COLORADO TICK FEVER AND DENGUE

AN EXPERIMENTAL IMMUNOLOGICAL AND CLINICAL COMPARISON

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The clinical and hematological similarities between Colorado tick fever and dengue are so striking that the possibility that they are the same disease must be considered. This similarity is further emphasized by the fact that both diseases are caused by a virus of approximately the same particle size (1,2). The two diseases differ in some respects, however. Dengue is transmitted by the Aedes mosquito, while Colorado tick fever is presumably spread by Dermacentor andersoni Stiles, in areas that are not coextensive. There is no rash nor prolonged convalescence with Colorado tick fever as observed in dengue.

The question of whether these two conditions are identical has become of more concern during the past several years with the occurrence of dengue in our armed forces abroad and Colorado tick fever in our soldiers stationed within endemic areas in the United States. The present paper is concerned with this matter.

Methods and Materials

There is at least a short immunity in both dengue (3) and Colorado tick fever (4). If they are identical, each disease should confer immunity against the other. At the time the experiments were planned to test whether this was the case, dengue virus had not been adapted to any laboratory animal; thus there appeared no immediate possibility of producing a vaccine. Colorado tick fever virus, however, had been propagated in hamsters and an animal source of virus had become available (4).

The problem was approached by the inoculation of human subjects, first with the virus of one disease, and, after a period long enough to build up an immunity, with the virus of the other.

Institutional patients suffering from central nervous system manifestations of syphilis who had been under constant observation for prolonged periods were the subjects. Inoculation

* This investigation was carried out in collaboration with the Commission on Neurotropic Virus Diseases, Board for the Investigation and Control of Influenza and other Epidemic Diseases in the Army, Preventive Medicine Division, Office of the Surgeon General, United States Army.
with the agents of these benign, self-limited virus infections was used to supplement malaria fever therapy which had proved inadequate.

Three strains of dengue virus were used, one from Hawaii\(^1\) and two from the southwest Pacific area identified as S.W.P. 1 and S.W.P. 2.\(^2\) On the basis of the disease characteristics in the donors and the clinical history of the passages made in the United States previous to this study, the strains are considered to be adequately identified. The strain of Colorado tick fever virus came from a naturally acquired infection and was passaged through 15 hamster groups and human volunteers 40 and 41 (2).

Attempts were also made to infect hamsters with dengue, since we know that these animals can be successfully infected with Colorado tick fever (2, 4).

**EXPERIMENTAL RESULTS**

Six human subjects were inoculated with dengue virus and each developed a fever, macular rash, reduction in the number of white blood cells, and an increase in the band forms. Patient 1, originally inoculated with the Hawaiian strain, was reinoculated 41 days later with the same strain. Patient 2, originally inoculated with the S.W.P. 2 strain was reinoculated 52 days later with the Hawaiian strain. They were both immune. There was no rash nor elevation of temperature. While the white blood cell count did tend to fall somewhat, the percentage of band forms did not alter significantly.

Patients 3, 4, 5, and 6 were inoculated with the virus of Colorado tick fever 40 to 84 days after their dengue inoculation. Patients 3, 4, and 5 developed a typical fever response, reduced white blood cell counts, and an increased percentage of band forms. The sixth patient did not develop a temperature elevation except for an unexplained rise to 39.2°C. on the 10th day. His white blood cell and differential counts remained essentially normal. This man had spent several years in areas of Colorado where this disease is endemic.

The source, amount, and mode of inoculation of the infective material for both dengue and Colorado tick fever, the physical findings, the temperature curves, and the white blood cell findings for patients 3, 4, and 5 are depicted in Text-figs. 1, 2, and 3.

No attempt has been made to describe subjective findings in most instances for all the patients were suffering from syphilitic general paresis. Seldom could subjective complaints be elicited, even during the acute phase of the diseases.

No improvement could be noted in any of the patients following Colorado tick fever and dengue.

Since patients 1, 3, 4, and 6 had previously received fever therapy with *Plasmodium vivax*, they were given suppressive atabrine from the time of inoculation through the duration of their dengue and Colorado tick fevers consisting of 0.1 gm. three times a day for 2 days and then 0.1 gm. daily. In cases 3 and 6, parasites were found on the day of inoculation with dengue virus, but not subsequently.

Patient 7 was first inoculated with Colorado tick fever and 69 days later with dengue. He developed typical disease in both instances as seen in Text-fig. 4.

Sabin and Schlesinger (1) have reported their inability to infect hamsters with dengue. One of us tried serial passages of dengue virus through hamsters and was unable to cause infection following inoculation of the hamster

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\(^1\) The Hawaiian strain of dengue was supplied to one of us by Lieutenant Colonel A. B. Sabin.

