ankle pulses, and suggests that with one reservation the inability to detect an ankle pulse by *one* observer is quite without significance, unless the finding is confirmed by careful examination by other observers. The reservation is with respect to the posterior tibial pulse in the over-60 age-group, where there is a very much higher probability that the single observer's findings will be confirmed.

There is, however, evidence that under certain circumstances the incidental finding of an absent ankle pulse may be of significance.

It can be seen (Table III) that the upward trend with age of the proportion of impalpable pulses is most striking in the case of the posterior tibial pulse. On the other hand, in the over-40 age-groups a preponderance of undetectable posterior tibial pulses occurred in females (Table III), which is unexpected if this is taken as an indication of arterial disease. In the 40-59 age-group, however, the observer error is very great (Table I). This we attributed to the high proportion of women in this age-group with a fat-pad behind the internal malleolus.

If the proportion of absent posterior tibial pulses in the different age-groups is recalculated on a basis of the findings when all *three* observers agree, a rather different result is obtained (Table VI).

TABLE VI.—Percentage of Limbs with Impalpable Posterior Tibial Pulses in Different Age-groups. The Results of One Observer, Compared with those when Three Observers Agree

Age-group	One Observer	Three Observers Agree
0-19	0.2%	0%
20-39	1.9%	0.9%
40-59	5.4%	0.7%
60-79	16.0%	13.6%

Thus of the 392 limbs of subjects under the age of 60 which were examined, all three observers agreed in being unable to feel a posterior tibial pulse in only 0.5%. If three observers of similar skill are unable to detect the posterior tibial pulse in a limb the probability is therefore very high that this represents an abnormality.

It is difficult to escape the conclusion that in some 13.6% of the limbs of those over the age of 60 such an abnormality existed. When it is remembered that this is a finding with which all three observers agreed, it is very difficult to explain it on a basis other than that of atheromatous narrowing or block of the artery. There is no absolute proof of this; nor, indeed, would any proof except arteriographic or necropsy findings be satisfactory.

Summary

The great observer error in the detection of the posterior tibial and dorsalis pedis pulses is demonstrated.

In the limbs of subjects under the age of 20, on the average a single observer failed to detect 0.24% of posterior tibial pulses and 8.7% of dorsalis pedis pulses.

In patients not presenting primarily with atherosclerosis the lack of significance of inability to detect the dorsalis pedis pulse is shown.

Evidence is produced that if three independent observers are unable to detect the posterior tibial pulse there is a high degree of probability that an abnormality is present.

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THERAPEUTIC TRIALS IN MULTIPLE SCLEROSIS

FINAL REPORT ON EFFECTS OF INTRATHECAL INJECTION OF TUBERCULIN (P.P.D.)

BY

HENRY G. MILLER, M.D., F.R.C.P.
Physician

D. J. NEWELL, M.A., Ph.D., F.S.S.
Statistician

ALAN R. RIDLEY, M.B., M.R.C.P.

AND

KURT SCHAPIRA, M.D.

Research Fellows

From the Department of Neurology and the Medical Research Council Research Group on Demyelinating Diseases, Royal Victoria Infirmary, and Medical School, Newcastle upon Tyne

In a previous communication (Miller, Newell, Ridley, and Schapira, 1961) the preliminary results were reported of a controlled trial of treatment with intrathecal P.P.D., which Smith, Espir, Whitty, and Russell (1957) had suggested might have a beneficial effect on the course of multiple sclerosis. At that time 82 of the intended 90 patients had been included in the trial, and the mean period between treatment and first assessment was 15 months. It was concluded that patients given intrathecal P.P.D. did not fare better than those who received intrathecal saline or others who had merely been subjected to lumbar puncture. This was also the experience of Kelly and Jellinek (1961); nor could Colover, Kremer, Lovelace, and Silver (1962) find any evidence from their uncontrolled observations that intrathecal P.P.D. had a favourable influence on the disease. Marshall and O'Grady (1959) investigated the changes in spinal fluid after the administration of intrathecal P.P.D. in multiple sclerosis and other chronic neurological diseases, but refrained from commenting on the therapeutic effect because of the small number of patients with multiple sclerosis in their series and the lack of controls. The present report is concerned with the follow-up trial of 90 trial patients reviewed annually for one to three years after treatment.

Material

The 90 patients were allocated to one of three treatment groups—lumbar puncture (L.P.), saline (S.), and P.P.D.—by a system of stratified randomization. Each patient was given a functional grade. The grades were grade I, symptom-free; grade II, with symptoms but unrestricted activities; grade III, moderately restricted; grade IV, markedly restricted; grade V, confined to home; grade VI, immobile at home; grade VII, bedridden. A separate randomization was carried out in

each of four groups defined by functional grades III and IV, and by durations of symptoms of less than or more than five years. Within each of the four groups randomization was further restricted to ensure that after each six patients had been admitted to each group, exactly two would be allocated to each treatment (Bradford Hill, 1961).

