EFFECT OF INTRATHecal PURIFIED PROTEIN DERIVATIVE OF TUBERCULIN IN MULTIPLE SCLEROSIS

JACK COLOVER,1 MICHAEL KREMER, R. E. LOVELACE, AND J. R. SILVER

From the Neurological Department and Clinical Research Institute of the Middlesex Hospital, London

In a preliminary report by Smith, Espir, Whitty, and Russell (1957) it was suggested that the intrathecal administration of purified protein derivative of tuberculin (P.P.D.) might be beneficial to patients with multiple sclerosis. It was also observed that apart from the immediate reaction no patient deteriorated who had experienced a definite response. These workers were unable to find evidence of any new lesions developing in patients who had been treated in this way although fluctuations were found in pre-existing symptoms. Attention was drawn to well-marked remissions and the change was noted from an expected fluctuating downhill course to moderate improvement. They, therefore, presented their preliminary report in the hope that others might expand this work.

PLAN OF THE TRIAL

In accordance with these suggestions we planned to administer P.P.D. intrathecally to a number of patients with multiple sclerosis and to observe their reactions and the subsequent course of the illness. Since the best régime for injecting P.P.D. has not yet been found, it was proposed to try a number of methods and to compare results. Thirty-six patients with multiple sclerosis were selected from the admissions to the Neurological Unit; all except one had had several episodes and showed clinical evidence of recent activity. The majority were ambulant. Patients with severe bladder disturbances, or permanently bed-ridden, or having marked mental changes, were excluded. Similarly no patient suffering from retrobulbar neuritis alone was selected. The details of the group selected are summarized in Table I. Their ages were between 18 and 56 years. Eleven were men and 25 were women. The duration of the illness varied between 22 years and three months, but 28 patients had a history of more than three years. Those who were deteriorating or had recently had fresh relapses were considered to be the most suitable for the treatment, as being in greatest need of an active therapeutie régime.

All were examined on admission and their physical capacity assessed. Routine investigations included a chest radiograph, full blood count, sedimentation rate, and urine examination. In addition, each patient was Mantoux tested using solutions of 1 in 10,000, 1 in 1,000, 1 in 100, and 1 in 10 P.P.D., and, if indicated, depot testing with tuberculin intradermally was also performed (Pepys, Bruce, and James, 1958). This was done on our behalf by Dr. Geraint James. All except two cases were Mantoux positive but these two were subsequently vaccinated with B.C.G. to ensure a positive tuberculin reaction. To mitigate some of the severe reactions which occurred, patients were treated with antipyretics, urinary antiseptics, or catheterization as required. To modify the deleterious effects seen in some cases adrenocorticotropic hormone (A.C.T.H.) was given intramuscularly. A small number of patients who had extreme skin sensitivity to P.P.D. were desensitized by means of increasing doses of intramuscular purified protein derivative.

For the intrathecal therapy, the standard dilution of P.P.D. solution prepared by Messrs. Allen and Hanbury from P.P.D. made at the Ministry of Agriculture and Fisheries, Weybridge, was employed. This was dissolved in borate buffer and contained 7·5 micrograms of P.P.D. per millilitre and it was used in strengths of 1 in 100, 1 in 10, and undiluted. The amount given initially was determined by the extent of the skin sensitivity in the Mantoux test. Before administering the P.P.D. a small amount of cerebrospinal fluid was taken off at lumbar puncture and this puncture was repeated, usually after 48 hours but in some cases also at 24 hours. Four patients had one injection of intrathecal P.P.D., 14 patients had two injections, 15 patients had three injections, two patients had four injections, and one patient had six injections (Table I).

The follow-up was carried out by seeing the patients at regular intervals but six were unable to attend for this purpose and information about their

