Laragh *et al.* (1960b) have measured secretion rates in a large number of patients with hypertension of various types. In 14 out of 15 patients with malignant hypertension the rate of secretion was greatly increased, lying between 600 and 2,000 $\mu\text{g.}/24$ hours (normal 150–330 $\mu\text{g.}$). Five patients with primary aldosteronism secreted slightly less aldosterone (510–1,690 $\mu\text{g.}/24$ hours), although the figures of the two groups overlapped. Patients with hypertension and renal or retinal complications other than papilloedema (grade III retinopathy) often had raised secretion rates, but the secretion rates of patients with uncomplicated essential hypertension were normal. Half the patients with malignant hypertension had their adrenal glands examined at subsequent operation or necropsy; no adrenal tumours were found, but bilateral cortical hyperplasia was present in several cases. This work constitutes impressive evidence that hyperaldosteronism is usual in malignant hypertension and common in hypertension of less severe degree. The rates of secretion are as high as those encountered in primary aldosteronism and might be expected to cause a similar hypokalaemia. Laragh *et al.* (1960b) remarked on the frequent finding of a hypokalaemic alkalosis in their patients; 6 out of 15 cases with papilloedema had a serum potassium below 3.5 mEq/l., and three cases had a plasma total carbon dioxide above 31 mM/l. In this respect Laragh's observations tally closely with mine.

From the observations cited above there can be little doubt that the hypokalaemia commonly present in severe hypertension is due to hyperaldosteronism. However, this condition is not primary aldosteronism. The present series and numerous earlier individual case reports (Wrong, 1957; Dollery *et al.*, 1959; Hoet and Molineaux, 1960; Laidlaw *et al.*, 1960; Gowenlock and Wrong, 1961) show that many such patients are discovered at investigation to have renal causes of hypertension—usually renal ischaemia. In such cases appropriate renal surgery alone has often resulted in cure both of hypertension and of the signs of hyperaldosteronism, which suggests that the adrenal hyperfunction is in some way the result of renal disease. Laragh *et al.* (1960a) have found that intravenous injection of angiotensin into normal subjects causes a marked increase in aldosterone secretion, and it may therefore be through the mediation of renin that renal disease brings about a state of hyperaldosteronism. Not all the hypokalaemia patients of this series were shown to have primary renal disease; but the above thesis is not thereby invalidated, for severe hypertension of any origin may damage the kidney and lead to focal areas of ischaemia. Alternatively, it may be that severe hypertension itself stimulates aldosterone secretion, but there is no experimental support for this hypothesis.

Conn (1960) has suggested that the diagnosis of primary aldosteronism would be made much more often if the plasma potassium were determined as a routine in cases of hypertension. While this conjecture is almost certainly true, the present study does suggest that the majority of untreated hypertensives who are found to have hypokalaemia are not, in fact, suffering from primary aldosteronism.

Summary

Of 64 patients with severe hypertension, 13 (20%) had a definite hypokalaemia (plasma potassium 2.7–3.4 mEq/l.), often accompanied by an alkalosis. The incidence of hypokalaemia was greatest in those with

papilloedema (43%). Possible renal causes of hypertension were discovered in two-thirds of those with hypokalaemia.

The hypokalaemia of severe hypertension seems to be due to hyperaldosteronism, which is caused by renal ischaemia, the hypertension itself, or some closely related phenomenon. The term "primary" aldosteronism is not applicable to this syndrome.

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INTRATHECAL TUBERCULIN IN DISSEMINATED SCLEROSIS

A CONTROLLED TRIAL

BY

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When Smith *et al.* (1957) published a hint of prolonged remissions in disseminated sclerosis after an experimental study of cerebrospinal fluid (C.S.F.) changes with intrathecal tuberculin injections (purified protein derivative—P.P.D.) we felt obliged to test this. For reasons which must be obvious (see also *British Medical Journal*, 1958) we set about a controlled trial.

