To achieve this there would have to be facilities for a very large number of barium meals.

ORGANISATION

There are roughly 15,000,000 people in this country between the ages of forty and sixty-five—i.e., 1,250,000 in each of the proposed health-service regions. If each year 1 in 25 of this age-group required a barium meal at the request of his general practitioner, 50,000 barium meals would be needed each year in each region. If one X-ray plant can deal with 20 barium meals a day, or 5000 a year, ten X-ray plants would be enough in each region. The provision of this equipment would not be impossible.

The service would naturally be directed by consultant radiologists holding appointments at the large hospitals, and they could decide whether to provide the additional facilities by enlarging their departments or by establishing additional regional centres. The chief difficulty would probably be the shortage of trained staff, since barium-meal work is one of the most skilled branches of radiology. The examinations could be carried out by junior radiologists in training as clinical assistants at the hospitals; they would get a wide experience of the radiology of the normal stomach and could submit any abnormal case to the radiologist in charge of the department. If this suggestion is impracticable, it would be necessary to make extended use of technicians, as in pathological laboratories. Whether such technicians could be trained to screen the stomach I am not competent to say, but they could prepare three films of each case for submission to the consulting radiologists. It will be objected that a proportion of small lesions would be missed by such a method; but as a surgeon my impression is that for every small lesion there are a great many obvious filling defects to be seen on the films. I feel sure that if every positive or doubtful case were referred for screening by the radiologist, comparatively few errors would be made.

This is obviously a controversial subject; but somehow radiology must get to closer grips with gastric carcinoma in the mass, instead of in selected cases. I have no doubt that, if the technical problem is put to them, our radiological colleagues will solve it. If the solution implies a modification of their technique of perfection, they may be assured that, in a situation where 5 out of 6 cases are lost from the start, an imperfect reform is better than none.

CONCLUSION

I do not suggest that the scheme outlined would completely solve the difficulties; there will always be cases of cancer of the stomach that are absolutely symptomless until they are inoperable, and there will always be sturdy beggars who refuse to consult a doctor. These we shall never save; but, if the general practitioners had direct radiological facilities at their call, and if the general public knew that they could be radiographed without being herded through the overcrowded outpatient departments of the hospitals, increasing numbers of patients would be referred for treatment at an operable stage.

As an operating surgeon I am appalled and depressed by the endless succession of hopeless laparotomies or desperate dissections of too extensive growths for lack of diagnostic facilities in general practice, and I see no other remedy for it. If, instead of 1 case out of every 6 that come to hospital we could save 3, no less than 3000 lives could be saved each year in this country. That is a challenge and an opportunity for the new organisation of the medical services, and an objective which fully justifies a clinical and radiological experiment on a regional scale.

STREPTOMYCIN TREATMENT OF TUBERCULOUS MENINGITIS

STREPTOMYCIN IN TUBERCULOSIS TRIALS COMMITTEE,* MEDICAL RESEARCH COUNCIL

IN September, 1946, the Medical Research Council appointed a committee to plan and direct clinical trials of streptomycin in the treatment of tuberculosis. Since the amount of the drug expected to be available for the trials was limited, the committee decided to restrict the tests at the outset to a few acute and usually fatal forms of the disease, including tuberculous meningitis in children and acute miliary tuberculosis. This report, the first to be made by the committee, is concerned with the results in tuberculous meningitis.

Three main centres were established in the first instance: Hammersmith Hospital (L.C.C.); Alder Hey Children's Hospital, Liverpool; and the Royal Hospital for Sick Children, Glasgow. Later, cases were also admitted under this scheme to the Hospital for Sick Children, Great Ormond Street; Guy's Hospital; the National Hospital for Nervous Diseases, Queen Square; and Highgate Hospital (L.C.C.). At the Radcliffe Infirmary, Oxford, some cases had been treated with streptomycin before the M.R.C. scheme was begun; this centre continued during 1947 to operate under M.R.C. auspices. Finally, when pressure for admission of cases was increasing, a few cases were admitted to centres established for other tuberculosis investigations in the M.R.C. streptomycin trials. Until July, 1947, only children under 9 years of age were admitted to the centres (except at Oxford, where there was no age limit); between then and the inception in September of the Ministry of Health scheme (see below) a few older children and adults were admitted as an emergency measure. In September, 1947, the centres at Alder Hey, Glasgow, Great Ormond Street, and Guy's were absorbed into the current Ministry of Health scheme, and the two largest centres, Hammersmith and Highgate, continued investigating special problems under M.R.C. auspices.

The first patients to be treated under the M.R.C. scheme were admitted in January, 1947, and 138 cases were admitted during 1947. This report is confined to the 105 proved cases admitted before Aug. 18, and the survivors observed to Dec. 15, thus giving a minimal observation period of 120 days (17 weeks). Of the 105 proved cases, 13 were treated at Oxford and are analysed in a separate report (Smith et al. 1948). For the other 92 cases the mean observation period in the survivors was 201 days (median 191 days), the maximum 325 days; the mean potential observation period (assuming survival of all cases) was 198 days (median 175), the maximum 334 days.

The centres kept uniform records and followed general recommendations regarding dosage, but there were necessarily considerable variations, particularly in rhythm of treatment, between different centres and between cases within each centre, because knowledge regarding optimal methods was so scanty that no hard and fast rules regarding treatment could be laid down.

This report does not present an exhaustive clinical analysis of the cases. By grouping the information from all centres it is, however, believed possible to reach conclusions more significant than could be derived from a study of a relatively small number of cases at one centre alone. It is hoped that the report may be followed by fuller clinical and pathological reports from individual centres.

The purpose of the present analysis is to ascertain the survival-rate in tuberculous meningitis under streptomycin treatment, to seek optimal techniques of treatment, to establish possible guides to prognosis, and to

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define the main outstanding problems. The general results (table I) and the over-all results of two methods of treatment (tables V and VI) refer to the total 105 proved cases; the more detailed analysis is concerned with the 92 cases treated in centres other than Oxford.

It had already become evident in the M.R.C. tests by the early summer of 1947 that streptomycin prolongs life and, at least temporarily, restores health in some cases of tuberculous meningitis, as previously reported from the U.S.A. The council thereupon recommended to the Ministry of Health that streptomycin should be made available for this condition as widely as supplies would permit. This recommendation led to the arrangement referred to above as the "Ministry of Health scheme," under which the streptomycin treatment of tuberculous meningitis (and acute miliary tuberculosis) can now be undertaken at many hospitals throughout the country (see *Lancet* 1947).

The streptomycin used in the present trials was in the form of the hydrochloride, obtained from one American producer; it had satisfied the requirements of the American Food and Drug Administration as regards identity, potency, purity, and toxicity (immediate lethal effects on mice, content of histamine-like depressor substances, content of pyrogens, &c.); tests on random samples at the National Institute for Medical Research gave confirmatory results. The potencies of the preparations were within the range 550–650 μg. of base per mg. of material. All weights of streptomycin given here refer to active base (1 μg. of base is the equivalent of 1 S unit and of 1 provisional British unit). So far as possible each patient received the same batch throughout his treatment.

Summary of Results on Dec. 15, 1947

Of the 105 patients admitted to M.R.C. centres for streptomycin treatment before Aug. 18, 1947, 67 (64%) have died and 30 (28%) are making good progress after 120 or more days' treatment and observation (table I). The condition of those making good progress is considered below.

It soon became obvious that the prognosis in children under 3 years of age was much worse than in older children; table I shows that the proportion of older children surviving and making good progress after four months

TABLE I—RESULTS OF STREPTOMYCIN TREATMENT RELATED TO AGE

Age (yr.)	No. of cases admitted before Aug. 18, 1947	Condition on Dec. 15, 1947			
		Good	Stationary or relapsed	Deteriorating	Dead
Under 3	33	4 (12%)	0	2 (6%)	27 (82%)
3–5 ..	26	10 (38%)	2 (8%)	0	14 (54%)
6–8 ..	25	11 (44%)	3 (12%)	0	11 (44%)
9 and over	21*	5 (24%)	1 (5%)	0	15 (71%)
All ages	105	30 (28%)	6 (6%)	2 (2%)	67 (64%)

*11 at Oxford.

was more than three times that in children under 3 years. An analysis of results reported by Debré et al. (1947) also shows a high fatality-rate in young children. The results in the age-group 9 years and over are not comparable with the rest, since 12 of the 21 received intramuscular treatment alone (see below).

