always asymptomatic in people with normal immunity, the virus establishes latency at sites which are unknown. The virus is probably maintained in this latent state by immune surveillance mechanisms since immunosuppression frequently leads to reactivation of virus.

Cytomegalovirus has been identified in most anatomical areas of the human body. The aim of this article is to define criteria for pathogenicity so that clinical and experimental data can be reviewed to determine if CMV is likely to cause disease at these various clinical sites. Thus, patients have been shown to die frequently *with* CMV but do they die *from* it?

POTENTIAL MECHANISMS OF PATHOGENICITY

There are several mechanisms whereby CMV could induce disease in its human host.

Direct viral lysis

Cytomegalovirus may cause tissue damage by infecting, replicating and ultimately lysing target cells. We believe that Class I HLA molecules represent the major cellular receptor for CMV (Grundy, Shanley & Griffiths, 1987) which exists in body fluids coated with the host protein β_2-microglobulin (McKeating, Griffiths & Grundy, 1987). Potentially, therefore, all nucleated cells within the body could be targets for CMV replication and lysis.

Immunopathology

Cytomegalovirus could initiate infection of target cells as above but without necessarily proceeding through a full replicative cycle. The expression of virus-specified immediate-early (IE) or early (E) antigens, either as whole proteins or peptide fragments on the cell surface, would be sufficient to make the cell vulnerable to attack by cytotoxic T-lymphocytes (Borysiewicz *et al.* 1983). In this case, the damage would be triggered by the virus but would be caused by the body's cell-mediated immune response. Cells supporting the full replicative cycle of CMV would also be targets for such responses since IE and E antigens appear in these cells prior to virus replication and since CMV structural proteins (or fragments thereof) could also be recognized by cytotoxic T-cells. Triggering of delayed-type hypersensitivity T cells could similarly lead to destructive inflammatory responses.

Triggering of 'autoimmunity'

By perturbing the cell membrane of a non-productively infected cell, CMV could induce cytotoxic T-lymphocyte responses against host antigens. Alternatively, CMV infection of or interaction with lymphocytes could induce a polyclonal activation of T or B cells, resulting in the expansion of clones with reactivity against self-antigens. Furthermore, interferon release, stimulated by CMV infection, would increase HLA display on uninfected cells leading to accentuation of graft rejection or graft versus host disease (GVHD).

Synergy

Synergism between CMV and another virus could induce disease not produced by either virus alone. For example, asymptomatic CMV infection of the brain could recruit to that organ macrophages bearing latent human immunodeficiency virus (HIV) which could then reactivate to cause encephalitis. Likewise, asymptomatic CMV or HIV infection of bystander lymphocytes or macrophages could induce release of lymphokines which could support the growth of neighbouring cells infected with the other virus. Alternatively, synergy between CMV and HIV could readily occur if one virus impaired the immune surveillance required for the suppression of replication of the other. Finally, expression of regulatory regions of the CMV genome (Stinski & Roehr, 1985) could lead to transactivation of latent HIV genomes resulting in viral lysis of the HIV infected cells.

Oncogenicity

Cytomegalovirus has a very large DNA genome with complex control mechanisms which lead to the ordered appearance of its specified proteins during replicative cycles (reviewed by Griffiths & Grundy, 1987). If integration of the CMV genome occurred into host DNA, these control sequences could influence expression of host oncogenes by the mechanisms of promoter insertion, enhancer insertion or genome translocation as has been described for other viruses (Weiss, 1985). Alternatively, partial expression of the CMV genome could lead to transactivation of host oncogenes. Two distinct subgenomic fragments have been reported to have transforming activity (Nelson *et al.* 1982; Clanton *et al.* 1983).

If CMV contains an oncogene homologue, as has been claimed (Spector & Vacquier, 1983), this potentially could directly induce altered growth characteristics in infected cells.

CRITERIA TO BE SATISFIED

In this section we define certain general criteria whose fulfilment for any given syndrome would support the concept that CMV is acting as a pathogen. Not all criteria would have to be met before pathogenicity was accepted but the strongest cases would be expected to meet most.

Table 1. *Association between CMV infection at particular anatomical sites and dysfunction of those organs*

Site of infection	Organ dysfunction?	Patient group*				
		Renal transplant	Marrow transplant	AIDS	Congenital infection	Infant infection
Salivary gland	No	+	+	+	+	+
Kidney	No	+	+	+	+	+
Retina	Yes	+	+	+	+	·
Liver	Yes	+	+	+	+	·
Lung	Yes	+	+	+	+	+
Brain	Yes	·	·	+	+	·
Colon	Yes	+	+	+	·	·

* + indicates infection at these sites.

