ABNORMAL IMMUNOLOGICAL REACTIONS IN DISSEMINATED SCLEROSIS*

A Preliminary Report

BY

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It is now established that the injection of tuberculin into the cerebrospinal fluid (C.S.F.) of a sensitized subject evokes a wave of inflammation involving the leptomeninges and, to some extent, the vessels of the brain and spinal cord. The properties of this reaction have been studied in both man (Smith and Vollum, 1950; Swithinbank, Smith, and Vollum, 1953) and animals (Bosanquet, Daniel, and Vollum, 1953; Taylor and Hunter, in the press). It is undoubtedly a true antibody-antigen response; it exerts a profound effect on the permeability of the blood-C.S.F. barrier (Smith, Taylor, and Hunter, 1955); and it has proved a useful adjuvant in the treatment of tuberculous meningitis (Smith, Vollum, Taylor, and Taylor, 1956).

About two years ago it was suggested to us by Dr. R. B. Bourdillon that these reactions might be beneficial in disseminated sclerosis, and accordingly in April, 1955, we began to study the effects of intrathecal tuberculin in this disease. Almost at once it became apparent that the local response, as judged by the changes in the C.S.F., were very different from anything we had been accustomed to see in either man or animals. Further experience showed that this departure from the normal pattern and relationships of the intrathecal tuberculin reaction was sufficiently constant to suggest a fundamental disturbance of certain immunological mechanisms. In this paper the peculiar reactions seen in disseminated sclerosis are described and contrasted with those obtained in a group of psychotic patients in whom the meninges were otherwise normal.

Case Material and Methods

The patients with disseminated sclerosis were selected from among those attending the Department of Neurology of the United Oxford Hospitals. A full explanation was given of the different factors involved, and volunteers

were obtained without difficulty. Most of the patients had been under observation for months or years, and all had been carefully investigated, while in every case the histories and findings were sufficiently typical to put the diagnosis beyond all reasonable doubt.

Serial Mantoux tests were done in the usual way with old tuberculin, diluted to 1 in 10,000, 1 in 1,000, and 1 in 100. The 1 in 10 dilution was not used because of the high incidence of non-specific reactions obtained with this solution. The tests were read at 48 hours and only recorded as positive if there was an area of palpable induration of from 5 to 10 mm. in diameter or more.

The purified protein derivative (P.P.D.) of tuberculin was used for the intrathecal injections. This was obtained from the Ministry of Agriculture and Fisheries Veterinary Laboratory, Weybridge, through the courtesy of Dr. Green. The same solutions were used as in the treatment of tuberculous meningitis (Smith *et al.*, 1956); that is to say, the original preparation was diluted to one part in 200 to make a solution containing 7.5 μ g per ml. This we have arbitrarily called the "standard" solution. The standard solution was then further diluted to 1 in 10 and 1 in 100. The 1 in 1,000 dilution was not used. As with all intrathecal solutions, the strictest sterility is obligatory.

The P.P.D. solutions were injected by lumbar puncture and immediately before the injection a sample of C.S.F. was withdrawn for analysis. Twenty-four hours later the puncture was repeated and the C.S.F. examined then and as often during the following fortnight as circumstances permitted. Total and differential cell counts were done, the protein was estimated, and in several cases the Lange curve was also studied.

In many cases the distribution of bromide between blood and C.S.F. was determined throughout the reaction. For this purpose 1 g. sodium bromide was given by mouth at least 48 hours before the P.P.D. was injected, and at each lumbar puncture from 2 to 5 ml. of C.S.F. and of venous blood was collected in dry, chemically clean test tubes. The bromide in both C.S.F. and serum was estimated by a micro-method (Hunter, 1955) and the results expressed as the ratio between the C.S.F. bromide and serum bromide. The upper limit of normal for this ratio for lumbar C.S.F. is 0.5. (In our earlier published work on the blood-C.S.F. barrier the results

* Based on a communication given to the Association of British Neurologists, November, 1956

are expressed as the reciprocal of this ratio, namely, serum bromide/C.S.F. bromide.)

The patients were examined at frequent intervals, and a four-hourly record was kept of the temperature, pulse, and respiration.