In order to obtain early results we deliberately selected 20 patients with undoubted disseminated sclerosis in whom we thought further demyelination probable—that is, we chose patients with at least three episodes occurring at a rate of more than one a year, or with evidence of unremitting progression over six months. They all had some signs of damage to the central nervous system, but were still useful members of society or of their household, with measurable faculties to lose. They were unaffected by pulmonary tuberculosis or general medical diseases or psychiatric disorders.

If after due explanation of the expected risks they agreed to this experimental course of treatment they were admitted under the care of one of us (R. E. K.) to Maida Vale Hospital or St. Thomas's Hospital. By kind permission of the other physicians at Maida Vale we selected from their much larger number of cases 20 controls who were matched as closely as possible for age, sex, length and activity of disease, and actual incapacity (see Table I).^{*} Two of the trial cases (Nos. 8 and 14) and one of the control cases (No. 4) had an

TABLE I.—*Clinical Histories up to Date of Trial*

No.	Trial Cases	Control Cases
1	Male shipping agent aged 37 in 1958. 4 episodes in 3 years. Good recoveries. Working.	Male lorry driver aged 42 in 1958. 4 episodes in 3 years. Good recoveries. Working.
2	Male photographic grader aged 30 in 1958. 4 years of progressive disability. Moderately disabled but working.	Male grocer aged 29 in 1958. Progressive disorder for 4 years. Part-time work. Walking limited to 50 yards.
3	Housewife aged 42 in 1958. 9 episodes in last 8 years. Fair recoveries. Some limitation of normal activities.	Male compositor aged 35 in 1958. 7 episodes in 7 years. Good recoveries. Full-time work.
4	Male insurance clerk aged 32 in 1958. 15 episodes in 9 years. Fair recoveries. Limited housework.	Housewife aged 32 in 1958. Brother died of disseminated sclerosis. 14 episodes in 9 years. Fair recoveries. Limited housework.
5	Clerk and housewife aged 35 in 1958. 8 episodes in 6 years. Fair recoveries. Full housework, but retired from clerical job.	Housewife aged 43 in 1958. 9 episodes in 9 years. Fair recoveries. Limited housework.
6	Housewife aged 43 in 1958. 3 episodes in 2 years. Good recoveries. Normal activity.	Housewife aged 43 in 1958. 4 episodes in 2 years. Good recoveries. Full domestic activity.
7	Schoolmaster aged 37 in 1958. 9 episodes in 8 years. Fair recoveries. Wheel-chair, but still doing literary work.	Male estimator in aircraft factory aged 43 in 1958. 6 episodes in 7 years. Fair recoveries. Moderately disabled, but still working.
8	Housewife aged 46 in 1958. Father died of disseminated sclerosis. 8 episodes with good recoveries 1940-52. Progressive disorder for last 6 years. Wheel-chair, but a fair amount of housework.	Housewife aged 48 in 1958. Episode with remission 15 years ago. Progressive disorder for last 4 years. Limited housework.
9	Housewife and secretary aged 35 in 1959. 6 episodes in 3 years. Good remissions. Full housework, but some limitation of secretarial work.	Housewife aged 25 in 1959. 10 episodes in 5 years. Good remissions. Slight limitation to housework.
10	Male electrician's mate aged 26 in 1959. 6 episodes in 2 years. Good recoveries. Full work.	Male instrument mechanic aged 23 in 1959. 6 episodes in 2 years. Good recoveries. Full-time work.
11	Housewife aged 38 in 1959. 4 episodes in 3 years. Poor recoveries. Limited housework. Wheel-chair.	Housewife aged 44 in 1959. 4 episodes in 3 years. Poor recoveries. Limited housework. Wheel-chair.
12	Businessman aged 44 in 1959. 5 episodes in 4 years. Fairly good recoveries. Full activities and only slightly disabled by giddiness.	Maintenance foreman aged 43 in 1959. 4 episodes in 2 years. Good recoveries. Some residual giddiness, but full activities.
13	Housewife aged 53 in 1959. First episode 36 years ago with complete recovery. During last 7 years 4 further episodes with incomplete recovery and progressive spasticity for last 3 years. Limited housework.	Housewife aged 64 in 1954. 3 episodes in 34 years with progressive paraplegia in last 9 years. Limited housework.
14	Housewife aged 45 in 1959. Mother afflicted with disseminated sclerosis. Remitting episode 23 years ago, but progressive illness for last 13 years. Limited housework.	Housewife aged 41 in 1959. 6 episodes in 15 years with slow progression over the last 11 years. Limited housework.
15	Female clerk aged 22 in 1959. 4 episodes in 3 years. Very good remissions. Normal work.	Housewife and typist aged 26 in 1959. 4 episodes in 3 years. Good recoveries. Well and working. Six months pregnant at time of trial.
16	Housewife aged 52 in 1959. More than 13 episodes in 13 years. Poor remissions during last 3 years. Limited housework.	Housewife aged 34 in 1959. 21 episodes in 12 years. Fair recoveries. Limited housework.
17	Female teacher aged 51 in 1959. Progressive disorder for last 6 years. Full housework only.	Female secretary aged 36 in 1959. Progressive paraplegia for 7 years. Motor wheel-chair and limited clerical work.
18	Milk roundsman aged 51 in 1959. 5 episodes in 4 years. Poor recoveries. Able to work as switchboard operator.	Male garage proprietor aged 50 in 1959. 7 episodes in 7 years. Poor recoveries. Still doing car repairs.
19	Retired police officer aged 43 in 1959. 6 episodes in 5 years. Fair recoveries.	Male local government officer aged 40 in 1959. 6 episodes in 6 years. Fair recoveries. Still working.
20	Male fishmonger aged 49 in 1959. 10 episodes in 15 years. Poor recoveries. Light manual work.	Housewife aged 56 in 1959. 6 episodes in 15 years. Poor recoveries. Limited housework.

