

# VIRUS INFECTIONS IN RENAL TRANSPLANT RECIPIENTS

by

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**VIRUSES** are obligate intracellular parasites which do not normally remain infective for long periods outside a living host cell. The associations between viruses and their hosts may take several forms (Fig. 1). Active replication of virus is followed by lysis of the infected cells and the duration of the illness is usually short. However, in some cases persistent production of virus may be observed over many months or years. Virus may also become latent in the host tissues and during this time there is no evidence of viral replication. However under favourable circumstances viral replication recommences and such 'reactivated' infection may become clinically apparent. The mechanisms of viral latency are not understood but it is possible that, as with some oncogenic animal viruses, the viral genome may become incorporated into the genetic material of the host cell.

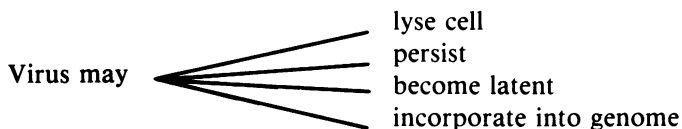


Figure 1. *Different ways in which viruses may behave. Note that it is possible that "latent" viruses may become incorporated into the genome.*

During the course of a viral illness specific antibody may limit the spread of the infection by neutralising extracellular virus whilst thymus derived lymphocytes (T lymphocytes) destroy virus infected cells. If the cell mediated immune response is selectively suppressed but humoral antibody responses remain unaffected then viruses whose mode of spread is to pass between cells in close contact, rather than via an extracellular route exposed to neutralising antibody, may be expected to flourish.

## THE VULNERABLE HOST

Clinical observation illustrates the practical importance of the different ways in which viruses are controlled in the normal host. Impaired T-cell function occurs in a number of congenital thymic dyscrasias, in Hodgkin's Disease and during immunosuppressive therapy—for example with azathioprine, anti-lymphocyte globulin and perhaps with corticosteroids.

In all these instances there are serious primary and frequent reactivation infections primarily with herpes group viruses.

Malnutrition and the metabolic changes of severe uraemia impair T-cell function, so a patient in renal failure is also vulnerable to viral infections before transplantation. The indefinite persistence of hepatitis B infection in patients on regular dialysis exemplifies the impaired immunity of the uraemic host. After transplantation good renal function may be restored, but immunosuppressive therapy maintains the hosts vulnerability to virus replication. In some instances the longterm requirement for immunosuppression provides conditions in which a latent virus such as Epstein Barr virus (EBV) may induce neoplastic transformation.

It is notable that humoral immune responses are much less severely impaired than cellular ones by azathioprine or anti-lymphocyte globulin, and so it might be predicted that infection with viruses readily controlled by circulating antibody would be less of a problem following renal grafting. This proves to be the case (Table 1).

TABLE 1  
*Viruses and Renal Transplantation*

<i>Infection</i>	<i>Days post-transplant</i>
CMV—primary	21— 90
—reactivation	30—500
HSV —reactivation	10— 90
HVZ primary	10—500
reactivation	50—365
papovavirus reactivation	30—500

*The viruses commonly detected following renal transplantation. It is those viruses which have the potential to be latent, or which may be persistent in the graft itself, which cause most infections.*

#### VECTORS FOR VIRUS INFECTION

There is little evidence that viral cross-infection is a significant problem in renal transplant units. This may in part be attributable to awareness by the renal staff of the hazards of immunosuppressive therapy. It is recognised that close physical contact is required for the spread of many virus diseases and patients with known infections are usually isolated and infected staff or visitors excluded from the unit. Indeed “common” virus infections such as those induced by respiratory or enteroviruses do not appear to be more common in renal transplant recipients than in the population as a whole.

It is now clear that the graft itself is an important vector of virus infection. Cytomegalovirus and papovavirus may be latent in donor renal tissue, probably in the urothelium while active infection in the donor with hepatitis B virus may be passively transferred with the graft. There is convincing evidence that renal donors without clinically apparent CMV infection, but who are seropositive for CMV in the complement fixation test, carry latent virus and that seronegative recipients become infected following renal grafting.