Findings in Psychotic Patients

The psychotic patients treated with intrathecal tuberculin were of different ages and both sexes, while the aetiology of the mental disorder was very varied, ranging from mental deficiency on the one hand to advanced schizophrenia on the other. In some, too, cingulectomy or leucotomy had been performed. In all cases the C.S.F. at the first examination was normal by the strictest standards, while in none was there any evidence of progressive organic disease of the nervous system. We therefore consider that our findings in these cases represent the normal response to intrathecal tuberculin, the more so as they were remarkably consistent. They have been fully described elsewhere (Swithinbank *et al.*, *loc. cit.*) but certain salient features are briefly recapitulated here in order to aid comparison with the findings in disseminated sclerosis.

In the first place, there was an obvious correlation between the intensity of the intradermal tuberculin reaction and that of the intrathecal response. When the Mantoux test was negative to O.T. 1 in 100 or more, no reaction was obtained, even when large amounts of P.P.D. were injected (Smith and Vollum, 1950, Fig. 6; Swithinbank *et al.*, 1953, Fig. 8). On the other hand, when the Mantoux test was positive to O.T. 1 in 1,000 or less, the intrathecal injection of 3.75 μ g. of P.P.D. never failed to provoke a well-marked diphasic reaction (Swithinbank *et al.*, *loc. cit.*, Table I). Occasionally, however, an unexpected intrathecal reaction was obtained in patients in whom the Mantoux test was by definition negative, but further observation showed that almost certainly these patients had at one time been sensitized to tuberculin. A typical example is the first reaction (Sch 1) shown in Fig. 4. Twenty-four hours after the injection the C.S.F. invariably contained many hundreds or, much more commonly, thousands of cells of which the great majority were polymorphonuclear leucocytes. The polymorphonuclears then disappeared almost as rapidly as they came, causing the total cell counts to fall sharply over the next two to four days. Thereafter the total count again rose, to reach a maximum some time between the fourth and eighth days, and this time the cells were virtually all lymphocytes. The concomitant rise in protein, though perfectly obvious, was more variable in degree and often less conspicuous than the pleocytosis. During the first phase of the reaction the protein content ranged from 90 to

600 mg. per 100 ml., and during the second phase it was invariably lower than it was during the first. Some idea of the typical relationships can be gained from the mean values for 13 such reactions set out at the bottom of the Table. The first phase was typically accompanied by a short-lived clinical disturbance consisting of fever and meningism. Nothing more than this was ever seen, and in every case the patient appeared as well as ever 48 hours after the injection.

During the first 24 hours of the reaction the permeability of the blood-C.S.F. barrier to bromide increased abruptly, as shown by the sharp rise in the ratio between the bromide content of the C.S.F. and of the serum. This rise persisted, to reach a maximum coinciding with the second, or lymphocytic, phase of the reaction, and thereafter declined, though it was often many weeks before it returned to within the limits of normal (Smith *et al.*, 1955, Table I and Fig. 1).

When, however, the Mantoux test was only positive to O.T. 1 in 100, then the intrathecal reaction was distorted, in that the second, lymphocytic, phase was usually lost, while the rise in protein was inconspicuous (Fig. 1 and Swithinbank *et al.*, *loc. cit.*, Fig. 11). The bromide ratio was less affected and returned more rapidly to normal (Smith *et al.*, 1955, Table III). The typical relationships in these weakly sensitized subjects are indicated by the mean values for six such reactions set out at the bottom of the Table.

Provided the recipient was sensitized to tuberculin, the intensity of the reaction also varied with the amount of P.P.D. given. Accordingly, in most of these observations the dose was kept constant

FIG. 1.—The total cell count and protein content of the C.S.F. during the 10 days following the introduction of the standard intrathecal dose of P.P.D. (3.75 μ g) in a control case, in which the Mantoux test was only positive to O.T. 1/100. Note the conspicuous rise in cell count 24 hours after the injection which overshadows the increase in protein content, and the absence of the second, or lymphocytic, phase of the reaction.

