PART XIII

Guest Lecture VIRAL INFECTION IN THE RENAL TRANSPLANT PATIENT

Chairmen

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VIRAL INFECTION IN THE RENAL TRANSPLANT PATIENT
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The past two decades have witnessed a remarkable achievement – the evolution of kidney transplantation from a fascinating experiment in human immunobiology into a practical therapeutic modality that offers the best chance for rehabilitation of the uremic patient. Whereas 20 years ago more than 50 per cent of transplanted patients were dying of fungal, bacterial, or protozoan infection in the first year post-transplant, today the one-year survival rate for recipients of kidneys from living related donors is greater than 95 per cent and from cadaveric donors 90 per cent, with one-year graft survivals of 85 per cent and 70 per cent respectively. These advances have been accomplished due to important achievements in a number of different areas (Table I) that together have been translated into less allograft rejection, better immunosuppressive therapy, and a decreased incidence of acutely life-threatening infection [1,2].

**TABLE I.** The major areas affecting the outcome of renal transplantation (modified from Rubin et al [2])

| A. Optimal tissue typing and matching of donor organ to potential recipient, thus minimising the incidence and extent of the rejection process |
| B. Careful procurement and preservation of the donor organ, and proper preparation of the recipient (including pre-transplant transfusion) |
| C. Impeccable surgical technique, resulting in a minimum of tissue injury, secure vascular and ureteral anastomoses, and the prevention of fluid collections, be they blood, urine, or lymph |
| D. Precise management of the immunosuppressive regimen to prevent allograft rejection but minimise depression of host defences against infection |
| E. Prevention, prompt diagnosis, and specific therapy of infection |

Concomitant with these advances in preventing and treating acute infections, however, has been the emergence of more chronic infections, those due to viral agents. Although there is nothing about the transplant patient that renders him
immune to the viral infections that affect the normal population (e.g. influenza, rhinovirus, enterovirus, etc) the combined effects of the rejection process and the immunosuppressive therapy administered make him particularly susceptible to four groups of viral agents: the herpesvirus group, hepatitis viruses, papovaviruses, and adenoviruses. The clinical illnesses produced by these viruses are particularly influenced by the two phenomena that are unique to the transplant experience — allograft rejection and a chronic state of immunosuppression. The effect is two-fold: those viruses (particularly the herpesviruses and papovaviruses) that latently infect much of the normal population will be reactivated, and the ability of the host to eradicate either reactivated virus or newly acquired virus will be greatly impaired, thus leading to a state of chronic or prolonged viral infection in many instances. The net effect is to produce four categories of clinical disease [1–3]:

1 A variety of clinical infectious disease syndromes produced by the virus itself, ranging from prolonged fevers to pneumonia, hepatitis, and a chronically progressive chorioretinitis.

2 An immunosuppressed state produced by the virus that is over and above that caused by the immunosuppressive drugs being administered but that contributes significantly to the net immunosuppressed state of the transplant patient and plays an important role in the pathogenesis of opportunistic superinfection due to fungi, Listeria monocytogenes, Pneumocystis carinii, etc.

3 A form of allograft dysfunction produced by the virus that has a different pathogenesis from that of classical allograft rejection.

4 Malignancy produced or made possible by the virus (Table II).

### TABLE II. Possible relationship between viruses and malignant disease in the renal transplant patient

<table>
<thead>
<tr>
<th>Virus</th>
<th>Possible virus-induced malignancy</th>
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<tr>
<td>Cytomegalovirus</td>
<td>Kaposi's sarcoma</td>
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<tr>
<td>Epstein-Barr virus</td>
<td>B-cell lymphoproliferative disease</td>
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<td>Herpes simplex virus</td>
<td>Squamous cell carcinoma of the cervix uteri and/or lip</td>
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<tr>
<td>Varicella-zoster virus</td>
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<tr>
<td>Hepatitis B</td>
<td>Hepatocellular carcinoma</td>
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<td>Non-A, non-B hepatitis</td>
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<tr>
<td>Papillomavirus (wart virus)</td>
<td>Squamous cell carcinoma of the skin</td>
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<td>Polyomaviruses</td>
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<td>Adenovirus</td>
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It is the purpose of this review to summarise current concepts of the pathogenesis and clinical impact of the four groups of viral agents listed above as they contribute to morbidity and mortality in these categories of clinical disease.

