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STREPTOMYCIN AND TUBERCULOUS MENINGITIS IN CHILDREN

PRELIMINARY NOTE

BY

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It is neither usual nor generally desirable to publish work on a new treatment before proof of its effectiveness and a knowledge of its limitations have been obtained. But the problem of tuberculous meningitis and of the first treatment known to have any effect on the disease is so important that it seems legitimate to draw attention to our preliminary trials, if only to point out our mistakes to our colleagues. We believe we have at the Hôpital des Enfants Malades in Paris one of the richest sources of experience in this field; the investigation is being carried out by a team of paediatricians, ophthalmologists, neurosurgeons, pathologists, bacteriologists, and chemists. In this article our preliminary work is being reported for the first time.

Importance of Early Diagnosis

We would at once emphasize that we make every effort to detect tuberculous meningitis in children at an early stage in order to be able to treat it in good time. Formerly no great haste was shown in obtaining the depressing confirmation of the disease in cases where meningitis was suspected and there was a risk that a lumbar puncture might even bring it on or be accused of so doing. It is known that tuberculous meningitis often becomes apparent in children at an early stage of the infection: out of 51 cases in our first series in which we were able to observe the onset of allergy 42 developed tuberculous meningitis within six months. The symptoms which should strike one at this stage are headache, vomiting (though this may be only occasional), sudden anorexia, fever, which is always present, and emaciation—but this last to a lesser degree only. If the tuberculosis is of longer duration, as was the case with 22 of our small patients, it is these same symptoms (with the addition of personality changes and insomnia), and here again not the emaciation, which should first attract the attention.

In acute or subacute miliary tuberculosis, which is often so difficult to detect and which is revealed by radiological examination of the lung, latent tuberculous meningitis is not uncommon. We therefore emphasize the fact that it is essential in such cases to employ lumbar puncture as a systematic routine procedure.

In these circumstances we cannot insist sufficiently on the absolute necessity, at the present time, of employing lumbar puncture in all cases where there is the slightest doubt, and, in some instances, of making repeated punctures. The examination of the fundus oculi, an excellent exploratory method, should also be widely used. Choroidal tubercles and changes in the optic disk are frequently discovered. (According to data supplied by our colleagues

Monbrun and Lavat, there were 18% of choroidal changes and 47% of disk changes in the cases of meningitis alone, 75% of choroidal tubercles and 56% of disk changes in the cases of miliary tuberculosis with established meningitis, no disk changes and 50% of chorio-retinal changes in the cases of miliary tuberculosis without meningitis.) The detection of these lesions is useful in determining the tuberculous nature of a neurological disturbance of which the diagnosis is indefinite, and observation of them makes it possible, to a large extent, to determine the effect of the treatment.

The importance of these indications lies in the fact that the immediate prognosis of tuberculous meningitis depends chiefly on early diagnosis, and also, undoubtedly, on the energy and duration of streptomycin treatment. Can the decision whether to employ streptomycin therapy, which carries with it grave risks, be based on direct observation of the bacillus in the cerebrospinal fluid? Our answer is "No." In our own statistics, which include 90 definite cases of tuberculous meningitis, direct examination showed acid-alcohol-resistant bacilli in 41 instances only—that is, in about half the cases. Nor can the line to be followed be based absolutely on negative Pirquet's reactions: in four out of 90 cases Pirquet's reaction was negative, but the intradermal reaction was positive. These facts, which have been a matter of common knowledge for some time, have, up to date, been of purely theoretical interest, but they have now come to be of great practical value. Such findings as these are not sufficient reason for refusing to undertake streptomycin therapy when the clinical conditions demand immediate energetic and prolonged action.

The decision is therefore taken after thorough discussion in which all the diagnostic elements are considered: history, knowledge of a recent contact, mode of onset, evolution, cytochemical abnormalities of the cerebrospinal fluid, and even, where necessary, examination of the ventricular fluid, which we found valuable in two cases in infants.

It is possible to determine the exact nature of the disease, with some delay but with absolute certainty, from the results of cultures of the cerebrospinal fluid on Loewenstein's medium, a test which practically never fails.

