Immobilization of Antiviral Antibody at the Cell Surface: a Novel Means for Preventing Virus Infection

WAYNE E. MAGEE

Experimental Biology, The Upjohn Co., Kalamazoo, Michigan 49001

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Methods for preparing bentonite-gamma globulin complexes and for determining their attachment to cells in tissue culture were investigated by use of human immunoglobulin G (IgG) labeled with \(^{125}\)I. For virus-inhibition studies, bentonite-IgG complexes were prepared by use of human IgG with high specific neutralizing activity against coxsackievirus A21. Much of the antibody in the complex remained available for virus neutralization, and the bentonite-IgG was at least 500 to 1,000 times as active as IgG alone in a plaque-reduction test. The complex appeared to function as a “shield” held at the surface of the cell, preventing initiation of infection.

In the animal or human, virus-specific antibody protects against a recurrent infection by neutralizing the infectious particle before it can penetrate susceptible cells of the host. Most cells of the body apparently do not adsorb antibody to their surfaces to any great extent. Consequently, protection by this route relies on a continuous level of gamma globulin circulating in serum and body fluids. Useful protective effects might be obtained by presenting cells with virus-specific antibody which is attached to particles rather than circulating as free protein. It was reasoned that by selecting particles that attach readily to cell surfaces, a coating of antibody might be held at the cell membrane, thereby preventing virus attachment and penetration. Additionally, phagocytosis of the particle-antibody complexes might be a means of introducing antibody into the interior of cells with interesting consequences. In the present experiments, these possibilities are examined by use of a model system employing cells in tissue culture.

**MATERIALS AND METHODS**

**Preparation of bentonite.** The method of Block and Bunim (1) was used. Amounts of 1 g of Wyoming bentonite were sterilized by ultraviolet light and homogenized in 200 ml of water by use of a Waring Blendor. The volume was made to 1 liter and, after standing for 1 hr, the suspension was decanted into centrifuge bottles. The bentonite particles sedimenting between 1,300 rev./min (15 min) and 1,600 rev./min (15 min) on an International centrifuge with a no. 284 swinging-bucket rotor were collected and resuspended in 100 ml of water. The suspension contained 0.5 to 1 mg (dry weight) of bentonite per ml (stock solution) and was concentrated 10-fold or more before use. Examination of the particles in the electron microscope showed a size range from 1 to 5 \(\mu\)m.

**Preparation of human immunoglobulin G (IgG).** Serum was prepared from individuals showing a high neutralization titer for coxsackie virus A21. Gamma globulins were twice precipitated with one-third saturated ammonium sulfate, dissolved in saline, and dialyzed against 0.015 M phosphate buffer (pH 6.5). IgG was separated from other globulins by chromatography on diethylaminoethyl cellulose. The fraction eluting immediately from the column with 0.015 M phosphate buffer was collected, dialyzed against 0.05 M tris(hydroxymethyl)aminomethane (Tris), pH 7.4, in saline, and stored at refrigerator temperature. Gamastan (Cutter Laboratories, Berkeley, Calif.) was used for some experiments.

**Preparation of \(^{125}\)I-IgG.** The reaction mixture (5) contained 2 ml [8 to 12 optical density (OD) units; 5.3 to 8.0 mg] of human IgG, 0.2 ml of 1 M phosphate buffer (pH 7.4), and 1.8 ml of water. The solution was chilled in an ice bath and stirred with a magnetic stirrer. Carrier-free \(^{125}\)I (Nuclear-Chicago Corp., Des Plaines, Ill.) was added (0.1 ml; 2 mCi), and 0.5 ml of a chloramine T solution (containing 100 \(\mu\)g) was injected into the stirred solution. The iodination was allowed to proceed for 15 min and then stopped with 0.5 ml of sodium metabisulfite solution (containing 100 \(\mu\)g). A 1-ml amount of 0.3 M glycine (pH 7) was added, and the sample was applied to a column (2.5 by 35.6 cm) of Biogel P-30 (Calbiochem, Los Angeles, Calif.) to separate radioactive protein from inorganic \(^{125}\)I; 33 to 35% of the \(^{125}\)I was incorporated into protein. The peak tubes containing the radioactive IgG were stored frozen.

