THE ROLE OF VIRUSES in predisposing the host to secondary bacterial infections has been most thoroughly examined for influenza A virus (IAV). In humans, infection with IAV has caused more than 10,000 excess deaths per year during each of the more than 20 epidemics that have occurred since 1957, and greater than 40,000 excess deaths have occurred in several of the most recent epidemics. The excess mortality is caused mostly by bacterial superinfections that occur mainly in people at either end of the age spectrum and those with underlying illnesses. Most of the mortality and morbidity are caused by secondary infections with *Streptococcus pneumoniae* and *Staphylococcus aureus*, but other pathogens including *Escherichia coli*, *Haemophilus influenzae*, and *Neisseria meningitidis* can also cause disease. For example, culture or serologic evidence of recent influenza illness has been noted in a large percentage of adults with pneumococcal pneumonia, and children with bacterial meningitis caused by *H influenzae*, *S pneumoniae*, and *N meningitidis*.

During a recent outbreak of meningococcal disease in the United Kingdom, the incidence of serologically confirmed recent influenza infection was fourfold higher than in controls. The mortality caused by IAV infection continues to be high despite the availability of influenza vaccine, antiviral agents (eg, amantadine), and antibacterial therapies.

Many viruses, including IAV, are known to cause immunosuppression. The polymorphonuclear leukocyte (PMNL) is the principal cell involved in the immune response to infection of the host by most bacteria, and multiple in vivo and in vitro studies involving animals and humans indicate that IAV has an immunosuppressive effect on PMNLs. PMNL dysfunction precedes and appears to predispose to the development of secondary bacterial disease in animals infected with IAV. Studies have shown that IAV depresses most PMNL end-stage functions (ie, oxidative, chemotactic, secretory, and bactericidal activities) and alters a number of intermediary steps (ie, actin polymerization, lysosome-phagosome fusion, and protein phosphorylation). While the exact mechanism by which IAV alters PMNL function remains to be elucidated, it is clear that IAV depresses PMNL function by altering a signal transduction pathway(s). Thus, agents that prime (enhance) the affected pathway, or augment a compensatory pathway, might be able to overcome the virus-induced PMNL dysfunction.

We recently reported that in vitro incubation of human PMNL with granulocyte-macrophage colony-stimulating factor (GM-CSF) can overcome the inhibition of PMNL function caused by IAV, probably by priming the cell's metabolic response to subsequent stimuli. The present study was performed to determine whether GM-CSF or G-CSF could reverse the virus-induced PMNL dysfunction and decrease the incidence of superinfections in an established animal model of IAV-induced secondary bacterial infection.

**Reagents.** Recombinant human preparations of G-CSF and GM-CSF were obtained as gifts from Amgen Inc (Thousand Oaks, CA) and Hoechst-Roussel Inc (Somerville, NJ), respectively.

**Animal model: Microbial inoculation, cytokine injection, and other procedures.** The use of the chinchilla animal model for the study of IAV-induced secondary bacterial infections has been previously described. Briefly, previously healthy 1- to 2-year-old chinchillas were intranasally inoculated with IAV or phosphate-buffered saline (PBS) (day 1) followed 3 days later by *S pneumoniae* (dual-infected animals). Nasopharyngeal colonization with IAV was accomplished by dripping 0.5 mL of virus into both anterior nares of each dual-infected animal used in this study. Similarly, pneumo-
coccal colonization was established by inoculating $1 \times 10^5$ *S. pneumoniae* into both nares of each dual-infected animal. Different groups of animals were used for the in vitro and initial in vivo studies that determined a cytokine dosing schedule for PMNL priming in uninfected animals. A separate group consisting of dual-infected animals was used to determine the ability of a cytokine to both overcome IAV-induced PMNL dysfunction and prevent bacterial superinfections (see Experimental Design section).

Prior studies had shown that IAV-induced PMNL dysfunction occurs 4 to 8 days after IAV inoculation. Therefore, animals were administered GM-CSF, G-CSF, or PBS by intraperitoneal injection using a dosing schedule designed to prevent IAV-induced PMNL dysfunction from occurring (ie, injection of a cytokine each day for 7 days starting on day 3 post-IAV inoculation).