Eight patients have been excluded from the analysis. In the L.P. group one patient defaulted, another could not be traced, and a female patient initially diagnosed as suffering from multiple sclerosis was later considered not to have this disease. Two patients in the S. group defaulted, and one died of pneumonia before the first review. Of the patients given P.P.D., one refused to complete the course of treatment and another declined to be reviewed.

A comparison of the patients receiving the three treatments and suitable for analysis is given in Table I. It will be seen that the randomization scheme was successful in providing three groups very similar in all of the recorded characteristics.

TABLE I.—Comparison of Groups Before Treatment

	Lumbar Puncture	Intrathecal Saline	Intrathecal P.P.D.
No. in group	25	28	29
Males	13	17	13
Females	12	11	16
Reviewed after two or three years	17	18	16
Reviewed after one year only	8	10	13
Course of disease { Rapidly progressive	1	2	4
{ Slowly	21	23	22
Exacerbation remission	3	3	3
Functional grading { III	16	18	19
{ IV	9	9	10
{ V	0	1	0
Mean age at onset of disease	33.7 years	32.5 years	32.2 years
" " " start of treatment	42.9 "	41.0 "	42.1 "
Average Alexander score before treatment	216.6 ± 17.5	229.8 ± 12.9	216.1 ± 14.4

± figures denote standard error of the mean.

Twenty-five patients were admitted to the L.P. group. Of these, eight had been in the trial only long enough for a single annual review, and the remainder had two or three reviews. The corresponding figures for the S. and P.P.D. groups are very similar.

In the majority of cases the disease was slowly progressive at the time of admission to treatment. In a few the course was rapidly progressive, or consisted of exacerbations and remissions. Table I shows that by chance four of the seven with rapidly progressive disease were allocated to the P.P.D. group. It will be seen that this had no effect on the outcome of the trial.

In each treatment group two-thirds of the patients were in functional grade III. The groups were also similar in mean age at onset of the disease, in mean age at the start of treatment (and hence in duration of the disease), and in clinical condition as assessed by Alexander's scoring system (Alexander, Berkeley, and Alexander, 1958).

Method

Details of the three treatments were described in the first report. Briefly, they were as follows: P.P.D. patients were given two intrathecal injections of P.P.D. (Weybridge), each of which produced a rise in spinal-fluid protein of over 100 mg./100 ml. Two patients were Mantoux-negative and were first "converted" with B.C.G. before starting treatment. Constitutional reactions to intrathecal P.P.D. were common, and were usually accompanied by an exacerbation of the existing neurological disability. Urinary retention was parti-

cularly troublesome, and six patients had severe P.P.D. reactions with meningitis and brain-stem signs: two became comatose. Patients in the S. group were given two intrathecal injections of 0.5 ml. and 1 ml. of normal saline separated by an interval of 7 to 10 days, and the L.P. group were subjected to a lumbar puncture, which was repeated 7 to 10 days later.

Results

Patients were reviewed and assessed by an observer unaware of the treatment group to which the patient belonged. Results are summarized in Table II. In every case the data refer to the final assessment of the patient between one and three years after beginning the treatment.

For each criterion the analysis has been carried out separately for patients with only one assessment (at one year after treatment) and for those with more than one assessment. For clarity of presentation the two sets of results have been amalgamated, again in Table II, for most of the variables.

Functional Grading.—The functional gradings by this time showed greater diversity than at the beginning of the trial. Several patients had deteriorated into grades V and VI; a few had improved into grades I and II. There was no significant difference in the average change in grade between the three treatments, the average deteriorations being 0.20, 0.21, and 0.45 grades for L.P., S., and P.P.D. respectively. For P.P.D. this deterioration was significantly greater than zero; for the other two treatments it was not.

Alexander Scores.—These changed considerably during the trial, ranging from an improvement of 270 points, with obvious clinical improvement in 28 months, to a deterioration of 235 points in 25 months. Both of these patients were in the L.P. group, which therefore showed greater variability in response than did the other two treatment groups. The overall finding is again that there was no significant difference between the mean deteriorations in Alexander scores for the three treatments. Examination of the separate results for each treatment group is interesting. With P.P.D. there were significant deteriorations of 38 and 58 points in the groups observed for one and two and a half years

TABLE II.—Comparison of Groups After Treatment

	Lumbar Puncture	Intrathecal Saline	Intrathecal P.P.D.
Period between treatment and assessment (mean):			
All patients	22.3 months	23.1 months	22.0 months
Patients reviewed after two or three years	26.6 "	29.6 "	30.8 "
Patients reviewed after one year only	13.3 "	11.6 "	11.2 "
Functional grading { I	1	0	0
{ II	1	1	0
{ III	11	13	11
{ IV	9	12	13
{ V	1	0	5
{ VI	2	2	0
Average deterioration in grading	0.20 ± 0.22	0.21 ± 0.16	0.45 ± 0.13*
Average deterioration in Alexander score:			
Patients reviewed after two or three years	10.5 ± 21.3	37.7 ± 12.4*	58.0 ± 12.1†
Patients reviewed after one year only	47.9 ± 36.5	16.0 ± 12.4	37.6 ± 9.6*
Patient's { Improved throughout assessment	3	2	2
{ Worse throughout	8	12	17
{ Unchanged or variable	14	14	10
Acute exacerbations { Reported since treatment	1	5	10
New symptoms	4	9	10
New signs	8	5	8

± figures denote standard errors of mean deteriorations.