**Preparation of bentonite-IgG complexes.** The bentonite particles contained in 10 ml of stock solution took up approximately 2 OD units of protein. A typical reaction mixture contained the following: bentonite stock solution (200 ml centrifuged and resuspended),
10 ml; 1 m Tris buffer (pH 7.4), 0.4 ml; and gamma globulin solution containing 800 to 2000 OD units of protein, 8.6 ml. The protein was allowed to adsorb to the bentonite for 30 min at room temperature with frequent swirling. The suspension was centrifuged at 2,000 rev/min for 10 min, and the supernatant was decanted. The pellet was resuspended in 100 ml of water and sedimented as before. Two more water washes were given, followed by one wash in 0.05 m Tris buffer. The pellet was resuspended in 10 ml of 0.05 m Tris (pH 7.4) and stored at 5°C. The particles could be stained with methylene blue during one of the first washes, if desired.

Attachment of bentonite-IgG complexes to cells. ML cells (a human cell line resembling HeLa cells) on 60-mm plastic petri plates were used. The cell monolayers were washed once with Hanks salts (HS) plus 0.5% bovine serum albumin (HS-A), and sufficient HS-A was added, together with the bentonite-gamma globulin suspension, to give a final volume of 2 ml per plate. Attachment was allowed to proceed for 30 min at 37°C without agitation. The cell monolayers then were washed three times with HS-A. The final wash was made with 0.05 m Tris buffer (pH 7.4), and the cells were scraped into Tris buffer if chemical analysis of the cells was planned. Radioactivity in the cells was determined by dissolving the cell pellet in 1 N NaOH and counting a sample of the digest on a Tri-Carb liquid scintillation spectrometer (Packard Instrument Co., Downers Grove, Ill.).

Microscopy of bentonite-IgG complexes attached to cells. ML cells were grown on cover slips in 60-mm plastic petri plates and exposed to bentonite-IgG as before. After being washed with HS-A, the monolayers were incubated for various lengths of time in growth medium, washed twice in HS, and fixed in 1% osmium tetroxide in HS for 30 min. After dehydration, the cells were embedded in methacrylate by the inverted-capsule method. The embedded cells were popped off the cover slip by use of dry ice. The capsule surface was trimmed and cut at an angle of 60 to 70° to the surface with a glass knife. Sections of 100 nm were prepared and examined by phase-contrast microscopy.

Virus neutralization test. Coxsackievirus A21 (Lennette) was grown in ML cells and stored frozen. Two-fold dilutions of antibody were made in 0.7 ml of HS-A. A 0.7-ml amount of virus dilution was added to each tube, the contents were mixed, and the tubes were incubated for 20 to 22 hr at 5°C. The dilution of antibody is expressed as the final dilution in the 1.4 ml. Duplicate 0.5-ml samples were plated on monolayers of ML cells for plaque assay. The cells were incubated with virus for 1 hr at 37°C and then overlaid with nutrient medium containing Tris buffer and agar. The original concentration of virus was adjusted so that, in the absence of neutralization, 50 to 100 plaques could be counted on each plate.

Plaque-reduction test for cells coated with bentonite-IgG. Cell monolayers were exposed to bentonite-IgG as before. After three HS-A washes, they were challenged with 100 to 200 plaque-forming units (PFU) of coxsackievirus A21 in 0.5 ml of HS-A. Cells were incubated with virus for 1 hr at 37°C with frequent rocking. Unattached virus was removed by one wash with HS-A, and the cells were overlaid with a Tris nutrient medium containing agar. Plaques were counted 2 days later.

RESULTS

Preparation of bentonite-IgG complexes and their attachment to cells. Portions (10 ml) of the bentonite stock solution were concentrated 10-fold and incubated with various amounts of human 125I-IgG. The amount of protein adsorbed was then calculated from the 125I uptake (Fig. 1A). At low protein concentration, most of the protein in solution could be adsorbed by the particles. At higher protein concentrations, a saturation level for adsorption could be approached. The reaction was essentially complete in 15 min, and the protein was tightly bound to the particles. Very little protein was detected in the washes, and that present was mostly bound to fine particles of bentonite. Little or no protein eluted off the particles, even after several weeks of storage at 5°C. The volume of the pelleted bentonite particles increased visibly after adsorption of protein, and the light-scattering properties of the suspension (measured at 340 nm) approximately doubled.

