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THERAPEUTIC TRIALS IN MULTIPLE SCLEROSIS

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

BY

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In 1957, Smith, Espir, Whitty, and Russell described what they regarded as characteristic changes in the spinal fluid of patients with multiple sclerosis following intrathecal injection of tuberculin (purified protein derivative, P.P.D.). They regarded these changes as indicating an abnormal and possibly specific immunological reaction, suggested that the administration of P.P.D. "might be beneficial in multiple sclerosis", and quoted initial clinical observations which seemed to lend some support to this view. The spinal fluid changes described were seen only in Mantoux-positive patients, and comprised an apparent suppression of the initial polymorphonuclear response seen in similar control (psychotic) patients similarly injected, with a subsequent exudation of mononuclear cells and a disproportionate biphasic rise in protein content. Marshall and O'Grady (1959) have subsequently demonstrated that spinal fluid changes similar to those encountered in multiple sclerotic cases are also seen after the intrathecal injection of P.P.D. in Mantoux-positive patients with other chronic neurological disorders such as motor neurone disease and Parkinsonism, an observation which they interpret as indicating the non-specific nature of the response without in any way "nullifying the suggestion that this treatment may be of benefit".

Although the reason for endowing this procedure with any possible therapeutic significance has never been clearly stated, we felt it important that the suggestion should be subjected to carefully controlled assessment, and it is with the preliminary results of such a trial that the present paper is concerned.

Material

The trial, which is still in progress, is to include 90 moderately disabled patients randomly allocated amongst three treatment groups whose management is conducted under similar conditions. One group is given intrathecal P.P.D., one intrathecal saline, and one is subjected to simple spinal punctures. During the treatment period each patient received in addition a three-week standardized course of physiotherapy.

Up to the present, 82 patients have been included in the trial, and the original intention was to defer assessment of results until two years after the treatment of the ninetieth patient had been completed. Our decision to report here the results of a preliminary analysis of 44 patients in whom more than 12 months have elapsed since the completion of treatment has been dictated by the considerable pressure to which neurologists in various parts of the United Kingdom have been subjected by patients who are anxious for them to undertake this form of treatment on the basis of present evidence.

In addition to the 44 cases in the trial proper, the present interim study includes 13 further patients with chronic multiple sclerosis to whom we had administered P.P.D. before the trial began. Because of death or unwillingness to participate further, four "trial" patients and three "pre-trial" patients could not be reviewed, and analysis is therefore based on the remaining 40 "trial" and 10 "pre-trial" patients. Of the 40 trial patients, 14 had lumbar puncture only, 12 received intrathecal saline, and 14 were given intrathecal P.P.D. The status of the patients before treatment was instituted is summarized in Table I.

The lumbar puncture (LP) group contained six men and eight women, the saline (S) group eight men and four women, and the P.P.D. group seven men and seven women. The pre-trial P.P.D. patients comprised six men and four women.

The mean age of onset of the disease was 33·5 years (LP), 31·3 years (S), 32·4 years (P.P.D.), and 26·3 years (pre-trial P.P.D.). At the onset of treatment the mean duration of the disease was 10·4, 8·0, 7·0, and 9·7 years respectively.

With regard to the course of the disease up to the time of the trial, the LP group comprised 11 patients in whom the disease had progressed slowly and three in whom the course showed exacerbations and remissions; the S group comprised one rapidly progressive, eight slowly progressive, and three exacerbating and remitting cases. In the P.P.D. group there were one rapidly progressive, 10 slowly progressive, and three exacerbation-remission cases; whilst among the pre-trial P.P.D. cases there were seven in whom the disease was of slow progression and three in whom its course had exhibited exacerbations and remissions.

The functional grade of patients was also recorded initially and at each subsequent examination. The

grades employed were grade I, symptom free; grade II, 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. At review, specific enquiry was made about any acute exacerbations experienced, and the patients were also asked if they thought their condition had improved, deteriorated, or remained unchanged.