The procedures for determining the incidence of bacterial superinfections (ie, otitis media, bacteremia, pneumonia, and meningitis) have been previously described. Briefly, bacteremia was detected by aseptically drawing blood via cardiac puncture every other day (at the same time when blood is being drawn for PMNL studies). Otoscopy also was performed every other day. Animals with a yellow tympanic membrane or fluid behind the ear underwent tympanocentesis through cranial bullae (this procedure allows for the detection of infection without disturbing the tympanic membrane) and bacterial cultures of middle ear fluid were done. On any day, an animal which appeared ill had a blood culture and otoscopic exam. All animals underwent an autopsy at the time of death or at the end of the study (day 21), and this included visual inspection and bacterial cultures of the lung, blood, CSF, and middle ear.

Blood for determining peripheral leukocyte counts and measuring PMNL function, as measured by the chemiluminescence (CL) assay (see Phagocytic Cell Assay section), was obtained by cardiac puncture. Leukocyte counts were performed using a micro cell counter (Symex CC-110, Carson, CA) and differential counts were determined manually under a microscope on a total of 100 cells.

**Experimental design.** To determine the optimal in vitro priming concentration of a particular cytokine, chinchilla PMNLs were exposed to various concentrations of one of the cytokines or buffer for 0 to 120 minutes followed by stimulation with N-formylmethionyl-leucylphenylalanine (FMLP). The concentration of each cytokine that caused maximal priming was then used to determine if the cytokine could overcome IAV-induced PMNL dysfunction. This was measured by exposing cells to IAV or PBS for 30 minutes, followed by a cytokine or buffer for 0 to 120 minutes followed by FMLP.

Using the above data an in vivo dosing schedule of each cytokine for priming chinchilla PMNL was determined. In these studies purified populations of PMNLs were obtained from uninfected chinchillas that had been treated with a specific dosing regimen of a cytokine to overcome the effect of the virus. More recent unpublished studies in our laboratory have confirmed this low incidence of disease in animals infected with pneumococcal disease. Thus, it was unnecessary to use animals infected with no, or only one, microbe to determine if overcoming PMNL dysfunction with the use of cytokines results in a decreased incidence of pneumococcal disease.

**Preparation of IAV and S pneumoniae.** The present study used the same influenza A/WSN/33 H1N1 virus used in our previous studies. This strain of virus causes PMNL dysfunction both in vitro and in vivo and the inhibition of cell function is equivalent to other strains of IAV, including A/PR/8/34 (H1N1) and A/Texas/77 (H3N2). Virus was grown as previously described. Harvests of virus had an egg infectivity dose (EID$_{50}$) between $10^7$ and $10^8$. The virus was diluted to an EID$_{50}$ of $10^6$ and stored in aliquots at $-70^\circ$C. When the virus is administered intranasally to chinchillas there is a 98% seroconversion (as determined by a fourfold increase in complement fixation antibodies) and less than 5% mortality.

Type 7F *S pneumoniae* was prepared and used as in our previous studies. Bacteria were passaged at regular intervals in mice to assure uniform encapsulation and the type 7 serotype was routinely confirmed by Quelling reaction with type-specific antibody (Statens Seruminstitut, Copenhagen, Denmark). Frozen aliquots are replaced every 2 months because no reduction in viable colony counts has been observed during this time interval. This method allows precise determination of viable colony counts before animal inoculation and standardization of the bacterial inoculum between different experiments.

**Phagocytic cell assays.** Purified populations of PMNLs (97%) were obtained as previously described. The luminol-enhanced CL assay was used to examine the ability of each cytokine to prime uninfected chinchilla PMNLs and to overcome the effect of the virus on PMNL function. Briefly, the CL reaction has 1 mL of $2.5 \times 10^7$ PMNLs, 1.8 $\mu$mol/L luminol (5-aminourea-2, 3-dihydro-1, 4-phtalazine-dione) and Hanks' balanced saline solution with Ca$^{2+}$, Mg$^{2+}$, and 0.1% gelatin. Vials containing cells, luminol, and buffer are placed in a liquid scintillation counter (Beckman LS-100; Beckman Instruments, Fullerton, CA) in the out-of-coincidence mode and after backgrounds are less than 30,000 cpm the cells are stimulated with FMLP ($10^{-6}$ mol/L). The vials are mixed and counts are analyzed for 12 seconds at 2-minute intervals. Time to reach peak CL activity and the cpm at peak activity of duplicate samples are recorded.