Prognostic Factors

The Clinique Médicale des Enfants has handled a very large number of patients, who often come from great distances, travelling in uncomfortable conditions, and presenting at very varied stages of the disease. This explains why we finally decided to base our preliminary conclusions on

Details of Cases of Tuberculous Meningitis Treated with Streptomycin

Case No.	Sex	Age (Years)	Weight (Kg.)	Diagnosis Confirmed	X-ray Findings in Lungs	Fundus Oculi	Dosage (g.)		Days of Treatment		Complications	Last Lumbar Puncture		Outcome	Days after Starting Treatment	Remarks
							I.M.	Spinal	Effective	Total		Cells per c.mm.	Protein (g./100 ml.)			
1 M		3	12	Clinically	Normal	No tubercles seen	104	2.2	105	180	None	1	0.45	Alive	240	Operated on for hydrocephalus; well
2 F		1	9	"	"	"	57	3.5	60	135	Eruption	20	1.20	Dead	135	Relapse
4 F		2	12	Bacteriologically	Primary infection	"	53	2.4	45	90	"	407	4.00	"	90	"
6 M		11	28	"	Normal	"	93	3.5	40	90	None	15	0.60	"	90	Relapse; operated on for hydrocephalus
7 F		9	20	"	Primary infection	"	60	1.7	42	85	"	60	1.40	"	85	Relapse
8 F		15	42	"	Miliary tuberculosis	"	320	4.0	150	210	Deafness	3	0.85	Alive	210	Well
9 F		14	38	"	Normal	Not examined	135	2.5	37	66	"	272	1.20	Dead	66	Died after slight improvement
10 M		3	11	"	Primary infection	"	14	1.2	15	15	None	71	0.60	"	15	Died without marked remission
11 M		9	21	"	Normal	No tubercles seen	32	1.8	30	30	Eruption	18	0.60	"	30	"
12 F		Under 1	4	"	Miliary tuberculosis	Not examined	2	1.4	7	7	None	161	—	"	7	Rapidly fatal issue
13 F		8	18	"	Normal	No tubercles seen	100	1.1	45	55	Eruption	141	3.60	"	55	Died after partial remission
17 F		5	15	Anatomically	Primary infection	"	86	3.0	48	81	Eruption; convulsions	148	1.30	"	81	Died in convulsions
18 F		4	12	"	Normal	"	12	0.9	8	8	None	8	0.80	"	8	Died after partial remission
19 F		4	10	Bacteriologically	"	"	37	1.1	23	23	Eruption; convulsions	57	1.65	"	23	Died without marked remission
20 F		1	9	Clinically	Primary infection	"	105	1.5	111	180	Eruption	8	0.30	Alive	180	Well
21 M		6	15	Bacteriologically	Normal	"	64	0.5	32	32	None	208	1.40	Dead	45	Hydrocephalus not operated on
23 F		3	12	"	"	"	7	0.5	5	5	"	29	1.00	"	60	Removed by her family 5 days after treatment started
24 M		3	12	"	Primary infection	"	145	6.0	150	180	Deafness; convulsions	4	1.30	Alive	180	Well
25 M		2	11	"	Normal	Not examined	28	0.6	21	21	None	161	1.80	Dead	21	Operated on for hydrocephalus
26 F		14	40	"	Miliary tuberculosis	Choroidal tubercles	274	5.0	150	180	Eruption; deafness	5	1.80	Dead	180	Well
27 M		7	20	"	Normal	No tubercles seen	269	3.2	105	135	Eruption	29	0.80	"	180	Condition good
29 M		5	15	"	"	"	17	1.1	8	8	None	—	—	Dead	8	Rapidly fatal issue
30 M		2	11	"	"	Not examined	30	1.5	20	20	Eruption; convulsions	—	—	"	20	Died in convulsions
31 M		7	25	"	Normal	No tubercles seen	45	1.9	19	19	Eruption	92	1.60	"	36	Died rapidly without noticeable improvement
32 F		4	14	"	Miliary tuberculosis	Choroidal tubercles	162	4.5	97	141	Convulsions	29	1.80	"	141	Hydrocephalus operated on
33 F		Under 1	7	Anatomically	Primary infection	Not examined	21	1.3	17	17	None	365	1.40	"	17	Hemiplegia; gross cerebral tubercle
34 M		9	21	Bacteriologically	"	"	15	0.5	5	5	"	161	2.80	"	5	Rapidly fatal issue
36 F		2	9	"	Primary infection	"	10	0.5	5	5	"	104	1.60	"	5	"
37 F		4	16	"	Normal	No tubercles seen	12.5	4.0	105	135	Eruption	0.2	0.20	Alive	165	Condition very good
38 M		1	8	"	Primary infection	"	12.5	1.1	11	11	None	21	0.25	Dead	35	Hydrocephalus operated on