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TABLE

CHANGES IN C.S.F. AFTER INJECTION OF DIFFERENT AMOUNTS OF P.P.D. IN CASES OF DISSEMINATED SCLEROSIS

Case	Age (Yr.)	Sex	P.P.D. (μg.)	24 Hours after Injection				Maximal Rise 3-8 Days after Injection			
				Total Cells (c.mm.)	Total Polymorpho- nuclears (c.mm.)	Protein (mg./100 ml.)	C.S.F. Bromide Serum Bromide	Total Cells (c.mm.)	Total Polymorpho- nuclears (c.mm.)	Protein (mg./100 ml.)	C.S.F. Bromide Serum Bromide
Group A: Mantoux Test Positive O.T. 1/10,000											
4. E.J.	43	F	5-625	120	0	50	—	45	0	30	—
3. A.L.	42	F	3-75	75	3	90	—	70	32	280	0-82
2. N.W.*	42	M	3-75	90	9	380	—	300	123	520	1-03
18. M.C.	28	F	0-375	950	427	960	0-53	618	6	400	0-72
24. G.H.	30	M	0-375	300	33	260	0-72	450	0	170	0-83
20. R.G.	48	M	0-225	—	Not estimated	—	—	180	36	250	—
12. R.A.	21	M	0-15	125	16	152	—	—	Not estimated	—	—
25. A.S.	17	M	0-15	81	0	118	0-65	285	2	106	0-52
9. P.G.	37	F	0-075	225	45	152	—	—	Not estimated	—	—
Group B: Mantoux Test Positive O.T. 1/1,000											
26. M.J.N.	37	F	3-75	418	350	750	0-87	1,500	0	360	—
27. S.K.	55	M	3-75	53	38	1,000	0-96	123	61	560	0-7
22. M.B.	31	F	3-75	620	180	339	0-7	725	0	336	0-92
14. J.P.	41	M	0-75	103	17	176	—	149	0	52	—
11. P.McD.	14	F	0-75	401	200	260	—	—	Not estimated	—	—
8. O.T.	31	M	0-15	180	0	550	—	—	Not estimated	—	—
Group C: Mantoux Test Positive O.T. 1/100											
19. S.S.	27	M	15-0	532	223	340	0-63	—	Not estimated	—	—
1. S.F.	22	F	3-75	30	0	375	0-77	75	54	132	0-53
5. K.P.*	21	M	2-25	21	4	190	—	120	0	340	—
21. K.M.	41	M	0-15	8	0	220	—	174	0	352	0-82
10. B.P.	33	F	0-075	3	0	170	—	5	0	52	—
Group D: Mantoux Test Negative O.T. 1/100											
7. L.T.	16	M	3-75	65	46	122	—	24	0	35	—
17. C.B.	35	F	3-75	37	0	70	0-33	—	Not estimated	—	—
13. C.M.	34	M	3-75	10	0	68	—	—	Not estimated	—	—
16. H.T.	26	F	3-75	7	1	22	0-29	46	0	35	—
23. R.T.	19	M	3-75	7	0	45	0-35	—	Not estimated	—	—
Mean Value in Psychotics Mantoux Positive O.T. 1/1,000 or More 13 reactions				2,548	1,862	296	—	631	2	213	—
Mean Values in Psychotics Mantoux Positive O.T. 1/100 or Less 6 reactions				1,289	818	85	—	152	8	42	—

*Severe delayed clinical reaction. Cortisone given 36-48 hours after injection.
All patients in Group D subsequently vaccinated with Wells' vole vaccine and/or B.C.G.

at 3.75 μg. Two patients, however, in whom the Mantoux test was strongly positive, received only a fifth part of this dose. In one the pattern of the reaction was unaltered, though the changes were smaller (Smith and Vollum, 1950, Fig. 7); in the other the first phase of the reaction was lost while the rise in protein was negligible. This was one of the only two occasions on which the polymorphonuclear component failed to develop. Increasing the dose of P.P.D. restored the typical pattern of the reaction (Swithinbank *et al.*, *loc. cit.*, Fig. 1). In one patient in whom the Mantoux test was only positive to 1/100 doubling the dose of P.P.D. merely increased the height of the initial cell spike (total cell count 3,980 per c.mm., polymorphonuclears 3,184 per c.mm., protein 90 mg. per 100 ml.).

The first, or polymorphonuclear, wave of pleocytosis thus proved to be much the most constant and stable part of the reaction. Moreover, once the result of the Mantoux test was known the character and intensity of the intrathecal response to P.P.D. could be predicted with reasonable certainty.

