

A second policy change is that we will no longer consider for publication letters that are not typed with double spacing between the lines. We have stated for the past two years in our instructions to authors that letters should be prepared in this way, but most of the letters we receive are not. Indeed, many of them are very poorly presented—in a way that would not be acceptable if they were papers. Many authors seem not to realise that their letters have to be subedited and then read by a printer who sets them in type.

While embarked on this moan, I want to point out two other policies that we have for our correspondence columns and to which many of our readers seem oblivious. Firstly, unlike many other scientific publications our correspondence columns are reserved primarily for letters that relate to articles that we have published. We try to avoid original publications (what we call "out of the blue")—these we consider as papers or short reports and so referee in the normal way. This rule does not apply to letters on political and policy matters.

Secondly, we are unenthusiastic about publishing letters more than six weeks after the article to which they refer. If a writer wants to take part in the argument about an article then he must be quick. One corollary to this policy is that our overseas readers who want to have letters published will need to make sure that they have access to an airmail edition of the journal.

We are not inflexible bureaucrats, and all of these rules may be broken. But their aim is to make our correspondence columns more readable and immediate and to give as many people as possible a chance to have their say. We hope, therefore, that our readers will cooperate.

RICHARD SMITH
Assistant editor

Cytomegalovirus infections in renal transplant recipients

After renal transplantation up to 60% of seronegative recipients and nearly 90% of seropositive recipients may show evidence of cytomegalovirus infection.¹ While many such patients remain clinically asymptomatic, the infection is associated with considerable morbidity and mortality.¹⁻³

Impairment of renal function developing after transplantation may be due to rejection or cytomegalovirus infection, and the distinction is vital clinically, since the former requires an increase in immunosuppressive drugs whereas in the latter the dose has to be decreased.⁴ Studies from Boston have shown that about half the patients with cytomegalovirus viraemia and renal impairment have diffuse glomerular lesions with only minimal interstitial damage. This finding helps to differentiate patients with cytomegalovirus infection from those having rejection episodes.^{4 5} Changes in the ratio of T lymphocyte subset populations may also help since the ratio of OKT4 (helper/inducer) to OKT8 (suppressor/cytotoxic) cells may be increased in rejection⁶ and reduced in clinically apparent cytomegalovirus infection.⁵ Some workers, however, have failed to confirm this finding⁷; the type and degree of immunosuppression may affect the OKT4:OKT8 ratio.⁸ Indeed, the degree of immunosuppression has a direct influence on cytomegalovirus infection—and in particular

treatment with antithymocyte globulin increases the risk of severe cytomegalovirus infection,⁹ possibly by causing T cell depression.¹⁰

Which patients, then, are at risk of developing severe cytomegalovirus disease? Firstly, reactivation of virus among patients who were seropositive before receiving their transplants is the more common form of infection and is usually less severe than primary infection.¹¹⁻¹⁴ The source of cytomegalovirus in primary infection is probably the donor kidney, since infection is rare in seronegative recipients given grafts from seronegative donors.^{11 14 15} Orsi *et al* isolated cytomegalovirus from donor kidneys¹⁶ and Wertheim *et al* showed by DNA restriction enzyme analysis that two recipients of kidneys from the same donor excreted cytomegalovirus strains with identical DNA profiles.¹⁷ Kidneys obtained from cadavers and parents carry a greater risk of infection among recipients than those obtained from child or sibling donors¹⁴—probably because the incidence of cytomegalovirus infection increases with age.

The risk of cytomegalovirus infection may, therefore, be lessened by careful matching of donor and recipients with respect to cytomegalovirus state. With the shortage of donor kidneys in Britain and with over half of all donors being seropositive this group cannot be excluded; but whenever possible allografts from seropositive donors should not be given to seronegative recipients.¹³ Surprisingly the protocols for neither UK Transplant nor Eurotransplant make any reference to cytomegalovirus state. All renal units have access to virology services for testing markers of hepatitis B virus infection, however, so they should be able also to determine the cytomegalovirus state of donors and recipients.