Space does not allow comparison of results with those reported by Hinshaw et al. (1946), Dubois and Linz (1947), Cocchi and Pasquinucci (1947), Council on Pharmacy and Chemistry (1947), and Mollaret (1948). The last is one of a symposium of twelve papers reporting on a total of 615 cases of tuberculous meningitis treated in France.

Clinical Condition of Patients on Admission

Nearly a third of the patients admitted were in a clinically advanced condition when submitted to the centres for streptomycin treatment: some cases, on the other hand, were diagnosed at a relatively early stage. To assess how far the prognosis depends on the clinical condition at the time treatment was started, the 92 cases

TABLE II—RESULTS OF STREPTOMYCIN TREATMENT RELATED TO STAGE OF DISEASE

Stage of disease at start of treatment	No. of cases admitted between Jan. 18 and Aug. 18, 1947	Condition on Dec. 15, 1947		
		Good	Stationary, relapsed, or deteriorating	Dead
Early ..	26	11 (42%)	3 (12%)	12 (46%)
Medium ..	38	10 (26%)	3 (8%)	25 (66%)
Advanced ..	28	2 (7%)	2 (7%)	24 (86%)
Total ..	92	23 (25%)	8 (9%)	61 (66%)

treated in centres other than Oxford have been classified as follows:

Early.—Patients with mainly non-specific symptoms, with little or no clinical signs of meningitis, with no pareses, in good general condition, and fully conscious. Diagnosis established mainly on findings in cerebrospinal fluid (C.S.F.).

Advanced.—Patients obviously extremely ill, deeply stuporose or comatose, or with gross pareses.

Medium.—Patients in a condition between those of the first two groups.

A little less than half the early cases, two-thirds of the medium cases, and six-sevenths of the advanced cases have proved fatal (table II). Only 2 of 28 advanced cases are making good progress,† compared with 11 of 26 early cases. Though some early cases never responded to treatment, and 2 advanced cases did respond, on the whole the prognosis is closely related to the condition on admission.

In this analysis the stage of disease has been assessed solely on the clinical condition on admission. In general, patients with a short history suggesting meningitis were clinically at an earlier stage than others, but there were many exceptions. Thus 8 patients with a suggestive history of more than a week's duration were still at an early stage on admission; on the other hand, 7 patients with a similar history of less than four days' duration were at an advanced stage. The development of clinical illness was sometimes very rapid, particularly in young children. Indeed the bad prognosis in children under 3 years is partly explained by the fact that so many of them (18/32 as against 10/60 older patients) were at an advanced stage on admission.

The length of non-specific history (with symptoms not suggesting meningitis) bore little relation to the condition on admission. In many cases a history of symptoms suggesting meningitis merges insensibly into a much longer non-specific history corresponding to a period of primary infection, or of miliary disease without meningitis. Thus 8 early cases had non-specific histories of over a month, whereas in 14 advanced cases there was no history of illness of any kind until a fortnight before admission.

Many patients showed on admission evidence of tuberculous lesions in other parts of the body. All were radiographed shortly after admission. In 25 (27%) the chest radiogram revealed typical miliary lesions; 23 (25%) had enlarged hilar glands or a recent or apparently active primary complex without associated miliary lesions; in 12 (13%) there were other lesions in lung, bone, or skin; only 32 (35%) had no other detectable

† One of the two has serious behaviour disorders (case 30); the other (case 37) has relapsed and died since December, 1947.

TABLE III—RESULTS RELATED TO X-RAY FINDINGS ON ADMISSION

X-ray findings	No. of cases admitted between Jan. 18 and Aug. 18, 1947	Condition on Dec. 15, 1947		
		Good	Stationary, relapsed, or deteriorating	Dead
Miliary or recent primary lesions ..	48	8 (17%)	4 (8%)	36 (75%)
Others ..	44	15 (34%)	4 (9%)	25 (57%)

lesions. Table III suggests that cases apparently caused by acute blood dissemination—i.e., those with miliary or recent primary lesions—have a higher fatality-rate.

Diagnosis

Nearly a third of the patients admitted to the centres were at an advanced stage. The proportion was much higher among the total cases submitted; at a time when beds and drug supplies were severely limited, selection necessitated refusal of cases so advanced as to offer little if any hope of response. The fact that so many were at an advanced stage when diagnosed, coupled with the finding that early cases offer the best prognosis, emphasises the importance of some features relevant to the diagnosis in the present series.

History.—The clinical history was often vague or misleading, and an early diagnosis of tuberculous meningitis could only be made by actively seeking supporting evidence.

A definite history of contact with diagnosed tuberculosis in the home was found in 35 of the 92 cases; but in three centres where it is known that a full inquiry was invariably made such a history was elicited in 23 of 42 cases (against 12/50 in other centres).

Tuberculin Reaction.—The tuberculin test has proved a highly significant aid to diagnosis, particularly in young children. It is commonly stated that the result is often negative in tuberculous meningitis, but in only 1 of 73 cases in this series with Mantoux tests completed—i.e., carried to a dilution of 1/100 where necessary—was the result negative; 5 showed positive reactions to O.T. 1/100 but not to 1/1000, and 67 to O.T. 1/1000.

Radiography.—Routine chest radiography proved another valuable aid. Of the 92 patients, 55 (60%) had tuberculous lesions in the chest demonstrable by radiography (5 more had previously diagnosed tuberculous lesions in other parts of the body).

C.S.F. Findings.—The general picture of C.S.F. changes was fairly characteristic in most cases. It is not possible from the present series to attach particular diagnostic importance to any one change in elements of the C.S.F., but a low sugar content had differential value when benign lymphocytic meningitis was in question.

All 92 cases reported here were proved either by isolating the tubercle bacillus from the C.S.F. by culture or guineapig inoculation, or by post-mortem histological examination. Cases with acid-fast bacilli in the C.S.F. smear not subsequently confirmed biologically are not included. Three survivors in whom the diagnosis is a most likely one, but in whom it was not confirmed by culture or guineapig inoculation, are excluded.

A diligent search for tubercle bacilli in the slide smears of C.S.F. deposit before the start of treatment gave positive results in 42 (46%) of the 92 cases. Direct examination of the C.S.F. smear is therefore of great value. Most patients, however, provided strong collateral evidence supporting the diagnosis; the general rule was therefore to start treatment even in the absence of immediate bacteriological proof, and the rule gradually adopted was to reserve the major part of the C.S.F. deposit for culture and guineapig inoculation, to provide later confirmation of the diagnosis and also to secure for sensitivity test specimens of the untreated strain of tubercle bacillus. The results of cultures for tubercle bacilli and guineapig inoculation of pretreatment specimens are analysed in table IV.

Guineapig inoculation was apparently more reliable than culture in those specimens of C.S.F. where acid-fast bacilli were not seen on direct examination. The difference is not statistically significant, but in addition 12 specimens, 11 of which were negative on direct examination, gave negative cultures but were positive on guineapig inoculation, whereas only 2 specimens were positive on culture but negative in guineapigs. It must, however, be emphasised that no controlled study along these lines was being made, and it is possible that where guineapigs were being inoculated only a small amount of the C.S.F. deposit was used for culture.

Only 1 of the strains from 33 cases was of bovine type, the rest being human.

