Prevention of Infections with Cytomegalovirus

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INTRODUCTION TO THE PANEL DISCUSSION

There is a need for prevention of cytomegalovirus infection. This is easiest to justify in the case of congenital infections with CMV that lead to severe congenital illnesses. In addition, the reactivation type of CMV infection has become increasingly a problem in persons who receive organ transplants and immunosuppressive therapy. One of the more striking situations is in bone-marrow transplantation where the recipients often die of interstitial pneumonitis 2 to 4 months after successful transplantation (4). This pneumonitis is strongly associated with and may be caused by CMV infection (5). Finally, there may be milder but nevertheless important congenital defects such as late onset of deafness or mild mental retardation initiated by CMV infection in utero, and there are other illnesses associated with CMV infection such as hepatitis, mononucleosis, and postperfusion syndrome. The majority of CMV infections are inapparent, and there is a good chance that we will come to recognize other syndromes that are caused by CMV infection.

It is worth noting that those conditions commonly assumed to be due to reactivation of latent CMV infection have in most cases not actually been proven to be due to reactivation; it has not been excluded that exogenous reinflection may play a role in some such cases.

Let us consider some of the factors that are likely to bear upon the approach to prevention of infection. First, reactivated infection presents quite a different problem in terms of what is required to prevent it than does primary infection. Primary infection is due to exogenous virus, whereas truly reactivated infection as opposed to reinfection with a different strain is due to endogenous virus. It is obvious that we can expect that the latter type of infection will be more difficult to abrogate than the former type.

A second important consideration would be the source or mode of transmission of infection. Virus might be spread by the respiratory or the venereal route, and this natural means of spread might be easier to prevent than infection transmitted by infected cells or cell-associated virus, for example, through transfusion or organ transplantation. Circulating antibodies should protect against the former but not against the latter mode of infection. Herpesviruses can spread from cell to cell in the presence of neutralizing antibodies.

A third consideration is the significance of circulating CMV antibodies. Are they in fact protective? Infection with cytomegaloviruses is not at all like infection with poliovirus and other infections in which immunization, especially active immunization, has been used successfully. Dr. Ho alluded to this point earlier. To indicate the complexity of the situation, in those very bone-marrow recipients who are dying of

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interstitial pneumonitis, presumed although not yet proven to be due to CMV infection, extraordinarily high titers of CF antibodies are often found (4). This fact alone tells us that we need to know a great deal more about the interplay between cellular and humoral immunity at work in symptomatic CMV infection.

Keeping these considerations in mind let us discuss the immunization procedures that might be feasible. First of all, let us consider passive immunization. We can anticipate that some protection could be achieved against primary infection with the use of CMV antibodies that are passively acquired. This I say because of the experience with Varicella-Zoster infections in which there is some evidence of protection (1). But this means of prevention might not work against reactivated infection. This mode of immunization might at least be tried during limited high-risk periods, again for example in the recipients of bone-marrow transplants. Indeed Neiman has proposed to use anti-thymocyte and anti-CMV globulin preparations in this situation (5). This combination is to counter the graft versus host reaction as well as provide a high level of CMV antibodies. Appropriate globulins could be prepared from animals that are inoculated with human thymocytes or T-cell lines and also immunized with purified cytomegalovirus. This is a special situation.

The reservation that passive immunization would have any merit at all comes in part from the fact that mothers who have CMV antibodies do give birth to infants who presumably have maternal antibody but nevertheless acquire neonatal and even congenital infection according to observations made by Alford’s group (8). There are other grounds for reservations whether this approach would work in preventing CMV infection, but a trial could be evaluated if properly conducted and should do little or no harm.

Active immunization opens a number of other possibilities. One is the use of a killed virus vaccine. This approach has not been effective or successful with herpes simplex virus nor with poxvirus vaccines. In fact, with measles virus the use of killed vaccine has actually proven to be hazardous. This is probably because the identity of the protective antigen in the virus is not really known and is likely to be lost during processing of the vaccine, as well as because of the heterogeneity of virion antigens as brought out later. Also, killed virus vaccines are probably not as effective at stimulating cell-mediated immunity.