39 F		7	18	"	Normal	"	80	1.8	36	80	Deafness	14	5.60	"	90	Died after partial remission
40 M		9	22	"	Primary infection	"	267	4.7	120	165	Eruption	10	0.50	Alive	165	Condition good
42 M		12	29	"	Normal	"	271	3.6	120	135	Eruption; deafness ± convulsions	26	2.40	"	165	Condition fairly good
43 F		2	8	"	Miliary tuberculosis	Choroidal tubercles	12	1.2	11	11	Convulsions	232	3.20	Dead	11	Rapidly fatal issue
44 F		Under 1	9	"	Primary infection	No tubercles seen	25	1.0	21	21	None	280	1.90	"	21	Died without marked remission
45 F		11	23	"	"	"	15	0.6	6	6	"	158	3.80	"	"	Removed by her family
46 M		10	24	"	Normal	"	262	4.15	134	165	Deafness	21	1.80	Alive	165	Condition good
49 M		11	30	Clinically	Primary infection	"	180	4.0	97	120	Eruption; deafness	11	0.40	"	150	"
50 M		9	31	Bacteriologically	"	"	227	4.7	120	150	Deafness	180	1.40	"	150	Hydrocephalus operated on; condition fairly good
51 M		9	20	Clinically	Miliary tuberculosis	Choroidal tubercles	253	2.0	90	105	Eruption	1	0.20	"	150	Received 83 g. in 10 days. Gross residual tubercle in fundus oculi. Condition very good
53 M		14	33	Bacteriologically	Normal	No tubercles seen	165	2.9	91	116	None	29	0.60	"	156	Condition good
54 F		6	15	"	"	"	80	3.1	105	120	Convulsions	3	0.20	"	150	Hemiplegia shows improvement. Condition good
55 F		10	25	"	"	"	145	4.15	110	151	"	2	0.25	"	151	Condition good
56 M		9	15	"	Primary infection	"	12	0.9	9	9	None	280	6.40	Dead	9	Rapidly fatal issue
57 F		14	40	"	Miliary tuberculosis	Choroidal tubercles	21	0.2	7	7	"	68	1.20	"	17	"
60 F		3	12	"	Normal	No tubercles seen	11.2	0.8	8	8	"	304	1.60	"	16	Removed by her family
61 F		5	15	"	"	"	42	2.0	21	21	"	121	2.00	"	21	Died without signs of improvement
62 F		11	29	"	"	"	154	3.4	124	149	"	5	0.60	Alive	149	Well
63 F		9	22	"	Miliary tuberculosis	Choroidal tubercles	62	1.1	11	11	Convulsions	208	0.80	Dead	15	Convulsions before treatment started
64 F		3	12	Clinically	Normal	No tubercles seen	193	5.3	141	149	None	6	0.40	Alive	149	Well
65 M		3	15	"	Primary infection	"	15	1.0	10	10	"	90	1.00	Dead	14	Rapidly fatal issue
66 M		17	60	Bacteriologically	"	"	250	2.3	120	120	"	1	0.30	Alive	150	Well
67 F		14	38	"	Normal	"	271	4.9	118	122	Eruption	3	0.20	"	146	"
69 M		7	18	"	"	Not examined	14	0.6	7	10	"	—	—	"	"	"
71 F		13	36	"	Miliary tuberculosis	No tubercles seen	17	0.6	6	6	None	181	2.40	Dead	10	Rapidly fatal issue
72 M		5	15	"	Normal	"	69	3.6	36	45	"	201	1.00	"	120	Removed by his family on the 36th day
73 F		4	14	"	Miliary tuberculosis	Choroidal tubercles	23	1.4	14	14	Eruption	91	1.20	"	14	Rapidly fatal issue
74 F		5	15	"	Normal	No tubercles seen	74	3.4	49	71	Deafness	38	32.00	"	105	Operated on. Tubercle on optic chiasma
76 M		10	31	"	"	Choroidal tubercles	264	3.25	129	135	"	4	0.70	Alive	135	Well
77 F		8	20	"	Primary infection	No tubercles seen	38	4.95	19	19	Eruption	—	—	Dead	21	Died without signs of improvement
78 F		7	18	"	Normal	"	83	3.0	27	45	Eruption; convulsions	12	6.40	"	45	Died after partial relief of symptoms
80 F		11	31	"	Primary infection	Choroidal tubercles	206	1.5	112	135	Eruption; deafness	12	0.45	Alive	135	Well
81 F		12	30	"	Normal	No tubercles seen	198	5.0	72	80	Deafness	26	19.20	Dead	98	Hydrocephalus operated on
82 M		3	12	Clinically	"	"	48	1.6	16	19	None	48	1.00	"	19	Rapidly fatal issue
83 F		4	10	Bacteriologically	Primary infection	"	107	3.3	104	127	Eruption	161	4.00	"	127	Hydrocephalus; condition poor
86 M		8	20	"	Normal	"	204	2.0	120	122	None	29	0.60	"	122	Well
87 F		7	18	"	"	"	142	1.7	112	123	Deafness	46	0.40	"	123	Not yet recovered

