An Attempt to Modify Scrapie in Mice by the Administration of Interferon

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Although the scrapie agent has for many years been considered a virus (Cuillé & Chelle, 1938; Eklund, Hadlow & Kennedy, 1963; Andrewes, 1964), recent work has emphasized the need for re-examining this classification (Pattison, 1965; Alper, Haig & Clarke, 1966; Pattison & Jones, 1967; Gibbons & Hunter, 1967). We thought it worth while, therefore, to determine the effect of interferon (Isaacs & Lindenmann, 1957) on scrapie, since previous experiments had demonstrated the efficacy of this antiviral factor in inhibiting the evolution of well-defined acute (Finter, 1964a; Finter, 1967; Gresser et al. 1968a) and subacute (Gresser et al. 1967; Gresser et al. 1968b) viral diseases of mice, and because, to the best of our knowledge, the action of interferon on the scrapie agent has not previously been examined.

Swiss and IC Villejuif mice were from inbred colonies maintained at the Institut du Cancer. After randomization, 1-month-old male and female mice were distributed in separate cages (6 to 8 mice/cage) and inoculated intracerebrally with 0.02 ml. of a 1/15 dilution (approximately 5000 LD50) in physiological saline of a pool of brains of strain BSvS mice clinically affected with the COMPTON strain of mouse-adapted scrapie (Chandler, 1961).

The techniques for the preparation and assay of concentrated mouse-brain interferon (Finter, 1964b) and concentrated normal brain extract have been previously described in detail (Gresser et al. 1967). The titre of the tenfold concentrated interferon used in these experiments was 1/48,000 per 2 ml. as assayed by 50% reduction of plaques of vesicular stomatitis virus on monolayer cultures of mouse embryonic fibroblasts. Interferon preparations of similar potency had proved effective in our laboratory in inhibiting the multiplication of encephalomyocarditis virus (Gresser et al. 1968a) and Friend and Rauscher viruses (Gresser et al. 1967, 1968b). Treatment of mice with interferon or normal extract was started 24 hr after inoculation of the scrapie agent, and continued daily for 5 days a week and thereafter for 3 months. Mice were inoculated with 0.25 ml. intraperitoneally or subcutaneously (alternating the route of inoculation every 2 weeks).

The brains of all mice were fixed in formalin, sectioned and stained according to techniques previously described (Pattison & Smith, 1963). All the brains were examined by one of us (I.H.P.) and graded according to the degree of pathological involvement. The first clinical signs of scrapie (Chandler, 1961) were observed 90 days after inoculation, and the majority of mice were killed 133 days (swiss strain) or 168 days (IC strain) after inoculation, at which time they were showing obvious clinical signs of the disease. The incubation period for the occurrence of clinical disease was somewhat longer in the IC than in the swiss strain of mice, but no other significant differences in the clinical course of the disease or in the severity of the histological lesions in the brains were observed between groups of mice inoculated with scrapie with or without treatment of interferon (Table 1).
The failure of repeated administration of interferon to modify the evolution of scrapie may have been related to the experimental conditions employed* and does not constitute final proof that the scrapie agent is resistant to interferon, although this possibility exists. To our knowledge, however, these concentrated mouse brain interferon preparations are among the most potent that have been used for in vivo experimentation.

Table 1

<table>
<thead>
<tr>
<th>Mouse strain</th>
<th>Uninoculated</th>
<th>None</th>
<th>Normal extract</th>
<th>Interferon</th>
</tr>
</thead>
<tbody>
<tr>
<td>swiss Male</td>
<td>0/5*</td>
<td>15/15</td>
<td>14/14</td>
<td>14/14</td>
</tr>
<tr>
<td>Female</td>
<td>0/4</td>
<td>15/15</td>
<td>15/15</td>
<td>15/15</td>
</tr>
<tr>
<td>IC Male</td>
<td>0/4</td>
<td>8/8</td>
<td>8/8</td>
<td>9/9</td>
</tr>
<tr>
<td>Female</td>
<td>0/4</td>
<td>9/9</td>
<td>8/8</td>
<td>8/8</td>
</tr>
</tbody>
</table>

* No. of mice with histological diagnosis of scrapie

Histological examination of the brains of all the clinically affected mice showed the characteristic extracellular vacuolation of scrapie (Pattison & Smith, 1963). However, it was interesting that although the vacuolation of the cerebellum and medulla/pons that is invariably present in scrapie-affected mice of the BSvS (COMPTON) strain was found in all the swiss mice, it was virtually absent in mice of the IC strain. In both strains there was vacuolation in the thalamus, hippocampus and cerebral cortex. This difference between the swiss and IC strains in the distribution of histological lesions was so constant that mice of each strain could be readily identified by microscopic examination of the brain. A recent report (Fraser & Dickinson, 1967) has noted similar histological differences in the brains of mice of different genotypes inoculated with one strain of scrapie agent.

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* For example, it was considered advisable to administer concentrated interferon throughout the entire incubation period. Since the stock of interferon available did not permit an intensive 5- to 6-month treatment, a relatively large dose of the scrapie agent was inoculated in order to shorten this incubation period to 3 months.
REFERENCES

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