**Statistical analysis.** For the in vivo studies, chinchillas were
USE OF CYTOKINES FOR BACTERIAL SUPERINFECTION

randomly assigned to a group with matching for the date received from the supplier. Previous experience has shown that the sex and weight of the animal does not affect the occurrence of phagocytic cell dysfunction or disease incidence. Therefore, animals were not matched for these factors except that cytokine doses were calculated on a per-kilogram basis. The chi-squared test was used to determine if the cytokines significantly altered the rate of pneumococcal disease. Pearson’s correlation coefficient was used to analyze the relationship between the capacity of a cytokine to overcome IAV-induced PMNL dysfunction and its ability to prevent pneumococcal superinfections. The Students’ t-test was used for all other analysis.

RESULTS

In vitro studies examining G-CSF– and GM-CSF–induced PMNL priming. PMNLs from uninfected chinchillas were exposed in vitro to various concentrations of recombinant human G-CSF, GM-CSF, or buffer for 0 to 120 minutes, stimulated with FMLP, and the CL response measured. PMNL priming caused by G-CSF and GM-CSF was significantly above control at all concentrations tested between 5 and 2,000 U/mL using a 90-minute incubation time (P < .05). The PMNL CL response was consistently greater than 40% above control at each concentration tested because of the priming effect of G-CSF, and maximal priming occurred at 2,000 U/mL (>twofold above control). Increasing the concentration of GM-CSF above 100 U/mL did not result in a significant increase in PMNL priming. Therefore, concentrations of 2,000 and 100 U/mL of G-CSF and GM-CSF, respectively, were used in the subsequent in vitro studies that examined the capacity of these cytokines to overcome IAV-induced PMNL dysfunction. Additionally, the data on the concentration range of these cytokines that caused priming in vitro were used to help estimate the dose of each cytokine administered to the chinchillas to prime their PMNL in vivo (see below).

Chinchilla PMNLs were next incubated in vitro with IAV or buffer for 30 minutes followed by exposure to the maximal priming concentration of G-CSF, GM-CSF, or buffer for 90 minutes. Thereafter, cells were stimulated with FMLP and the CL response measured. As expected, IAV caused significant inhibition of the CL response compared to cells treated with buffer (Fig 1). Both cytokines were able to significantly enhance the PMNL CL response compared to cells treated with IAV alone. Furthermore, both cytokines enhanced the CL response in IAV-treated PMNL to a degree that made the CL response similar to that seen in control cells.

Determining a dosing schedule of each cytokine that caused PMNL priming in uninfected animals. The PMNL CL response to FMLP stimulation was measured in uninfected chinchillas before and 6 hours after they were administered G-CSF or GM-CSF intraperitoneally. Initial experiments examined the effect of various doses and time intervals for intraperitoneal injection of these cytokines, to determine a satisfactory dosing schedule for priming PMNL in uninfected chinchillas. The manufacturers of these cytokines have animal and human data that relate the dose of the cytokine administered to the serum concentration obtained. This information was combined with our in vitro data on the concentrations of these cytokines that results in maximal PMNL priming to estimate a dosing range for each cytokine that would yield serum concentrations which cause priming in vivo. For example, using an estimated volume of distribution of 350 mL in chinchillas (animals weigh ~500 g and their volume of distribution is ~0.7) and a conversion factor of 100,000 U/µg, an intraperitoneal dose of G-CSF between 4 and 16 µg/kg was predicted to cause a serum concentration of G-CSF in the 500 to 2,000 U/mL range that caused priming in vitro. Previously reported data suggested that this serum concentration of G-CSF would affect only the granulocytic cell line.25 Our studies showed that an intraperitoneal dose of 15 µg/kg of G-CSF had the maximum priming effect on PMNL. Similar studies with GM-CSF showed that the best PMNL priming dose was 8 µg/kg (data not shown).