Figure 1. Timetable for the occurrence of infection in the renal transplant patient. (From Rubin et al [2] published by permission of the American Journal of Medicine)

Herpesvirus group

There are four recognised human herpesviruses: cytomegalovirus (CMV), Epstein-Barr virus (EBV), herpes simplex virus (HSV), and varicella-zoster virus (VZV). All are common in the transplant patient with the first two of these having major systemic effects. The herpesviruses are double-stranded DNA viruses, approximately 200nm in size, whose internal core is surrounded by an icosahedral capsid of 162 capsomeres and a lipid-containing viral envelope. Three important characteristics of these viruses play a significant role in determining their clinical manifestations in transplant patients [1–3]:

1. All four viruses share the property of latency; that is, following recovery from primary infection, infectious virus is no longer detectable in the patient utilising conventional virologic techniques. However, these viruses do remain in a dormant state within particular cells (neural tissue for HSV and VZV, lymphocytes for EBV and leucocytes for CMV), capable of being reactivated so that infectious virus is again produced. Prominent among those factors that
produce reactivation are immunosuppression and allograft rejection. For all practical purposes, anyone sero-positive for each of these agents harbours latent virus, which is capable of being reactivated, for the remainder of his life.

2 All four viruses are highly cell-associated, with infection spreading from cell to cell by direct contact. Thus, neutralising antibody is rendered inefficient as a host defence and cell-mediated immunity more important. Therefore, any situation, such as transplantation, in which cell-mediated immunity is impaired, will be associated with an increased incidence and increased severity of infection due to these viruses.

3 All four viruses have to be thought of as potential oncogenic agents. These all cause cellular transformation in tissue culture, the in vitro correlate of oncogenesis, and similar agents have been clearly shown to be oncogenic in other species.

It is little wonder, then, that herpesviruses are the most important class of viruses affecting the transplant patient.

_Cytomegalovirus_

CMV is the most common form of infection identified in renal transplant patients, being demonstrable in 60–96 per cent of patients in the first year post-transplant. Virtually all such infections have their onset 1–4 months post-transplant, although a few examples of clinically important infection with disease onset as late as two years post-transplant have been reported. Two epidemiological patterns of CMV disease have been noted. The first is primary CMV disease, in which the transplant recipient has had no previous experience with this virus (and is sero-negative for CMV before the transplant) and develops infection with virus that is transmitted in latent fashion with either the kidney allograft (90 per cent of cases of primary infection) or leucocyte-containing transfusions (10 per cent of cases) — both from sero-positive donors. Perhaps reflecting the close cell association of the virus, person-to-person spread among dialysis and transplant unit patients and personnel appears not to occur. The second pattern is that of reactivation disease, in which the transplant recipient who has been infected with CMV previously (and is sero-positive for CMV before the transplant) reactivates endogenous latent virus [1,2,4–6].

With both epidemiologic patterns, the immunosuppressive therapy employed in transplantation and the rejection processes that follow placement of the allograft appear to activate latent virus and make it clinically manifest. Since the recipients of cadaveric kidneys undergo more rejection and receive more immunosuppression than those individuals receiving kidneys from living related donors, it is not surprising that CMV appears to have a greater impact among cadaveric graft recipients. In particular, anti-thymocyte globulin (ATG), when administered in addition to conventional immunosuppression, has been associated with an increased incidence and severity of clinical disease due to CMV [7,8]. That this is not due to a unique effect of ATG but rather is due to the ‘net state of immunosuppression’ induced is suggested by a recent study. In
this study, ATG, when administered with approximately half the usual amount of prednisone and azathioprine, was associated with an identical incidence of CMV viraemia and clinical disease as patients receiving conventional amounts of prednisone and azathioprine [9].

The asymptomatic infection rate associated with CMV infection is relatively high. Approximately 65–75 per cent of sero-negative patients who receive kidneys from sero-positive donors (and thus are at risk for primary CMV) develop symptomatic illness, whereas only 20–25 per cent of patients at risk for reactivation disease (they are sero-positive prior to transplant) develop symptoms. Overall, since at many transplant centres 60–90 per cent of patients receiving transplants are sero-positive prior to transplantation, reactivation disease has an effect that is at least equal to that of primary disease on the outcome of clinical renal transplantation. In distinguishing trivial from potentially important CMV infection, viraemia, as opposed to peripheral excretion of the virus or changes in antibody titre, appears to be a useful laboratory marker [1,2,6].