1. *CMV should be found at the clinically involved site in the absence of other pathogens*

Table 1 shows the sites of the body from which CMV has been isolated regularly. The data, as presented, suggest that CMV infection of the salivary gland and kidney does not produce disease but that this virus is pathogenic at all other sites. However, a selection bias may be present. Since only diseased organs are biopsied, any agent, such as CMV, which is found in most organs will be associated with that disease but may not be the aetiological agent.

2. *Disease should occur in those with high CMV titres*

If CMV is damaging by way of lytic infection then disease should be directly correlated with high CMV titres. There are problems of course in attempting to measure virus titres in biopsies from affected organs such as inner ear or brain. We have therefore accepted data on virus titres in urine as fulfilling this criterion.

3. *Effective antiviral chemotherapy should suppress disease*

Therapy with ganciclovir is fairly effective at reducing the titre of CMV in humans (Collaborative Study, 1986). If disease was caused by lytic infection, then one would expect therapy to hasten resolution of disease.

Notice that failure to satisfy this criterion does not indicate that CMV is not pathogenic. As discussed earlier, CMV may be causing disease by expression of only IE or E antigens on infected cells which can then act as targets for immunopathological processes. Since drugs like ganciclovir operate only at the DNA replication stage (Tocci *et al.* 1984), which occurs after IE and E gene expression, these drugs would not be expected to inhibit immunopathological conditions.

4. *Animal models should reproduce the CMV syndromes*

This criterion is difficult to satisfy for human CMV since the virus is highly species-specific and so animal experiments with the human virus cannot be performed. However, all species so far tested have their own species-specific cytomegaloviruses and murine CMV infection of mice, rat CMV infection of rats

Table 2. *Induction by murine CMV of organ dysfunction in various groups of mice*

Syndrome	Effect of MCMV seen in: Normal mice	Newborn mice only	Immunocompromized mice only	Effect of immunity
Hepatitis	+	·	·	Protective
Eye infection	+	·	·	Protective
Microcephaly	·	·	·	·
Ear infection	·	+	·	Protective
Mononucleosis	+	·	·	·
Immunosuppression	+	·	·	·
Pneumonitis	·	·	+	Damaging
Gastrointestinal infection	+	·	·	·
Allograft effects	+	·	·	Damaging
Encephalitis	·	+	+	Protective

and guinea-pig CMV infection of guinea-pigs have all been used as animal models of the human infection. The mouse model has been studied intensively (reviewed by Osborn, 1982; Hamilton, 1982) and murine CMV (MCMV) has been shown to infect all of the organs associated with the human disease (see Table 2). However, since murine CMV does not cross the placenta in mice (Johnson, 1964), congenital infection cannot be studied in this model (this is thought to be due to differences in the structure of the placenta in the mouse and man rather than differences between the two viruses).

Note that not all of the mouse models mirror the human conditions exactly. For example, MCMV causes labyrinthitis in the mouse which is different histologically from the endolymphatic labyrinthitis seen in humans (Davis & Strauss, 1973) and also infects the vascular tissues of the eye rather than the retina and choroid as seen in humans (Hudson, 1979). These discrepancies may be due to differences in the route of infection in the experimental and natural situations and so we have accepted virus infection of the same organ as fulfilment of this criterion.

5. *Immunity against the virus should prevent disease*

If the virus infection is the cause of the syndrome then prevention of infection should be associated with control of disease Unfortunately, however, the live passaged vaccine strains used to date have not provided convincing evidence of protection against CMV infection (Plotkin *et al.* 1984). We have therefore evaluated this criterion by reference to the ability of naturally induced immunity to moderate the pathology found in each syndrome.