Findings in Patients with Disseminated Sclerosis

Our findings in disseminated sclerosis during both phases of the reaction are summarized in the Table. Since in the normal the intensity of the intrathecal response varies with both the sensitivity of the recipient and the dose of P.P.D., these cases are arranged in four groups in descending order of intradermal sensitivity, Group A, comprising those in which the Mantoux test was positive to O.T. 1 in 10,000, and Group D, those in which the Mantoux test was negative. Within each group the cases are arranged in order of decreasing dosage of P.P.D. When more than one injection of P.P.D. had been given it is the effects of the largest dose that are shown here. At the foot of the Table are set out the mean values for 13 reactions obtained in psychotics in whom the Mantoux test was strongly positive, and for six reactions in psychotics in whom the Mantoux test was only positive to O.T. 1 in 100.

As in the normal, no definite reaction was obtained when the Mantoux test was negative (Group D). (In one case in which the Mantoux test was negative an injection of 0.1875 μg P.P.D. produced 246 cells

per c.mm. and 160 mg. protein per 100 ml. 48 hours later. As this was the only observation made, this case cannot be included in the Table.) For the rest, however, the intensity of the reaction cannot be correlated with either the Mantoux test or, within limits, the dose of P.P.D. Thus, the reactions shown in Group A are not consistently brisker than those in Group B, nor even, dose for dose, than those in Group C. (Both phases of the reaction should be considered when making this comparison.) How strongly this contrasts with the normal may be seen by comparing the two sets of mean values given at the foot of the Table.

The relative unpredictability of the reaction in terms of the dose of P.P.D. is seen when the cases in any one group are compared with one another. Thus, in Group A, a 50% increase over the standard dose of P.P.D. failed to produce any significant reaction in Case 4, E.J., while in Case 18, M.C., there was a brisk reaction to only a tenth part of the standard dose. Again, in Group C a fourfold increase in the standard dose produced a moderate reaction in Case 19, S.S., while three-fifths of the standard dose in Case 5, K.P., produced a clinical reaction of such severity that cortisone had to be given in an attempt to abort it (see also Fig. 3, K.P.). Compare, too, Case 14, J.P., in Group B with Cases 11, P. McD., and 8, C.T.

Other striking anomalies are seen in the altered pattern of the reaction. Throughout the reaction there is a marked tendency for the increase in protein to outstrip the pleocytosis, an exact reversal of the normal relationship. Particularly good examples of this reversal are seen when Cases 26, M.J.N., 27, S.K., and 8, C.T., in Group B, and Cases 1, S.F., 5, K.P., 21, K.M., and 10, B.P., in Group C are compared with the relevant set of mean values for reactions in psychotics.

FIG. 2.—The cell counts, protein content, and bromide ratio throughout the reactions provoked by giving variable amounts of P.P.D. in eight cases of disseminated sclerosis in which the Mantoux test was positive to 1 in 1,000 or less. The percentage of polymorphs (P) and lymphocytes (L) is indicated. Note the absence, relative or complete, of the initial spike of cells and the marked, sustained increase in protein content (contrast Fig. 4; reaction Sch I). Note also the lack of correlation between the intensity of the reaction and the dose of P.P.D. and the sharp rise in the bromide ratio accompanying each reaction.

This reversal is brought about partly by an exaggeration of the normal increase in protein and partly by a failure of the polymorphonuclear leucocytes to make their expected appearance. The protein can on occasions rise to surprising levels, and this rise tends to persist and may even increase during the second phase of the reaction (compare Cases 5, K.P., and 21, K.M., in Group C.) In consequence, the second phase is usually conspicuous, even in those cases in which the Mantoux test was only weakly positive and where the first phase of the reaction failed to develop.

The complete or partial suppression of the polymorphonuclear component is equally remarkable. As a result of this, the initial spike of cells that is such a constant and striking feature of the normal reaction is no longer seen. Figs. 2 and 3 show in detail certain reactions obtained in patients in whom the Mantoux test was positive to O.T. 1 in 1,000 or less, and to O.T. 1 in 100, respectively. It is largely the absence of the initial cell spike that gives these reactions their very peculiar pattern as compared with those shown in Fig. 4 (Sch I) and Fig. 1.

As in the normal reaction the permeability of the blood-C.S.F. barrier to bromide is greatly increased, though probably not to quite such an extent. Thus, in the reactions listed in the Table the bromide ratio has only once risen to unity, whereas in the psychotics ratios of unity or above were the rule in patients in whom the Mantoux test was strongly positive (Smith *et al.*, 1955).