This information was then used in studies designed to determine a dosing schedule of each cytokine that caused significant PMNL priming. Animals were injected intraperitoneally once with G-CSF (16 µg/kg), GM-CSF (8 µg/kg), or PBS (equivalent volume). The PMNL CL response was examined before injection and every 6 hours thereafter for 24 hours. The CL response was enhanced by greater than twofold through 12 hours in animals receiving G-CSF and 24 hours with GM-CSF compared to control animals.

Our previous studies had shown that PMNL dysfunction occurs 4 to 8 days post-IAV intranasal inoculation and, therefore, it was important to examine whether the cytokines were capable of priming PMNL for this period of time. Therefore, 44 animals were administered G-CSF, GM-CSF, or PBS intraperitoneally for 7 days, at the doses noted in the previous paragraph. The CL response was measured before the first dose and then on days 1, 3, 5, and 7; blood
was drawn for the PMNL studies 4 to 6 hours after the injection. For animals treated with G-CSF or GM-CSF the mean CL response was equivalent before the initial dose and was greater than 45% (range 47% to 279%) above control animals on each day tested throughout the 7-day period. The peripheral WBC counts and absolute neutrophil counts were not significantly different on any of the days for chinchillas injected with either cytokine compared with animals receiving PBS (data not shown). No morbidity or mortality was noted in the cytokine-treated groups. These data are consistent with a prior study which found that ethanol-induced suppression of rat PMNL chemotactic and bactericidal functions was overcome by pretreating these animals for 2 days with 50 μg/kg of recombinant human G-CSF subcutaneously.26

**Effect of these cytokines on PMNL function and the incidence of superinfections in dual-infected animals.** These cytokines were next examined in 59 dual-infected chinchillas that were intranasally inoculated with IAV (day 1) and *S pneumoniae* (day 3). G-CSF (16 μg/kg), GM-CSF (8 μg/kg), or PBS was IP injected into 21, 15, and 23 animals, respectively, beginning on day 3 for 7 consecutive days. Blood was obtained for WBC counts and PMNL function studies on 3 separate days before inoculation with IAV and on days 3, 7, 10, 14, 17, and 21 post-IAV infection. When compared with their mean pre-inoculation values, the CL response was significantly decreased in control animals on day 7 (Table 1); this finding is consistent with our previous studies showing that IAV caused PMNL dysfunction 4 to 8 days after viral inoculation of animals. Importantly, the CL response was significantly increased at least through day 10 in those animals receiving GM-CSF (Table 1). No significant increase in their CL response was noted at any time during the study period in chinchillas injected with PBS. Similarly, when the data were analyzed by comparing the CL response on a given day in animals treated with either cytokine compared with control, a significant increase in PMNL function was noted on many of these same days. The peripheral WBC counts and absolute neutrophil counts of animals injected with either cytokine were not significantly different on any of the days studied when compared with the mean of their own preinjection values or to animals receiving PBS. These same animals were also observed to determine if the cytokines were able to decrease the incidence of superinfections caused by *S pneumoniae*. The incidence of pneumococcal disease and mortality was similar in animals in the G-CSF, GM-CSF, and placebo-treated groups (Table 2). The use of these cytokines did not significantly affect the time of disease onset or death. No significant correlation was found when the data were analyzed to determine if the mean PMNL priming for an animal during the time that the cytokine was administered was related to their risk of developing pneumococcal disease (r = .01, P = .9). Similarly, when the data were analyzed as to whether the peak priming (defined as the greatest amount of priming seen on any of the days when a cytokine was administered) was associated with a decreased incidence of pneumococcal infection, no correlation was noted (r = .08, P = .5). Equivalent results were obtained when the relationship between PMNL priming and mortality was examined. In additional experiments the dose of *S pneumoniae* administered to the animal was decreased by up to 3 logs, but no significant effect of the cytokines on decreasing the incidence of pneumococcal disease was noted; the incidence of pneumococcal disease was greater than 60% in cytokine- and placebo-treated animals even at an inoculation dose of 10^7 bacteria.