The most common clinical manifestation of CMV infection is an unexplained fever — indeed, CMV is by far the most common infectious cause of fever in the period one to six months post-transplant. These patients resemble normal hosts with CMV mononucleosis, even to the presence of five to 10 per cent atypical lymphocytes on peripheral blood smear. Approximately one third of patients with fever due to CMV will develop respiratory symptoms. By far the most common radiological correlate of these symptoms is a bilateral, symmetrical, peribronchovascular (interstitial) process predominantly affecting the lower lobes. Less commonly, a focal consolidation more suggestive of bacterial or fungal disease, or even a solitary pulmonary nodule may be caused by CMV. Although a few transplant patients with CMV pneumonia progress to total lung ‘whiteout’ and respiratory failure, in the majority of individuals the lung involvement is relatively minor and would go unappreciated if a chest X-ray had not been obtained. Indeed, if respiratory distress and/or rapid radiological progression occur, such superinfecting agents as Pneumocystis carinii, Gram-negative bacilli, or fungal agents should be suspected [1,10–13]. It is important to note that a relapsing form of CMV pneumonia may occur when immunosuppression is re instituted after recovery from serious CMV infection [14].

Leucopenia and/or thrombocytopenia can be important concomitants of CMV infection, the former predisposing to serious superinfection and the latter to a major bleeding diathesis [1,12]. This last becomes a major concern in the presence of gastrointestinal bleeding — a frequent complication of serious CMV infection. Typical CMV inclusions have been found in cells along the gastrointestinal tract of such patients, with virus being isolated from such sites. In particular, several authors have now associated life-threatening caecal haemorrhage with CMV-induced ulcerations at this colonic site in patients with a full-blown CMV clinical syndrome [15–17].

Approximately 50 per cent of patients with acute CMV infection will continue to excrete the virus in their saliva and/or urine two to five years post-transplant, with 20 per cent continuing thereafter, although clinical effects of such viral excretion are not apparent. In contrast, an occasional patient will
will have chronic CMV viraemia demonstrable, with this being associated with progressive CMV chorioretinitis [18]. Chorioretinitis is the major ‘late’ manifestation of CMV infection, usually being noted for the first time more than six months post-transplant [19].

In most transplant patients with clinical CMV disease, the direct effects of the virus itself are short-lived, with the major problem for the clinician being a differential diagnostic one, i.e., distinguishing fever and/or pneumonitis due to CMV from that due to more dangerous agents. Far more important are the ‘indirect’ infectious disease consequences of CMV infection – CMV predisposes patients to potentially lethal superinfection with a wide variety of infectious agents, but most particularly Pneumocystis carinii, Aspergillus and Candida species, Listeria monocytogenes, and Gram-negative bacilli. A variety of host defence defects are produced by CMV that account for this propensity for superinfection. The most noticeable of these is CMV-induced leucopenia, which can be quite profound. Severe leucopenia (white cell count <1500/mm³) in conjunction with symptomatic CMV disease of five days duration is associated with a 50 per cent mortality caused by superinfection of the lung and/or bloodstream [1,2,12].

In addition to the abnormalities in leucocyte number and, possibly, function induced by the virus, a major defect in cell-mediated immunity is produced. Both in normal individuals with CMV mononucleosis and transplant patients with CMV infection, cell-mediated immunity, whether measured by skin testing with recall antigens or by in-vitro lymphocyte stimulation testing, is markedly impaired [20,21]. Recently, studies have been performed in both normal individuals with CMV mononucleosis [22] and transplant patients with CMV infections to delineate the circulating T-lymphocytes into their helper/inducer and suppressor/cytotoxic subsets [23]. Such studies, employing flow cytometry and monoclonal antibody techniques, have shown in both populations that CMV infection is associated with a decrease in the helper cells and an increase in the suppressor/cytotoxic cells. These changes in the so-called ‘immunoregulatory T-cells’ are important markers for risk of opportunistic superinfection. Thus, over the past two years 10 of 11 instances of opportunistic superinfection have occurred in the subset of patients with these viral-induced changes in T-cell populations. Thus, these viral-induced changes are both a marker for those patients at high risk for opportunistic infection and at least a partial explanation for the defect in cell-mediated immunity that accounts for such superinfection [23]. For the clinician, both leucopenia and these changes in the T-cell subsets are important warnings of the need to decrease immunosuppressive therapy.