Streptomycin Administration

When the first centres for streptomycin treatment of tuberculous meningitis were opened in January, 1947, little was known except that some patients treated in the U.S.A. were still alive; no detailed treatment technique could be recommended. It was decided that all cases should be treated both by the intramuscular route and intrathecally, that the intramuscular injections should be given 6-hourly for at least three months, and that frequency and total duration of intrathecal treatment should be left to the discretion of the clinician in charge. The 24-hourly intramuscular dose was to be 1 g. for children under 3 years, and 2 g. for older children; with the first few cases it became evident that this dosage was too high, particularly for children at the lower age limits, and the 24-hourly dosage adopted for the rest of the trials was 0·02 g. per lb. of body-weight. The maximal 24-hourly dose was 2 g. The intrathecal dose has been between 0·05 g. and 0·1 g.; the dose was given in 5–10 ml. of normal saline, not more often than once daily.

TABLE IV—EXAMINATION OF PRETREATMENT SPECIMENS OF C.S.F. FOR TUBERCLE BACILLI

C.S.F. findings	Cultures (85 specimens)		Guineapig inoculation (53 specimens)	
	Pos.	Neg.	Pos.	Neg.
Direct examination positive	33	3	17	2
Direct examination negative	24	25	23	11
Total ..	57	28	40	13

Toxic effects attributable to excessive dosage were seen in the first few children treated; in some of these albuminuria developed and blood and casts were found in the urine. After the dosage was reduced, toxic symptoms rarely necessitated cessation of treatment. Transient rashes which disappeared while treatment was continued were seen in 13 patients; as isolated phenomena they appear to be of little significance. In 15 cases there was a low pyrexia which persisted throughout streptomycin treatment and only disappeared after the end of the course; this was true particularly during courses of intrathecal treatment. Persistent vomiting during treatment occurred in many cases, but its frequent combination with other evidence of unsatisfactory progress made it difficult in any instance to assign responsibility to toxicity or to progressive hydrocephalus.

Tests of effects on the vestibular apparatus were too few to bear analysis; but in the survivors little subjective

effect persisted. Children had an ataxic gait on beginning to walk, but after several weeks their gait became normal.

A disturbing feature manifest in some patients was meningeal irritation attributable to the intrathecal treatment. Thus case 78, a girl of 7 years, made a good general response in the first two weeks of treatment, though clinical signs of meningitis persisted; meningism became much more severe in the third week and persisted until after the 28th day, when intrathecal treatment was stopped; from that time she made rapid uninterrupted progress. Similarly case 29 improved dramatically after cessation of intrathecal treatment lasting seven weeks, during which period her clinical state had been stationary or deteriorating.

The irritant effect of streptomycin on the meninges was often demonstrated in the C.S.F. by a well-marked pleocytosis (predominantly polymorphonuclear); in 20 cases this reaction was seen after the first injection, with cell-counts rising as high as 3250 per c.mm. in 1 case; in 13 cases the sharp rise appeared only after several intrathecal injections had been given. In patients whose progress was favourable, after cessation of intrathecal therapy the cell-count fell steeply at first and then gradually reached a low level.

TRIAL OF INTRAMUSCULAR TREATMENT ALONE

These facts led the committee to consider whether in some cases the trauma of intrathecal injections repeated over a long period, and the irritant effect of streptomycin on the meninges, might not more than counterbalance the possible benefits of introducing the drug directly to the site of the disease. Moreover, it was found that by intramuscular injections alone streptomycin levels of 2–4 μg. and sometimes 8 μg. or more per ml.‡ could be reached in the C.S.F. in meningitis. After full discussion in June, 1947, at a meeting of clinicians of the centres concerned, it was concluded that the question could be answered only by conducting a parallel investigation with cases treated by intramuscular injection alone. Accordingly from mid-June alternate patients admitted to M.R.C. centres received streptomycin by the intramuscular route only; also the few patients over the age of 9 years admitted to centres other than those established specifically for treatment of tuberculous meningitis had intramuscular therapy only.

Including those treated in the Oxford centre, 33 of the 105 patients were treated with a course of streptomycin given intramuscularly only; 5 of these who did not respond were later given intrathecal treatment. In table v the results of combined therapy (intramuscular plus intrathecal) are compared with those of intramuscular treatment alone. The first group includes cases admitted since the start of the trials (mean potential observation period 223 days); the second, only cases admitted since mid-June, 1947 (mean potential observation period 148 days). The type of case admitted was similar in the two groups, with a similar distribution of cases in an advanced stage on admission.

‡ Levels of 2–8 μg. per ml. represent a satisfactory bacteriostatic range, according to present knowledge.

TABLE V—RESULTS RELATED TO MODE OF TREATMENT

Age	Treatment	No. of cases admitted before Aug. 18, 1947	Condition on Dec. 15, 1947		
			Good	Stationary, relapsed, or deteriorating	Dead
Under 3 yr.	Combined ..	24	4 (17%)	2 (8%)	18 (75%)
	Intramuscular only ..	9	0	0	9 (100%)
3 yr. and over	Combined ..	48	21 (44%)	3 (6%)	24 (50%)
	Intramuscular only ..	19	3 (16%)	3 (16%)	13 (68%)
	Intramuscular plus intrathecal later	5	2	0	3
All ages	Combined ..	72	25 (35%)	5 (7%)	42 (58%)
	Intramuscular only ..	28	3 (11%)	3 (11%)	22 (78%)

The results are considerably better in the series on combined therapy. About a third of these were doing well after a minimum of 120 days' observation and treatment, as compared with a ninth of those on intramuscular treatment only. The difference between the two series is statistically significant. Of the 28 patients on intramuscular treatment alone 22 (78%) died, compared with 42 (58%) of 72 patients on combined therapy. The results were particularly disastrous in children under 3 years; not one of the 9 patients on intramuscular therapy alone survived—indeed not one of them survived more than two months, whereas in 10 of the 18 fatal cases under 3 years on combined therapy life was prolonged over two months.

TABLE VI—RESULTS OF COMBINED INTRATHECAL AND INTRAMUSCULAR STREPTOMYCIN TREATMENT IN CHILDREN OF 3 YEARS AND OVER AND ADULTS

Stage of disease on admission	No. of cases admitted before Aug. 18, 1947	Condition on Dec. 15, 1947		
		Good	Stationary or relapsed	Dead
Early ..	15	9 (60%)	2 (13%)	4 (27%)
Medium ..	21	9 (43%)	1 (5%)	11 (52%)
Advanced ..	12	3 (25%)	0	9 (75%)
All stages ..	48	21 (44%)	3 (6%)	24 (50%)

The difference in results is even more definite if account is taken of the fact that the mean observation period in the group on combined therapy was longer than in the other group. Taking the results in all cases four months after treatment had been started, in the group on combined therapy 43% had died, whereas of those having only intramuscular therapy 70% had died.

The superiority of combined treatment is illustrated in another way by the 5 cases in which it was applied at a late stage following unsuccessful intramuscular treatment. Of these 5 patients 2 improved after intrathecal treatment was added, one of them responding dramatically, as follows:

Case 81.—A girl of 4 years admitted with seven days' history of headache, vomiting, and constipation, and a history of close contact with a case of open tuberculosis. Neck-rigidity, positive Kernig's sign, fully conscious but irritable, general condition fair. Mantoux positive. Chest radiogram: enlarged hilar glands, and patch of consolidation left mid-zone. C.S.F.: 75 lymphocytes per c.mm., protein 90 mg. per 100 ml., chlorides 710 mg. per 100 ml. Smear negative for tubercle bacilli (later culture positive).

The patient responded very rapidly to intramuscular streptomycin treatment; within two weeks meningeal signs and irritability had disappeared, and lymphocytes and protein content in the C.S.F. were falling. After this her clinical condition remained satisfactory for two months, though without further improvement; the only abnormal neurological sign was an extensor plantar reflex (doubtful until the fourth week), but from the end of the third week cells and protein in the C.S.F. increased progressively, reaching on the 75th day of treatment 480 cells per c.mm. and 350 mg. of protein per 100 ml. (chlorides were within normal limits). The C.S.F., negative for tubercle bacilli since the first week, showed tubercle bacilli on direct examination and on culture between the 60th and 70th days.