\(^2\) The southwest Pacific strains of dengue were supplied to one of us by Lieutenant Colonel Cornelius Philip as acute phase blood serum from typical naturally acquired cases. Subsequent human passages produced a typical dengue syndrome with rash in all patients.
### Dengue

**Case 3**

- **Patient:** White Female, Age 38
- **Method of inoculation:** 0.5 cc. Serum Intravenously
- **Strain:** Hawaiian Strain

<table>
<thead>
<tr>
<th>Days After Inoculation</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
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<th>11</th>
<th>12</th>
<th>13</th>
<th>14</th>
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<tbody>
<tr>
<td>Leucocytes in Thousands per c.mm.</td>
<td>9.00</td>
<td>8.00</td>
<td>8.10</td>
<td>4.30</td>
<td>4.00</td>
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<tr>
<td>Segments %</td>
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<td>39</td>
<td>23</td>
<td>50</td>
<td>27</td>
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</tr>
<tr>
<td>Band Forms %</td>
<td>5</td>
<td>10</td>
<td>15</td>
<td>4</td>
<td>4</td>
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<tr>
<td>Lymphocytes %</td>
<td>33</td>
<td>41</td>
<td>56</td>
<td>32</td>
<td>31</td>
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</tr>
<tr>
<td>Monocytes %</td>
<td>8</td>
<td>9</td>
<td>3</td>
<td>6</td>
<td>9</td>
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<tr>
<td>Eosinophils %</td>
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<td>2</td>
<td>7</td>
<td>6</td>
<td></td>
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<tr>
<td>Basophils %</td>
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<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
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### Colorado Tick Fever

**Case 3**

- **Method of inoculation:** 0.5 cc. Serum Subcutaneously
- **Strain:** From Volunteer 41

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<th>Days After Inoculation</th>
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<th>5</th>
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<tbody>
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<td>5.30</td>
<td>5.25</td>
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<td>5.00</td>
<td>6.00</td>
<td>3.30</td>
<td>4.10</td>
<td>4.50</td>
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<td>Segments %</td>
<td>30</td>
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<td>46</td>
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</tr>
<tr>
<td>Band Forms %</td>
<td>2</td>
<td>17</td>
<td>15</td>
<td>11</td>
<td>17</td>
<td>17</td>
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<tr>
<td>Lymphocytes %</td>
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<tr>
<td>Monocytes %</td>
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<tr>
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<td>2</td>
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<tr>
<td>Basophils %</td>
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<td>0</td>
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**Text-Fig. 1.** Dengue followed by Colorado tick fever in patient 3.
COLORADO TICK FEVER AND DENGUE

Text-FIG. 2. Dengue followed by Colorado tick fever in patient 4.
Text-Fig. 3. Dengue followed by Colorado tick fever in patient 5.
COLORADO TICK FEVER AND DENGUE

40 Days Following Inoculation with Colorado Tick Fever Serum Intravenously

DAYS AFTER INOCULATION

Leucocytes in Thousands per c.mm.

Days After Inoculation 0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
Leucocytes % 820 516 360 185 244 230 364 420 480 660 640
Segmenters % 44 13 6 21 16 18 25 17 17 19 11 4 7
Band Forms % 6 10 14 25 17 17 13 11 4 7
Lymphocytes % 43 8 16 46 45 44 54 20 49 45
Monocytes % 5 5 6 7 4 8 8 6 5 5
Eosinophils % 2 3 3 2
Basophils % 1 1 1

TEXT-Fig. 4. Colorado tick fever followed by dengue in patient 7.
serum into human volunteers. The same methods were employed as those reported for Colorado tick fever virus (4).

SUMMARY AND CONCLUSIONS

Six human beings were inoculated with dengue and developed typical disease. Two of these were reinoculated and proved immune. The remaining four were later inoculated with Colorado tick fever. Three developed typical disease. The fourth, who remained well, has previously lived in an endemic area (Colorado). One patient was inoculated with Colorado tick fever first and later with dengue. He developed both diseases.

Colorado tick fever and dengue do not give a cross-immunity.

Hamsters can be infected with Colorado tick fever but not with dengue.

Colorado tick fever and dengue appear to be distinct disease entities.

We wish to thank the human subjects and Dr. K. M. Bowman, Director of the Langley Porter Clinic of the California State Department of Institutions, and Dr. T. K. Miller and his staff of Napa State Hospital, California, for their cooperation in this study.

BIBLIOGRAPHY