Details of Cases of Tuberculous Meningitis Treated with Streptomycin (cont.)

Case No.	Sex	Age (Years)	Weight (Kg.)	Diagnosis Confirmed	X-ray Findings in Lungs	Fundus Oculi	Dosage (g.)		Days of Treatment		Complications	Last Lumbar Puncture		Outcome	Days after Starting Treatment	Remarks
							I.M.	Spinal	Effective	Total		Cells per c.mm.	Protein (g./100 ml.)			
88	F	8	20	Bacteriologically	Primary infection	No tubercles seen	57	2.0	28	32	Eruption; deafness	51	1.00	Dead	75	Hydrocephalus operated on
89	F	1	7	"	Miliary tuberculosis	"	31	0.8	13	13	Convulsions	248	0.40	"	13	Rapidly fatal issue
91	M	1	7	"	"	Choroidal tubercles	123	2.0	90	120	Eruption	59	2.00	"	120	Hydrocephalus; condition poor
92	M	21	52	"	"	"	310	1.7	115	138	"	101	7.00	Alive		
93	F	4	13	"	"	"	39	1.3	13	13	None	85	1.00	Dead	13	Rapidly fatal issue "
94	M	14	54	"	Primary infection	No tubercles seen	134	1.4	78	94	"	30	3.20	Alive	135	Exploration of optic chiasma; well
95	F	10	25	Clinically	Miliary tuberculosis	Choroidal tubercles	83	0.6	48	55	Eruption	5	0.45	"	97	Well
97	M	8	17	Bacteriologically	Normal	"	120	1.3	75	75	None	21	3.20	"	75	Fairly well
98	M	4	13	"	"	No tubercles seen	47	1.1	66	66	"	31	0.90	"	66	Well
99	F	10	20	"	Miliary tuberculosis	Choroidal tubercles	113	3.5	64	64	"	12	2.40	"	64	Hydrocephalus not yet operated on
100	M	13	34	"	Pulmonary tuberculosis	No tubercles seen	156	0.6	63	63	Eruption	28	0.60	"	63	Well
101	M	12	34	"	"	"	21	1.1	7	7	None			Dead	7	Rapidly fatal issue
102	F	16	44	"	Pleurisy	"	218	1.5	45	45	"	30	1.40	Alive	45	Well
103	M	6	21	Clinically	Primary infection	"	90	0.7	45	45	"	3	0.20	"	45	"
104	M	4	14	Bacteriologically	Normal	"	61	1.0	46	46	"	21	1.00	"	46	"
106	F	11	22	"	"	Choroidal tubercles	108	1.3	36	36	"	17	1.20	"	36	"
107	M	1	7.5	"	Primary infection	"	48	1.6	64	64	"	29	1.60	"	64	"
108	F	3	12	"	Normal	No tubercles seen	64	0.9	33	33	"	12	0.40	"	33	"
109	M	4	15	"	"	Choroidal tubercles	42	1.8	28	28	"	3	0.40	"	28	Hydrocephalus not yet operated on
110	F	14	42	"	"	No tubercles seen	121	1.1	28	28	Deafness	21	2.00	"	28	Fairly well
112	M	13	26	"	Miliary tuberculosis	Choroidal tubercles	81	2.4	27	27	None	22	0.80	"	27	Well
113	M	20	54	Clinically	Normal	"	72	0.7	24	24	"	21	2.40	"	24	"
114	F	13	25	"	"	No tubercles seen	65	0.95	26	26	Eruption	13	0.80	"	26	"
115	M	17	47	Bacteriologically	"	"	86	0.9	22	24	None	372	1.75	"	26	Fairly well
117	F	2	9	"	Miliary tuberculosis	Choroidal tubercles	20	0.9	20	20	"	38	1.10	"	20	Very ill; disturbance of consciousness
118	F	14	52	Clinically	"	"	59	0.7	14	14	"	29	0.70	"	14	Well