Henceforth the patient began slowly to deteriorate clinically, becoming apathetic and then irritable, vomiting occasionally and then repeatedly, until finally she presented a typical picture of tuberculous meningitis more severe than on admission. Intrathecal treatment was started on the 90th day.

She continued to deteriorate for three weeks, when she suddenly began to improve and she has continued since then to make good progress. On Dec. 15, six weeks after the start of intrathecal treatment, meningism had disappeared and she was afebrile, cheerful, and sitting up out of bed. She was still having treatment, and the C.S.F. contained 256 cells per c.mm., with 692 mg. of protein and 670 mg. of chlorides per 100 ml.

This case-history is characteristic of the favourable initial response to intramuscular therapy, uncomplicated by the irritation that intrathecal therapy can produce; this type of response led to the hope in the first two months of this part of the investigation that intramuscular therapy alone might be effective. The case follows the pattern also of the late progressive deterioration observed in cases on intramuscular therapy only, and finally it demonstrates the effect of introducing streptomycin intrathecally. The 3 fatal cases to whom intrathecal streptomycin was given after a course of intramuscular treatment received it terminally, too late to be of use.

Manifestly, even though 3 patients who have had only intramuscular therapy have done well, intrathecal treatment must for the present be considered indispensable as a working rule.

With the superiority of combined therapy established, the results of this method related to the stage of disease on admission yield an interesting analysis, and the results are given in table VI (with the exclusion of patients under 3 years because of their generally bad prognosis).

It is seen that only 4 of 15 early cases have died. Taking together the cases admitted at early or medium stages, 18 out of 36 were making good progress after 120 days or more.

RHYTHM AND DURATION OF STREPTOMYCIN THERAPY

Since various modes of streptomycin treatment were adopted in different centres, an attempt has been made to see if one method was more efficacious than another.

The regimens of treatment in the 23 patients (table II) who have done well are set out in fig. 1. A first impression is confusing, for it appears that these patients were treated in very different ways: some with combined therapy maintained for nearly three months; some with continuous intramuscular treatment but interrupted courses of intrathecal treatment; and some with long rest periods in which they had no streptomycin by either route. Consideration of the 69 patients who responded less well or not at all (not charted here) reveals a similar multiplicity of techniques.

However, on analysing the results in different centres, it was found that in the centre where the least intrathecal treatment was given, and where all streptomycin treatment was interrupted frequently and for relatively long periods, the highest proportion of good results was obtained—i.e., 5 doing well and 5 deaths among 11 patients on combined therapy. By contrast, in a centre where treatment was maintained fairly continuously by both routes, 1 did well and 9 died among 10 patients on combined therapy. The age-distribution was similar in these two centres, as also was the condition of patients on admission.

The results of this comparison between the two centres are suggestive but obviously not conclusive. Note in fig. 1 the treatment given in the 5 successful cases (11, 23, 28, 38, and 69) at the first centre; one of these is of particular interest:

Case 38 is remarkable in that the patient had only 11 days' streptomycin treatment in the first two months. A boy aged 2 years, he had been ill on and off for ten days. On admission he had mild meningeal signs, and the C.S.F. contained 300 cells per c.mm. (99% lymphocytes); protein 302 mg. per 100 ml.; chlorides 652 mg. per 100 ml. His tuberculous mother had died four months previously, he was Mantoux-positive, and a chest radiogram showed enlarged hilar glands. Streptomycin treatment, started immediately, was stopped after five days because no tubercle bacilli had been seen in the C.S.F. He continued to improve, except that three weeks after admission he developed paresis of the right arm. When the culture of a pretreatment specimen of C.S.F. gave a positive result, treatment was started again on the 42nd day, but was discontinued again after five days (because he had a well-marked pyrexial reaction). He remained well and apyrexial until about the 75th day, when his general condition began to deteriorate, his temperature rose, and the lymphocyte-count and protein in the C.S.F. increased; treatment was started again on the 86th day. His condition improved slightly during the two-month treatment course that followed, and improved more still after the end of the course. On Dec. 15, 1947, his general condition was good, though he still had occasional rises in temperature to 99°F.

The general impression voiced by clinicians at the centres has been that daily intrathecal treatment sustained over a long period ceases to be beneficial and is probably harmful. Another impression that emerges is that periods of complete rest from streptomycin treatment are beneficial. The clinical evidence in favour of this is strong; some children, while improving slowly under streptomycin treatment, did not gain weight and remained pyrexial and apathetic, but during periods of suspension of all streptomycin treatment they improved dramatically.

STREPTOMYCIN LEVELS IN THE C.S.F.

Very high concentrations of streptomycin in the C.S.F. were reached by intrathecal injection. Between 1 and 3 hours after injection of 0·1 g. the level was 750–2000 μg./ml.; it fell rapidly between 4 and 10 hours after injection, and 24 hours after was in most cases between 2 and 16 μg./ml. (range 1–75 μg./ml.). High concentrations were reached also in the ventricles; in one case ventricular puncture 4 hours after injection of 0·05 g. intrathecally showed a level of 500 μg./ml. A cisternal puncture 10 min. after 0·1 g. given by the lumbar route showed a level of 1200 μg./ml.

Concentration in the C.S.F. was studied in patients who had received intramuscular treatment only, or who had not had intrathecal treatment for some weeks. An important finding is that levels varied according to the degree of disease. In the early stages of treatment the level was 3–16 μg./ml.; in patients making good progress the range was 0·125–4 μg. in 7 cases, and 8–16 μg. in 1 case only.

In patients deteriorating on intramuscular treatment only, the range of streptomycin concentration in the C.S.F. was 1–32 μg./ml.; the following 4 cases showed rising levels as the disease progressed.

Case 59 appeared to improve clinically for the first month; but the C.S.F.-streptomycin level, which was 4·3 μg./ml. on the 2nd day and fell on the 6th day to 1·6, rose again to 5·5 on the 12th day, 11·0 on the 37th day, and 20·0 μg./ml. on the 58th day.

Case 70, who clinically improved slightly in the first week and was stationary until the 90th day, subsequently deteriorating rapidly, had C.S.F.-streptomycin levels as follows: 4·6 μg./ml. on the 3rd day, 8 on the 27th, 13 on the 25th, 20 on the 47th, and 27 μg./ml. on the 58th day; the levels fell slightly subsequently when there was a spinal block.

Case 47 improved clinically during the first three months, but after this his condition remained stationary or slightly deteriorating, with a C.S.F. showing a rising cell-count and falling sugar level. The C.S.F.-streptomycin level was 0·5–1 μg./ml. in the first four days, 2–4 during the next five weeks, and 32 μg./ml. on the 57th day.

Case 81, already described, also showed a steady rise in C.S.F.-streptomycin level after the third week of treatment.

It is interesting to note also that in a case of miliary tuberculosis treated with streptomycin and developing meningitis while under treatment (case 77) the C.S.F. level was 0·125–0·25 μg./ml. before the onset of meningitis, 0·5–1·0 during the first week of meningitis, and 2 μg./ml. subsequently.

These observations provide evidence that, as the meningeal process progresses, streptomycin passes with

increasing facility from the blood circulation into the thecal space; and conversely, as the condition improves, the barrier becomes less permeable. In other words, while a patient is on intramuscular treatment only, the C.S.F.-streptomycin level may be regarded as a valuable prognostic index, and a rising level should perhaps be an indication for a fresh course of intrathecal treatment.

In 4 patients blood and urine levels were studied after intrathecal injection of 0·1 g. The level in the blood-serum was 2–4 μg./ml. after an hour, and 4–16 μg./ml. after 4 hours. The maximal urinary excretion occurred from 1 to 12 hours after injection; $^1/_4$–$^1/_2$ the dose injected was recovered in the urine in 24 hours. The conclusion seems to be that, if intramuscular injections are spaced out to a 12-hourly or 24-hourly rhythm, intrathecal injections should be given not at the same time but in the middle of the period between one intramuscular injection and the next, since the streptomycin given intrathecally helps to maintain a good blood-serum level.