An important question is whether transfusion of stored blood transmits cytomegalovirus or EB virus. There is convincing evidence that cytomegalovirus is transferred in *fresh* blood; babies given exchange transfusion or patients subjected to open heart surgery may become infected as evidenced by seroconversion and isolation of virus. It is not yet clear if the transfusion of stored blood is a significant source of virus infection.

## SPECIFIC VIRUS INFECTIONS

### *Cytomegalovirus (CMV)*

Evidence of the replication of CMV, as measured by fourfold rise in specific complement fixation (CF) antibody and/or isolation of the virus, has been found in up to 95% of renal transplant recipients.<sup>1</sup> The results of CMV replication may vary from the asymptomatic infection to fatal disease.<sup>2</sup> It is widely accepted that renal transplant recipients who reactivate their endogenous CMV are usually asymptomatic whereas patients having a primary infection with this virus following transplantation have clinically apparent disease (Table 2).

TABLE 2

### *Cytomegalovirus Induced Illness*

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<i>Primary infection</i>	
(rarely if ever symptomless)	
fever	
leucopenia	
'glandular fever' (Paul-Bunnell negative)	
liver cell damage	
pneumonia	
myocarditis	
chorioretinitis	
<i>Reactivation</i>	%
symptomless seroconversion or virus excretion or	
leucopenia and/or fever	90—95
any 'primary' manifestation	5—10

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Attempts are being made to protect the seronegative recipient by vaccination with live attenuated CMV.<sup>3</sup> A potential drawback is that the vaccinated subject (when immunosuppressed) may reactivate the vaccine virus and there is also the theoretical risk that CMV may be oncogenic. A simple and effective course of action would be to avoid transplanting kidneys from CMV seropositive donors into seronegative patients. All transfused blood might also be checked for evidence of previous CMV infection, indicated by the presence of specific antibody, and only seronegative blood given to seronegative recipients.

There is no convincing evidence that CMV infection makes graft rejection more likely or affects the long term survival of the graft. However, it has been suggested<sup>4</sup> that a recipient who already carries CMV may transfer it to a grafted kidney derived from a previously uninfected donor and that impaired renal function may result. The authors have seen a case in which a graft removed for primary poor function was heavily infected with CMV although there was no evidence of irreversible rejection.

### *Herpes Simplex Virus (HSV)*

The emergence of HSV infection following renal transplantation is usually the result of reactivation of latent virus, often within 30 days of transplant. Sixty to 70% of renal graft recipients may excrete HSV within the first three months. For example, Korsager et al,<sup>5</sup> in a prospective study, found that 20 of 30 patients reactivated their latent HSV infections between 23 and 71 days after transplantation.

HSV disease following renal graft is usually confined to the oral or genital regions (Table 3); rarely disseminated, often fatal, infections are observed. Anuras and Summers<sup>6</sup> describe such a case, with severe hepatitis developing in a 37 year old male, 3 months after a live donor renal transplant. Recently we have observed disseminated HSV infection in a 37 year old female renal graft recipient who excreted HSV in her urine 10 days after transplantation and then followed a rapidly deteriorating course, with fever, florid stomatitis, vaginal ulceration, herpetic vesicles on the hands, arms and trunk and evidence of hepatitis. She eventually succumbed to heart failure caused by ischaemic heart disease 23 days after transplantation.

TABLE 3

### *Herpes Simplex Virus (HSV)*

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*HSV—1*

84% positive by 40 years.

Lifelong inhabitant.

Latent in cranial ganglia.

Infection:-

Asymptomatic

Mouth

Eye

Finger

Generalised—especially liver

*HSV—2*

Genital infection.

Latent in sacral ganglia.

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### *Varicella-zoster virus (Herpesvirus varicella HVZ)*

Reactivation of latent HVZ expressing itself as herpes zoster, is common after renal transplantation, although the time of appearance of the lesions may vary greatly. For example, Rifkind<sup>7</sup> noted that 6 of 73 (8.2%) renal graft recipients

developed herpes zoster lesions from 12 to 511 days after transplantation. These infections usually clear spontaneously.