Cells in monolayers were treated with each of the preparations shown in Fig. 1A to determine whether attachment to cells was influenced by the amount of protein adsorbed to the bentonite. The results showed (Fig. 1B) that adsorption declined somewhat when the particles were heavily coated with IgG. Another experiment showed that bentonite alone was adsorbed slightly less than were the complexes. The amount of bentonite-IgG attached to cells was a linear function of that added (Fig. 1C), with a leveling off at higher concentrations. More bentonite-IgG was attached to the cells than would be expected by diffusion, and it was found that the particles were large enough to settle onto the monolayer during the 30-min attachment. Firm attachment to the cells was an active metabolic process that took place much better at 37°C than at 8 to 10°C (Fig. 1D). Agitation also reduced adsorption (Fig. 1D). Treatment of coated cells with ethylenediaminetetraacetate did not cause release of the particles. The medium in which attachment took place (normally HS-A) was not critical. Good attachment was obtained with Eagle’s medium, Eagle’s medium plus 10% calf serum, or medium 1066.

Bentonite-IgG that became attached to cells did not elute back into the medium to any great extent (Fig. 2).

Examination of vertical sections of cells coated with bentonite-IgG showed the particles attached to the surface of the cells in fairly even patterns (Fig. 3). All of the particles were at or near the
The effect inside the normal was incubation nite-IgG was 20 hr cell surface growth was washed, Preparation HS-A of attachment IgG to amount (1.8 ml) and 0.2 ml each of preparations 1–4 [from (A)] were incubated with cells at 37 C. (C) Relationship between the amount of bentonite IgG added and the amount attached to cells. The total volume was adjusted to 2.0 ml with HS-A. Preparation 3 [from (A)] was used. Incubation was for 30 min at 37 C. (D) Influence of temperature on attachment of bentonite-IgG to cells. One sample was shaken gently at 37 C.

cell surface for 1 to 3 hr after attachment, but by 20 hr considerable numbers of particles were seen inside the cells.

Metabolic effects of bentonite-IgG in complexes. The effect of coating cells with bentonite-IgG on normal ribonucleic acid (RNA) and deoxyribo nucleic acid (DNA) metabolism was examined by measuring the uptake of 3H-uridine and 3H-thymidine. Measurement of 3H-uridine uptake showed a dose-dependent, transitory stimulation of RNA metabolism. There was a slight depression in DNA synthesis that was dose-dependent (Fig. 4). The complexes did not appear to be severely toxic, and cells could grow and divide at least once after bentonite-IgG treatment. Longer times were not studied.

Antiviral effects of bentonite-IgG complexes. For these experiments, bentonite particles were coated with a high-titer, purified human IgG directed toward coxsackievirus A21. The starting serum had a neutralization titer of 1:20,000, and the final IgG (a three times concentrate from the serum) had a titer of 1:64,000 and 35 OD units of protein/ml.

Cells were treated with various amounts of the bentonite-antibody complex for 30 min as usual and then were challenged with coxsackievirus A21. Plaque numbers were markedly reduced, and
those that were visible were much smaller than normal in size. The dose-response curve (Fig. 5) shows that a 50% reduction in plaque numbers was equivalent to approximately 0.02 ml of the complex. Bentonite alone, bentonite-bovine serum albumin and bentonite-Gamastan complexes were inactive and served as controls. The Gamastan had an anticoxsackievirus A21 titer of approximately 1:12,000, but because of a high protein content (16.5%) the final bentonite-Gamastan complex was approximately 60-fold diluted. The resulting titer of about 1:200 evidently was inadequate.

IgG itself was ineffective in the plaque reduction...
At various times cated amounts IgG. ML cells were incubated for 30 min with the indicated amounts of bentonite-Gamastan, washed, and returned to the incubator with normal medium (0 time). At various times thereafter, 3H-uridine or 3H-thymidine was added, and incorporation of isotope was allowed to continue for 1 hr before harvest. The times indicated were the midpoints of the 1 hr incubations.

test. Application of up to 1.0 ml of the undiluted IgG antibody to a monolayer gave less than half reduction in plaques.