NOTE.—As the table was received some time after the text, cases treated since the article was written have been included.

70 cases only, leaving aside those patients who died almost at once and in whom the treatment could not have begun to take effect.

So far as one can at the present time attempt to define the new clinical picture of tuberculous meningitis, there are three possible ways in which the disease may develop: (i) some cases deteriorate whatever action is taken; (ii) others, after an encouraging improvement, seem to become stabilized, but gradually the disease, from being subacute, becomes chronic; (iii) others develop favourably and present every clinical appearance of good—even excellent—health, but we do not yet know whether it is possible to describe them as cured or whether relapses will occur.

In the first group were included the cases which developed fatally within a few days (13 of our first 50 patients), those which did so a little more slowly but without showing the slightest improvement (14), and those which succumbed after a very transitory abatement of symptoms (2). These were nearly all cases whose treatment was started too late. At the beginning of the experiment we gave up all idea of instituting streptomycin treatment in patients whose condition seemed to us beyond hope. Of all the unfavourable signs there is only one, in our opinion, which has an absolute value, and that is coma, by which we mean complete abolition of consciousness, absolute insensitivity to the strongest stimuli. This is the only condition in which we consider all hope to be lost. One cannot be so completely pessimistic when confronted by somnolence or torpor, even when this is marked, if one manages to lift the child out of it, even temporarily, and to drag a few coherent answers from him. One must also be on one's guard, in estimating disturbances of consciousness on the child's admittance to hospital, against the transitory aggravation due to being moved and to travelling.

Early Essays in Treatment

While we were still clarifying these elements in the prognosis we instituted, at an early stage of our investigation, a method of treatment of which the general principles were: (i) employment of large doses of the order of 100,000 to 200,000 units per kilogram of body weight per day; (2) administration of the drug by both the intraspinal and the systemic route; (3) prolonged treatment, with the highest doses compatible with tolerance for as long as possible.

This method of *large doses administered both systemically and locally over a prolonged period* was instituted at a time when we had only very vague data on the dosage and toxicity of streptomycin. With experience we found it to be dangerous, as it was the cause of severe—sometimes extremely severe—toxic disturbances. In future the method can only be accepted with reserve. Certain conclusions can be drawn from these results, and above all they provide a profitable lesson for those who may have to handle streptomycin for the first time.

When tuberculous meningitis is treated in this way an embarrassing situation arises out of the concurrence of symptoms and signs caused on the one hand by the disease and on the other by the drug.