Another approach to preventing cytomegalovirus infection is to use relatively low dose steroid regimens.¹⁸ McGeown *et al* noted that though infections caused 37.5% of deaths after renal transplantation reported to the European Dialysis and Transplant Association none of their 100 patients died of infection.¹⁹ One of the reasons suggested for this disparity was the sparing use of steroids. Whether or not the use of cyclosporin will reduce the incidence of cytomegalovirus infection is not clear. Since cyclosporin acts primarily on T cell functions one might expect that cytomegalovirus infection would occur more frequently and perhaps be more severe.²⁰ So far, however, the findings have been variable. Dummer *et al*²¹ and the European Multicentre Trial Group²² found no difference in the incidence of cytomegalovirus infection between patients treated with cyclosporin and azathioprine. Petersen *et al* reported that patients given cyclosporin had responded beneficially—but they used antilymphocyte globulin in the control group.²³

High titre globulin has been used for the prophylaxis and treatment of cytomegalovirus infection; three reports all found a beneficial effect.²⁴⁻²⁶ Meyers *et al* found that bone marrow recipients who had received prophylactic globulin had significantly fewer infections than controls, provided that the granulocyte transfusion donors were seronegative for cytomegalovirus.²⁵ Winston *et al* showed that, though giving cytomegalovirus immune plasma resulted in a similar incidence of cytomegalovirus infection in the treated and control groups of bone marrow recipients, the infection was less severe in the treated group.²⁴ Recipients of bone marrow transplants are more profoundly immunosuppressed than renal transplant recipients, in whom comparable results might be expected: Condie *et al* treated 52 such patients with high titre globulin in an uncontrolled trial and concluded that some benefit had occurred.²⁶

A further method of prevention is the use of cytomegalovirus vaccine. A trial in 1979 showed that all 12 seronegative patients seroconverted, but six excreted cytomegalovirus in their urine after transplantation.²⁷ Restriction enzyme studies conducted on strains isolated from four of the patients showed that the DNA pattern was different from that of the vaccine, which had not therefore prevented the patients from becoming infected with different strains of cytomegalovirus. Studies in Minneapolis compared live attenuated vaccine with placebo.²⁸ Ninety out of 119 previously seronegative recipients seroconverted. Forty one patients were given transplants, and 17 developed cytomegalovirus infection, seven in the vaccinated group and 10 in the placebo group. Preliminary evidence, however, suggested that the cytomegalovirus infection was less severe among the vaccinees. Similar results have been reported by Plotkin and colleagues.²⁹ Perhaps the development of subunit vaccines or vaccine prepared by DNA recombinant techniques will remove the hazards associated with the potential oncogenicity of cytomegalovirus vaccine.³⁰ To be effective, however, a cytomegalovirus vaccine must induce an immune response, both humoral and cellular, which persists over the period (unfortunately, often long) that patients remain on a transplant waiting list.

The prophylactic use of acyclovir may provide a further approach to the prevention of cytomegalovirus infection. Gluckman and colleagues recently reported a double blind trial of acyclovir in 39 bone marrow transplant recipients.³¹ In the group treated with acyclovir none developed cytomegalovirus infection while having treatment but four did so later when the drug was stopped. In the placebo group 12 developed cytomegalovirus infection during the study. Recently encouraging results have also been achieved with α interferon.³²

Treatment of established infection is unsatisfactory, though in a small trial Balfour *et al* showed that patients treated with acyclovir had low viraemia and improved clinically more rapidly than those given placebo.³³ Perhaps a higher dosage or the use of a derivation of acyclovir such as DHPG (G-(1,3-dexhydroxy-2-propoxymethyl)-guanine; Wellcome 759) may provide more impressive results. Laboratory studies have shown that cytomegalovirus is considerably more sensitive to DHPG than acyclovir; it is also likely to be more toxic.

Several potentially useful methods are, then, available for preventing and treating cytomegalovirus infection in patients with renal transplants, though the studies published have usually been on relatively few patients. Within the not too distant future the optimum method of management may be clearly established, perhaps using a combination of some of these regimens.

T O NUNAN
Senior medical registrar
J E BANATVALA
Professor of virology

St Thomas's Hospital,
London SE1 7EH

Requests for reprints to: Professor J E Banatvala.

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