Clinical Course of Tuberculous Meningitis under Streptomycin Treatment

It has already been indicated that streptomycin is the first drug known to have modified the course of tuberculous meningitis, hitherto almost invariably fatal. What amounts practically to a new form of the disease, chronic tuberculous meningitis, is now being observed. A study of the various types of clinical response to streptomycin treatment may help us to understand this new form and its complications, and lead to a consideration of the elements of prognosis and possibly to an improvement in treatment techniques. It is possible also that whatever emerges from this study may apply also to other more potent chemotherapeutic agents that may be discovered in the future.

A—FATAL CASES

Of the 92 patients 61 have died. In many of the fatal cases survival was prolonged far beyond the period normally expected. The different types of response to treatment are discussed below.

(1) *No response to treatment.*—Twenty patients deteriorated rapidly and died within the period expected for untreated cases, without showing any response to treatment. Of these, 12 were under the age of 3 years; 15 were at an advanced stage on admission; and 11 died within five days of admission.

(2) *Slow progressive deterioration, with no period of improvement.*—In 19 cases the effect of streptomycin treatment seems to have been to delay death, sometimes for a considerable period (over four months in 2 cases) but without effecting any clinical improvement. In some of these the temperature fell after treatment was begun and tubercle bacilli could no longer be isolated from the C.S.F. In at least 2 instances (cases 27 and 72) the clinical impression was that the tuberculous infection was more or less under control, but that the patient went steadily downhill with progressive hydrocephalus. In case 27, a child of $2^1/_2$ years, on the 70th day of treatment the C.S.F. chlorides were within normal limits, protein 80 mg. per 100 ml., cells 30 per c.mm.; on the 120th day chlorides were normal, protein as before, cells 5 per c.mm. No tubercle bacilli had been isolated from the C.S.F. at any time during treatment. Miliary lesions in the lungs, obvious on admission, had cleared radiographically on the 110th day. Clinically, however, the child was in a "terminal state" two weeks after admission, and continued to deteriorate slowly. Necropsy revealed gross distension of all four ventricles.

In other cases to a picture of continuing gross infection was added one of increasing hydrocephalus, with or without manifest spinal block.

Case 82, not included in the above figure of 19 cases, improved slightly from the 60th to 80th day, during a

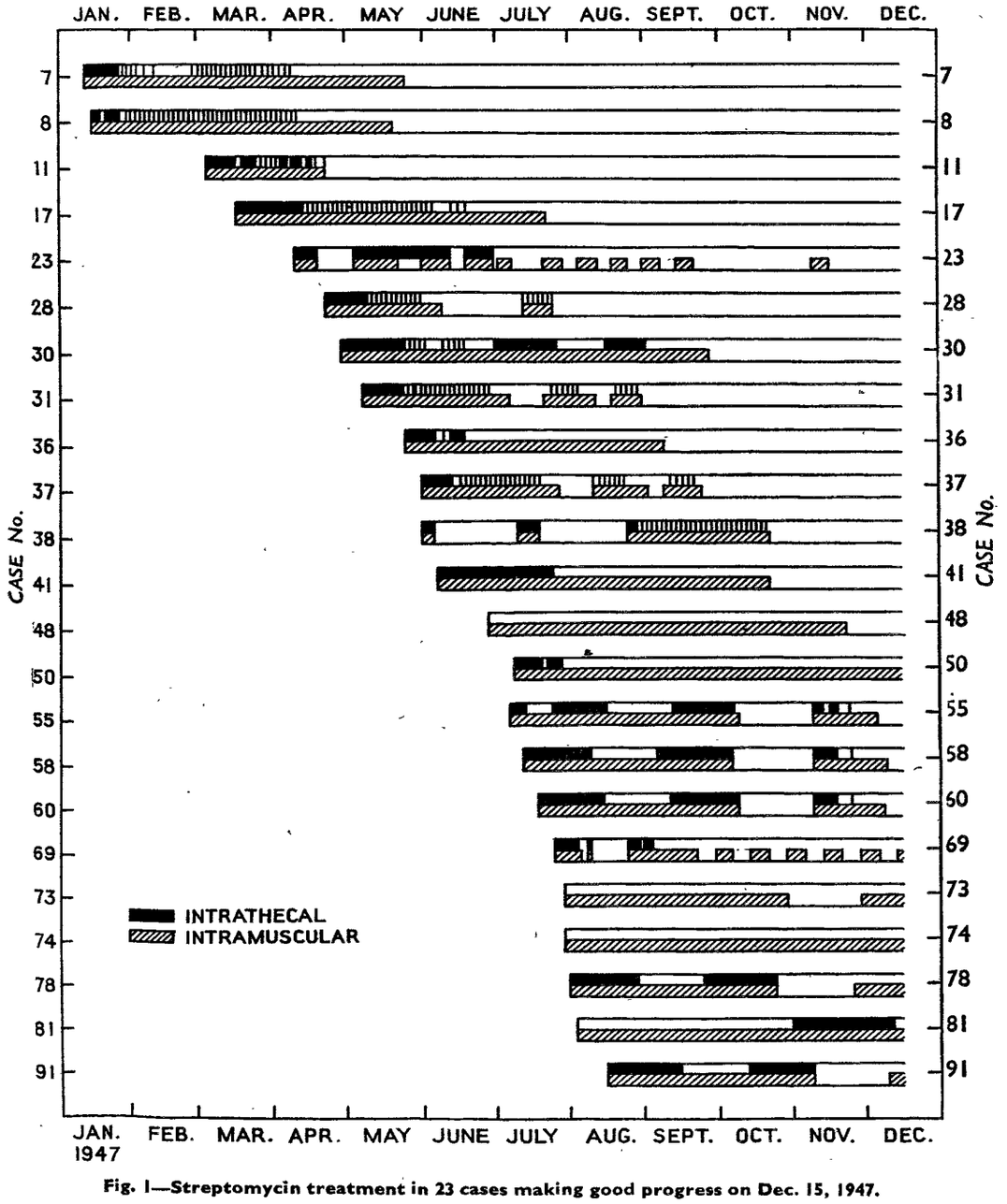

Fig. 1—Streptomycin treatment in 23 cases making good progress on Dec. 15, 1947.

second course of intrathecal treatment. Miliary lesions in the lungs cleared radiologically. She too developed spinal block with hydrocephalus.

(3) *Progressive deterioration after short initial period of improvement or no change.*—In 9 cases there was an obvious favourable reaction during a short initial period of treatment, but this was followed by progressive deterioration terminating in death.

Case 92.—A boy of 5 years responded well at first to intramuscular treatment alone. Clinically he was improving for the first two or three weeks; his temperature fell rapidly to normal limits, tubercle bacilli disappeared from the C.S.F., and the cell-count was lowered. In the third week he began to vomit, then slowly to lose weight; his pupils became dilated, and bilateral severe papillœdema was seen, with an area of venous hæmorrhage. A diagnosis of internal hydrocephalus was confirmed by ventricular puncture, and the child went rapidly downhill and died on the 44th day; intrathecal treatment initiated on the 30th day had no effect.

(4) *Relapse after long period of improvement.*—This group of 12 cases is differentiated from the preceding group in that here the improvement gave good grounds for believing that the patient might recover; the subsequent deterioration may therefore be termed a relapse. This is a most important series to consider, since the prognosis in cases responding well is severely limited by the possibility of such relapses.

(*a*) In a first subgroup of 7 cases the relapse occurred more or less suddenly, 130, 110, 110, 75, 77, 198, 150 days after the start of treatment. The first 5 were still having intramuscular therapy when relapse was observed, one of them having intrathecal therapy also; the other 2 had been off all treatment for 16 and 88 days. In 5 of them the temperature had been within normal limits for some time before the relapse—for 80, 30, 90, and 50 days in 4 of them, while in the 5th it had been normal since admission. In 3 of them the C.S.F., though not normal, had appeared to be progressing towards normal; in the 4 others the C.S.F. had remained grossly abnormal.