1Member of the external scientific staff, Medical Research Council.
### Table I

**RESULTS OF INJECTIONS OF P.P.D. IN PATIENTS WITH MULTIPLE SCLEROSIS**

<table>
<thead>
<tr>
<th>Serial No.</th>
<th>Duration of Disease</th>
<th>No. of P.P.D. Injections</th>
<th>Interval between Injections</th>
<th>Dose of P.P.D. (ml.)</th>
<th>Ancillary Treatment</th>
<th>Follow-up Period in Months</th>
<th>At One Year</th>
<th>Final State</th>
<th>No. of Relapses after P.P.D.</th>
<th>C.S.F. Changes</th>
<th>Initial Cells¹</th>
<th>Protein (mg. %)</th>
<th>Maximum Protein (mg. %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1 ½ years</td>
<td>2</td>
<td>2 months</td>
<td>1-0, 1/100</td>
<td></td>
<td>34</td>
<td>Relapse</td>
<td>Worse</td>
<td>1</td>
<td></td>
<td>2L</td>
<td>110</td>
<td>425</td>
</tr>
<tr>
<td>2</td>
<td>22 years</td>
<td>2</td>
<td>2 months</td>
<td>0-5, 1/100</td>
<td></td>
<td>31</td>
<td>Relapse</td>
<td>Improve</td>
<td>0</td>
<td></td>
<td>2L</td>
<td>50</td>
<td>1,200</td>
</tr>
<tr>
<td>3</td>
<td>10 years</td>
<td>2</td>
<td>2 months</td>
<td>0-5, 1/100</td>
<td>A.C.T.H. Cortisone</td>
<td>31</td>
<td>Relapse</td>
<td>Worse</td>
<td>1</td>
<td></td>
<td>12L</td>
<td>90</td>
<td>600</td>
</tr>
<tr>
<td>4</td>
<td>4 years</td>
<td>2</td>
<td>2 months</td>
<td>0-5, 1/100</td>
<td>A.C.T.H.</td>
<td>31</td>
<td>Much better</td>
<td>Improved</td>
<td>0</td>
<td></td>
<td>2L</td>
<td>110</td>
<td>1,100</td>
</tr>
<tr>
<td>5</td>
<td>6 years</td>
<td>2</td>
<td>3 weeks</td>
<td>0-5, 1/100</td>
<td>A.C.T.H.</td>
<td>30</td>
<td>Relapse</td>
<td>Worse</td>
<td>1</td>
<td></td>
<td>1L</td>
<td>80</td>
<td>300</td>
</tr>
<tr>
<td>6</td>
<td>8 years</td>
<td>3</td>
<td>2 weeks</td>
<td>0-5, 1/100</td>
<td>A.C.T.H.</td>
<td>30</td>
<td>Relapse</td>
<td>Worse</td>
<td>2</td>
<td></td>
<td>10L</td>
<td>70</td>
<td>200</td>
</tr>
<tr>
<td>7</td>
<td>2 years</td>
<td>3</td>
<td>2 months</td>
<td>0-5, 1/100</td>
<td></td>
<td>27</td>
<td>Static</td>
<td>Improved</td>
<td>0</td>
<td></td>
<td>4L</td>
<td>45</td>
<td>350</td>
</tr>
<tr>
<td>8</td>
<td>3 months</td>
<td>2</td>
<td>5 days</td>
<td>0-5, 1/100</td>
<td></td>
<td>27</td>
<td>—</td>
<td>Much worse</td>
<td>14L</td>
<td></td>
<td>60</td>
<td>300</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>14 years</td>
<td>4</td>
<td>1 week</td>
<td>0-5, 1/100</td>
<td>A.C.T.H.</td>
<td>27</td>
<td>Relapse</td>
<td>Slightly worse</td>
<td>1</td>
<td></td>
<td>2L</td>
<td>50</td>
<td>750</td>
</tr>
<tr>
<td>10</td>
<td>9 years</td>
<td>2</td>
<td>2 weeks</td>
<td>0-5, 1/100</td>
<td>A.C.T.H.</td>
<td>2½</td>
<td>Died</td>
<td></td>
<td>3L</td>
<td>70</td>
<td>750</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>3½ years</td>
<td>3</td>
<td>4 days</td>
<td>0-5, 1/100</td>
<td></td>
<td>27</td>
<td>Worse</td>
<td>Worse</td>
<td>1L</td>
<td>75</td>
<td>500</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>7½ years</td>
<td>3</td>
<td>9 days</td>
<td>0-5, 1/100</td>
<td>A.C.T.H.</td>
<td>27</td>
<td>Static</td>
<td>Worse</td>
<td>1L</td>
<td>80</td>
<td>1,200</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>8 years</td>
<td>3</td>
<td>3 weeks</td>
<td>0-5, 1/100 x 3</td>
<td>A.C.T.H.</td>
<td>26</td>
<td>Relapse</td>
<td>Much worse</td>
<td>1L</td>
<td>60</td>
<td>530</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>6 years</td>
<td>2</td>
<td>2 weeks</td>
<td>0-5, 1/100</td>
<td>A.C.T.H.</td>
<td>26</td>
<td>Relapse</td>
<td>Static</td>
<td>2L</td>
<td>35</td>
<td>375</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>9 years</td>
<td>3</td>
<td>2 months</td>
<td>0-5, 1/100</td>
<td>A.C.T.H.</td>
<td>26</td>
<td>Relapse</td>
<td>Static</td>
<td>3L</td>
<td>60</td>
<td>260</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>6 years</td>
<td>6</td>
<td>2 weeks</td>
<td>0-5, 1/100</td>
<td>B.C.G.</td>
<td>25</td>
<td>Relapse</td>
<td>Worse</td>
<td>2L</td>
<td>55</td>
<td>150</td>
<td></td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>10 years</td>
<td>1</td>
<td>0-5, 1/100</td>
<td>A.C.T.H.</td>
<td>24</td>
<td>Worse</td>
<td>Numerous</td>
<td>1L</td>
<td>90</td>
<td>110</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