The Alexander scoring system (Alexander, Berkeley, and Alexander, 1958) was used to record the results of clinical examinations carried out before treatment and at the time of re-assessment.

Eight patients had received previous medication. This consisted of vitamin B_{12}, liver injections, or arsenical therapy, and this group included one patient in the LP group, four in the S group, one P.P.D. case, and two pre-trial P.P.D. patients. No patient was included in the trial who had received any such treatment during the preceding year.

The random allocation had thus produced three trial groups comparable in all the relevant respects mentioned.

Method

P.P.D. and Pre-trial P.P.D. Patients.—Before beginning intrathecal injections the following preliminary investigations were carried out: (1) Chest radiograph; (2) serial Mantoux testing, using dilutions of 1 : 10,000, 1 : 1,000, 1 : 100 (since only Mantoux-positive patients will show the described response to intrathecal tuberculin, any Mantoux-negative patients were first "converted" with B.C.G.); (3) E.S.R., full blood count, and blood urea estimations; (4) microscopic examination of urine to exclude infection.

The tuberculin (P.P.D.) obtained from the Ministry of Agriculture and Fisheries Veterinary Laboratory at Weybridge was made up into "standard" P.P.D. (Smith *et al.*, 1957) which contains 7·5 μg. of P.P.D. per ml.

At lumbar puncture a specimen of spinal fluid is collected for cell count and protein estimation, and 0·5 ml. of 1 in 10 standard P.P.D. introduced into the lumbar sac. Temperature and pulse are recorded four-hourly. Twenty-four hours after the administration of the P.P.D., spinal fluid is collected to determine whether cells and protein have risen. A "satisfactory reaction" is considered to have taken place if the rise in spinal fluid protein exceeds 100 mg. per 100 ml. If the protein rise is less than this figure, a further lumbar puncture is carried out three days later, and if the increase in the protein level of the fluid has still not exceeded 100 mg. % the response is recorded as "no reaction". Should there have been no reaction, 1·0 ml. of 1 in 10 standard P.P.D. is given, and if this dose fails to produce a reaction, 1·5 ml. of 1 in 10 standard P.P.D. solution is injected.

When a reaction has occurred, no more P.P.D. is given until the spinal fluid protein content has fallen to below 100 mg. %. Two reactions constituted a "course" of P.P.D. In the pre-trial P.P.D. group, three reactions were induced in two patients. All the reactions in both P.P.D. and pre-trial P.P.D. groups fulfilled the above criteria, and the mean increases in the spinal fluid protein induced by both first and second injections of P.P.D. were 260 mg. % (P.P.D. group) and 290 mg. % (pre-trial P.P.D. group).

The "P.P.D. reaction" was usually accompanied by a constitutional illness with some degree of meningism, and occasional more alarming complications included severe clinical meningitis with troublesome vomiting (four cases), retention of urine (four, including one requiring three weeks' catheterization), coma (two), dysphagia and dysarthria. In three further patients severe exacerbations of the chronic disease caused some alarm during treatment, and in one of these instances a profound difficulty in walking did not fully recover.

Saline Group.—These patients received two intrathecal injections of 0·5 ml. and 1·0 ml. of normal saline separated by an interval of seven to 10 days, and each injection was followed 24 hours later by lumbar puncture for estimation of cell and protein content of the spinal fluid. The changes observed were trivial and evanescent.

Lumbar Puncture Group.—Patients in this group had one lumbar puncture followed by a further puncture seven to 10 days later.

