Mouse Strain Selectivity in the Endotoxin-induced Hypersensitivity to Histamine

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We have previously shown that, although bacterial endotoxins can sensitize mice to histamine, this effect is more feeble than, and qualitatively different from, that of the characteristic histamine-sensitizing factor (HSF) of pertussis vaccine (R. E. Pieroni, E. J. Broderick, and L. Levine, J. Bacteriol. 91:2169, 1966). HSF is a heat-sensitive, proteinaceous substance closely associated with, or identical to, the immunogen of pertussis vaccine (J. Munoz and B. M. Hestekin, Proc. Soc. Exptl. Biol. Med. 112:799, 1963; R. E. Pieroni, E. J. Broderick, and L. Levine, J. Immunol. 95:643, 1965; A. C. Wardlaw and C. M. Jakus, Can. J. Microbiol. 12:1105, 1966). A further characteristic of HSF is that its activity can be demonstrated in only certain strains of mice. It is well established, for example, that, whereas the CFW mouse strain displays a greatly increased sensitivity to histamine after pertussis vaccination, the CF1 strain fails to respond (J. Munoz, p. 460, in M. Landy and W. Braun [ed.]. Bacterial endotoxins, Rutgers Univ. Press, New Brunswick, N.J., 1964; R. E. Pieroni and L. Levine, J. Allergy 39:25, 1967). The natural sensitivity of these strains to histamine, however, is not markedly different (R. E. Pieroni and L. Levine, unpublished data). Since the responsive CFW strain was used in our earlier work on endotoxin-induced histamine sensitivity, we considered it of interest to determine the response of the CF1 mouse strain to histamine after injection of bacterial endotoxin. We also wished to determine whether host responsiveness to the intrinsic lethality of endotoxin played a major role in endotoxin-induced histamine sensitivity.

Groups of 18 CF1 and CFW mice (Carworth Farms, Inc., New City, N.Y.) were injected intraperitoneally (ip) with five graded doses of Salmonella typhosa 0901 endotoxin. The low dose consisted of 50 μg, increased by successive doubling to a high dose of 800 μg. Because of a handling error, the CFW group that received the highest endotoxin injection comprised 10 mice instead of the 18 assigned to the other 9 groups. Groups of 10 CFW and CF1 mice were inoculated ip with 13 × 10⁹ Bordetella pertussis organisms, and similar groups of 10 were set aside as uninoculated controls. The results shown in Table 1 indicate that mice of both strains showed a similar susceptibility to the lethal effect of typhoid endotoxin. Most of these deaths occurred within the first 48 hr after injection of endotoxin. There were no toxic deaths among the vaccine-injected mice. In 4 days, all of the surviving mice were challenged ip with 1 mg of histamine dihydrochloride (Nutritional Biochemicals Corp., Cleveland, Ohio). In contrast to the similar susceptibility of these strains to endotoxin lethality, the response of the survivors to histamine was quite different. None of the 58 CF1 mice available for challenge died, whereas 13 of the 62 CFW mice died in histamine shock. In confirmation of previous findings, pertussis sensitization showed a parallel strain contrast. All 10 CF1 mice survived the histamine in-

### Table 1. Toxic and histamine death rates of CF1 and CFW mouse strains sensitized with Salmonella typhosa endotoxin or Bordetella pertussis vaccine

<table>
<thead>
<tr>
<th>Sensitizing agent</th>
<th>Mouse strain</th>
<th>CF1 mice</th>
<th>CFW mice</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Toxic deaths</td>
<td>Hista-mine⁶ deaths</td>
<td>Toxic deaths</td>
</tr>
<tr>
<td>S. typhosa endo-toxin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50 μg</td>
<td>0/18</td>
<td>0/18</td>
<td>0/18</td>
</tr>
<tr>
<td>100 μg</td>
<td>0/18</td>
<td>0/18</td>
<td>1/18</td>
</tr>
<tr>
<td>200 μg</td>
<td>2/18</td>
<td>0/16</td>
<td>2/18</td>
</tr>
<tr>
<td>400 μg</td>
<td>12/18</td>
<td>0/6</td>
<td>9/18</td>
</tr>
<tr>
<td>800 μg</td>
<td>18/18</td>
<td>--</td>
<td>8/10</td>
</tr>
<tr>
<td>B. pertussis or-ganisms (thimerosal-killed, 13 × 10⁹)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uninoculated controls</td>
<td>0/10</td>
<td>0/10</td>
<td>0/10</td>
</tr>
</tbody>
</table>

* One milligram of histamine dihydrochloride.
oculation, whereas 80% of the CFW strain died within 2 hr of histamine challenge. There were no deaths among the uninoculated control CF1 and CFW mice.

This experiment indicates that if a strain of mouse can be sensitized to histamine shock by one agent, the HSF of pertussis vaccine, it can also be sensitized by another agent, bacterial endotoxin; but if a strain is refractory to sensitization by one agent, it is similarly refractory to the other. An analogous selectivity of the two mouse strains has been reported following blockade of the β-adrenergic receptors of the autonomic nervous system (R. E. Pieroni and L. Levine, J. Allergy 39:25, 1967) as well as after adrenalectomy (J. Munoz and L. F. Schuchardt, J. Allergy 25:125, 1954). Bergman and Munoz (Proc. Soc. Exptl. Biol. Med. 122:428, 1966) recently offered convincing evidence that the hypersensitivity to histamine in pertussis-sensitized, β-adrenergically blockaded, or adrenalectomized mice is caused by an impairment in catecholamine function. We are currently investigating the possibility that this may also be the case with endotoxin-induced hypersensitivity to histamine. The lethal potential of the endotoxin apparently does not play a major role in its sensitizing effect, since the CF1 mouse strain, which was at least as susceptible as the CFW strain to the lethal effect of typhoid endotoxin, was nevertheless refractory to its histamine sensitizing effect.

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