Case 40.—A boy of 6 years, admitted with early meningeal signs and bilateral papillœdema, drowsy but coöperative, responded slowly to treatment and then more definitely after streptomycin treatment had been stopped on the 63rd day because of persistent vomiting. The temperature was normal from the 60th day onwards. Spinal block had developed between the 20th and 40th day and persisted until after the 80th day, when it appeared to resolve gradually. The C.S.F. cell-count had fallen progressively after cessation of intrathecal therapy on the 27th day. On the 150th day, after a long period of continuous improvement with only occasional vomiting, he suddenly began to deteriorate, with evidence of acute hydrocephalus, and died 15 days later.

Case 44.—A man of 21 years developed meningitis while in hospital with acute miliary tuberculosis. He was admitted to a streptomycin centre and treated by the intramuscular route only. His clinical condition improved rapidly, though mild meningeal signs persisted; the temperature was down to normal on the 25th day, chlorides in the C.S.F. rose to nearly normal levels, proteins varied between 80 and 100 mg. per 100 ml., tubercle bacilli were no longer isolated from the C.S.F. On the 75th day the miliary lesions in the lungs had almost completely cleared. At this time, however, he began to deteriorate, vomiting daily and complaining of intense headache; his C.S.F. pressure was high, there was bilateral papillœdema, and he died on the 96th day.

Case 21.—A girl of $7\frac{1}{2}$ years, an early case when admitted, appeared to respond well to treatment within 3 days. Meningeal signs gradually disappeared, she became mentally quite alert, and in the fourth month was up and able to walk a little. The C.S.F., however, remained grossly abnormal, with chlorides persisting below 600 mg. per 100 ml., protein 200–400 mg. per 100 ml., and cells up to 870 per c.mm. during intrathecal therapy but also reaching 340 per c.mm. when intrathecal treatment had been stopped. On the 110th day she began to vomit, and from that date she deteriorated rapidly, became drowsy and confused, wasting increased, she developed convulsions with gross vasomotor disturbance, and died on the 125th day. At necropsy all ventricles were grossly distended, and the right vertebral artery was thrombosed.

(*b*) In a second group of 5 cases, deterioration after a period of improvement was more slow and progressive. In 4 of these the clinical relapse occurred between the 30th and 50th days after start of treatment; all 4 were still under treatment at the time, 2 of them having intramuscular therapy only. In 1 patient the relapse occurred on the 130th day, when he had been off all treatment for 33 days; this was the only case in which the C.S.F. elements were nearing normal at the time of relapse.

B—CASES MAKING GOOD PROGRESS

On Dec. 15 23 of 92 patients were reported to be making good progress. Fig. 1 shows the treatment in these cases, the date of admission, and the total observation time since admission and since treatment ceased (where applicable). Table VII shows the main features of the condition of each patient as reported in December, 1947; in 9 of the 23 the C.S.F. contained less than 15 cells per c.mm., and the fluid was in other respects normal or nearly normal. In some cases improvement was continuous from the start of treatment; in others a more uneven course was followed.

(1) *Uninterrupted improvement* was observed in 12 cases (nos. 7, 8, 17, 23, 31, 37, 58, 60, 69, 73, 74, 78). The following are representative case-records:

Case 7.—A girl of 6 years, treated in hospital for a tuberculous ischial lesion, became at the beginning of February morose and apathetic; a few days later she had definite meningeal signs. On admission to a streptomycin centre she was delirious and had well-marked meningism and a characteristic C.S.F. For three days after treatment started there was little change, but after this she responded dramatically. Meningism rapidly disappeared, within a week she was lucid and well oriented, and there was a substantial reduction in the discharge of a labial sinus from the bone lesion. Papillœdema resolved during the first three months. Spinal block developed at the end of the first month of treatment, and was present for some two months, but subsequently resolved. The C.S.F. cell-count remained high until the end of the third month of treatment and then gradually fell. Clinically she continued to improve steadily. On the 205th day after treatment started the C.S.F. contained 15 cells per c.mm., protein 100 mg. per 100 ml., chlorides 760 mg. per 100 ml. In September she was transferred to another hospital for convalescence and for treatment of her bone lesion. In December she was reported to be in good general condition, apyrexial for the past month. She was still in bed, in a spinal frame for treatment of her ischial lesion; the labial sinus was discharging slightly; a radiogram showed healing round the bone cavity. On psychometric tests she was of normal intelligence, alert, and coöperative.

Case 74.—A girl of 7 years is one of the 3 cases which have responded well to intramuscular treatment alone. She was admitted to a streptomycin centre in July, very ill, toxic, with well-marked symptoms and signs of meningitis; she had been under observation for miliary tuberculosis at home for a month; the C.S.F. was characteristic. Within two weeks of starting treatment all meningeal signs apart from slight neck-rigidity had disappeared, and the child was now fully conscious and alert. The C.S.F. cell-count continued to rise until the 45th day of treatment and then fell progressively. The protein level followed a similar course. Her condition continued slowly to improve, though a low-grade pyrexia persisted. At the end of three months the miliary lung opacities had almost subsided; the primary lung focus and enlarged paratracheal gland shadows were unchanged. In December her condition was reported to be good; she was bright and rational; C.S.F. examination showed 7 lymphocytes per c.mm., protein 30 mg. per 100 ml., chlorides 716 mg. per 100 ml. A slight pyrexia and tachycardia were attributed to the primary tuberculous process still obvious.

(2) *Continuous improvement after initial stationary or deteriorating period* was observed in 8 cases. Of these, 4 cases (nos. 28, 41, 48, and 91) improved after an initial stationary period of 60, 30, 15, and 15 days; whereas 4 others (nos. 30, 36, 50, and 55) improved after at first

appearing clinically to be deteriorating for 45, 50, 21, and 42 days.

Case 41.—A girl of $3^1/_2$ years, undergoing treatment for lupus, became listless at the end of May, and a few days later developed signs of meningeal irritation. The C.S.F. contained 350 cells per c.mm., protein 100 mg. per 100 ml., chlorides 660 mg. per 100 ml. On admission to a streptomycin centre she was listless. During the whole of the first month of treatment there was little change clinically; she became rather less drowsy but more irritable and she developed an ocular paralysis. The C.S.F. protein remained for 50 days at a level of about 200 mg. per 100 ml., the chlorides about 600 mg. per 100 ml., and the cell-count high. Subsequently she improved steadily, the ocular paralysis regressed, she became steadily less irritable and brighter, fever subsided, and the C.S.F. elements slowly reverted to normal. She was discharged home at the beginning of November, and readmitted in December for review. She was then very well, active, gaining weight, afebrile, and mentally normal; the old lupus had healed; C.S.F. (Dec. 9): 9 lymphocytes per c.mm., protein 20 mg. per 100 ml., and chlorides 750 mg. per 100 ml.