SYNDROMES REPORTED TO BE ASSOCIATED WITH CMV

CMV mononucleosis

Although most cases of primary CMV infection in apparently healthy individuals remain asymptomatic, occasional cases of a mononucleosis-like illness are seen. CMV mononucleosis is a febrile illness accompanied by a lymphocytosis and atypical lymphocytes are found in the peripheral blood (Klemola &

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Kääriäinen, 1965; Kantor *et al.* 1970; Jordan *et al.* 1973). However, when compared to infectious mononucleosis caused by Epstein-Barr virus, exudative pharyngitis is not a feature of CMV mononucleosis, the Paul Bunnell test is negative and lymphadenopathy is less commonly seen (Klemola & Kääriäinen, 1965; Kantor *et al.* 1970; Jordan *et al.* 1973). Hepatomegaly and splenomegaly are often seen in patients with CMV mononucleosis (Kantor *et al.* 1970; Jordan *et al.* 1973) and hepatitis can be a presenting symptom (see below). Haemolytic anaemia, thrombocytopenia and myocarditis can also be features of CMV mononucleosis (discussed below). In addition, various immunologic abnormalities have been observed which disappeared when the mononucleosis-like syndrome resolved; these include the presence of autoantibodies, cold agglutinins, rheumatoid factors and cryoglobulins (Kantor *et al.* 1970). It is estimated that 10–14% of cases of mononucleosis are due to CMV (Hamilton, 1982). When infectious mononucleosis is transmitted by blood transfusion following open-heart surgery it is termed the 'post-perfusion syndrome'.

Mononucleosis can be reproduced in the mouse model (Grundy, 1979), as can the production of autoantibodies (Bartholomaeus *et al.* 1983) and, being a manifestation of primary CMV infection, can be moderated by immunity. Criteria 4 and 5 are therefore satisfied (see Table 3).

Hepatitis

Patients with CMV mononucleosis often have some degree of hepatitis, as indicated by raised serum levels of liver enzymes. In particular, transaminases are elevated with variable changes in alkaline phosphatase (Klemola & Kääriäinen, 1965; Hanshaw *et al.* 1965; Jordan *et al.* 1973). In addition, hepatitis can be the major presenting symptom of CMV infection in previously healthy adults (Lamb & Stern, 1966; Carter, 1968; Shusterman, Frauenhoffer & Kinsey, 1978) and this may be accompanied by jaundice (Lamb & Stern, 1966; Shusterman, Frauenhoffer & Kinsey, 1978). Cytomegalovirus hepatitis has also been described following blood transfusion (Toghill *et al.* 1967; Fiala *et al.* 1974). Cytomegalovirus has not been found to be associated with chronic liver disease (Toghill, Williams & Stern, 1969).

Immunosuppressed adults (reviewed by Glenn, 1981; Meyers, Flournoy & Thomas, 1986) may develop hepatitis alone. More frequently, hepatitis is part of disseminated infection with viraemic spread to multiple organs. Thus, although the hepatitis itself is not life-threatening, it represents a poor prognostic sign for the patient.

Hepatitis is frequently found in cases of congenital CMV infection. The hyperbilirubinaemia is in both the direct and indirect fractions and is rarely sufficient to cause kernicterus (Hanshaw, Dudgeon & Marshall, 1985). The condition usually resolves during the first year of life.

Cytomegalovirus has been cultured from liver biopsies and the hepatitis appears to respond to ganciclovir (Collaborative Study, 1986). The syndrome can be reproduced in the mouse model (Mohamed, 1974; Grundy, 1979; Papadimitriou, Shellam & Allan, 1982) and pre-existing immunity against CMV protects against hepatitis. Criteria 1, 3, 4 and 5 are therefore considered proven.

Table 3. *Criteria for pathogenicity which have been satisfied in specified clinical syndromes*

Syndrome	Criteria + 1	2	3	4	5	Is CMV pathogenic?	Mechanism of pathogenicity
Mononucleosis	·	·	·	+	+	Yes	·
Hepatitis	+	·	+	+	+	Yes	Lytic
Haemolytic anaemia	·	·	·	+	+	Yes	·
Thrombocytopenia	·	·	·	+	+	Yes	·
Retinitis	+	·	+	+	·	Yes	Lytic
Gastrointestinal infection	+	·	+	+	·	Yes	Lytic?
Microcephaly	+	+	·	·	+*	Yes	·
Hearing loss	+	+	·	·	+*	Yes	·
Immunosuppression	·	·	·	+	+	Yes	·
Pneumonitis-allografts	+	·	·	+	·	Yes	Immunopathology?
Pneumonitis-AIDS	·	·	·	+	·	Possibly	Lytic?
Allograft effects	·	·	·	+	·	Possibly	·
Encephalitis	·	·	·	+	·	Possibly	Viral synergy?
Kaposi's sarcoma	·	·	·	·	·	Unlikely	·
Prostatic carcinoma	·	·	·	·	·	No	·
Colonic carcinoma	·	·	·	·	·	No	·

+ See text for details. * Maternal immunity.