The problem now becomes an extremely difficult one to solve, as streptomycin itself, introduced in this way in massive doses, creates an experimental disease that must be recognized in order to avoid therapeutic errors the consequences of which may be fatal to the patients. The disease thus created comprises (a) general toxic disturbances, (b) cutaneous reactions, and (c) meningeal reactions.

(a) The general toxic disturbances completely upset the temperature and weight charts, so that if treatment with large doses (more than 50,000 units per kg. per day) is carried out

no reliance can be placed on either fever or weight as a guide. Streptomycin produces very varied temperature curves: sometimes large waves, or, more especially, wide daily oscillations of the order of $1-2^{\circ}$; sometimes only moderate fever; but the temperature is never normal. Under the same therapeutic conditions the patient does not gain weight: he may lose weight at an extraordinary rate (10 kg. in about a fortnight). Still under the same therapeutic conditions, it is impossible to use the state of consciousness as a basis for estimating the progress of the meningitis. The somnolence and clouding of the mind may be caused by the toxic effects of the drug. If one interprets the fever, emaciation, and somnolence as indications for continuing the treatment, convulsions may well ensue, and these often end fatally or, at best, give rise to that well-known complication of streptomycin therapy, deafness, which has occurred in 15 of our cases, and the onset of which is particularly difficult to detect in the presence of such serious disturbances of consciousness. We should add toxic vomiting to this picture, a symptom which may occur even without intraspinal treatment. We would also mention, as symptoms of less frequent occurrence whose mechanism is still unexplained, tetany (in two cases), hyperazotaemia, and sometimes slight albuminuria.

(b) The cutaneous reactions, in spite of the fact that they may be chronologically independent of the general toxic manifestations, often give some warning: there may be transient erythema resembling that of scarlet fever, measles, or rubella; this is usually accompanied by fever and is in itself a painful complication.

(c) The meningeal reactions are characterized by stiff neck, sharp pain at each fresh injection of the drug, and special symptoms of sudden onset, i.e., severe convulsions with opisthotonos.

We must also mention a point which in our opinion is very important: the fact that repeated large doses of streptomycin introduced into the meninges always produce a violent histological reaction (wide daily variations in the lymphocyte count of the order of 50 to 400 and even 800 cells per c.mm.).

If one adds to the intoxication and meningeal reactions the sufferings caused by local injections whose high concentration makes them irritant and liable to produce abscesses and scars, one finds that practically every case presents a pitiful picture. If, unaware as we were at the beginning of our researches of the general toxicity of streptomycin, one perseveres in the belief that these symptoms constitute a development of the meningitis one is heading straight for disaster. In practice it is essential sooner or later (within from one to three weeks) to cease treatment, possibly for some time if the patient is threatened with deafness. Cessation of treatment is accompanied by improvement or, to be more correct, a veritable resurrection: the temperature falls with surprising rapidity, the weight increases as quickly as it decreased, and the disturbance of consciousness disappears.

If there is too much delay in resuming treatment a probably fatal relapse ensues sometimes after an interval as short as a week, sometimes after the patient has been normal for as long as 85 days. This may happen with devastating rapidity.

It is impossible, therefore, to adopt such a method; that is the first point to be learnt from this therapeutic trial. It is a great strain for the patient, and causes numerous toxic manifestations and sometimes permanent infirmity. It also necessitates, sooner or later, stopping the treatment in circumstances such that one hesitates to resume the administration of the drug. It is essential to recognize all these disadvantages. On the other hand, it should be remembered that such energetic treatment seems to ensure the most rapid improvement in the cellular reaction of the cerebrospinal fluid: we shall see the importance of this later. In order both to exploit the advantages and to avoid

the disadvantages of this method, we finally adopted a new therapeutic procedure, which we will now describe in its principles and applications.

Treatment in Present Use

The treatment which we are now using against tuberculous meningitis comprises two distinct phases: the *phase of attack*, followed by the *phase of maintenance*.