Assessment

Disability was assessed and scored by an observer who was unaware of the patient's treatment group

TABLE I

COMPA RISON OF GROUPS BEFORE TREATMENT

		Trial Treatment			Pre-trial Group P.P.D.
		Lumbar Puncture	Intrathecal Saline	Intrathecal P.P.D.	
Number in Group		14	12	14	10
Males		6	8	7	6
Females		8	4	7	4
Mean age at onset of multiple sclerosis		33·5 yr.	31·3 yr.	32·4 yr.	26·3 yr.
Mean age at start of treatment		43·9 yr.	39·3 yr.	39·4 yr.	36·0 yr.
Course of disease	Rapidly progressive	—	1	1	—
	Slowly progressive	11	8	10	7
	Exacerbation-remission	3	3	3	3
Functional grading	III	10	8	10	7
	IV	4	4	4	1
	V	—	—	—	—
	VI	—	—	—	2
Alexander classification (mean)		200·3	219·0	201·6	241·0

TABLE II

COMPARISON OF THE GROUPS AFTER TREATMENT

	Trial Treatment			Pre-trial Group P.P.D.
	Lumbar Puncture	Intrathecal Saline	Intrathecal P.P.D.	
Period between treatment and assessment (mean)	14 mth.	16 mth.	15 mth.	33 mth.
Functional grading III	9	5	9	3
Functional grading IV	3	7	4	2
Functional grading V	1	—	1	1
Functional grading VI	1	—	—	3
Functional grading VII	—	—	—	1
Deterioration score	+27·6	+34·2	+33·4	+74·2
Number of acute exacerbations since treatment	1	1	6	1
Patients' assessment after treatment Improved	5	3	3	1
Patients' assessment after treatment Same	4	3	5	2
Patients' assessment after treatment Worse	5	6	6	7

at the time of his examination. Seven patients were not available for this initial review. Of these, three declined to be re-examined, one could not be traced, and three had died. One male patient died suddenly after an attack of bronchopneumonia 18 months after receiving intrathecal saline, and the other two deaths occurred in pre-trial P.P.D. patients, three and 13 months respectively after receiving this form of treatment. In each instance death occurred in toxaemia associated with intractable chronic urinary infection which originated during catheterization necessitated by treatment.

Results

These are summarized in Table II.

Acute Exacerbations.—Discounting the immediate neurological exacerbation which often accompanied a "reaction" in patients injected with P.P.D., six patients in the three trial groups experienced eight subsequent exacerbations during the period of observation following treatment, which has so far covered a total of 580 patient-months. This indicates that one acute exacerbation occurred during every 73 patient-months: in a trial of maintenance treatment with prednisolone, salicylate, and dummy tablets recently concluded (Miller, Newell, and Ridley, 1961) the comparable figure during 18 months' observation in 79 patients who had suffered from the disease for an average period of about 12 years was 75 patient-months per exacerbation. Four of the patients who relapsed had received P.P.D., and one exacerbation occurred in each of the other groups. One of the P.P.D. cases had three exacerbations. These figures are too small to be statistically significant.

Alexander Scores.—A positive change in the Alexander score indicates clinical deterioration. All three of the trial group scored an average of about +30 points on the Alexander scale, and the changes in score did not differ significantly between the three treatments.

The pre-trial P.P.D. patients, with an average deterioration score of +74·2 points, were significantly different from the trial patients ($t=2{\cdot}27$, $P<0{\cdot}05$). This result is consistent: after twice as long these patients had deteriorated twice as much.

Functional Grading and Patients' Subjective Assessments.—In neither instance did comparison in these respects reveal any significant difference between the three trial groups.

Conclusions

These observations have failed to reveal any influence of the injection of intrathecal tuberculin on the subsequent clinical course of multiple sclerosis by comparison with that of saline injection or simple spinal puncture. In more than half the patients treated, the injection of tuberculin provoked an immediate clinical exacerbation of the chronic disease, with the reactivation of old symptoms and the provocation of new, but the present observations lend no support to the contention that the procedure influences the subsequent progression of the disease for good or ill once the immediate effects of treatment have subsided. It is possible that further observations may lead us to revise this assessment, but in the meantime it seems hardly justifiable to regard the intrathecal administration of tuberculin as a form of treatment for this disease.

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