A central question in assessing the importance of CMV in renal transplantation is whether or not CMV induces renal allograft dysfunction. Some investigators have found no relationship between these two events [8,24] while others, particularly those who use intensive ATG regimens, report a striking correlation [1,10,24–30]. Recently, we have described a group of patients with allograft dysfunction in association with CMV infection. Their renal biopsies failed to reveal the typical tubulointerstitial changes of rejection, but instead had a
unique glomerular lesion. This glomerulopathy was diffuse and characterised by enlargement or necrosis of endothelial cells and accumulation of mononuclear cells and fibrillar material in glomerular capillaries [30]. Of 12 patients with the glomerulopathy who have been appropriately studied thus far, all have had the previously described viral induced changes in the immunoregulatory T-cells. Thus, monitoring of T-cell subsets not only pinpoints those patients at risk for superinfection but those in whom allograft dysfunction could be due to causes other than classical rejection. That this may be of more than academic interest is suggested by preliminary data that suggest that such patients do poorly with the increased amount of immunosuppression conventionally used to treat rejection, and may improve by decreasing the amount of immunosuppression. This last hypothesis requires more extensive testing [23–30].

Direct evidence that CMV is oncogenic in man is currently lacking. However, recent epidemiological studies, DNA hybridisation studies of tumour tissue, and immunofluorescence demonstration of CMV antigen on tumour cells have all suggested a causative role for CMV in Kaposi’s sarcoma [31–33]. There is an unexpectedly high incidence of Kaposi’s sarcoma in both transplant patients and male homosexuals with the newly described acquired immunodeficiency syndrome – two populations of patients with a high incidence of CMV infection [34,35].

Epstein-Barr virus

The role of EBV in causing morbidity and mortality in renal transplant patients has been less easy to discern. On the one hand, the ubiquity of CMV makes it difficult to study patients with EBV alone; on the other hand, since EBV and CMV are both herpes viruses that cause similar clinical syndromes in the non-immunosuppressed individual, one would predict that they would have similar effects on the transplant patient. There is little doubt that there is abundant evidence of EBV activity post-transplant: one half to two thirds of all transplant patients excrete EBV post-transplant, virtually all such viral excretion being due to viral reactivation (as with CMV both rejection activity and immunosuppressive therapy, particularly the addition of ATG to conventional immunosuppressive protocols, is correlated with viral reactivation). Such viral reactivation may occur in the absence of changes in antibody titre. In particular, heterophile antibodies do not appear in renal transplant patients with either viral excretion or rises in specific antibody titre [1,36–38].

Despite this evidence of viral activity, it has been unclear as to the consequences of EBV infection in renal transplant patients. A few children with primary infection have been described with a mononucleosis-like syndrome, hepatitis, and/or pneumonia [1]. Two studies in adults have noted several patients with evidence for reactivation of EBV and clinical findings of leucopenia, fever, atypical lymphocytes, and/or pulmonary infiltrates — all in the absence of any evidence for CMV [37,38]. In addition, EBV has been shown in normal patients and a few transplant patients to produce identical T-cell subset changes to CMV [23,39]. Also in normals EBV has been noted to be associated
with glomerulonephritis [40]. Therefore, it is not unreasonable to postulate that EBV could both predispose to superinfection and be associated with a non-rejection form of allograft injury.