¹Relapse in this column indicates a relapse during the preceding six months.

L = lymphocytes, P = polymorphonuclear leukocytes.

condition has been obtained from their medical practitioners. As a part of the follow-up many patients were re-admitted to have their condition reassessed. In judging the course of the illness, the opinions of their relatives were obtained whenever possible.

At the beginning of the trial patients were informed that this method of treatment was an experimental undertaking but that it had been claimed to be beneficial.

**IMMEDIATE COMPLICATIONS AND REACTIONS**

As noted by Smith et al. (1957) most patients developed acute reactions which took the form of severe headache, drowsiness, pyrexia, nausea, pains in the limbs, neck stiffness, photophobia, and other signs of meningeal irritation. Sometimes these symptoms began as late as 36 hours after the intrathecal injection. Many showed a transient exacerbation of the physical signs which gradually subsided. Bladder complications were so common as to be regarded as part of the reaction, and usually took the form of acute retention. Carbachol was given for this but was often unsuccessful so that catheterization became necessary. As is common in bladder disturbances of this type a high incidence of urinary infection followed and prophylactic urinary disinfectants were administered as a routine when the
frequency of this complication was realized. Later in the investigation patients were given sulpha-
methizole and a self-retaining catheter was inserted before the administration of the P.P.D. to diminish
the effects of the acute retention. Nevertheless some patients who before P.P.D. had adequate bladder
function, were left with impairment of the vesical sphincters, urinary infection, frequency, and small
spastic bladders. One patient completely lost bladder function and eventually required permanent cathe-
terization.

Another immediate complication of an alarming kind was hyperpyrexia associated with a gross con-
fusional state. This was observed in five patients and in two of them it was associated with respiratory
failure. One of these had to be resuscitated with a hand respirator and the other required tracheotomy.
Herpes zoster developed in one patient. Two developed erythematous rashes at the site of lumbar
puncture believed to be due to a tuberculin type of reaction brought on by leakage of P.P.D. at the
injection site.

Fresh lesions developing immediately or very soon after P.P.D. occurred in two patients, in one retro-
bulbar neuritis and in the other a Brown-Séquard syndrome associated with a psychotic episode. One
man became apathetic, more spastic, and also developed gross sepsis of the skin. A tremor of brain-
stem type became more marked in another patient. Another complication was a complete block of
cerebrospinal fluid which appeared in one man. One patient who had had some renal complications before receiving P.P.D. developed renal colic. One woman, whose main complaint was backache, became worse and would not continue her treatment. Another patient similarly refused further treatment after a single injection. A few patients showed increasing weakness.

RESULTS OF FOLLOW-UP

The results are shown in Table I. The appearance of new symptoms and signs after the initial reaction had subsided is described in this table as a relapse, as is the sudden marked deterioration compared with the previous state. Transient disturbances were not taken into account in this assessment. Gradual deterioration leading to a change in the patient's functional capacity is recorded as a worsening of the condition. Table I shows the state of the patients at one year and also the last known condition.\(^1\) Thirty-four months after the beginning of this investigation the position was as follows:—Out of the 36 patients five were improved, one was unchanged, four were slightly worse, 19 were worse, five much worse, one could not be traced, and one had died. The last was a man who had been grossly restricted in physical activity leading a wheelchair existence at the beginning of the treatment. He died within a few months of pyelonephritis.