^{*}Full clinical histories may be obtained from the authors.

affected parent or sibling. Table II summarizes the main data of the two groups.

TABLE II.—*Summary of Clinical Features of the Two Groups*

	Trial Group	Control Group
Average age	40½	40
Males	9	8
Females	11	12
Relapsing-remitting course	11	11
Relapses with poor or no remissions	5	5
Relapsing-remitting followed by progressive course	2	2
Progressive course	2	2
Patient-years of disease	174	162
Episodes of demyelination	121	123

Methods

Mantoux tests were done: in the four Mantoux-negative trial cases the reactions were converted to positive by B.C.G. inoculation. Two of the control cases were also inoculated with B.C.G., but otherwise the control cases were treated only by the palliative measures of current neurological practice, and remained under the care of their physicians. The trial cases were assessed clinically, psychometrically, and by the physiotherapists, and were given a course of physiotherapy on admission, if indicated, before the actual treatment.

P.P.D. (Ministry of Agriculture and Fisheries) was injected by lumbar puncture; 0.375 µg. (0.5 ml.) was given at first in all 20 cases. If the C.S.F. protein rose to over 300 mg./100 ml. in the next week or if the clinical reaction was severe no more was injected (11 cases). Nine patients had a second injection of 0.375 to 1.5 µg., and one of these had a third injection of 0.75 µg.

Apart from careful clinical observations serial studies were made of the C.S.F., usually on the first and fifth days after the P.P.D., and then weekly until the reaction was clearly subsiding. C.S.F. and plasma protein changes were also studied electrophoretically and serial E.E.G. recordings were made in most cases.

After discharge all the trial cases were seen by us personally at intervals of three months or less. Nineteen of the control cases were also seen by us during and at the end of the follow-up period, but a little less often as they remained under the care of their own physicians. We are obliged to the family doctor for the follow-up of control case No. 17, who moved to the North of England. Psychometric tests were repeated about the sixth and twelfth months.

Results

Ten cases were treated at St. Thomas's Hospital and 10 at Maida Vale Hospital between August, 1958, and September, 1959.