The next experiment examined whether the virus itself adsorbed to bentonite. Bentonite alone or bentonite-IgG was incubated with 400 or 800 PFU of coxsackievirus A21 in 4 ml of HS-A overnight with gentle shaking in a cold room. Samples (0.5 ml) were assayed for virus before and after the bentonite complexes were pelleted by centrifugation. The results showed that very little virus became attached to the bentonite (Table 1). Likewise, the bentonite-IgG was very effective in neutralizing coxsackievirus A21 (titer, 1:3,000), and the non-neutralized virus did not become attached to the bentonite-IgG complex.

Table 2 summarizes these comparisons between IgG and bentonite-IgG. From the protein content, the titer of the bentonite-IgG should have been approximately 1:7,000; thus, there was about a 55% loss or masking of antibody as a result of the binding between bentonite and IgG. Nonetheless, the bentonite-IgG preparations were at least 500 times as effective as IgG alone in the plaque-reduction assay. Evidently, free IgG does not adsorb to the cells but is almost completely removed by the three washes with HS-A before virus challenge. This was found to be the case in a direct test with 125I-IgG. Obviously, if IgG were present with the virus or added with the agar overlay, plaque suppression would result.

An experiment was run to determine how long the protective effect of the bentonite-IgG complexes would persist after they were added to the cells. Monolayers were treated with bentonite-IgG for 30 min to allow attachment and were washed and incubated for various lengths of time in growth medium before challenge with virus. The results (Fig. 6) show that the protective effect was relatively short-lasting and was totally absent 4 hr after application of the particles.

**Effect of bentonite-IgG complexes on virus growth.** The experiments described in the previous section suggested that the bentonite-IgG was active for only a limited time at the cell surface, and thus might be thought of as a shield over the cells which complexed and inactivated virus before it reached the cell surface. Determining the subsequent rate of growth of virus within the cells which did become infected should indicate whether or not the presence of complexes had any additional effects on virus maturation. Cells in monolayers were treated with bentonite-IgG (0.2 ml, preparation no. 12; 50% plaque-reduction titer of 0.05 ml) for 30 min at 37 C as usual, challenged with various multiplicities of virus for 1 hr, and washed three times with HS-A. Warm growth medium was added, and the plates were returned to the incubator. Cells were harvested at various times after infection for virus assay by scraping into the medium. From the results (Fig. 7), it is apparent that the treated cells made less virus than the controls, but the virus was produced at normal rates. The effect of the complex was the same as that obtained by lowering the multiplicity of infection (MOI). The apparent
Table 1. Test for adsorption of coxsackievirus A21 to bentonite, and neutralization of virus by bentonite-IgG complexes

<table>
<thead>
<tr>
<th>Sample</th>
<th>Virus</th>
<th>PFU in 0.5-ml sample</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Before centrifugation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ml</td>
</tr>
<tr>
<td>Bentonite alone</td>
<td>1.0</td>
<td>54, 44, 55</td>
</tr>
<tr>
<td>(volume)</td>
<td></td>
<td>0.1 ml</td>
</tr>
<tr>
<td></td>
<td>0.2 ml</td>
<td>55, 60</td>
</tr>
<tr>
<td></td>
<td>0.5 ml</td>
<td>55, 55</td>
</tr>
<tr>
<td>Bentonite-IgG (dilution)</td>
<td>1:12,800</td>
<td>95, 87</td>
</tr>
<tr>
<td></td>
<td>1:6,400</td>
<td>67, 77</td>
</tr>
<tr>
<td></td>
<td>1:3,200</td>
<td>54, 48</td>
</tr>
<tr>
<td></td>
<td>1:1,600</td>
<td>29, 22</td>
</tr>
<tr>
<td></td>
<td>1:800</td>
<td>19, 10</td>
</tr>
<tr>
<td></td>
<td>1:400</td>
<td>6, 7</td>
</tr>
<tr>
<td></td>
<td>1:200</td>
<td>1, 1</td>
</tr>
<tr>
<td>None</td>
<td>2.0</td>
<td>83, 88, 89</td>
</tr>
</tbody>
</table>

* All dilutions were made in HS-A, and the total volume for each tube was 4.0 ml. Samples were incubated overnight with shaking in the cold before assay. Dilution of bentonite-IgG refers to final dilution in the 4 ml. Centrifugation was for 10 min at 2,000 rev/min.

The maximal drop in virus titer was 10- to 30-fold over the control, indicating that 90 to 97% of the cells which ordinarily would have become infected were protected by the bentonite-IgG.