\(^1\) Fuller clinical details will be sent to those interested, on request.

RELAPSE RATES During the first year after the injection of P.P.D. 30 relapses were noted and these occurred in 24 out of the 36 patients. In the first six weeks after therapy three relapses occurred. Eight relapses took place in the second six weeks, five relapses from 12 to 26 weeks, and 14 relapses from six months to one year.

In Tables IIA and IIB these rates have been analysed. Table IIA shows the number of first relapses in the above periods. Table IIB shows the incidence of all the relapses during the same intervals. As can be seen, the period from seven to 12 weeks inclusive had the highest incidence of first relapses and also of the total number of relapses. In Table IIB the patient who could not be traced has been omitted.

DISCUSSION

Smith et al. (1957) state that in order to produce a beneficial effect in multiple sclerosis by this treatment

TABLE IIA

<table>
<thead>
<tr>
<th>Time after First Injection</th>
<th>Correction Factor for Time</th>
<th>No. of Patients</th>
<th>No. of First Relapses Observed</th>
<th>Mean First Relapse Rate per Patient per Annum (M)</th>
<th>Standard Error of Differences</th>
<th>Difference of Means (M1 - M2)</th>
<th>Ratio Last Two Columns</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-6 weeks inclusive</td>
<td>8-666</td>
<td>36</td>
<td>3 (8-333%)</td>
<td>0-722</td>
<td>0-734</td>
<td>1-116</td>
<td>1-52</td>
<td>P&gt;0-1</td>
</tr>
<tr>
<td>7-12 weeks inclusive</td>
<td>8-666</td>
<td>33</td>
<td>7 (21-21%)</td>
<td>1-838</td>
<td>0-674</td>
<td>1-244</td>
<td>1-94</td>
<td>0-05&lt;P&lt;0-1</td>
</tr>
<tr>
<td>13-26 weeks inclusive</td>
<td>3-714</td>
<td>25</td>
<td>4 (16-00%)</td>
<td>0-594</td>
<td>0-349</td>
<td>0-358</td>
<td>1-0</td>
<td>P&gt;0-1</td>
</tr>
</tbody>
</table>

TABLE IIB

<table>
<thead>
<tr>
<th>Time after First Injection</th>
<th>Correction Factor for Time</th>
<th>No. of Patients</th>
<th>All Relapses Observed</th>
<th>Mean Relapse Rate per Patient per Annum (M)</th>
<th>Standard Error of Differences</th>
<th>Difference of Means (M1 - M2)</th>
<th>Ratio Last Two Columns</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-6 weeks inclusive</td>
<td>8-666</td>
<td>36</td>
<td>3 (8-333%)</td>
<td>0-722</td>
<td>0-733</td>
<td>1-259</td>
<td>1-72</td>
<td>0-05&lt;P&lt;0-1</td>
</tr>
<tr>
<td>7-12 weeks inclusive</td>
<td>8-666</td>
<td>35</td>
<td>8 (22-85%)</td>
<td>1-981</td>
<td>0-653</td>
<td>1-435</td>
<td>2-19</td>
<td>0-02&lt;P&lt;0-05</td>
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<tr>
<td>13-26 weeks inclusive</td>
<td>3-714</td>
<td>34</td>
<td>5 (14-70%)</td>
<td>0-546</td>
<td>0-281</td>
<td>0-277</td>
<td>0-99</td>
<td>P&gt;0-1</td>
</tr>
</tbody>
</table>
a marked rise in the level of protein in the cerebrospinal fluid was necessary. They found that they could give repeated injections of P.P.D. intrathecally without ill effects. Our technique was to give multiple injections of this material. Most patients had two or three such injections. In view of the considerable difficulty in predicting the severity of the reaction, the amount of the first injection was often of the order of 0.5 ml of a 1 in 100 dilution of the standard solution of P.P.D. (7.5 micrograms per ml) which is 10 times less than that employed by the Oxford workers. To modify the severe reactions A.C.T.H. intramuscularly was administered. Similarly the Oxford workers had given cortisone for the same purpose. The use of A.C.T.H. as a therapeutic measure was only employed if the severity of the reaction necessitated it.