Immediate Clinical Reaction.—A febrile reaction with signs of meningeal irritation occurred after 19 out of the total of 30 intrathecal injections. This subsided in one to three days and never gave cause for anxiety. Nine patients experienced exacerbation of their symptoms and signs, and six required catheterization of the bladder. Eight recovered to their pretreatment state, usually within a few days, but Case 2 remained more spastic. The severity of the clinical reaction was not mirrored in the C.S.F. changes.

Clinical Progress Until Discharge

Fourteen patients progressed uneventfully. Bladder infections occurred in six cases (Nos. 4, 5, 9, 14, 16, and 20)—in four of these in association with neurological setbacks. Episodes of further plaques of

demyelination occurred in five cases after the immediate clinical or meningeal reaction had subsided.

Case 5 became much more ataxic with increasing weakness of the lower limbs on the twelfth day after treatment, and this had not resolved at the time of discharge. Case 14 developed increasing weakness of the upper limbs between the eleventh and the twentieth day after treatment. She also developed retention of urine and had not recovered her pretreatment state at the time of discharge three months later, although improved. Case 19 developed a complete left foot-drop 10 days after the first injection of tuberculin. This had resolved completely at the time of discharge.

In two other cases the new episodes were alarming.

Case 9 was given 0.375 μ g. of P.P.D. without much reaction. On the eighth day she developed numbness of the second division of the trigeminal nerve on the right and the left side, apparently a reactivation of an old plaque 11 months previously. She was given a second injection of 0.75 μ g. 12 days after the first. The immediate meningeal reaction was not severe. On the third day after the second injection she developed motor and sensory signs in her left lower limb; these increased gradually up to the 20th day, by which time she had loss of anal sensation, complained of bladder symptoms, and was in a state of agitated depression. On the 24th day she also developed motor and sensory symptoms in the right leg and was frankly suicidal; a course of E.C.T. was started. On the 30th day she presented the picture of an ascending myelitis with intercostal paralysis and a respiration rate of 28. On the 34th day the paraplegia was complete, and she had a fourth plaque with right-sided facial paralysis and dysarthria. On the 41st day there was a fifth plaque with left-sided deafness and a bulbar palsy. Treatment with prednisone, 60 mg. daily, was started. She had a fourth E.C.T. for her persistent depression. On the 46th day the bulbar palsy was improving but she had a sixth plaque in the form of an acute attack of left retrobulbar neuritis, having been on a large dose of prednisone for the previous five days. Thereafter she improved slowly: visual acuity had returned to normal three months after the tuberculin and she was discharged home, still incontinent and paraplegic, four months later.

Case 20 was given 0.375 μ g. of P.P.D. and had a brisk meningeal reaction lasting three days with transient retention of urine. Thereafter he returned to his pretreatment state until the 19th day. On this day he lost control of his bladder and the following day he had signs of a spinothalamic plaque in the dorsal region. By the 23rd day he required catheterization and had signs of a complete cord transection in the mid-dorsal region. On the same day he developed increasing weakness of his left upper limb and visual acuity in the right eye diminished from J1 to J8. Two months later there was some recovery of spinothalamic sensation in the lower limbs, but he still had an indwelling catheter and a chronic urinary infection. He was transferred to a hospital for chronic cases four months later, still completely paraplegic.

The trial cases were discharged between 4 and 18 weeks after the tuberculin injections (mean 7½ weeks). At the time of discharge 13 of the patients were improved or unchanged and seven were worse than on admission.

Serial E.E.G.s were done before and during the reactions and at the time of discharge in all the Maida Vale cases, and showed no significant change.

C.S.F. Changes

The C.S.F. protein increased with the reactions: in 10 patients the peak occurred on the first day, in the rest about the fifth day except in Case 5, where it was delayed till the twelfth day, and in Case 20, where a second higher peak was observed on the fiftieth day

(Table III). A second or third injection, even of the same amount, produced a higher rise of protein on all but one occasion (Case 10).