In disseminated sclerosis, therefore, it is the increase in the protein content, and not the initial polymorphonuclear spike of cells, that has proved the most characteristic and constant part of the reaction.

The Effect of Cortisone

It is interesting to compare the reactions seen in disseminated sclerosis with those obtained in highly sensitized psychotics in whom the intrathecal tuberculin reaction was covered by a single small dose of cortisone given at the same time as the P.P.D. Full details of two such reactions have been published elsewhere (Smith *et al.*, 1955, Table IV). In both there was a striking suppression of the polymorphonuclear response: in one case, in which

50 mg. cortisone was given by mouth, the C.S.F. 24 hours later only contained 24 polymorphonuclears per c.mm.; in the other, in which 50 mg. cortisone was given intrathecally, there were 118 polymorphonuclears per c.mm. The increase in protein was much less affected, and the second phase of the reaction developed normally. The increase in barrier permeability still occurred, but was less marked than in the unmodified reaction and returned more rapidly to normal.

In certain respects, therefore, these modified reactions closely resemble the reactions seen in disseminated sclerosis. This resemblance is exemplified in Fig. 4. Reaction Sch 1 shows the characteristic, unmodified response in a well-sensitized subject, and reaction Sch 2 shows the response to the same dose of P.P.D. in the same patient when 50 mg. cortisone was given by mouth. The third reaction, D.S., was obtained to the same dose of P.P.D. in a patient with disseminated sclerosis. At least as far as the cell curve is concerned, the resemblance is striking. The rise in protein content and bromide ratio in the case of disseminated sclerosis

FIG. 2

FIG. 3.—As in Fig. 2, except that in these cases the Mantoux test was only positive to O.T. 1 in 100. The reactions show the same features as those in Fig. 2 and contrast strongly with that shown in Fig. 1.

is rather more marked than in reaction Sch 2, but it should be noted that the second and larger dose of P.P.D. was given before the delayed effects of the first small dose had subsided. It is possible, therefore, that the two injections were to some degree additive.

The Effects of Vaccination

In the past we have vaccinated four psychotics in whom the Mantoux test was negative with Wells' vole vaccine. In every case the skin and meninges converted rapidly, unequivocally, and simultaneously. An example of this conversion is shown in Fig. 5 (Swithinbank *et al.*, *loc. cit.*, Fig. 9). When, therefore, it was found that the intrathecal injection of P.P.D. failed to elicit any definite response in the five Mantoux-negative cases of disseminated sclerosis listed in Group D (Table), the patients

were vaccinated with Wells' vole vaccine or B.C.G.

Two patients (17, C.B., and 13, C.M.) were vaccinated with B.C.G. Three months later both skin and meninges were found to have converted, but unfortunately in neither case had it been possible to make any observations in the interval. The other three patients were vaccinated with Wells' vole vaccine and observed from the time of vaccination. In all three the response was anomalous. In one, Case 23, R.T., the Mantoux test became positive within three weeks, but it was another month before any response was obtained to the intrathecal P.P.D.

In the other two cases the response to vaccination was more unexpected. The events in one of these, Case 7, L.T., are shown in detail in Fig. 6.

Initially, the Mantoux test was negative to O.T. 1 in 100, and the standard intrathecal dose of P.P.D. produced only 65 cells per c.mm. and 122 mg.

FIG. 4.—The total cell counts, protein content, and bromide ratio throughout three separate reactions. The total polymorphonuclear count is shown also by the dotted line. The first two (Sch 1 and Sch 2), were produced in the same control patient to the same dose of P.P.D. but before the second, 50 mg. cortisone were given by mouth. Reaction Sch 1 exemplifies the normal intrathecal response in a subject in whom the Mantoux test is strongly positive (O.T. 1 in 1,000). The third reaction, D.S., was obtained in a patient with disseminated sclerosis. Note the almost complete suppression of the polymorphonuclear response by the cortisone in Sch 2, and the close resemblance in the pattern of Sch 2 and D.S. For further explanation, see text.

protein per 100 ml. Whether or not this represents a small but genuine reaction is uncertain, but in any event the response was insignificant, and consequently the patient was vaccinated with Wells' vole vaccine. Four weeks later the Mantoux test was still negative and the response to the intrathecal P.P.D. unchanged. After another nine days (38 days from vaccination) the intrathecal injection was repeated, and this time was followed by a sharp rise in the protein content of the C.S.F. to 376 mg. per 100 ml., while the bromide ratio rose from 0.29 to 0.53. Sixty-five days after vaccination another injection of P.P.D. produced essentially similar results except that the increase in pleocytosis was rather more definite. In spite, however, of this obvious increase in intrathecal sensitivity, the Mantoux test remained steadfastly negative. Accordingly, 92 days after the first vaccination the patient was revaccinated with B.C.G. A Koch's phenomenon developed at the vaccination site, 10 days later the Mantoux test was found to be already strongly positive, while a final intrathecal dose of P.P.D. given 116 days after the original vaccination was followed by a well-marked reaction.

