THE EFFECTS OF MAPHARSIDE ON THE WHITE CELL COUNT OF EARLY SYPHILIS

BY

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Neutropenia, following the use of arsphenamines, is a well-recognized condition and, apart from infective or idiopathic causes and exposure to X-rays and other radio-active substances, such an event may follow the administration of other drugs as amidopyrine, barbiturates, dinitrophenol, sulphonamides, thiouracil and the heavy metals, to name but a few. It is with this complication in mind that white cell counts are regularly performed as a routine in any antisyphilitic schedule involving intensive rather than long-term methods of treatment with organic arsenical compounds.

The white cell counts of 405 adult male cases of early syphilis have already been studied [1]. These showed no startling distinctions between seronegative primary, seropositive primary and secondary syphilis apart only from a very slight tendency to a lymphocytosis and perhaps a minimal increase in the large mononuclears as the disease progresses. These 405 cases comprised 166 patients with seronegative primary syphilis, 164 with seropositive primary syphilis and 75 with secondary syphilis and the object of this paper is to show how the white cell counts of these patients reacted to a regime consisting of ten daily intravenous injections of 0.06 gramme of mapharside. Commercial penicillin in doses of 40,000 units, injected intramuscularly every three hours to a total of 2·4 million units, was given concurrently.

The initial blood-counts were usually performed within twenty-four hours of admission, often a few hours after penicillin therapy had begun but before any arsenical compound had been administered. In uncomplicated cases the counts were repeated on the fourth to fifth and the eighth to ninth days. These will be referred to as the second and third counts respectively. All examinations were performed to a standard method and vital staining was not employed.

Under treatment the third counts, like the first, were practically indistinguishable as to the type of disease present, though the second count showed some lag in respect of seropositive primary syphilis which had, however, quite evened out in the third and final count.

THE TOTAL WHITE CELL COUNT

The average number of white cells per c.mm. in the first count was 8,950, the second 8,190 and the third 7,620. Thus there was an overall drop of 14.9 per cent, which was caused mainly by a fall in the neutrophil polymorpho-
nuclears though there was also a decrease in the other elements. The same tendency was noticed in whatever manner the cases were grouped, though certain individual counts, especially in the lower ranges, actually increased while under treatment. The blood-count is well known to fluctuate under normal conditions. These cases were therefore at the lower levels of normal at the time the first count was performed and had ascended to, or towards, the higher levels at the time the subsequent observations were made.

**Polymorphonuclear Neutrophils**

<table>
<thead>
<tr>
<th></th>
<th>Absolute</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>First count</td>
<td>5,560</td>
<td>62</td>
</tr>
<tr>
<td>Second count</td>
<td>4,910</td>
<td>60</td>
</tr>
<tr>
<td>Third count</td>
<td>4,505</td>
<td>59</td>
</tr>
</tbody>
</table>

There was an overall drop of 19 per cent in the absolute polymorph count which was reflected to a lesser degree in the percentage calculation. This fall is also manifest if the figures are arranged to show the proportions of the absolute counts falling in the different ranges.

<table>
<thead>
<tr>
<th></th>
<th>First count Percentage of counts</th>
<th>Third count Percentage of counts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Above 9,000</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>7,000-9,000</td>
<td>22</td>
<td>12</td>
</tr>
<tr>
<td>4,000-6,000</td>
<td>62</td>
<td>57</td>
</tr>
<tr>
<td>Below 4,000</td>
<td>12</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

**Lymphocytes**

<table>
<thead>
<tr>
<th></th>
<th>Absolute</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>First count</td>
<td>2,830</td>
<td>31.5</td>
</tr>
<tr>
<td>Second count</td>
<td>2,740</td>
<td>33.5</td>
</tr>
<tr>
<td>Third count</td>
<td>2,590</td>
<td>34.0</td>
</tr>
</tbody>
</table>

There was thus a smaller, but none the less present, decrease in the absolute lymphocyte count amounting to 8.5 per cent. The proportionately greater fall in the numbers of polymorphonuclear neutrophils, however, makes this appear as a small increase in the relative percentage. This decrease is also shown in the table depicting the proportions of the absolute lymphocyte counts falling in the different ranges.