Another possibility, still in the future, would be the use of so-called subunit vaccines consisting of fractions of the protein coat. Such preparations would be of course preferable to killed virus vaccines in that the viral genome could be eliminated so that there is no possibility of phenomena such as multiplicity reactivation. There would also be no defective genome that might be retained in cells. Indeed, it might be possible to dissociate the protective antigen from the putative sensitizing antigen and preserve the protective activity in quantities that are still efficacious. This brings up the other problem that we might have to deal with. We do not know whether there are sensitizing antigens in the complex antigenic structure of CMV as apparently exist in measles and rubella viruses, but there may well be. Certainly it would be desirable to identify both sensitizing and protective components and to be able to separate them.

The big problem with subunit vaccines is the quantity of virus required; certainly it will be great, even once the identity of the protective components has been established.

Now let’s move on to consideration of attenuated virus vaccines. Theoretically, such preparations would be ideal if they were possible to prepare with safety. The at-
tenuated virus could be administered deliberately, produce asymptomatic infection, and confer immunity that would be long lived, presumably life long.

There are many problems with this approach. Some of them have been encountered before, but some are newly posed by the herpes group of viruses. The first question is how do we attenuate cytomegalovirus? Does it really follow that passage of the virus through human diploid fibroblastic cells leads to attenuation, and why do we think that that is so? Mouse CMV becomes attenuated upon passage in mouse cell culture, but once the virus has been inoculated in mice it becomes virulent again (6).

The second point is related to the first. What is the index of attenuation that we should use? Attenuation must exclude virulence in terms of clinical illness and congenital infection yet retain antigenicity in terms of humoral, cell-mediated, and local immunity. Here we feel strongly the lack of an animal model for human cytomegalovirus infections. There is no way to gauge the virulence of strains of human CMV except in man.

The third point would be the strain differences that are now becoming well defined among isolates of CMV. It is increasingly clear that we will find that immunization with some strains of CMV would not provide full cross protection against certain other strains, although there would be a degree of cross protection. This is being brought out by the work of Huang as well as the earlier work of Weller et al. (9). We would have to be sure that we are dealing with key strains to generate immunity.

The most important problem with the use of "attenuated" CMV strains both from the theoretical side as well as the practical point of view arises from the habit of herpes-group viruses of latency in man and other species. Biologically, these viruses are unlike other viruses of man that have been used successfully in the preparation of attenuated virus vaccines. The genome of cytomegalovirus as well as other herpes-group viruses apparently persists for life after the initial infection. There is no reason to think that an "attenuated" virus would not also produce persistent carriage of the virus genome. We are then forced to consider not only whether the initial infection with the vaccine virus is harmless and asymptomatic, but also what will happen when that virus is reactivated. We know nothing about the relation, if any, between degree of symp'toms upon primary infection and likelihood of serious or symptomatic reactivated infection. It is almost certain that many silent primary infections do result in symptoms, sometimes severe, during reactivation. I see no way at present to assess this hazard in a risk versus effectiveness analysis. It would seem to be imperative that we learn more about the epidemiology with respect to mode of transmission and the pathogenesis of infections with CMV in man. It seems to me that with the herpes group of viruses this consideration must be more than a pious hope.

Related to this problem is the possibility, considered fairly remote but not excluded at present, that cytomegalovirus may have oncogenic potential (7). Any time one introduces into human cells foreign DNA which remains capable of being transcribed and translated, then the possibility that some portion of that genome might code for a transforming factor or in some other way induce malignant change has to be considered. Indeed it is well within the realm of biological possibility that the selective process involved in attenuating a strain of virus might also select for a more strongly oncogenic strain. Here we are doubly confounded because we have markers neither for attenuation nor for oncogenicity of CMV. I think it is premature to work with such viruses in man until we have some reasonable basis of knowledge on these points.
Fortunately the outlook is not entirely bleak. The discovery by Huang of a cytomegalovirus-induced DNA polymerase which is separable from host cell polymerases (2) and which can be specifically inhibited in tissue culture systems by the antiviral compound, phosphonoacetic acid (3), offers quite another route apart from immunization that offers real promise for control of cytomegalovirus infection. Perhaps we will end up attempting to provide short-term protection against primary infection with subunit vaccine to be used in selected high-risk groups, let us say at the time of pregnancy, and use antiviral substances during reactivated infections when it is too late to attempt immunization.

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