From the response to the intrathecal tuberculin, and from the Koch's phenomenon and rapid conversion of the Mantoux reaction that followed the second vaccination, it is clear that the first vaccination had in fact produced some degree of sensitization. Why this acquired sensitivity could not show itself in the classical way by Mantoux conversion until after the extra stimulus of revaccination is not yet clear. It is, however, interesting that the chain of events in the remaining case, No. 16, H.T., is similar, in that vaccination caused the meninges to convert though the Mantoux test was still negative more than three months later.

The Immediate Clinical Effects and Dosage of P.P.D.

The clinical component of the reaction in disseminated sclerosis has proved as unpredictable as the changes in the C.S.F. In some cases there was little or no clinical disturbance, even though well-marked changes in the C.S.F. might develop some days later. More commonly, the first phase of the reaction has been accompanied by the usual short-lived fever, headache, nausea, and pain in the back and legs. In a few cases focal neurological signs have been accentuated during the reaction. Thus, one patient developed nystagmus and another a troublesome retention of urine. Two patients showed signs of a low pressure state following the first small dose of P.P.D., but without any fever or changes in the C.S.F.

FIG. 5.—The effects of vole vaccination in a psychotic patient in whom the Mantoux test was negative. Ten days after vaccination the Mantoux test is positive and the intrathecal injection of 3.75 µg P.P.D. evokes a brisk response. Note the rapid and simultaneous conversion of skin and meninges and the small increase in protein content during the reaction relative to the increase in cells.

In two of our early cases, however, in both of which brain-stem and cerebellar signs predominated, the reaction was extremely alarming. Twenty-four hours after the injection the patients showed no more than the expected fever and meningism. The temperature then began to subside in the usual way, but then, about 36 hours after the injection, it rose abruptly, and both patients suffered a violent exacerbation of their cerebellar signs and became first stuporous, then comatose, with periodic respirations. Lumbar puncture showed that the intracranial pressure was not raised but that the fluid contained a great excess of protein. In both cases cortisone was given in an attempt to abort the reaction. One patient recovered consciousness within a few hours and the following day seemed none the worse. The other improved much more slowly, and it was several days before his temperature returned to normal.

Since the intensity of the intrathecal reaction is so unpredictable, while the reaction itself is potentially dangerous, finding the safe yet effective dose in any individual case of disseminated sclerosis has proved a matter of considerable difficulty. This difficulty is

reflected by the great variation in the dosage of P.P.D. shown in the Table. At present, our practice is to inject 0.375 µg P.P.D. (0.5 ml. of the 1 in 10 dilution of the "standard" solution) in the first instance, and then, if no reaction is obtained, to give a fivefold (0.25 ml. of the standard solution) or tenfold (0.5 ml. of the standard solution) increase at the second injection. The smaller dose is preferred in cases in which the brain-stem appears to be heavily involved. An interval of about a week is allowed to elapse between the injections, in case the response to the first dose is delayed.

Possible Effect of the Reactions on the Course of the Illness

We have naturally been anxious to determine whether, apart from the immediate disturbance associated with the reaction itself, these injections have any effect on the clinical condition, or modify in any way the expected course of the illness over the following months or years. It has seemed to us that the incidence of relapses during the next few years will give the best indication of the value of any form of treatment. Since, however, it

FIG. 6.—The effects of vaccination in a patient with disseminated sclerosis in whom the Mantoux test was negative. Contrast Fig. 5. For full explanation, see text.

is only 2 years since we gave intrathecal P.P.D. to a patient with disseminated sclerosis, and since only 35 patients, including those who are at present in hospital, have so far been treated in this way, it is still much too soon to attempt any valid appraisal of the late effects. It must also be pointed out that until fairly recently the patients to receive P.P.D. were selected from among our most advanced cases; that is to say, most of them had been completely disabled for months or years. It is, however, true to say that we have yet to see evidence of a new lesion developing in any case in which a reaction has been obtained though fluctuations in pre-existing symptoms have been seen. Further, in several cases the pattern of the illness appears to have been changed, in that a slow but steady, if only moderate, improvement has been substituted for a fluctuating downhill course. Finally, in certain cases a reaction has been followed by a well-marked remission. Whether or not the two are causally related, it is at the least possible to say that the reactions neither prevent nor delay the natural remissions.