<table>
<thead>
<tr>
<th></th>
<th>First count Percentage of counts</th>
<th>Second count Percentage of counts</th>
</tr>
</thead>
<tbody>
<tr>
<td>3,500 and above</td>
<td>26</td>
<td>18</td>
</tr>
<tr>
<td>2,000-3,000</td>
<td>67</td>
<td>71</td>
</tr>
<tr>
<td>1,500 and below</td>
<td>7</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>
Effects of Mapharside on the White Cell Count of Early Syphilis

LARGE MONONUCLEARS

<table>
<thead>
<tr>
<th>Absolute</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>First count</td>
<td>410</td>
</tr>
<tr>
<td>Second count</td>
<td>390</td>
</tr>
<tr>
<td>Third count</td>
<td>375</td>
</tr>
</tbody>
</table>

A similar state of affairs is shown in the reaction of the large mononuclears. There was a fall of 8.5 per cent in the absolute numbers, though the drop in the other elements made it appear as an increase in the percentage counts. For example, the proportion of the counts in which the mononuclears reached, or exceeded 7.5 per cent was 8.4 per cent for the first count, 11.9 per cent for the second, and 12.6 per cent for the third count.

EOSINOPHILS

The same tendency, though less marked, was evidenced in the case of the eosinophil cells, the absolute totals for the three counts averaging 125, 120 and 120 respectively and the percentages all being in the region of 1.5 per cent. Owing to the greater fall in the numbers of the other types of cell, there was a progressive increase of the proportion showing a percentage eosinophil count of 2.5 per cent or over. This was 16 per cent for the first count, 18.6 per cent for the second and 25.4 per cent for the third count.

BASEOPHILS

The basophils seemed to be the only component which actually showed some, if small, signs of increase while under treatment, though the average absolute counts compared only at 25, 30 and 30 and this increase was within the limits of experimental error. There was, however, a noticeable drop in the proportion of the counts showing zero basophils and an increase in the number showing a percentage of basophils greater than 0.5 per cent.

<table>
<thead>
<tr>
<th>Percentage of zero counts</th>
<th>Percentage exceeding 0.5 per cent</th>
</tr>
</thead>
<tbody>
<tr>
<td>First count</td>
<td>54.3</td>
</tr>
<tr>
<td>Third count</td>
<td>43.6</td>
</tr>
</tbody>
</table>

LEUCOPENIA

It was customary definitely to discontinue treatment with mapharside, and increase the penicillin, if the total white count fell to 4,000, or the polymorphonuclear neutrophil count to 40 per cent. Total counts of below 5,000 and polymorphonuclear counts below 50 per cent were very suspect and treatment usually modified.

14 of the 166 seronegative primaries, 8 of the 164 seropositive primaries and 8 of the 75 secondary cases had their treatment with mapharside suspended or modified on this account. 12 of these cases arose during the first four days and 18 after this time. The initial blood counts of this series were drawn generally from the lower total white count ranges, though this was by no means always the case. The average first counts were thus lower than
average, possessed markedly fewer polymorphs and showed a higher percentage of lymphocytes than the average for the whole, viz.:

<table>
<thead>
<tr>
<th></th>
<th>Absolute</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polymorphonuclear neutrophils</td>
<td>4,060</td>
<td>57.0</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>2,600</td>
<td>36.5</td>
</tr>
<tr>
<td>Large mononuclears</td>
<td>350</td>
<td>5.0</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>65</td>
<td>1.0</td>
</tr>
<tr>
<td>Basophils</td>
<td>25</td>
<td>0.5</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>7,100</strong></td>
<td><strong>100.0</strong></td>
</tr>
</tbody>
</table>