Case 50.—A boy of 2 years, with 10 days' history of irritability, vomiting, and pyrexia, and a story of family contact, had clinical signs of meningitis, was Mantoux-positive, and the C.S.F. contained 130 cells (90% lymphocytes) per c.mm., protein 90 mg. per 100 ml., chlorides 660 mg. per 100 ml., and culture proved positive for tubercle bacilli after four weeks. During the first three weeks of treatment, while he was having intrathecal injections, he deteriorated rapidly, became semi-comatose, with increased meningism, and apparently blind, with pupils widely dilated and a sluggish reaction to light. He then suddenly began to improve, meningeal signs

TABLE VII—ANALYSIS OF 23 CASES MAKING GOOD PROGRESS ON DEC. 15, 1947

Case no.	Age (yr.)	Days of observation since treatment began	Treatment status	General condition	Temperature	C.S.F. (most recent specimen)					Comments
						Date	Cells per c.mm.	Chlorides (mg. per 100 ml.)	Protein (mg. per 100 ml.)	Sugar (mg. per 100 ml.)	
7	7	306	Nil for 171 days	Good	Normal	Sept. 4, 1947	15	760	100	..	See text
8	3	302	„ 177 „	Good	Normal	Aug. 8, 1947	2	780	30	..	Persistent slight squint. At home. Excellent progress
11	6	289	„ 242 „	Good	Normal	Nov. 15, 1947	81	724	112	..	See text
17	1	276	„ 151 „	Good	Normal	Jan. 8, 1948	40	740	140	"Normal"	Deaf. Resolving bronchopneumonia. Still in hospital
23	3	252	„ 27 „	Good	Normal	Nov. 17, 1947	13	745	40	..	In convalescent home. Excellent progress
28	6	239	„ 147 „	Good	Normal	Oct. 3, 1947	78	657	87	..	Enlarged hilar glands. Behaviour problems. In hospital
30	8	231	„ 76 „	Good	Normal	Jan. 1, 1948	12	740	60	50	Sensory aphasia, and serious behaviour disorders. In convalescent home
31	5	221	„ 106 „	Fair	Normal	Sept. 24, 1947	..	720	90	..	Slow progress. Has had whooping-cough. In convalescent home
36	7	205	„ 100 „	Good	Normal	Aug. 28, 1947	28	627	5830	..	Absent knee-jerks. At home. Steady improvement
37	4	198	„ 83 „	Good	Normal	Dec. 3, 1947	2	725	35	61	Miliary shadows cleared, hilar glands smaller. In convalescent home
38	2	198	„ 56 „	Good	Occasional 99°	Oct. 19, 1947	90	740	60	..	See text
41	3	195	„ 60 „	Good	Normal	Dec. 9, 1947	9	750	20	..	See text
48	3	172	„ 22 „	Good	Normal	Nov. 22, 1947	55	729	73	..	Mild behaviour disorders. Still in hospital
50	2	161	Still under treatment	Good	Normal	Dec. 16, 1947	6	710	40	..	See text
55	4	164	„	Good	Normal	Dec. 1, 1947	85	725	250	..	Deaf. Miliary shadows clearing. In hospital
58	7	156	„	Good	Still pyrexial	Dec. 1, 1947	400	645	500	..	Slight squint. In hospital
60	5	151	„	Good	Normal	Dec. 1, 1947	46	690	200	..	Absent knee-jerks. Miliary shadows clearing. In hospital
69	5	141	„	Good	Normal	Dec. 15, 1947	12	692	68	..	In hospital
73	8	140	„	Good	Normal	Dec. 22, 1947	8	735	60	..	Excellent progress. In hospital
74	7	140	„	Good	Low pyrexia	Dec. 18, 1947	7	716	30	..	See text
78	7	138	„	Good	Normal	Dec. 15, 1947	26	750	30	..	In hospital
81	4	135	„	Fair	Still pyrexial	Dec. 23, 1947	256	670	692	..	See text
91	6	120	„	Good	Normal	Dec. 30, 1947	94	735	80	..	In hospital

disappeared, vision returned, and a week later he was alert, bright, and fully conscious. From that time onward he improved steadily, and in December was gaining weight, afebrile since October, continent, and with no abnormal physical signs, and optic discs normal; the C.S.F. contained 6 lymphocytes per c.mm., protein 40 mg. per 100 ml., and chlorides 710 mg. per 100 ml. He was reported to be mentally normal, intelligent, vivacious, with only behaviour problems attributable to long stay in hospital.

(3) *Improvement after relapse.*—Case 81, who relapsed on the 75th day of intramuscular treatment and began to improve again on combined therapy, has already been described. In 2 other cases the word "relapse" is perhaps excessive.

Case 11.—A boy of 6 years began to improve clinically shortly after start of treatment. Spinal block began on the 6th day and became complete on the 10th day. Fluid was freely obtained by cisternal puncture for 18 days; the ventricles were then tapped, and streptomycin was administered by that route until the 49th day, when all streptomycin treatment was discontinued. During this time he had remained clinically well until the 40th day, but from that time and for about three weeks he was more ill and disoriented, and crying was more "cephalic" in character. From the 60th day onwards he improved steadily, and from the 85th day he was afebrile and the spinal block resolved. On Dec. 15 he was very well, "wildly active," afebrile, and completely continent of urine and fæces; vision was 6/36, 6/36, and fundi still showed blurring of disc margins; the C.S.F. (Nov. 15) was under low pressure, and contained 81 cells (all lymphocytes) per c.mm., protein 112 mg. per 100 ml., chlorides 724 mg. per 100 ml. On psychological examination he was reported as "mildly elated and showing obsessive compulsive thinking; improving."

Case 38.—A boy of 2 years, who had made good progress with very little treatment but began to deteriorate on the 75th day, has already been described. In December he was reported to be very well, increasingly active, standing and moving about in a play-pen, using his right arm much more, though paresis of the forearm and hand persisted. He was, however, still totally incontinent, and reported to have a severe intellectual defect, probably permanent. The C.S.F. had not been examined since Oct. 19, at the end of a course of combined therapy; it then contained 90 cells per c.mm., protein 60 mg. per 100 ml., and chlorides 740 mg. per 100 ml.

In only 1 (case 38) of the 23 patients was intelligence seriously affected; 2 others (cases 17 and 37) were reported to be slightly below normal. Serious behaviour disorders, indicating possibly permanent damage, developed in 1 patient (case 30), who was at an advanced stage on admission; 2 other patients (cases 11 and 28) presented behaviour disorders which were improving; in 3 others mild problems arose which were attributable to prolonged stay in hospital.

C—OTHER CASES

After a long period of deterioration, 3 patients were in December in a more or less stationary condition, with evidence of gross cerebral lesions. The following case-record is typical:

Case 42.—A boy of $2^1/_2$ years was comatose on admission in June, 1947, and had a right hemiplegia. His clinical condition continued to deteriorate under treatment, but the temperature gradually fell and the elements of the C.S.F. slowly reverted towards normal, particularly after cessation of treatment on the 65th day. On the 95th day the C.S.F. contained 10 cells per c.mm., protein 30 mg. per 100 ml., and chlorides 720 mg. per 100 ml. He remained comatose, with generalised rigidity and bilateral optic atrophy, and was in this state in December. The impression was that the meningeal infection had been controlled, and the child was surviving with gross residual lesions.

In a similar case an impression of severe internal hydrocephalus was confirmed by needling; the cortex was about 0·5 cm. thick.

In 5 other cases the patients were in a condition of uncertain progress at the time of reporting, 4 of them having recently relapsed; 3 of the 5 had had intramuscular treatment only. Relapse occurred in the 4 cases after periods of improvement lasting 150, 150, 140, 135 days. The last 2, treated intramuscularly only, had been off treatment for 45 and 15 days. The 2 cases on combined therapy are particularly important:

Case 29.—A girl of 5 years, when admitted with a history of about 12 days' illness, was drowsy and had a bilateral 6th-nerve palsy, with dilated pupils reacting poorly to light; the C.S.F. was typical of tuberculous meningitis. Her condition remained stationary during the first month of treatment. She developed bilateral optic atrophy and remained completely blind subsequently. From the 30th to 40th day there was definite deterioration, with onset of left flaccid hemiplegia and pronounced mental apathy. After the end of the first course of intrathecal treatment she improved remarkably, fever subsided, elements of the C.S.F. reverted towards normal, and she began to gain weight and was mentally bright and rational. Treatment was stopped on the 115th day. On the 150th day she was walking with minimal support, and on the 175th day the left hemiplegia had regressed almost entirely. Her C.S.F. then contained 40 cells per c.mm., protein 80 mg. per 100 ml., and chlorides 730 mg. per 100 ml. She was sent to another hospital for convalescence apparently very well, but was readmitted two weeks later with headache, vomiting, and drowsiness; the C.S.F. then contained 78 cells (87% lymphocytes) per c.mm., protein 110 mg. per 100 ml., chlorides 710 mg. per 100 ml., and sugar 62 mg. per 100 ml., and an acid-fast bacillus was seen on examination of the deposit (guineapig inoculated developed tuberculosis). Intrathecal and intramuscular treatment was resumed. During the following month the C.S.F.-protein level rose, and the sugar level fell progressively. Her general condition improved slightly, but she continued to vomit and had persistent headache. The clinical impression was that the child had a communicating hydrocephalus.