Much more convincing, however, is the emerging evidence that EBV is an important cause of malignant disease in the renal transplant patient. Approximately 20 per cent of the malignancies reported to occur after renal transplantation are malignant lymphomas, of which 65 per cent have been classified as reticulum cell sarcomas (or, more recently, immunoblastic sarcoma). Many of these lymphoproliferative diseases demonstrate a polyclonal B-cell proliferation [41]. It has been suggested that these patients may be grouped into two categories: 1) young patients presenting with fever, pharyngitis, and lymphadenopathy soon after transplantation or antirejection therapy who develop a rapidly fatal multi-organ lymphoproliferative disease reminiscent of that seen in boys with the X-linked lymphoproliferative disorder after EBV infection; 2) older patients several years post-transplant who develop manifestations of solid tumours involving the central nervous system, oropharynx, liver, small bowel, or transplanted kidney. Their clinical course is more slowly progressive but still ultimately fatal. EBV specific antibody titres, immunofluorescence staining of tumours for the presence of EBV nuclear antigen, and DNA hybridisation studies all strongly implicate EBV as the probable aetiological agent in these disorders [42,43]. Additional confirmation of this hypothesis comes from a recent paper describing a patient with a polyclonal B-cell lymphoma thought to be secondary to EBV who responded clinically on two occasions to acyclovir, an anti-viral agent with potent anti-EBV effects in vitro but no inherent anti-lymphoma properties [44]. Loss of acyclovir responsiveness in this patient was associated with evolution of the tumour from a polyclonal B-cell disease to a monoclonal one.

It is clear the immunosuppression is playing an important role in the pathogenesis of these EBV-related lymphoproliferative syndromes. Our current understanding would suggest that specific memory T-cells in normal individuals who are sero-positive for EBV mount a vigorous cytotoxic response against EBV-infected B-cells. In vitro, it can be shown that such T-cells cause regression of proliferating foci of B-cells, preventing the establishment of immortalised B-cell lines (an in-vitro correlate of malignant transformation). In the absence of such T-cells, EBV-infected B-cells regularly give rise to such immortal B-lymphoblastoid cell lines. Similar events are presumed to occur in vivo. Thus, immunosuppression would be postulated to interfere with this T-cell surveillance mechanism, leading to unchecked B-cell proliferation. Such events appear to be particularly common in renal transplant patients receiving such innovative forms of immunosuppression as cyclosporin A and total lymph node irradiation. This has been most extensively investigated with cyclosporin A, where it has been demonstrated that this drug can interfere with the T-cell-mediated cytotoxic response that normally keeps EBV-infected B-cells under control [44–46]. As these and other innovative forms of immunosuppression for renal transplantation are developed, it will be essential to determine the effects of such treatment on EBV infection and the occurrence of virus induced lymphoma.
Herpes simplex virus

HSV is probably second only to CMV among viral agents causing clinically recognised disease after renal transplantation. Virtually all such infections are a result of reactivation disease. Current information would suggest that approximately three fourths of sero-positive patients will excrete the virus in their oral secretions, with approximately two thirds of them developing mucocutaneous lesions [7]. The clinical syndromes caused by HSV in the renal transplant patient may be summarised as follows:

1 Most common is a severe form of herpes labialis (due to HSV Type 1), usually beginning in the second week post-transplant, peaking in severity by the fourth week and then healing. Intraoral and oesophageal infection may occur in association with the herpes labialis, particularly if the mucosa has been traumatised by endotracheal or nasogastric tubes [1].

2 Less commonly, anogenital infection, caused predominantly by HSV Type 2, may occur. This may be unusually severe in renal transplant patients, presenting as large, coalescing ulcerated lesions that may provide a portal of entry for invasive bacteria [47].

3 Occasionally zosteriform lesions on the buttocks due to HSV Type 2 may be observed. Rarely, eczema herpeticum (Kaposi’s varicelliform eruption), a disseminated HSV infection restricted to the skin, may be observed in transplant patients whose skin was previously injured [1].

4 More serious consequences of HSV infection are most unusual. With the immunosuppressive protocols that are presently employed, systemic dissemination is exceedingly rare. Reflecting this lack of systemic involvement, there is no evidence that HSV infection has an important effect on allograft function. Similarly, although HSV may act as a secondary pathogen in an intubated patient with severe pneumonia caused by other agents, it is rarely a primary cause of pneumonia in renal transplant patients [1,48].

5 Two of the most common malignancies seen in renal transplant patients are squamous cell carcinoma of the lip and carcinoma in situ of the cervix uteri [34]. It is not unreasonable to postulate that HSV may be playing a pathogenetic role in the development of these tumours.