The phase of attack consists of large doses: 100,000 units per kilogram per day by the parenteral route and at the same time two intraspinal injections per day of 50,000 to 100,000 units. This treatment is continued for about a week, with some variations to suit individual reactions. In the second phase, treatment is maintained at doses below 50,000 units per kilogram per day by means of parenteral injections alone, no intraspinal injections being given as a rule.

Carried out in this way the phase of attack takes place without any serious disturbances. It may, on occasion, be modified if meningeal intolerance makes this necessary; this would involve giving the intraspinal injections at longer intervals or even stopping them altogether.

The dosage to adopt in the maintenance phase of treatment is a difficult question to settle. Its level may be lowered if there are manifestations of intolerance and particularly if signs of intoxication appear (the much rarer cases of deafness may be encountered even with small continuous doses). What is more difficult still is to assess the progress of the meningitis. It very often happens that the patient appears at this stage to be in excellent condition. What points reveal the state of his meninges? For our part, setting aside the information derived from the comparison of the x-ray plates in the case of associated miliary tuberculosis of the lungs, we note, among the clinical elements, the development of the pyrexia: any rise in temperature or any wave modifying a curve which has normally been following a progressively downward trend should arouse attention once the possibility of drug fever has been eliminated.

We attach the greatest importance, however, to the essential supplementary examinations—i.e., those of the fundus oculi and the cerebrospinal fluid.

For the observation of a case of meningitis the collaboration of the ophthalmologist is indispensable, as the examination of the fundus oculi is one of the most delicate methods by which it is possible to keep a watch on the progress of the meningitis: the choroidal tubercles, under the influence of the treatment, lose their original aspect and gradually heal or disappear, leaving residual pigmentation. At the same time it often happens that the specialist detects the appearance of fresh tubercles well before the clinician has noticed anything abnormal.

The second indispensable method of investigation is the examination of the cerebrospinal fluid. It required a whole series of accidental circumstances, comparisons of estimations, and discussions before we accorded to the lymphocyte count the importance which it now seems to us to merit. If one takes the trouble to work out the significance of the changes in the lymphocyte count incidental to local treatment, and to study the general trend of the count from a curve plotted from estimations at suitable intervals (about every eight days), one cannot fail to be struck by the importance of the evidence afforded by this means. Thus in favourable cases it is possible to obtain a count which remains normal or subnormal; in 16 of the cases at present under observation the number of cells per cubic millimetre is always below 10, and generally of the order of 4 or even less. On cessation of treatment a sudden rise in the number of lymphocytes may be observed; this appears to precede

clinical recurrence of the infection. If the dosage is diminished a sudden or progressive increase in the number of leucocytes may be noticed. To obtain this return of the cerebrospinal fluid to normal, which we consider indispensable, the minimum dosage varies from one patient to another; in certain cases the minimum effective dose is very close to or even exceeds the toxic dose. This is the eventuality to be dreaded most in practice, and though the situation may not be conclusive it is too soon to be certain on this point.

These are the broad outlines of the treatment which is at present being tried out at the Clinique Médicale des Enfants. The immediate results of the method are good. At the present moment 46 children who have been undergoing treatment for from 2 to 10 months are behaving like normal beings. The tuberculous meningitis ward is like a playroom, where the liveliness provides a constantly touching scene.

The problem arises, or will arise sooner or later, of when to stop the treatment, and this is the most difficult question of all. In every country doctors are asking themselves, When and on what indications can one stop the treatment? For our own part, forewarned by our early mistakes of the gravity of premature cessation of treatment followed by fatal relapses, we have not yet dared to make the decision. We are treating the children continuously, as diabetics are treated with insulin. Here, to be honest, we come up against an unfavourable factor in the occurrence of streptomycin resistance in the tubercle bacilli, but we have not arrived at any definite conclusions on this still very obscure problem; at the same time there is a favourable factor in the tendency shown by the lesions to heal by degrees as the duration of the tuberculosis increases. We have now decided not to cease treatment until we have the support of a large number of reassuring signs: absence of all clinical meningeal symptoms, an ascending weight curve, complete apyrexia, normal sedimentation rate, and a spinal lymphocyte count below 10 per c.mm. at repeated examinations. We would add to this, absence of tubercle bacilli in culture and, if possible, a normal quantity of cerebrospinal albumin. This last point is justified by an extremely important observation concerning the evolution of certain cases of meningitis treated by streptomycin.