**HERXHEIMER REACTIONS**

27 seronegative primaries, 30 seropositive primaries and 13 secondary cases showed a Herxheimer effect with primary fever. There was thus no significant difference in the incidence of this reaction according to how long the patient had had syphilis. The initial counts showed no marked differences from the normal and the third counts too, regarding the total count, were a good sample of the average though there was a greater tendency to lymphocytosis (36 to 38 per cent). Treatment was not suspended in these cases though the mapharside was usually withheld for twenty-four to forty-eight hours until the temperature had returned to normal.

**SECONDARY FEVER**

While under treatment, 14 of the seronegative primaries, 19 of the seropositive primaries and 11 secondary cases showed a secondary pyrexia as a major symptom, and the treatment was altered accordingly. These patients showed a higher initial count (9,800) but they dropped 14.7 per cent as compared with 14.9 per cent for the whole and were thus apparently only geared at a higher level.

**DERMATOLOGICAL COMPLICATIONS**

Only 9 cases exhibited cutaneous reactions. The number is too small for strict comparison, though the average of the initial counts was similar to the average of the whole as regards the total number of cells, though there was a slight lymphocytosis (37 per cent). Under treatment the total counts dropped no less than 26 per cent to 6,400, the differential remaining unaltered except for an increase in the percentage of large mononuclears from 3.5 to 5 per cent.

**ARSENCIAL ENCEPHALOPATHY**

This was fortunately a rare complication. There was one established case and two others each had an epileptic fit, one after seven injections and the other at the termination of treatment. The latter case also showed vomiting, headache and a temperature of 99°F and was thought to be a mild case of arsenical encephalopathy. The other case, showing headache and a temperature of 98.8°F, had had such fits before and was considered as doubtful. The mild case, suffering from seronegative primary syphilis, was treated
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with B.A.L. He had an initial total white cell count of 9,000 which had fallen to 5,700. The doubtful case, a patient with secondary syphilis, had an initial total white count of 5,800. He received no specific treatment, apart from discontinuance of the mapharside, and the white cell count in this case fell to 4,100 with a polymorphonuclear neutrophil percentage of 36 per cent.

The severe case arose in a man with late secondary syphilis after only four injections of the drug. He exhibited slight fever, headache, photophobia, extreme lethargy and inability to respond to the spoken voice or other external stimuli, associated with a markedly raised protein in the cerebrospinal fluid. He was never unconscious and had no epileptiform seizures. He received B.A.L. and made a steady, if slow, recovery. The initial white cell count in this case was 14,500 which fell in three days to 5,100.

Thus in all these three cases the fall in the blood-count was more accentuated than that of the average for the whole.

SUMMARY

The white cell counts of 405 cases of early syphilis treated with ten daily injections of 0.06 grammes mapharside combined with penicillin have been studied. There were no significant differences in the responses of seronegative primary, seropositive primary and secondary syphilis.

There was a general fall in the total count amounting to approximately 15 per cent. This decrease was most noticeable in respect of the neutrophil polymorphonuclear cells but was also present in the case of the lymphocytes and large mononuclears. The eosinophils remained about stationary but the basophils appeared slightly to increase.

Owing to the larger fall in the neutrophil polymorphonuclears there was a relative increase in all the other elements.

Cases showing leucopenia necessitating modification of treatment had lower initial counts, those showing Herxheimer reactions had average and those showing secondary pyrexia had somewhat higher initial counts than the average for the whole.

A very marked drop was noticed in the white cell count of patients manifesting dermatological complications and also in those who suffered from arsenical encephalopathy.

Grateful acknowledgments are expressed to Private J. Mullis, R.A.M.C., for his performance of the blood-counts, and to Private J. Tomkins, R.A.M.C., and Sergeant L. Badger, R.A.M.C., for their help with the analysis.

REFERENCE

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