Like Smith et al. (1957) we observed two patients with respiratory failure. These had previously shown signs of brain-stem damage, and it seems reasonable to suppose that an extension of a pre-existing lesion in this region was responsible for the failure of respiration. In the natural course of multiple sclerosis respiratory complications have been observed.

Urinary disturbances were very common. They took the form of increased frequency, urgency or precipitancy of micturition, or incontinence. Retention with or without overflow occurred in many patients. This was most serious as it led to severe infection. Such disturbances of micturition were very persistent, lasting many months and leading to marked physical deterioration and loss of morale. The pathological changes responsible for the sphincter disorders are not known, but one possibility which should be considered is that the P.P.D. becomes absorbed or fixed near the site of injection on the lumbosacral roots and conus medullaris and that the subsequent meningeal reaction which is of an immunological nature, tends to be very severe at these sites. An alternative possibility is that pre-existing lesions of the spinal cord flared up. There was evidence that fresh spinal lesions might occur, as one patient developed a Brown-Séquard syndrome from which she took many months to recover. Previously she had not had any clinical evidence of a lesion at the affected level of the spinal cord.

A rising level of protein after intrathecal P.P.D. has been described but one patient in this series developed manometric evidence of a complete spinal block which subsequently remitted. It is considered that if the protein level in the cerebrospinal fluid becomes greatly raised the possibility of a spinal block should be suspected. It is also of interest that in two patients symptoms suggestive of spinal arachnoiditis appeared at a late stage. The details of the changes found in the cerebrospinal fluid with particular reference to the protein fractions will be discussed in another paper but Table I shows the highest level of protein which developed and also the findings preceding treatment.

If the relapse rate is compared with that noted by McAlpine, Compston, and Lumsden (1955) then it will be seen that the average relapse rate in this series for the 12 months following treatment was 0.83 as against 0.39 observed by McAlpine et al. The two series may not be strictly comparable as our patients were selected because they were having frequent relapses and it is possible that their natural relapse rate would have been higher than that recorded by McAlpine et al. Because of this, we analysed the relapse rate in our series in relation to the time following treatment (Tables IIA and IIB). The figures show that the period of six to 12 weeks was a very hazardous one and that at this time the relapse rate became greatly increased compared with the preceding or following periods.

If the figures are analysed statistically by the \( \chi^2 \) test then the values are not sufficiently large to show a significant change in the relapse rate over the whole year. On the other hand, if the figures are analysed according to the means and standard errors, then a significant drop is suggested between the second and third periods of Table IIB in which \( P \) lies between 0.02 and 0.05 and this is suggestive of a real difference and might imply that the high relapse rate between the seventh and twelfth week could have been related in some way to the treatment. For the corresponding period in Table IIA where only the first relapse is considered \( P \) lies between 0.05 and 0.1. If the above figures are significant then it would seem that our technique of injecting P.P.D. may have fired off the same mechanisms as those which are responsible for relapse in multiple sclerosis, and this might indicate that an immunological stimulus occurring about six to 12 weeks before a relapse may be the cause.

Our findings are very different from those noted by Smith et al. The severe initial complications, the high relapse rate, and the large percentage of patients whose condition became worse has been a striking feature in this series. The source of P.P.D. was the same in both series (Weybridge) but it is conceivable that when dealing with such complex biological material as P.P.D. there may be variations in its composition. The dose of P.P.D. given to our patients on the whole seems to be smaller than that given by the Oxford workers. We have considered the possibility that the A.C.T.H. which was given to ameliorate the acute reaction could be responsible for the differences in the findings but our own experience of the use of A.C.T.H. would not support this view. Nor is this borne out by the work of
Alexander, Berkeley, and Alexander (1958). The worsening of the clinical status of many patients was a gradual deterioration quite independent of obvious relapses. It is probable that the urinary infections may have contributed towards this.

