Reduced Interferon Response in Mice Congenitally Infected with Lymphocytic Choriomeningitis Virus

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Congenital or neonatal infection of mice with lymphocytic choriomeningitis (LCM) virus results in a life-long virus carrier state (Traub, 1936; Hotchin, 1962). In a number of mouse strains, but not in all, this persistent infection may result in a slowly progressing disease. Generally the disease does not manifest itself before the animals are several months old (Hotchin, 1965). A chronic, non-cytopathogenic infection can also be established in mouse cells in vitro. After an initial high virus yield, infected cultures continuously produce virus at a variable but restricted rate, without impairment of cell growth (Lehmann-Grube, Slenczka & Tees, 1969).

The chronic virus carrier state of mice may result in altered susceptibility to infection with other viruses, e.g. eastern equine encephalomyelitis (Wagner & Snyder, 1962), Rauscher leukaemia virus (Young & Barski, 1966), polyoma virus (Hotchin, 1962; in other instances susceptibility may not be changed, e.g. yellow fever (Volkert, Larsen & Pfau, 1964) or ectromelia (Mims & Subrahmanyan, 1966).

The mechanisms responsible for regulation of LCM virus production in vivo or in vitro, as well as for the heterologous interference phenomena, are unknown. A possible role of interferon has been explored, but interferon has not been demonstrated in virus carrier mice or in chronically infected cells in vitro (Wagner & Snyder, 1962; Traub & Kesting, 1963). Since this chronic virus infection might have an influence upon the interferon response itself, a comparison was made of the interferon response of uninfected and congenitally infected CFW mice.

Chronic virus carrier animals were established by neonatal inoculation with the CA 1371 strain of LCM virus. The congenitally infected progeny of these mice were used. No more than three generations separated the infected animals from the uninfected controls. When used, the mice were 8 to 10 weeks old. At this age no disease symptoms had yet developed in the congenitally infected animals. Interferon was induced by intravenous injection of 0.2 ml. of a stock of Newcastle disease virus (NDV), having a titre of $4 \times 10^6$ p.f.u./ml. The animals were bled 6 hr later and the blood from two or three individuals was pooled. The sera were dialysed against a HCl + KCl solution at pH 2.2 for 24 hr at 4°C. Neutral pH was restored by dialysis against Hanks's balanced salt solution. Interferon was assayed by a modification of the plaque reduction method described by Wagner (1961), using Earle's mouse cells. The serum titres were expressed as the reciprocal of the dilutions resulting in 50% plaque reduction of the challenge virus.

No interferon could be demonstrated in sera from four pairs of congenitally infected mice (without challenge with NDV). This finding is compatible with those of others (Wagner & Snyder, 1962; Traub & Kesting, 1963). After challenge with NDV, the interferon titres of the sera from ten groups of congenitally infected and ten groups of uninfected mice showed reproducible differences (Table 1). The animals infected with LCM had consistently five- or sixfold lower titres than the uninfected controls.

The mechanism for the observed impaired interferon production is not clear. The possibility of a hyporeactivity analogous to that following interferon induction in other systems
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(Ho, Kono & Breinig, 1965; Youngner & Stinebring, 1965) is not supported by the lack of demonstrable interferon in unchallenged LCM virus carrier mice. However, we cannot exclude the possibility that interferon could have been present in quantities too small to be detected.

The interferon response to virus challenge may be influenced by a number of factors such as hormones (Kilbourne, Smart & Pokorny, 1961), stress (Postic et al. 1966; Tokumaru, 1967), age (Vilcek, 1964) and the bacterial microflora (Considine & Starr, 1967). Our results indicate that indigenous virus infection might be an additional factor able to influence the magnitude of the interferon response.

Table 1. Serum interferon titres of LCM virus-infected and uninfected mice

<table>
<thead>
<tr>
<th>Group number</th>
<th>LCM virus-infected</th>
<th>Uninfected</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>890</td>
<td>5900</td>
</tr>
<tr>
<td>2</td>
<td>980</td>
<td>6300</td>
</tr>
<tr>
<td>3</td>
<td>890</td>
<td>6150</td>
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<td>4</td>
<td>1000</td>
<td>6000</td>
</tr>
<tr>
<td>5</td>
<td>890</td>
<td>6300</td>
</tr>
<tr>
<td>6</td>
<td>960</td>
<td>4700</td>
</tr>
<tr>
<td>7</td>
<td>1150</td>
<td>5120</td>
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<td>1000</td>
<td>4700</td>
</tr>
<tr>
<td>10</td>
<td>1050</td>
<td>4500</td>
</tr>
<tr>
<td>Mean</td>
<td>959</td>
<td>5437</td>
</tr>
</tbody>
</table>

Mice congenitally infected with LCM virus and uninfected control mice were challenged with an intravenous injection of NDV. Serum interferon concentrations were determined on blood taken 6 hr after challenge.

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REFERENCES


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