Until recently, therapy of HSV infection in renal transplant patients has been quite difficult, consisting of local analgesia and decreasing the level of immunosuppressive therapy. Recent trials of intravenous acyclovir in such patients have been quite promising, with localised disease responding quite nicely [49,50]. However, if the immunocompromised state that led to severe herpetic infection cannot be corrected, then the HSV infection may recur as soon as the acyclovir is discontinued. Whether or not resistance to acyclovir will become a significant clinical problem remains to be established.

Varicella-zoster virus

Some seven to nine per cent of renal transplant patients will develop clinical zoster post-transplant, usually between two months and three years post-trans
plant. Two clinical syndromes are commonly recognised in renal transplant patients as being due to VZV:

1. Typical localised dermatomal zoster due to reactivation of latent virus present in dorsal root ganglia since childhood chickenpox. It is important to emphasise that the renal transplant patient differs significantly from the lymphoma patient in that in the renal transplant patient systemic dissemination rarely occurs;

2. A syndrome of unilateral pain without skin rash associated with rises in specific antibody to VZV has been described in the renal transplant patient and is presumably also caused by this virus [1,51].

In contrast to the rather benign course of zoster (a reactivation infection) in renal transplant patients, primary varicella infection can be quite virulent. Therefore, particularly for paediatric renal transplant recipients with no previous history of varicella, serious exposure to VZV should be considered an indication for immediate zoster immune globulin prophylaxis [1].

**Hepatitis viruses**

The two major causes of viral hepatitis in the renal transplant patients are hepatitis B and so-called non-A, non-B hepatitis. Prior to the universal deployment of HBsAg by blood banks in the early 1970s, hepatitis B was thought to be the major cause of viral hepatitis in this patient population, as it is still an important factor at many transplant centres today. Most renal transplant patients who develop hepatitis B infection acquire their infection while they are still on haemodialysis prior to transplantation. Approximately 70 per cent of infected dialysis patients become anicteric chronic carriers of the virus. Particularly in transplant programmes where there is a close association between dialysis and transplant patients, an occasional transplant patient will acquire his hepatitis B post-transplant [1,52]. It is probable that hepatitis B infection may also be transmitted with the allograft if the donor is HBsAg-positive at the time of organ procurement [53].

There remains considerable controversy concerning the impact of hepatitis B on the transplant patient. It would appear that in the first six to 24 months post-transplant, patients with chronic HBsAg antigenaemia prior to transplant continue to have this, only a minority of them (probably less than 15 per cent) developing significant clinical hepatitis, and there is no adverse effect on either graft or patient survival [1]. Indeed, it has been suggested that the host response to hepatitis B infection prior to transplant is a useful predictor of transplant graft survival: Those patients able to clear hepatitis B infection and develop antibody to HBsAg while on dialysis ('good immunologic responders') had a high rate of rejection and poor graft survival; those patients with chronic hepatitis B antigenaemia ('poor immunologic responders') had a low rate of rejection and good graft survival [54].

Beginning approximately one to two years post-transplant, it would now appear that HBsAg-positive patients do not do as well as those free of this
infection. An increased patient mortality is being observed in these patients because of chronic liver disease and other conditions [55–57]. It has been suggested that the inability to clear HBsAg from the blood is a marker not only for chronic liver disease but also for an increased mortality from other infections or from fatal cardiovascular events beginning approximately nine months post-transplant [57]. It also appears that renal transplant patients surviving for prolonged periods with chronic active hepatitis due to hepatitis B are at risk for developing hepatocellular carcinoma [58].

Even in the absence of hepatitis B, significant hepatic dysfunction develops in some 10–30 per cent of renal transplant patients. It is now clear that the major cause of this is non-A, non-B hepatitis [1,59]. Such infections are characterised by the following [59]:

1. More than 80 per cent of patients who develop non-A, non-B hepatitis develop chronic liver disease.

2. The mortality rate in patients with hepatitis is approximately three times as great as that in non-hepatitis patients (p < 0.01), with the chief cause of death (approximately 80 per cent of the deaths) in the hepatitis patients being due to extra-hepatic infection.

3. In addition to those deaths, more than 50 per cent of the survivors survived life-threatening extra-hepatic infection (as compared to 20 per cent of the non-hepatitis patients (p < 0.01).

4. Conversely, graft survival was significantly increased among the hepatitis patients (73 per cent one-year cadaveric allograft survival as compared with 50 per cent for the non-hepatitis patients (p < 0.01)).