**DISCUSSION**

Agents that enhance phagocytic cell function may prevent or mitigate the severity of microbial infections in the immunosuppressed host. G-CSF and GM-CSF have the capacity to increase PMNL numbers and function.27,28 These cytokines

<table>
<thead>
<tr>
<th>Day</th>
<th>Treatment</th>
<th>% Change in CL (post v pre)*</th>
<th>% Change in CL (cytokine v placebo)t</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>G-CSF</td>
<td>3 ± 21</td>
<td></td>
</tr>
<tr>
<td></td>
<td>GM-CSF</td>
<td>4 ± 19</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>G-CSF</td>
<td>183 ± 33t</td>
<td>207 ± 69t</td>
</tr>
<tr>
<td></td>
<td>GM-CSF</td>
<td>109 ± 24t</td>
<td>125 ± 35t</td>
</tr>
<tr>
<td></td>
<td>PBS</td>
<td>23 ± 27</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>G-CSF</td>
<td>160 ± 33t</td>
<td>181 ± 50t</td>
</tr>
<tr>
<td></td>
<td>GM-CSF</td>
<td>203 ± 51t</td>
<td>162 ± 18t</td>
</tr>
<tr>
<td></td>
<td>PBS</td>
<td>−60 ± 305</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>G-CSF</td>
<td>214 ± 57t</td>
<td>194 ± 33t</td>
</tr>
<tr>
<td></td>
<td>GM-CSF</td>
<td>152 ± 46t</td>
<td>422 ± 206t</td>
</tr>
<tr>
<td></td>
<td>PBS</td>
<td>−60 ± 34</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>G-CSF</td>
<td>149 ± 62t</td>
<td>145 ± 73</td>
</tr>
<tr>
<td></td>
<td>GM-CSF</td>
<td>−13 ± 26</td>
<td>175 ± 95</td>
</tr>
<tr>
<td></td>
<td>PBS</td>
<td>−17 ± 18</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>G-CSF</td>
<td>112 ± 22t</td>
<td>−27 ± 43</td>
</tr>
<tr>
<td></td>
<td>GM-CSF</td>
<td>−54 ± 32</td>
<td>156 ± 55t</td>
</tr>
<tr>
<td></td>
<td>PBS</td>
<td>−37 ± 15t</td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>G-CSF</td>
<td>−51 ± 18t</td>
<td>−7 ± 26</td>
</tr>
<tr>
<td></td>
<td>GM-CSF</td>
<td>−27 ± 20</td>
<td>98 ± 24t</td>
</tr>
<tr>
<td></td>
<td>PBS</td>
<td>−23 ± 13</td>
<td></td>
</tr>
</tbody>
</table>

Dual-infected animals were administered G-CSF (16 μg/kg), GM-CSF (8 μg/kg), or PBS intraperitoneally on days 3 through 9 post-IAV inoculation. The PMNL CL response was measured in response to FMLP stimulation 3 days before IAV inoculation (the pre-inoculation value is the mean of those 3 days) and days 3, 7, 10, 14, 17, and 21 thereafter. The peak CL response in each animal was used in determining the mean CL response for each group on a given day. Blood was always drawn 4 to 6 hours after the cytokine or PBS was injected. The total number of animals studied in each group is noted in the text.

*The percent change (mean ± SEM) in the PMNL CL response when the value on a given day is compared with the mean of the 3 previral inoculation days in the same animals.
†The percent change (mean ± SEM) in the PMNL CL response when animals injected intraperitoneally with a cytokine are compared with control animals administered PBS on the same day.
‡P < .05 by Student's t-test when the percent increase in the PMNL CL response in chinchillas injected with a cytokine is compared with control animals.
§P < .05 by Student's t-test when the percent decrease in the CL response in control animals is compared with their mean pre-inoculation value.
have been reported to improve host defenses and survival in bacterial-infected animal models that are immunosuppressed because of burn injury, young age, and exposure to ethanol. Furthermore, improved PMNL function occurred in some patients with acquired immunodeficiency syndrome (AIDS) who were treated with GM-CSF.