### *Epstein Barr virus (EBV)*

Excretion of EBV, usually as a result of reactivated infection occurs 3 to 12 months after transplantation.<sup>8</sup> The excretion of virus is mainly asymptomatic but primary infection can be associated with fever and pneumonitis.<sup>9</sup> Evidence of EBV replication has been found in up to 74 per cent of renal transplant recipients.<sup>10</sup>

### *Papovaviruses*

Papovavirus infections following renal transplant are usually regarded as asymptomatic, although Hogan et al<sup>11</sup> have suggested that the excretion of papovavirus in urine may be associated with urothelial swelling and obstruction of the transplanted ureter. Two papovaviruses, designated BK and JC viruses have been isolated or seen by electron microscopy in the urine of renal transplant recipients.<sup>11, 12</sup> These viruses may be reactivated after transplantation as a result of immunosuppression, as papovaviruses have also been found in patients undergoing chemotherapy for malignancies.<sup>13</sup>

### *Hepatitis B*

Since, in Britain at least, all renal graft recipients, all blood donors and all potential organ donors are screened for hepatitis B, the risk of its being transmitted by tissue transfer is very small. There is the interesting possibility that hepatitis B may, rarely, become latent and develop as a reactivated infection after grafting and immunosuppression.<sup>14</sup> Analysis of the evidence for this illustrates the difficulty in differentiating 'latency' from 'persistence'; the latter requires evidence of active viral replication which may be difficult to obtain with very low grade infections.

### *Virus infections and oncogenic disease in renal graft recipients*

There are strong associations between some oncogenic conditions and virus infections particularly in animals. In man the best documented are the associations between Burkitt's lymphoma, nasopharyngeal carcinoma and Epstein Barr virus (EBV).<sup>15</sup> Less well documented are the relationships between primary liver cell carcinoma and hepatitis B virus and between CMV and adenocarcinoma of the colon.<sup>16, 17</sup>

Crawford et al<sup>18</sup> and Nagington and Gray<sup>19</sup> have recently drawn attention to a possible association between EBV and lymphoma, following renal transplantation. The incidence of lymphoma in renal graft recipients may be higher in patients immunosuppressed with cyclosporin A than in those in whom conventional immunosuppression agents are used. Three patients with lymphoma were shown to have rising antibody to EBV,<sup>19</sup> and a fourth patient had EBV nuclear antigen in cells of a lymphoma present in his groin.<sup>18</sup> The latter case is the first definitive report linking EBV with a lymphoma other than Burkitt's lymphoma.

## THERAPY FOR VIRUS INFECTIONS

During the past twenty years, optimism about virus chemotherapy has never ceased to grow. In particular, a number of drugs can be shown to be effective both in vitro and in vivo against viruses of the herpes group. Idoxuridine, cytarabine, vidarabine and more recently acyclovir, all have a place in the management of herpes simplex virus and varicella-zoster virus disease. Therefore, it is particularly disappointing that very little, if anything, has been achieved in the case of cytomegalovirus (CMV). One of the problems appears to be that some of the drugs are effective in controlling CMV replication but not in clearing the infection. When therapy is withdrawn, virus excretion rapidly returns to the level existing before treatment. Idoxuridine and cytarabine are very toxic and prolonged courses impossible. Vidarabine does not have such serious side effects and is the advocated drug for the control of zoster in immuno-compromised patients, but there is little evidence that it achieves very much in the face of CMV. Indeed, recent reports have suggested that vidarabine is specifically contra-indicated in this group of individuals because of central nervous system problems.

Acyclovir is a new drug of remarkable promise, because of a highly favourable therapeutic ratio. Unfortunately, CMV does not code for the kinase which must phosphorylate acyclovir before it can interfere with the synthesis of virus DNA, and it does look as though CMV will not be amenable to this drug. In any event, even in the case of herpes simplex and varicella-zoster, care will be necessary if acyclovir is used in kidney graft patients, because it can precipitate in the proximal tubules if renal function is inadequate.

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