Two additional questions were asked in the next experiment. The first was whether cells protected with bentonite-IgG might become infected during a second cycle of virus growth. The second question was whether the bentonite-IgG present in the cells was sufficient to inactivate appreciable amounts of newly formed virus and thus result in an underestimation of the amount of virus produced. The experiment was performed as described for Fig. 8, except that harvests were taken over a 24-hr period. The results (Fig. 9) suggested that some of the protected cells could become infected during a second cycle. The difference between the control and treated cells diminished with time from 33-fold at 16 hr to 7.2-fold at 24 hr. Treatment with bentonite-IgG also may have resulted in an improved synchrony of infection, because this group showed a more clear-cut second cycle than did the untreated cells. To

Table 2. Comparison of the antiviral properties of IgG and bentonite-IgG

<table>
<thead>
<tr>
<th>Sample</th>
<th>Protein (OD units/ml)</th>
<th>Neutralization titer (ml)</th>
<th>Plaque-reduction titer (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgG</td>
<td>35</td>
<td>1:64,000</td>
<td>&gt;1</td>
</tr>
<tr>
<td>Bentonite-IgG</td>
<td>4</td>
<td>1:3,000</td>
<td>0.02-0.05</td>
</tr>
</tbody>
</table>

* Dilution or amount for a 50% reduction.

Figure 8 shows an experiment similar to that described above, except that the cells were all infected with the same amount of virus (MOI = 0.1) but the amount of bentonite-IgG used to treat the cells was varied. A given amount of bentonite-IgG produced an approximately equal drop in virus titer at all points along the growth curve. Dose-response curves for these data at each time could be drawn as a series of parallel lines when both virus titers and milliliters of bentonite-IgG were plotted on logarithmic scales. The effect appeared to be leveling off with the highest dose used (0.8 ml).

All of these data suggest that inactivation of the initial infecting virus is the only mode of action of the bentonite-IgG.
must be considered, since the samples (in 5 ml) were stored at −70 C, thawed, and sonically treated before dilution for assay.

**DISCUSSION**

The Wyoming bentonite used in these studies is well known for its remarkable adsorptive properties. The clay particle is principally an aluminosilicate (montmorillonite). The open-lattice structure of the clay consists of alternating sheets of silica and aluminum oxide together with appreciable amounts of metal impurities. The clay swells 10 to 12 times its volume in water, and adsorbed materials are held in the lattice by extensive hydrogen bonding and charge neutralization. The use of these particles for serological tests has been popular, the most notable example being the flocculation test for rheumatoid arthritis, in which bentonite particles are coated with human gamma globulin (1, 2). Other antigens, such as polysaccharides, also may be attached to the particles (8) and made the basis of specific flocculation tests for detection of antibodies. Bentonite

![Graph](http://iai.asm.org/)

**Fig. 7.** Inhibition of virus growth in cells treated with bentonite-IgG. Single-step growth curves obtained with various MOI. Solid symbols, no bentonite-IgG treatment; corresponding open symbols and dashed lines, cells treated with 0.2 ml of bentonite-IgG.

approach the second question of how much virus was bound to bentonite-IgG, and thus not available for assay, the 16-hr samples were treated at low pH (pH 2.5), a procedure which dissociated virus and antibody (Table 3). The incubation at pH 2.5 caused less than a twofold drop in virus titer in the absence of antibody. The sample of bentonite-IgG-treated, infected cells showed a doubling in titer as the result of the pH 2.5 treatment, indicating that the observed initial titration was about four times too low. Even so, the virus yield was still well below that of the control (ninefold). Since these cells were infected with a low dose of virus (5 × 10⁴ PFU) for an MOI of 0.01, it is obvious that most of the bound virus which could be liberated by pH 2.5 treatment must have been newly synthesized during the infection. It is not known whether the virus might bind to the bentonite-IgG as it is liberated from the infected cell, be adsorbed from the medium, or represent binding and neutralization during processing of the sample. The latter possibility

![Graph](http://iai.asm.org/)

**Fig. 8.** Inhibition of virus growth by increasing amounts of bentonite-IgG.
particles coated with proteins also have been used to study phagocytosis by macrophages and other cells of the reticuloendothelial system (3, 4, 7).