This constellation of findings would suggest that non-A, non-B hepatitis is an important cause of chronic disease in renal transplant patients, and that this virus or group of viruses has a major immunosuppressing effect that is reflected in an increased rate of life-threatening infection on the one hand and an increased rate of graft survival on the other.

Papovaviruses

There are two genera of these viruses, both of which can significantly affect the transplant patient: papillomavirus (the wart virus) and the polyomaviruses (BK and JC virus).

Approximately 40 per cent of renal transplant patients will develop warts, with one to five per cent having extensive, disfiguring disease. Immunosuppressive therapy apparently causes reactivation of latent papillomavirus in most instances of wart disease in the transplant patient, with the incidence and extent of such lesions being related to the intensity and duration of immunosuppression. Malignant transformation is not uncommon in such warts, particularly in sun-exposed areas [60]. Squamous cell carcinomas of the skin, which tend to be multiple, recurrent, and aggressive, are the most common form of malignancy affecting the renal transplant patient [61]. Recently, human papillomavirus DNA has been demonstrated in both primary and metastatic cutaneous
squamous cell carcinomas, suggesting a pathogenetic role for this virus (presumably in conjunction with sunlight) in the development of this form of post-transplant malignancy [62].

The human polyomaviruses BK virus (BKV) and JC virus (JCV) infect most normal individuals during childhood, apparently without demonstrable clinical illness. These agents have come under increased scrutiny in recent years for several reasons: 1) Post-transplant, approximately 40 per cent of renal transplant patients either excrete one or both of these viruses or manifest a rise in antibody titre; 2) BKV, JCV, and the simian viruses SV 40 are closely related both antigenically and structurally; 3) SV 40 and JCV have been linked to the development of the devastating neurological illness progressive multifocal leucoencephalopathy in monkeys and man, respectively; 4) All three agents are oncogenic outside their normal host [1,63–67].

Other than being thought to be the cause of progressive multifocal leucoencephalopathy, the clinical effects of the polyomaviruses in renal transplant patients are not clearly delineated. Some attempt has been made to associate them with the development of ureteral strictures, pancreatic disease, accelerated atherosclerosis, and malignancy post-transplant, but this work is in its infancy [1,65–67].

**Adenoviruses**

Adenoviruses are a group of DNA viruses commonly causing infection in the normal population, in whom they produce asymptomatic infection or such clinical illnesses as upper and lower respiratory tract infection, conjunctivitis, and haemorrhagic cystitis. It would appear that this class of virus may have a special relationship with renal transplant recipients [1,3]. Three patients have now been described with diffuse interstitial pneumonia secondary to adenoviruses previously not recognised (Types 34 and 35). Five other renal transplant patients have had adenovirus 35 isolated from their urines. An additional three renal transplant patients have had adenovirus type 11 isolated from their urines in the setting of a haemorrhagic cystitis [1,68–71].

The implications of these findings are several: 1) Hitherto unrecognised adenoviruses types are being isolated and should be looked for among immunosuppressed patients, particularly renal transplant patients. The full extent of their clinical impact remains to be established; 2) The major effects of these adenoviruses in renal transplant patients thus far appear to be on the respiratory tract and bladder; 3) Since adenoviruses in other species have been shown to be oncogenic, the role of these agents, particularly the newly isolated types, need to be carefully explored in this patient population [1,3].

**Summary**

With the advances that have occurred over the last two decades in the prevention and treatment of bacterial and fungal infection, viral infection has been recognised as an important problem in renal transplant patients. Four groups of viruses —
the herpesviruses, hepatitis viruses, papovaviruses, and adenoviruses — appear to have a particular impact on this patient population, especially the first two of these. The effects of these viruses can be categorised as follows: the production of infectious diseases by the virus itself; the production of an immunosuppressed state that predisposes to opportunistic superinfection; the production of a unique form of allograft injury; and the production of malignancy. It is the recognition of these last three categories of viral effect that has led to a reawakening of interest in these agents in recent years. In particular, the interaction among rejection, innovative forms of immunosuppression, and reactivated viral infection in the pathogenesis of malignant disease, which occurs at a markedly increased rate in this patient population, offers a major frontier of human biology whose importance extends far beyond the renal transplant population.

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