The cellular reaction was variable; it was maximal on the first day on nine occasions but delayed until

TABLE III—*Predominant C.S.F. Changes After Intrathecal P.P.D.*

Case No.	Dose of P.P.D. (μ g.)	1st Day			Maximum 3–8 Days	
		Total Cells	% Polymorphs	Protein	Total Cells	Protein
1	0.375	1	0	83	24	52
	1.5	38	15	490	320	225
2	0.375	21	26	98	150	480
3	0.375	249	87	80	190	232
	1.125	400	14	380	103*†	194
4	0.375	65	0	210	239	400
5	0.375	63	0	105	255	220†
6	0.375	6	0	65	217	90
	1.125	2,025	80	240	178	120
7	0.375	29	0	200	260	570
8	0.375	9	60	65	113	320
9	0.375	15	0	60	181	140
	0.75	Not counted	—	185	99	220
10	0.375	30	0	80	218	160
	0.75	Not counted	—	70	—	95
	0.75	31	?	400	—	110
11	0.375	3,300	85	220	440	295
12	0.375	247	0	190	—	210
13	0.375	282	76	60	131	35
14	0.375	705	38	90	240	57
	0.375	1,343	95	114	93	77
15	0.375	2	?	25	61	75
	0.75	543	?	300	91	80
16	0.375	30	?	50	65	155
	0.75	>1,000	90	475	203	165
17	0.375	192	?	340	578	325
18	0.375	—	—	—	358	325
19	0.375	—	—	—	195	110
	0.75	565	?	850	290	475
20	0.375	176	68	116	286	600‡

* 5th day: 64% polymorphs. † 12th day: protein 326 mg./100 ml. ‡ 50th day: protein 650 mg./100 ml.

the third to eighth day in 14 reactions. Three patients with a delayed cellular response to the first P.P.D. injection gave a first-day response to a second injection.

The maximum cell count in each case ranged between 100 and 1,000 in 16 cases, and over 1,000 in four cases (No. 6, 2,025; No. 11, 3,300; No. 14, 1,343; No. 16, >1,000). The cell count had usually subsided to fewer than 100 after a month.

The cellular reaction of the first day was mainly polymorphic in six patients. In another case polymorphs predominated on the fifth day (No. 3). Otherwise the first-day reactions were lymphocytic, as were all later cell-counts in all cases.

Follow-up Period

The periods of observation in the two groups from the date of the first P.P.D. injection ranged from 16 to 29 months (mean 22½ months). Table IV gives the events and end-results in the two groups. In summary, these were as shown in Table V at the end of the follow-up period.

Serial psychometric tests showed evidence of deterioration in 9 out of 16 trial cases during the year after the P.P.D.

Discussion

The results indicate quite clearly that the trial group did not benefit from P.P.D., whether one assesses the results from the point of eventual degree of disability or from the number of new episodes. By the first criterion there is probably no significant difference between the two groups.

The number of new episodes was indeed much higher in the treated group (52:31), but this score is inevitably

TABLE IV.—*Clinical Progress of the Two Groups During Follow-up Period*

	Worse on Discharge	Trial Group					Control Group				
		Better or Unchanged	Slightly Worse	Much Worse	Steady Deterioration	New Episodes	Better or Unchanged	Slightly Worse	Much Worse	Steady Deterioration	New Episodes
1		X				1			X		4
2	X			X	X	10		X	(X)	X	5
3				X		2					2
4			X	X		2					3
5	X			X		4	X		X		5
6			X			3			X		3
7	X			(X)	X	3			X	X	1
8				X		7	X	X			1
9	X			X		1			X	X	1
10				X		3					1
11			X	X	X	1					1
12				X		1		X			1
13				X	X	1		X			1
14	X			X	X	2		X			3
15			X	X		1			X		1
16	X			X	X	1			X		1
17			X			1	X				1
18		X				1			X		1
19						3	X				3
20	X			(X)	X	3	X				1

(X) Died.