The suspended bentonite took up an amount of protein (purified human IgG) almost equal to its own dry weight. The particles with protein attached doubled in volume and in light-scattering. The protein was very firmly bound and did not elute during washing or over several weeks of storage in the cold.

Up to 60% of the bentonite-IgG added became firmly attached to cells in monolayers during 30 to 60 min of incubation at 37 C. The particles were dense enough so that appreciable settling onto the monolayers occurred during this period, allowing intimate contact between cells and particles, and accounting for the high percentage of attachment. The attached particles did not subsequently elute from cells, but, instead, were rather slowly phagocytized. Cells with bentonite-IgG attached showed a transitory rise in RNA synthesis and a depression in DNA synthesis. The cells were able to grow and divide at least once, and the bentonite-IgG did not appear to be very toxic.

For studies of virus inhibition, bentonite particles were coated with a purified human IgG with a high neutralizing titer against coxsackie-

virus A21. The antibody retained much of its virus-neutralizing activity after binding to the bentonite, and the bentonite-IgG was shown to be very active in a plaque reduction assay. Various preparations gave a 50% plaque reduction when 0.02 to 0.05 ml was used (equivalent to 0.04 to 0.1 OD units of protein).

The purified IgG alone was almost inactive in this same test, indicating that the bentonite-IgG was at least 500 to 1,000 times as effective. The reason for this result appeared to be that free IgG was almost totally removed from the cell monolayers by three rinses with buffer before virus challenge, whereas the attached bentonite-IgG was retained at the cell surface. The results of subsequent experiments are all compatible with the idea that the chief mode of action of the bentonite-IgG is a physical shielding of the coated cells, resulting in neutralization of the invading virus particles as they approach the cell surface. Those coated cells that did become infected produced virus at normal rates, and virus growth curves were not distinguishable from those observed by lowering the multiplicity of infection. By using increasing amounts of bentonite-IgG, it was calculated that over 90% of the cells in the monolayer could be protected from infection. The protective effect of bentonite-IgG was relatively short-lived, and normal plaque numbers resulted if 4 hr was allowed to elapse between treatment and virus challenge. Also, a second cycle of virus multiplication appeared to take place if the coated cells were incubated for sufficient time. The reason for the short protective effect is not clear, as phagocytosis of the attached particles appeared to take place slowly, and numerous particles were still observed on the outside of the cells after 20

**TABLE 3. Test for coxsackievirus A21-antibody complexes in infected cells treated with bentonite IgG**

<table>
<thead>
<tr>
<th>Sample</th>
<th>Total PFU</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before pH 2.5</td>
</tr>
<tr>
<td>16 hr, untreated cells</td>
<td>1.7 X 10^4</td>
</tr>
<tr>
<td>16 hr, bentonite-IgG- treated cells</td>
<td>5.2 X 10^4</td>
</tr>
<tr>
<td>Ratio, untreated/ treated                              33</td>
<td>9</td>
</tr>
</tbody>
</table>

* Samples (0.1 ml) of 16-hr harvested cells (sonically treated) were incubated with 0.9 ml of 0.1 M glycine buffer (pH 2.5) for 2 hr at room temperature. The samples then were diluted immediately, the pH was adjusted to neutrality, and the dilutions were assayed for virus. Same experiment as Fig. 9.
hr of incubation. A virus-antibody dissociation study (by low pH) showed that much more virus was bound to antibody at 16 hr than had been added initially as the inoculum, indicating that the IgG still was capable of complexing with virus.

Selection of particles of different sizes and charge (to vary phagocytic rates) and different physical properties (to vary interaction with virus) can be expected to give a wide spectrum of results when the particles are complexed with IgG or other virus-inhibitory materials and tested for antiviral effects. As yet, no effect has been seen in viral multiplication which could be attributed to intracellular action of the complexes, but it is possible that these will appear after suitable manipulation of the variables.

It should be emphasized that these experiments were confined to effects in tissue culture, and extrapolation of the results to the intact animal is uncertain. It is well documented that virus-antibody complexes are phagocytized at an accelerated rate by the macrophages which protect various ports of entry (6). The phagocytized particles presumably are carried to the lymphatic system where they are handed over to antibody-producing cells, resulting in a stimulation of the immune response. Similar effects might be anticipated for certain particle-antibody-virus complexes during the course of an infection.

ACKNOWLEDGMENTS

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LITERATURE CITED