THE ABSENCE OF THE HETEROPILE REACTION IN THE SPINAL FLUID IN INFECTIOUS MONONUCLEOSIS

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THE DEMONSTRATION in 1932 by Paul and Bunnell\(^1\) that the blood serum of patients with the sporadic form of infectious mononucleosis contained antibodies against sheep erythrocytes in concentrations far above a normal titer was an important advance in the study and diagnosis of this disease. It gave a good test for the recognition of the individual case, allowed the linking of the sporadic and the epidemic forms of the disease\(^2\) and permitted the establishment of certain epidemic fevers as infectious mononucleosis.\(^3\) The test has been reported to be positive in 92 per cent of the sporadic cases,\(^4\) and is consistently negative when performed in many diseases.\(^5\) Recently, Gutner and Fisher\(^6\) have described a case of chronic melioidosis with a persistently high heterophile titer. (None of the differential absorption tests described below were done.) Even in those cases in which horse serum was previously administered, the reaction can be differentiated from infectious mononucleosis by the appropriate conditions.\(^9\) Conditions producing Forssman type antibodies (such as E. coli bacteremia, the use of parenteral liver extract, etc.) can be distinguished by the fact that the antibodies are not absorbed by ox cells.\(^11\) In infectious mononucleosis, the antibodies are absorbed by ox cells but not by guinea pig kidney, whereas, in normal serum the antibodies are absorbed by guinea pig kidney but not by ox cells. These differential absorption tests distinguish the various types of heterophile antibodies.\(^9\)\(^14\)

Formerly, it was thought that the antibodies of infectious mononucleosis were of the Forssman type, but now, it is definitely known that they are not. The differential absorption tests described above distinguish the heterophile antibodies occurring in various conditions from those of infectious mononucleosis. Warren\(^14\) believes that the two types are interrelated, but this view is not widely held.

The spinal fluid has on occasion shown abnormalities. The pressure may be moderately elevated. Cell count increase is variable, ranging from twenty-five to three hundred cells. Lymphocytes usually predominate\(^11\)\(^12\) This is not at all uncommon, as was found in our cases. The spinal fluid sugar, and the chloride content are usually normal. The protein, however, may be increased and the Pandy Test strongly positive. Usually, the increase in the protein is out of proportion to the cell count.

It is interesting to note that although spinal fluid abnormalities have been studied in infectious mononucleosis,\(^17\)\(^20\) little attention has been directed as to whether or not the heterophile antibody is present. Slade\(^21\) and Landes, Reich and Perlow,\(^22\) respectively, found a negative spinal heterophile in one case. Ab
normal spinal fluid findings of pleocytosis and increased protein, however, were present.

We have examined the spinal fluids in 20 cases with positive heterophile agglutinations in the serum. These findings are summarized in table 1.

The spinal fluid abnormalities that occur are similar to those reported in the literature by Thelander and Shaw, and Shafer and Weir, with pleocytosis and increased protein as the outstanding features. The cases described in this paper were free of any central nervous system manifestations. As will be seen from the table, there is no correlation between the serum heterophile agglutination titer and the other spinal fluid changes. Each case revealed an absence of heterophile agglutinins in the spinal fluid.

Landes commented on the lack of reports of spinal fluid examinations for heterophile agglutinins. As noted above, he and Slade demonstrated a lack of

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**Table 1.** — Blood Serum and Spinal Fluid Findings in Infectious Mononucleosis

<table>
<thead>
<tr>
<th>Blood Serum</th>
<th>Spinal fluid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heterophile Agglutination</td>
<td>Case</td>
</tr>
<tr>
<td>1. J. B.</td>
<td>1:111</td>
</tr>
<tr>
<td>2. G. H.</td>
<td>1:111</td>
</tr>
<tr>
<td>3. I. G.</td>
<td>1:488</td>
</tr>
<tr>
<td>4. M. M.</td>
<td>1:28*</td>
</tr>
<tr>
<td>5. T. S.</td>
<td>1:1340</td>
</tr>
<tr>
<td>6. D. J.</td>
<td>1:28*</td>
</tr>
<tr>
<td>7. C. H.</td>
<td>1:1340</td>
</tr>
<tr>
<td>8. R. H.</td>
<td>1:1792</td>
</tr>
<tr>
<td>9. A. M.</td>
<td>1:1792</td>
</tr>
<tr>
<td>10. A. S.</td>
<td>1:1992</td>
</tr>
<tr>
<td>11. L. S.</td>
<td>1:89*</td>
</tr>
<tr>
<td>12. R. E.</td>
<td>1:14*</td>
</tr>
<tr>
<td>13. R. M.</td>
<td>1:896</td>
</tr>
<tr>
<td>14. W. O. H.</td>
<td>1:14*</td>
</tr>
<tr>
<td>15. P. P.</td>
<td>1:14*</td>
</tr>
<tr>
<td>17. D. J.</td>
<td>1:56</td>
</tr>
<tr>
<td>18. P. D.</td>
<td>1:448</td>
</tr>
<tr>
<td>19. R. N.</td>
<td>1:1340‡</td>
</tr>
<tr>
<td>20. S. K.</td>
<td>1:4970</td>
</tr>
</tbody>
</table>

