Prolonged Allograft Survival In Newcastle Disease Virus-Treated Mice

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There was persistent lymphocytopenia and prolonged survival of C57Bl skin allografts when recipient BALB/c mice were injected daily with Newcastle disease virus.

The size of the circulating pool of thymus-dependent (T) lymphocytes decreases rapidly in mice and rats injected with the paramyxovirus Newcastle disease virus (NDV). One day after virus inoculation, there is a marked depletion of lymphocytes in the blood, thoracic duct lymph, and thymus-dependent areas of lymphoid tissues. However, these deficits are largely corrected 1 to 2 days later. Evidence has been obtained which suggests that NDV induces lymphocytopenia by interrupting T lymphocyte recirculation rather than by destroying these cells. Alterations induced by NDV are dependent on the dose of virus injected but are not mediated by viral replication or by adrenal cortical hormone (7, 9, 10).

The influence of NDV on host immune responsiveness is not known, although delayed hypersensitivity is depressed in individuals infected with measles virus (6), which is also a paramyxovirus. Addition of NDV to lymphoid cells in vitro does, however, suppress production of immunoglobulins (4) and responsiveness to phytohemagglutinin (5). In the present study, the survival of skin allografts was used to test cell-mediated immunity in NDV-treated mice. Since clearance of NDV in mice is very rapid, we first determined whether repeated viral challenge would persistently depress the size of the circulating lymphocyte pool.

Adult male BALB/c and C57Bl mice were obtained from Jackson Memorial Laboratory, Bar Harbor, Me. NDV (Hickman strain) in allantoic fluid was prepared and titrated as described previously (7). BALB/c mice were injected daily (intraperitoneally) with 4 x 10⁴ mean egg infectious dose (EID₅₀) of NDV or with phosphate-buffered saline (control), and at intervals tail vein blood was obtained for lymphocyte counts. In other experiments, virus-treated BALB/c mice were grafted with C57Bl ear skin by the standard method (1). Dressings were removed on day 8 or 9; grafts were inspected daily for evidence of destruction and were scored as rejected when 50% of the tissue was sclerotic.

Mice were lymphocytopenic throughout the period when virus was inoculated daily. Blood lymphocyte counts of virus-treated mice ranged from 30 to 71% of normal (Fig. 1). The marked degree of lymphocytopenia found 24 h after the first injection of virus was not maintained by subsequent injections of virus. This may have been due to stimulation of antibody against NDV, since specific antiserum mixed with virus before inoculation diminishes its effect on lymphocytes (7).

Allograft survival was prolonged by approximately 2 days (P < 0.01) when recipients were injected daily with NDV beginning on the day of grafting (Table 1). Approximately the same effect was observed when the dose was 4 x 10⁴ or 4 x 10³ EID₅₀ of NDV. In contrast, daily injections of virus-free allantoic fluid had no apparent influence on allograft survival. Similarly, grafts were rejected normally when recipients were challenged with virus from the day before to the 4th day after grafting.

T lymphocytes play a major role in cellular immune reactions, and alteration in their function by NDV could be an important factor in the prolongation of allograft survival. Previous experiments showed that murine lymphocytes have receptors for NDV (8) and that virus attachment can disrupt the normal route of T cell traffic through the body (9, 10). Since migration of circulating lymphocytes into antigen-stimulated lymphoid tissues promotes immune reactivity (2, 3), the effect of NDV on T lymphocyte recirculation through draining lymph nodes could delay interaction of immunocompetent cells with alloantigen and thereby
Fig. 1. Mean blood lymphocyte counts in mice injected daily with $10^{3.3} \text{EID}_{50}$ of NDV or with phosphate-buffered saline (control). Values in control animals expressed as 100%. Five animals per group per day. Differences between mean counts were significant; days 1, 3, 7, $P < 0.01$, and days 11 and 14, 0.02 $> P > 0.01$.

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**LITERATURE CITED**


![Graph showing mean counts as percent of control values over days](image)

**TABLE 1. Effect of Newcastle disease virus (NDV) on allograft survival**

<table>
<thead>
<tr>
<th>Expt No.</th>
<th>No. of recipients</th>
<th>Treatment of recipients</th>
<th>MST (days)</th>
<th>$P^*$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8</td>
<td>None</td>
<td>10.9</td>
<td></td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>NDV</td>
<td>12.6</td>
<td>&lt;.01</td>
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<tr>
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<td>11</td>
<td>None</td>
<td>10.6</td>
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<tr>
<td></td>
<td>16</td>
<td>NDV</td>
<td>13.2</td>
<td>&lt;.001</td>
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<td></td>
<td>12</td>
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<td>.02 $&gt; P &gt; .01$</td>
</tr>
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<td>11</td>
<td>None</td>
<td>10.6</td>
<td></td>
</tr>
<tr>
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<td>11.9</td>
<td>.02 $&gt; P &gt; .01$</td>
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<tr>
<td></td>
<td>9</td>
<td>NDV*</td>
<td>10.9</td>
<td>.6 $&gt; P &gt; .5$</td>
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<td></td>
<td>12</td>
<td>Virus-free allantoic fluid</td>
<td>10.7</td>
<td>$P &gt; .9$</td>
</tr>
</tbody>
</table>

*C57Bl → Balb/c mice.

*NDV ($10^{3.3} \text{EID}_{50}$ except dose noted in parentheses) or virus-free allantoic fluid injected daily beginning at the time of grafting until rejection.

*MST, mean survival time.

*Mean survival time.

*P, variance analysis comparing values found in untreated versus treated animals.

*NDV injected daily for 5 days beginning 1 day before grafting.