Haemolytic anaemia

Haemolytic anaemia is occasionally seen in infants with congenital CMV infection (Hanshaw, Dudgeon & Marshall, 1985) but has also been reported during CMV infection in previously healthy individuals (Harris, Meyer & Brody, 1975; Coombs, 1968) and more frequently in adults who had received blood transfusions (Kantor *et al.* 1970; Kantor & Goldberg, 1971; Holt & Kirkham, 1976). Both Coombs'-positive and Coombs'-negative anaemias have been reported (Zuelzer *et al.* 1970).

Thrombocytopenia

Thrombocytopenia is a common feature of congenital CMV infection (Hanshaw, Dudgeon & Marshall, 1985). In CMV infection of adults, thrombocytopenia has been described either accompanying (Harris, Meyer & Brody, 1975) or in the absence (Chanarin & Walford, 1973; Fiala, Kattlove & Lemkin, 1973) of haemolysis.

Haemolytic anaemia (Grundy, 1979) and thrombocytopenia (Osborn & Shahidi, 1973) can be reproduced in animal models and are often manifestations of primary infections; criteria 4 and 5 are therefore satisfied for both.

Retinitis

Cytomegalovirus retinitis is seen in cases of congenital CMV who are born with symptoms but not in those who are asymptomatic at birth (Pass *et al.* 1980). Retinitis is found frequently in AIDS patients (Egbert *et al.* 1980) and is occasionally seen in other immunosuppressed individuals. The lesions are frequently sight-threatening.

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Cytomegalovirus DNA has been detected in the retina (Kennedy *et al.* 1986), ganciclovir can effectively suppress the disease process (Collaborative Study, 1986) and animal models are available (Hudson, 1979). Criteria 1, 3 and 4 are therefore satisfied.

Gastrointestinal infection

Cytomegalovirus has been detected in most parts of the gastrointestinal tract from the oesophagus to the anus (Wong & Warner, 1962; McDonald *et al.* 1985). It is frequently found in the base of ulcers and may be associated with severe haemorrhage. Such ulcers have been described in patients with normal immunity, immunosuppressed patients and those with ulcerative colitis.

The clinical response to ganciclovir therapy and the absence of other recognized pathogens (criteria 3 and 1) indicate that CMV is probably acting as a pathogen in the gastrointestinal tract.

Microcephaly

Cases of cytomegalic inclusion disease may have microcephaly at birth (Pass *et al.* 1980). Others may develop microcephaly during infancy but may also have impaired intellectual development in the absence of formal microcephaly.

Disease correlates with high viral titres (Stagno *et al.* 1975). No clear dissociation has been shown between damage to the ear or brain and it must remain likely that both organs can be affected by virus lysis although immunopathological processes can also be implicated (Griffiths *et al.* 1982). Maternal immunity is partially protective (Stagno *et al.* 1982) so we consider criterion 5 to be satisfied (see Table 3).

Hearing loss

Sensorineural hearing loss can occur in congenitally infected babies who are born with or without symptoms. It may be unilateral or bilateral and may be profound (Hanshaw, Dudgeon & Marshall, 1985; Pass *et al.* 1980). Children with high CMV titres in the urine are at increased risk of hearing loss (Stagno *et al.* 1975) but immunopathological processes may also be involved (Griffiths *et al.* 1982).

Cytomegalovirus has been isolated from the inner ear of a fatal case of congenital infection (Davis *et al.* 1979) and from the middle-ear effusion of a 12-month-old child with conductive hearing loss (Embil, Goldbloom & McFarlane, 1985). Since MCMV can infect the ear (Davis & Strauss, 1973), CMV can be found at the affected site and maternal immunity is protective (Stagno *et al.* 1982), criteria 1, 2 and 5 are considered to be satisfied.

Immunosuppression

Immunosuppression has been described in patients with CMV mononucleosis as evidenced by decreased responses of peripheral blood lymphocytes to mitogenic stimulation (Rinaldo *et al.* 1980). Accessory macrophages were reported to be responsible for this defect (Carney & Hirsch, 1981) and recently Rodgers *et al.* (1985) described an inhibitor of interleukin 1 released by monocytes after exposure to CMV. However, the latter effect could not be reproduced using stocks of CMV free from contamination with mycoplasma (Scott & Sissons, 1987) and so it must

be concluded that the inhibitory action on interleukin 1 was caused by mycoplasma.