In dual-infected chinchillas treatment with either G-CSF and GM-CSF significantly enhanced PMNL function compared with placebo-treated animals. However, these cytokine-treated animals did not have a decreased incidence of secondary bacterial infections. There are a number of potential reasons for this finding. IAV-induced PMNL dysfunction might have only a minor role in causing secondary bacterial disease. While the importance of the PMNL in controlling viral infections is often minimal compared with that of mononuclear cells, the PMNL is the principal cell involved in the immune response to infection of the host by most bacteria. Multiple in vivo (eg, refs 13, 14, 32-34) and in vitro (eg, refs 17, 19, 35-38) studies involving animals and humans indicate that IAV has a major immunosuppressive effect on PMNLs. PMNL dysfunction precedes and appears to predispose to the development of secondary disease in animals infected with IAV. These data support the concept that virus-induced PMNL dysfunction has an important role in the development of superinfections.

The priming induced by G-CSF and GM-CSF may have been inadequate to overcome the PMNL dysfunction caused by the virus. This seems unlikely because the enhanced PMNL function caused by these cytokines was sufficient to overcome the amount of depression caused by the virus in vitro (Fig 1) and in vivo (Table 1; PMNL function on those post-IAV inoculation days when either cytokine was administered was above the pre-IAV inoculation values).

The mechanism by which priming augments PMNL function is not well defined. Whether these cytokines corrected the virus-induced defect or augmented nonaffected pathway(s) is unclear; if the latter is true it is possible that the enhanced alternate pathway(s) are not as effective in killing S pneumoniae. While in general the CL response correlates well with bactericidal activity, whether priming-induced enhancement of the CL response directly correlates with increased killing of S pneumoniae is unknown. Additionally, even if the metabolic defect was corrected, decreased chemotactic-related activities (eg, adherence and cell movement) caused by IAV may still be present. The quantity of blood required to examine these types of activities precluded studying all of these functions in the same set of animals.

At the doses of G-CSF and GM-CSF used in the present study PMNL metabolic function was enhanced, but the number of circulating PMNL was not significantly increased. These data are not surprising, because the dose required to induce the maximal in vitro proliferative effect on bone marrow cells is approximately 1,000 times higher than that needed to stimulate PMNL function. However, even though the animals were not neutropenic in our study, increasing the number of circulating PMNL could potentially help decrease the incidence and mortality from superinfections. Additional studies are needed to determine whether increased doses of these cytokines can prevent bacterial superinfections by either augmenting other PMNL functions (eg, chemotaxis) or increasing the absolute neutrophil count.

The time when the cytokines were started (day 3 post-IAV inoculation), the amount of cytokine administered, and/or the route that they were injected may not have been optimal. For example, a recent report suggests that intranasal administration of GM-CSF is more effective than subcutaneous or intravenous injection for preventing Sendai virus infection in mice. Future studies should examine whether administering these cytokines earlier in the time course of IAV infection, at higher doses, or by another route prevents bacterial superinfections from occurring. While these cytokines now have an established place in treating neutropenic patients, their role in the treatment of non-neutropenic patients with microbial infections remains to be determined.

ACKNOWLEDGMENT

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Table 2. Incidence of Pneumococcal Disease in Dual-Infected Animals Treated With G-CSF, GM-CSF, or PBS

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. With Pneumococcal Disease*</th>
<th>No. Without Disease†</th>
</tr>
</thead>
<tbody>
<tr>
<td>G-CSF†</td>
<td>15 13 (21)</td>
<td>6 6 0</td>
</tr>
<tr>
<td>GM-CSF‡</td>
<td>11 11 (11)</td>
<td>4 1 1</td>
</tr>
<tr>
<td>PBS</td>
<td>16 14 (21)</td>
<td>8 14 7 1</td>
</tr>
</tbody>
</table>

*The number of animals that developed pneumococcal disease, how many died, and the sites that S pneumoniae was cultured. Some animals had pneumococcal disease detected at more than one site.
†The number of animals that did not develop pneumococcal disease.
‡The incidence of pneumococcal disease and mortality was not significantly different, as determined by the chi-squared test, between the groups of animals receiving either cytokine versus placebo.
§The total number of animals that died before day 10 (ie, when cytokine treatment was completed) is indicated in the parentheses.

See Table 1 and text for information on the dosing schedules for the cytokines and placebo.


Effect of priming polymorphonuclear leukocytes with cytokines (granulocyte-macrophage colony-stimulating factor [GM-CSF] and G-CSF) on the host resistance to Streptococcus pneumoniae in chinchillas infected with influenza A virus

JS Abramson and HR Hudnor

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