A preliminary report by Miller, Newell, Ridley, and Schapira (1961) at the meeting of the Association of British Neurologists of a controlled series of patients treated with intrathecal P.P.D. did not indicate any differences in patients treated in this way and those who received intrathecal saline. Kelly and Jellinek (1961) reported similar findings. Marshall and O’Grady (1959) injected P.P.D. intrathecally into 17 patients with multiple sclerosis but did not consider that they had sufficient data to assess the effects of the treatment. They reported loss of sphincter control persisting for several weeks.

A recent publication by Smith, Hughes, and Hunter (1961) states that there was diminution of the relapse rate in patients with multiple sclerosis treated in this way if they developed a protein exceeding 550 mg. in cerebrospinal fluid with a low cell count. Table I does not indicate that patients who develop a high protein level fared any better than the others. Owing to different times at which lumbar puncture was performed it is not possible to compare the results in relation to the cellular reactions.

Purified protein derivative is made (Paterson, 1957) by treating the steamed culture filtrate of M. tuberculosis grown on a synthetic medium with trichloracetic acid. The precipitated protein is washed with diluted trichloracetic acid, redissolved and then clarified by filtration or by Sharples centrifugation. Its stability is affected by storage conditions and it is unstable in high dilution. Magnus, Guld, Waaler, and Magnusson (1956) drew attention to loss of its potency by absorption on to the glass ampoules. The known components of P.P.D. include nucleic acid, polysaccharide, lipopolysaccharide, lipid, and a number of proteins. Some of these substances are present in small amounts as impurities. Seibert (1950) noted the partial degradation of P.P.D. by the heating process used in its preparation, and in unheated P.P.D. material which she prepared she found three separate proteins of different potencies, one of which was more active in higher dilutions. Later Seibert, Soto Figueroa, and Dufour reported (1955) that variable amounts of these proteins were produced in culture filtrates from time to time regardless of the strain (of the organism), the time of growth, medium used, or method of isolation, and that to obtain protein fractions with reproducible and constant compositions special methods of preparation would be necessary.

It might appear that these conclusions would be equally applicable to P.P.D. prepared from steamed culture filtrates as used here. For this reason it is not possible to state with certainty that different investigators have been using P.P.D. samples which are chemically identical as regards the proportions of the different constituents. Also, the question now arises whether P.P.D. may contain encephalitogenic material. One of us (Colover, 1954) failed to produce experimental allergic encephalomyelitis with P.P.D. in guinea-pigs although two animals out of 10 died. However, it is now known (Colover, 1958) that the method of injection used in those early experiments, although quite adequate for very active materials, might not have recognized weak encephalitogenic activity. Using immunological and immunochemical methods Burtin, Kourilsky, Uriel, and Ternynck (1959) and Burtin, Uriel, and Ternynck (1959) reported the presence of both polysaccharide and lipopolysaccharide derivatives in culture filtrates of tubercle bacilli. In 1958 Colover showed that purified tubercle bacillus lipopolysaccharide had encephalitogenic properties in guinea-pigs, and it is therefore conceivable that P.P.D. may contain small quantities of such encephalitogenic substances. The amounts, however, which might be injected in humans according to the dose scale shown in Table I would be much less than those which were employed experimentally in guinea-pigs.

It is considered that in regard to P.P.D. treatment of multiple sclerosis there is a state of uncertainty concerning the chemical composition of this material. The results of this therapy will be variable until purified preparations of P.P.D. of known biochemical composition and immunological behaviour are obtainable and it is understandable that with the material as at present available different observers may obtain different results and that these will be unpredictable. If it is confirmed that the P.P.D. complex as made at present contains encephalitogenic substances then it is clearly undesirable that it should be administered intrathecally.

SUMMARY

Thirty-six patients with multiple sclerosis were treated with intrathecal P.P.D. and their condition observed over a period varying from 16 to 34 months.

No evidence was found of any favourable effects, most deteriorated, and there was a high relapse rate.

The highest relapse rate was noted between the sixth and twelfth week after P.P.D. injection. Statistical analysis of the results suggested that this high relapse rate could have been related to the treatment. If this were so, then it could be evidence that some naturally occurring relapses in multiple sclerosis might similarly be caused by an immuno-
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Logical stimulus preceding them by the same time interval.

Attention is drawn to the variability of composition of P.P.D. and to the theoretical possibility of encephalitogenic substances being present in it. Until this question is clarified it is doubtful whether this material should be injected intrathecally.

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