* Mean significantly different from zero at 1% level.

† Mean significantly different from zero at 0.1% level.

respectively. With saline the corresponding deteriorations were 16 and 38 points, the deterioration at one year not being significantly different from zero. In the L.P. group the two very large changes mentioned previously obscured the expected pattern of mean deterioration increasing with time. In view of the non-homogeneity of variances, the changes in Alexander score were analysed by a number of methods (including ranking tests and t-test on homoscedastic pairs), none of which indicated any significant differences between results on the three treatments. Nor was there any significant difference in the number of new symptoms and signs occurring during the trial.

Patients' Subjective Assessment.—At each review each patient was asked for his opinion of the change in his condition since he was last seen. In Table II these results are summarized by showing those who consistently reported an improvement, those who consistently reported that they were worse, and the remainder who either remained unchanged or reported an improvement at one review and a deterioration at another. Seven patients, evenly divided amongst the treatments, reported improvement, and 37 reported a deterioration. Eight of these were in the L.P. group, 12 in the S. group, and 17 in the P.P.D. group. Again there is no significant difference between the groups.

Acute Exacerbations.—A significant difference was found in the number of acute exacerbations. One and five occurred in the L.P. and S. groups respectively, but 10 among those receiving P.P.D. ($\chi^2=6.45$, d.f.=2, $P<0.05$). The numbers of patients suffering these acute exacerbations were one, three, and seven respectively for L.P., S., and P.P.D.

It was mentioned earlier that four of the seven patients with rapidly progressive disease were admitted by chance to the P.P.D. group. Although the number of patients is not statistically significant, some comment is called for to indicate that they did not invalidate the results. These four patients showed no change in functional grading in the course of the trial, and their average change in Alexander score was slightly less than that for the remainder of the P.P.D. group. Exclusion of these patients would change none of the conclusions of the trial: they have therefore been retained in the analysis.

Conclusions

The findings lend no support to the suggestion that intrathecal P.P.D. has a beneficial effect on the course of multiple sclerosis. There were no significant differences between the three treatment groups by the following criteria: change in functional grading, change in Alexander score, number of new symptoms or signs, or the patients' own assessment of improvement or deterioration. There was, however, a significant increase in the number of acute exacerbations experienced by patients in the P.P.D. group. Smith, Hughes, and Hunter (1961) claim that if a rise of spinal fluid protein of 550 mg./100 ml. or more is induced the chance of relapse during the next year is lessened. In the present trial such high levels of spinal protein were not reached, but the study of Colover *et al.* (1962), in which protein rises of the order recommended by Smith *et al.* were produced, did not reveal that the clinical course in patients with marked spinal-fluid-protein reactions was more favourable than that of patients with a smaller increase in protein content.

Summary

The intrathecal administration of P.P.D. to patients with multiple sclerosis failed to exert any favourable influence on the course of the disease; it appeared to induce an increased number of exacerbations during the succeeding one to three years; and it evoked an immediate reaction which was always uncomfortable and sometimes alarming. Such findings hardly serve to establish it as an acceptable form of treatment.

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CONTROLLED CORD TRACTION IN MANAGEMENT OF THE THIRD STAGE OF LABOUR

BY

PAMELA M. SPENCER, M.B., F.R.C.S.
M.R.C.O.G.

Consultant Obstetrician and Gynaecologist, Elizabeth Garrett Anderson Hospital, London; formerly First Assistant, Obstetric Unit, University College Hospital, London

The Third-stage Problem

Complications in the third stage of labour remain the major unpredictable hazard facing an expectant mother. Nixon (1955) stated that "in England to-day a conservative estimate would be that one in five thousand mothers dies from haemorrhage." The Report of Confidential Enquiries into Maternal Deaths in England and Wales, 1955-57 (Ministry of Health, 1960), found that haemorrhage was the fourth most common cause of maternal death. Avoidable factors were thought to be present in 37 of the 70 records examined where the patient died from post-partum haemorrhage.

It is very likely that for every maternal death due to haemorrhage there are many instances where death is averted by efficient treatment. The obstetric flying squad is called to most of the serious third-stage complications that occur at home. Lloyd (1949) showed a steady fall in maternal deaths in Birmingham during the years in which the flying squad had operated in the city. Dewhurst (1952) reviewed 489 calls dealt with by the Manchester squad: 79% were to patients with third-stage complications. He wrote: "Many of the patients treated were near to death—so near in fact as to cause the gravest concern to even the most experienced of the flying squad." In London 62% of the calls to St. James's Hospital, Balham (Fraser and Tatford, 1961), in Edin-