An immunosuppressive syndrome associated with CMV infection has been seen in renal transplant patients. It follows an AIDS-like course with opportunistic superinfections but often resolves spontaneously in those individuals who survive the acute episode. It is possible that a similar effect may occur with CMV infection of bone marrow transplant or AIDS patients but the underlying severe immunosuppression makes this difficult to identify with certainty.

Since this syndrome can be reproduced in mice (reviewed in Griffiths & Grundy, 1987) and is a manifestation of primary infection, criteria 4 and 5 are considered to be satisfied.

Pneumonitis

Interstitial pneumonitis is a frequent complication of CMV infection in renal and bone-marrow transplant recipients (Rubin *et al.* 1981; Meyers, Flournoy & Thomas, 1986). Histologically, it resembles interstitial pneumonitis seen in patients with collagen vascular disease (Hammer *et al.* 1983) and is characterized by a mononuclear cell infiltrate in the lung septae with perivascular cuffing and endothelial cell swelling (Beschorner *et al.* 1980; Hammer *et al.* 1983). Radiologic changes may or may not be present (Milburn, Prentice & du Bois, 1987). Cytomegalovirus pneumonitis in transplant recipients has a case-fatality rate of approximately 85% and has been reported to be the single most common cause of death in bone marrow transplant patients (Watson, 1983; Meyers, Flournoy & Thomas, 1986).

Most cases of perinatal CMV infection are asymptomatic but occasionally infant pneumonitis may occur (Stagno *et al.* 1981). This resembles pneumonitis caused by *Pneumocystis carinii* and the patient may require ventilatory support.

AIDS patients frequently have CMV detected in the lung by culture of BAL fluid but *P. carinii* is often found in the same specimen (Murray *et al.* 1984; Stover *et al.* 1985). Such patients frequently respond promptly to treatment with co-trimoxazole irrespective of whether or not CMV was co-infecting the lung.

The mouse model shows that a host immune response is required for CMV-induced pneumonitis (Shanley, Pesante & Nugent, 1982; Grundy, Shanley & Shearer, 1985) and that the syndrome can be prevented by continued immunosuppression. All of the clinical findings in human allograft patients are consistent with these data so we have hypothesized elsewhere that CMV pneumonitis in allograft patients is an immunopathological condition while in AIDS patients lung infection may be asymptomatic or may cause disease through extensive cell lysis (Grundy, Shanley & Griffiths, 1987). Thus, CMV pneumonitis in allograft patients fulfils criteria 1 and 4 while the same syndrome in AIDS patients fulfils only criterion 4 because such patients also have *P. carinii* in their lungs.

Allograft effects

Cytomegalovirus infection is often closely associated with rejection episodes in renal transplant patients (Lopez *et al.* 1974; May *et al.* 1978; Pass *et al.* 1979). It is a moot point whether the virus triggers the adverse response or whether the

immunosuppressive effect of the treatment required for the suppression of renal rejection episodes induces reactivation of CMV. However, in the mouse model MCMV infection has been shown to enhance the cytotoxic T-cell response to alloantigens (Grundy & Shearer, 1984; Grundy & Reid, 1985).

Likewise, patients with GVHD following bone-marrow transplantation have more severe CMV infection, especially pneumonitis (Appelbaum *et al.* 1982; Meyers, Flournoy & Thomas, 1986; Miller *et al.* 1986). However, it is not clear whether CMV triggers GVHD or whether the profoundly immunosuppressive effect of GVHD (and that of its treatment) are responsible for CMV reactivation. In the mouse model, CMV has been shown to accentuate the GVH reaction (Grundy, Shanley & Shearer, 1985).

Since only the mouse data provide evidence of CMV actually causing these allograft effects, we cannot conclude that CMV is pathogenic in humans, although this remains a strong possibility (see Table 3).

Encephalitis

Encephalitis due to CMV has been described in AIDS patients but not in other immunosuppressed individuals. The patients present with memory loss and impaired intellectual function. Human immunodeficiency virus is frequently also found in brain macrophages from AIDS patients with encephalitis (reviewed by Carne, 1987). Cytomegalovirus may be pathogenic in this setting but we consider it to be unproven at this time, with support only for criterion 4 following intracerebral inoculation of MCMV (Lussier, 1973, 1975; Hudson, 1979).