L = Lymphocyte.
S = Segmented cell.
— = Not done.
1:56 positive dilution was considered a positive test.
Heterophile titer was negative in all instances.
* 1st week of illness.
† 2nd week of illness.
‡ Also had in the right lung a solitary lesion of coccidioidomycosis with a positive complement fixation and precipitin titers for coccidioidomycosis.
heterophile agglutinins in the presence of other abnormalities. This finding has been confirmed in the 20 cases in the table, and if their 2 cases are included, it is true for twenty-two cases.

Each case had a diagnostic titer of heterophile agglutinins in the blood serum, although agglutinins were lacking in the spinal fluid, even when other abnormalities were present. Even in the presence of spinal fluid abnormalities, clinical evidence of central nervous system symptoms or signs were lacking, but this certainly does not preclude central nervous system involvement by the disease. The converse also is true of infectious mononucleosis with cerebral signs and symptoms. Such cases may yield normal spinal fluid studies or may parallel the neurologic involvement.

The central nervous symptoms that occur are identified by various authors as meningitis, serous meningitis, lymphocytic meningitis, metastatic encephalomyelitis, encephaloneuronitis, encephalomyelitis, neuronitis, and Guillain-Barré syndrome. These various designations merely indicate the varied ways that the central nervous system is involved in infectious mononucleosis. Bercel has demonstrated with electroencephalograms that encephalitic foci are present with or without demonstrable cerebral symptoms.

The abnormal spinal fluid findings may thus be associated with various types of involvement of the nervous system, or with none. Whatever the heterophile antibody is in infectious mononucleosis, it does not appear to pass from the blood serum into the cerebrospinal fluid. Likewise, whatever the mechanism is in infectious mononucleosis that produces the not infrequently positive Wassermann reaction in the serum, it does not affect the spinal fluid, for in all the studies this reaction has been consistently negative. In what manner the other abnormal spinal fluid changes are brought about is not known. They may be due to the virus which is the probable etiologic agent of the disease or to a possible allergic reaction. The abnormal number of lymphocytes in the spinal fluid may simply be a reflection on blood lymphocytosis, or the lymphocytes may be squeezed out from the perivascular spaces.

Jervis, in keeping with the allergic concept, produced an acute disseminated encephalomyelitis by injection of Forssman antibodies into the carotid arteries of guinea pigs. He believed the Forssman antibody passed through an impaired blood-brain barrier. However, in the experiments of Jervis, the guinea pig tissue, including the brain, probably contains Forssman antigen with which the injected antibody might well react. Human tissues do not contain Forssman antigen.

Recent electrophoretic studies of the serum proteins throw some light on the subject of antigen-antibody reaction, but have not as yet been extensively studied in the spinal fluid. It has been shown that the beta and gamma globulin serum proteins are elevated, and that the heterophile reaction, like all antibody reactions, is due to this elevation.

Because of the protein manifestations of infectious mononucleosis, and the delayed development of the heterophile reaction or the lack of its presence in the serum, abnormal spinal fluid findings might be misleading. The fact that a heterophile antibody does not occur in the spinal fluid reveals that this cannot aid in the diagnosis.
Summary

The spinal fluid was studied in twenty cases of infectious mononucleosis proved by clinical picture, blood studies and serological examination. It may be concluded that in acute cases of infectious mononucleosis, the heterophile antibody does not pass into the spinal fluid, but that there may be an increase in cell count, particularly lymphocytes, and in protein content, which is not necessarily proportional to the cell count elevation. These findings have no correlation with central nervous system signs or symptoms.

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