Discussion and Conclusions

Since the intrathecal tuberculin reaction must be accepted as a true antibody-antigen response, it follows that a consistent distortion of its pattern in one particular disease indicates that in that disease the normal immunological processes are disordered. Such a consistent distortion of the pattern of the reaction has now been demonstrated in disseminated sclerosis, and it is of considerable interest that a very similar distortion can be produced artificially by the exhibition of cortisone. Most of our findings, except possibly the exaggerated protein response, could be accounted for on the hypothesis that in this disease some substance is at work exerting a cortisone-like effect. This might explain not only the particular distortion seen in the intrathecal reactions, but also the very unusual results of vaccination. In this connexion, it is interesting to note that in those two reactions in which the clinical disturbance was alarmingly severe, cortisone seems to have little, if any, effect on the evolution of the changes in the C.S.F. (Fig. 2, N.W.; Fig. 3, K.P.). It is as though the cortisone-like effect was already

exerted and so no further modification was possible. It is also perhaps worth recalling the disappointing results reported for cortisone in the treatment of disseminated sclerosis as compared with its effect in acute encephalitis (Miller and Gibbons, 1953). Whether this cortisone-like effect is confined to the central nervous system or affects the body as a whole we do not yet know, though the results of vaccination would indicate that it is not strictly confined to the central nervous system.

It may be objected that, in spite of the reasons adduced, we are not justified in treating our findings in psychotics as controls. It is true that we have made no observations in other chronic progressive diseases of the nervous system, such as motor neuron disease or paralysis agitans. On the other hand, we are very familiar with the intrathecal reaction as seen in tuberculous meningitis, we have studied the C.S.F. changes during the reaction in rabbits (Taylor and Hunter, in the press), and the histological changes in guinea-pigs (Bosanquet *et al.*, 1953). In all these the reaction appears similar in kind to that seen in the psychotics; in fact, there is a far greater resemblance between the reaction in the rabbit and in the psychotic patients than between the psychotics and the patients with disseminated sclerosis, and this in spite of the species difference.

As to the possible therapeutic effect, it is obvious that no proper assessment can yet be attempted. Moreover, owing to the natural history of the disease, and the limited facilities available at any one neurological centre, it may be a long time before the evaluation of this treatment becomes possible. Excluding the immediate disturbance of the reaction itself, no patient has yet grown worse who has experienced a definite reaction, while others have improved. We therefore consider ourselves justified in pursuing this research, and are presenting this preliminary report in the hope that others may extend and expand this work.

Summary

The effects of the intrathecal injection of tuberculin in disseminated sclerosis have been studied and compared with the findings in cases of psychosis of mixed aetiology.

Reasons are advanced for accepting the findings

in the psychotic patients as valid control observations.

Striking and consistent differences are described between the intrathecal tuberculin reaction in disseminated sclerosis and in the controls.

In particular, the correlation seen in the controls between the intensity of the intrathecal reaction and both the result of the Mantoux test and the dose of tuberculin is not apparent in disseminated sclerosis. The pattern of the reaction also is distorted, in that the characteristic polymorphonuclear leucocyte component is suppressed, while the increase in protein is exaggerated.

A similar suppression of the polymorphonuclear component can be artificially produced in controls by administering cortisone.

The response in tuberculin-negative cases of disseminated sclerosis to vaccination with Wells' vole vaccine or B.C.G. is anomalous, in that—contrary to experience with the controls—sensitization of the skin and of the meninges may be markedly dissociated.

The immediate clinical effects of the intrathecal injection of tuberculin have been very alarming in two brain-stem cases, but have otherwise been associated with little immediate change in the clinical picture.

Follow-up studies suggest, however, that the course of the illness may have been modified for good; and this aspect of the subject is being investigated further.

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