Symptoms after Apparent Cure

A fourth group of patients develops in a very peculiar manner, and a knowledge of the facts involved constitutes an indirect advance in the streptomycin therapy of tuberculosis. Though apparently cured of meningitis in so far as they no longer present any clinical syndrome of the infection, are practically free from fever, and there is no longer any serious cellular reaction in their cerebrospinal fluid, these patients do not recover their liveliness like the others, and do not regain weight. Sometimes their neurological examination is not completely negative (there may be cutaneous hyperaesthesia, Babinski's sign, or slight tremor). In this case very careful attention must be given to the examination of the eye and of the cerebrospinal albumin. In these patients the possibility of a mechanical lesion, particularly the setting up of hydrocephalus secondary to meningeal adhesions, should be considered. This is where the neurosurgeon is called in to deal with the new situation; we are not yet certain whether this is the result of tuberculous meningitis or the consequence of a cerebral tubercle against which streptomycin does not seem so far to be as completely effective as against meningitis. The decision to operate was taken in 6 cases. In 5 of these the findings were widespread leptomeningitis or pachymeningitis of the cisterna pontis; in the sixth case there was a large

meningeal tubercle round the chiasma. In two of these cases the results were remarkable, one patient, who was comatose and blind at the time of operation, being one of those who are now giving us the greatest hope. In the new treatment of tuberculous meningitis the neurosurgeon is associated with the physician, as the chest surgeon is associated with the phthisiologist in certain cases of chronic pulmonary tuberculosis.

THE TROPICAL LICHEN PLANUS SYNDROME

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An unusual disease with striking cutaneous manifestations has been observed in Australian, American, and New Zealand troops serving in widely scattered areas of the Pacific. Because of its geographical distribution, and from some clinical and histological resemblances, it has become commonly known as tropical lichen planus. The condition was briefly referred to by Myers (1944) in the course of a review of skin diseases affecting Australian troops in New Guinea. A detailed account of the findings in some American cases has been given by Bagby (1945).

The aetiology is not definitely established, but there is substantial evidence that the disease has some relation to the use of mepacrine as a malaria suppressive. The public revelation that an identical syndrome has been observed for some time in military forces using mepacrine suppression in Europe and the Middle East substantially confirms this belief (*Lancet*, 1945, 2, 711).

In his account Bagby mentions that the total number of cases in American troops would be impossible to estimate. A reasonable assessment of the incidence, as well as some conclusions from the geographical distribution, can be made from an analysis of the figures for a New Zealand force which operated in the Pacific Zone. This was a relatively small force of some 18,000 men, and it maintained independent medical services. Divisional troops comprised about 12,000 men, and all evacuations from this group came ultimately to a single base hospital, where all skin cases were seen by me. Most of the men in the force had served for periods of six months to two years in Fiji prior to November, 1942. Individual battalions had been stationed also in Tonga and Norfolk Islands. In November, 1942, the force proceeded to New Caledonia. Although some of these islands are quite tropical in climate, none of them is malarious, and therefore no mepacrine suppression was employed. No case of tropical lichen planus, or any condition resembling it, was seen at that time, though the usual tropical dermatoses were prevalent.

In August and September, 1943, the combatant part of the force moved to Guadalcanal, one of the Solomon Islands, some units spending a few weeks on the New Hebrides en route. In the following 12 months they were divided into two groups, which operated independently on various islands in the Solomon region. All these islands are highly malarious, and suppressive mepacrine was started when troops left New Caledonia, being maintained continuously until their return. The rate of administration was 0.1 g. of mepacrine daily for six days in each week.

The first case of tropical lichen planus in this force was evacuated to the base hospital in early December, 1943, and five further cases were received in the following five months. This suggests, at first consideration, a steady trickle of cases, but examination of the histories shows that