TABLE V.—*Comparison of Follow-up Results*

	Trial Cases	Control Cases
Better or unchanged	2	5
Slightly worse	6	6
Much worse (including deaths)	12	9
Deaths	2	1
Continuous deterioration	6	3
New episodes	52	31
No sign of activity of the disease	1	3

directly related to the closeness of medical supervision, and if the 12 episodes observed in the trial group while in hospital after the P.P.D. treatment are subtracted the numbers are more comparable in the two groups. However, the same 12 episodes so soon after the P.P.D. led us to stop the trial in September, 1959.

No significant difference in the clinical progress was observed in two subgroups: (1) *B.C.G. cases* (Nos. 13, 14, 15, and 19 in the trial group, and Nos. 11 and 14 in the control group). (2) Cases with a maximal *C.S.F. protein of more than 500 mg./100 ml.* (Cases 7, 19, and 20), of whom two had died and one was unchanged at the end of the follow-up period.

We were struck by the great variability in the individual C.S.F. reactions in our cases. This seemed to differ from two previous studies. Smith *et al.* (1957), who tended to use larger doses of P.P.D., emphasized a single pattern of response with relatively high protein levels and apparent absence of an early polymorphonuclear reaction. Marshall and O'Grady (1959) described two patterns of response of either a slow rise in protein and cells or of an early peak followed by a later and smaller rise in protein and cells; these patterns were also observed in motor neurone disease, Parkinsonism, and Huntington's chorea.

The significance of the changes in the protein fractions on electrophoresis of the serum and C.S.F. has been discussed elsewhere (Gavrilescu *et al.*, 1961).

Finally, we can unfortunately claim success only for our choice of cases with measurable activity of their disease; our series must not be taken as representative of disseminated sclerosis; as seen generally, this is a much more benign disorder.

Summary and Conclusions

A trial of intrathecal tuberculin (P.P.D.) was made on 20 patients with disseminated sclerosis in whom the disease seemed active and in whom new episodes of demyelination or deterioration were anticipated.

On comparing their fate with a group of 20 carefully matched control cases we conclude that intrathecal tuberculin in disseminated sclerosis is a form of treatment which confers no benefit on the patient, despite the unpleasantness of the reaction and the length of the stay in hospital. Indeed, we are not satisfied that it may not lead to reactivation of the condition during the month after the treatment.

We hope that trials like ours and the similar results of Miller *et al.* (1961) will prevent the use of P.P.D. as a placebo in a condition where there is great pressure for some active form of treatment. Other untested and potentially harmful methods such as intravenous "pyrifer," or arsenic and bismuth, should similarly be abandoned for truly harmless placebos.

We thank the patients who agreed to participate in this trial and the other members of the staff of Maida Vale Hospital who allowed us to follow the progress of the control cases. We are obliged to Dr. Honor Smith for her kind advice on the technique of the P.P.D. course during the planning of this trial; to Miss Marjorie Durward for the psychometric tests; to Dr. H. Townsend for analysis of the many E.E.G. tracings; and to Dr. M. H. Russell for his help in the follow-up of control case No. 17.

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FAECAL EXCRETION OF ADENOVIRUS IN A CLOSED COMMUNITY

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The adenoviruses are a large group of viruses possessing a common soluble antigen but divisible into no fewer than 23 serological types, of which 18 are of human and five are of simian origin. Since the observation of a spontaneous degenerating agent in human tonsils growing in tissue culture (Rowe *et al.*, 1953), many family and institutional outbreaks of adenovirus infections have been described among civilians (Munro-Ashman *et al.*, 1958). Serological evidence suggests that infection is widespread and probably occurs in children (Huebner *et al.*, 1954), although the exact role of these agents in causing clinical symptoms is not yet clear. Some types, such as 3, 4, and 7, are associated with acute respiratory disease (Berge *et al.*, 1955), type 8 (Jawetz *et al.*, 1955, 1956) is associated with epidemic keratoconjunctivitis. Others, such as 1 and 2, are more often found in human adenoids and tonsils removed at operation. Maternal antibodies to many of these agents are

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