Kaposi's sarcoma

Fifteen years ago, cultures of cells derived from Kaposi's sarcoma (KS) tissue were found to contain a herpesvirus which resembled CMV (Giraldo, Beth & Haguenau, 1972; Giraldo *et al.* 1972). Serological studies later revealed that 100% of patients with KS have IgG antibodies against CMV. The geometric mean titre of these antibodies was significantly raised above that of controls in European cases of KS but not in African cases of KS (Giraldo *et al.* 1975). Subsequent publications reported that CMV could not be cultured from KS tissue but that virus DNA, RNA or proteins could be detected (Giraldo, Beth & Huang, 1980; Boldogh *et al.* 1981; Drew & Mintz, 1984).

Unfortunately, the studies reported to date have all used nucleic acid probes prepared from whole virion DNA. Since regions of CMV DNA are now known to bind avidly to human DNA (Peden, Mounts & Hayward, 1982; Ruger, Bornkamm & Fleckenstein, 1984), the results claiming to detect CMV DNA or RNA must be assumed to be unreliable until the experiments have been repeated using cloned sequences of the virus genome which lack cross-reactivity with host DNA. Likewise, the studies of virus-specified proteins within KS tissue must be repeated using monoclonal antibodies of defined specificity before the results can be accepted. Thus, at the time of writing, the CMV/KS association is based upon some early seroepidemiology together with the coincidence of KS developing in AIDS patients who also have CMV infection (Marmor *et al.* 1984). Clearly, those who believe that KS may be caused by CMV (Giraldo & Beth, 1986) require more convincing evidence.

Prostatic carcinoma

Albrecht & Rapp (1973) showed that CMV irradiated with ultraviolet light could transform hamster fibroblasts and that these cells could produce tumours in mice. Rapp *et al.* (1975) reported that cell cultures derived from normal prostate developed cytopathic changes and that CMV antigens and DNA were detectable in these cells. Similarly, Geder *et al.* (1976) showed that unirradiated CMV prepared from the prostatic tissue described above could transform human embryo lung fibroblasts and that these could also produce tumours in nude mice (Geder, Kreider & Rapp, 1977). Passage of the tumour cells *in vitro* led to identification of a herpesvirus which was rather confusingly given the initials HMCV (Hershey Medical Center Virus); this virus has been identified as infectious bovine rhinotracheitis virus (Geder *et al.* 1978).

It seems safest to assume that the whole CMV/prostatic carcinoma story is an unfortunate example of an adventitious virus presumably acquired from fetal calf serum despite strenuous attempts (Geder *et al.* 1978) to maintain sterile conditions. Curiously, however, this interpretation is not discussed in a recent review (Rapp & Robbins, 1984) where the reference identifying HMCV as infectious bovine rhinotracheitis is not quoted.

Colonic carcinoma

Cytomegalovirus has been isolated from surgical specimens of colonic adenocarcinomas (Hashiro, Horikami & Loh, 1979) and CMV DNA has been reported to be detectable using whole virus genomic material (Huang & Roche, 1978). In contrast, Hart, Neill & Norval (1982) could find no association between CMV and carcinoma of the colon using *in situ* hybridization and explant techniques.

CONCLUSIONS

It will be seen from Table 3 that some CMV syndromes satisfy several of the proposed criteria and so we suggest that CMV is causally associated with these conditions.

Others meet none or only one criterion and so we are reluctant to conclude at this point that CMV is pathogenic in these settings. In particular, the suggestion that CMV may be naturally oncogenic is far from proven. The association between CMV and KS certainly falls far short of that between Epstein–Barr virus and Burkitt's lymphoma or nasopharyngeal carcinoma. The best that can be said about the data suggesting that CMV DNA can transform cells or may contain an oncogene homologue is that it argues against immunization with CMV vaccines which contain DNA.

Despite the difficulties of working with different viruses, the animal models have provided good evidence to support the many pathogenic roles of CMV and perhaps deserve to be read more widely by human virologists. Indeed, the murine models may give examples of organ-specific damage which have not yet been recognized in man. For example, Shanley (1987) has shown that athymic nude mice can develop necrotizing adrenalitis. The possibility that human AIDS patients may have a similar disease inducing Addisonian crises is an intriguing one which deserves further study.

In preparing this review it is clear to us that some of the conclusions in Table 3, although probably supported by most virologists, are still somewhat subjective and need to be placed upon firmer scientific ground. Perhaps this will only happen when controlled trials of subunit CMV vaccines show which 'CMV syndromes' can be prevented.

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