Case 53.—A boy of 7 years had a history of headache and vomiting for $2^1/_2$ weeks but was at an "early" stage of disease on admission, with mild meningism, no pareses, and full consciousness. He responded well to treatment, particularly after the first month; meningeal signs had then disappeared, and he was bright, coöperative, and gaining weight. In the C.S.F. there had been a well-marked cellular response to streptomycin treatment, but the cell-count fell slowly when intrathecal treatment was stopped; C.S.F.-protein level, however, rose slowly and was 240 mg. per 100 ml. on the 75th day. The temperature fell progressively and was almost normal, with occasionally 99°F, from the 80th day. Treatment was stopped on the 95th day. He continued to improve, physically and mentally, and at the time of transfer to a sanatorium on the 150th day was clinically well apart from a slight persistent tachycardia. His C.S.F. then contained 48 cells (85% lymphocytes) per c.mm., protein 95 mg. per 100 ml., chlorides 710 mg. per 100 ml., and sugar 37 mg. per 100 ml. On Dec. 6, the 160th day, he was readmitted from sanatorium, with drowsiness, headache, vomiting, and photophobia, and with clinical signs of meningitis. The C.S.F. now contained 244 cells (83% lymphocytes) per c.mm., protein 140 mg. per 100 ml., chlorides 690 mg. per 100 ml., and sugar 24 mg. per 100 ml.

One patient, in a condition reported as stationary in December, must be considered apart from the 4 patients who relapsed:

Case 77.—A girl of 6 years was admitted to a streptomycin centre for treatment for acute miliary tuberculosis of the lungs. Her temperature fell rapidly, but on the 18th day it rose again and she became rather irritable, though otherwise apparently well; lumbar puncture was then performed for the first time, and the C.S.F. contained 75 cells per c.mm., protein 40 mg. per 100 ml., and chlorides 700 mg. per 100 ml.; tubercle bacilli were seen on direct examination and later on culture. Intramuscular injections were continued, without additional intrathecal therapy. Clinically the child continued to be very well, without signs of meningitis; she became much less irritable and gained weight, and her temperature slowly fell to normal. Tubercle bacilli were cultured several times from the C.S.F. during the first two weeks after onset of meningitis but not subsequently; the C.S.F. cell-count rose to 260 per c.mm. on the 10th day of meningitis, then fell slightly and varied subsequently between 100 and 200 per c.mm.; the protein level rose slowly. On the 90th day of meningitis she was still gaining weight and was afebrile; the

C.S.F. contained 69 cells (94% lymphocytes) per c.mm., protein 120 mg. per 100 ml., chlorides 790 mg. per 100 ml., and sugar 32 mg. per 100 ml. On Dec. 12, the 135th day of meningitis, her general condition was unchanged and she was still afebrile, but the C.S.F. now contained 163 cells per c.mm., protein 160 mg. per 100 ml., chlorides 715 mg. per 100 ml., and sugar 15 mg. per 100 ml. She was still having intramuscular treatment only.

D—SPECIAL FEATURES

In most patients life was prolonged by streptomycin therapy; over the longer course of the disease certain complications were observed with a frequency much greater than in the untreated rapidly progressive disease, and relapses were observed in cases that had been improving.

Spinal block was diagnosed clinically in 20 of the 92 cases. It developed at different stages of the disease—sometimes within a few days of admission, sometimes as long as one or two months after treatment started. It developed in 5 of 30 patients on intramuscular therapy only, in 14 of 61 on "combined" therapy, and in 1 patient two weeks after start of intrathecal therapy following a long course of intramuscular therapy alone. The block appeared to resolve spontaneously in 4 patients: 2 of these (cases 7 and 11) made satisfactory progress subsequently; the other 2 died. In another patient making good progress in December (case 58) the spinal block appeared to be resolving. Another patient who did well (case 36) still had a definite block when the C.S.F. was last examined in September, 1947.

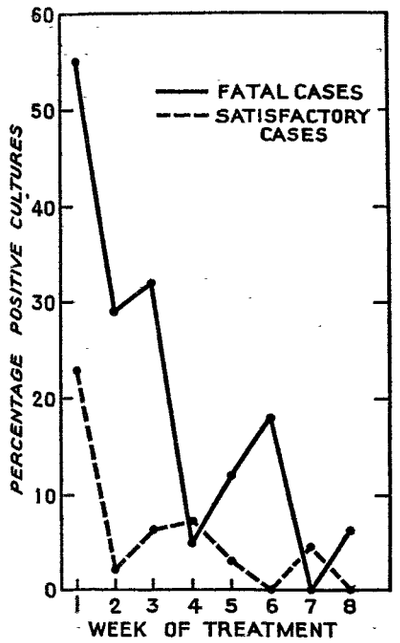

Fig. 2—Results of culture of C.S.F. for tubercle bacilli

In 7 cases streptomycin was administered by the cisternal or ventricular routes after the diagnosis of spinal block had been established. All were severely ill at the time; 6 of the 7 died within 18 days of start of treatment by these routes; case 11 responded well, and his spinal block resolved several weeks after cessation of treatment. In an 8th patient (case 36 mentioned above) cisternal puncture was performed once, but owing to the severe clinical reaction produced it was not repeated.

Clinical relapse is considered to have taken place when deterioration occurred after a period of continuous good progress lasting at least a month. The clinical histories of several patients who relapsed have already been given. Clinical relapse had been observed in 17 cases before Dec. 15: 11 among the 61 on "combined" therapy, and 6 among the 31 on intramuscular treatment only. In 5 of these cases miliary lesions were present in the lungs on admission; 8 had other probably active lesions in the chest; and only 4 had no other tuberculous lesions diagnosed on admission. 4 were under 3 years of age, 10 were aged 3–7 years, and 3 were adults (all 3 on intramuscular treatment only).

In 7 patients the relapse occurred between the 30th and 75th days after starting treatment; in 6 between the 110th and 140th days; and in 4 between the 150th and 198th days. In 8 patients the temperature had been normal for six to twelve weeks when the clinical relapse occurred. In 9 patients the clinical deterioration was more or less sudden; vomiting was the most frequent heralding symptom, followed by character changes, irritability, and apathy. In the 8 other cases deterioration was slow, insidious, and preceded by a stage during which the clinical condition seemed stationary.

In none had the C.S.F. elements returned to normal before relapse occurred, but in 7 there had been a steady progression towards normal until the time of relapse.

A study of C.S.F. changes in the period immediately preceding clinical relapse has revealed fewer factors of prognostic value than expected. Fall in the chloride level was usually the last element to reflect deterioration and in some cases did not occur at all. A sudden steep rise in the protein level usually indicated onset of spinal block, but in several cases this occurred without clinical deterioration; a slow and less pronounced rise was more significant of impending relapse, but the protein level rose slowly during the first stages of treatment in many cases, including those who did well; and, on the other hand, relapse occurred in some cases with a normal protein level. Changes in the C.S.F.-sugar level were more significant, for in 3 cases (nos. 26, 47, and 53) the level fell progressively before clinical relapse was obvious (in many cases the sugar level was not tested). The lymphocyte-count in the C.S.F. in some cases reflected progression of the disease, though in only 2 cases was a rising lymphocyte-count detected before progression was diagnosed clinically. The clearest premonitory evidence of relapse was provided, in cases recently on intramuscular treatment only, by a rising streptomycin level in the C.S.F. (see above).

Bacteriology during Streptomycin Treatment

CULTURES

In 81 of the 92 cases tubercle bacilli were isolated from the C.S.F. by culture or guineapig inoculation before treatment, during treatment, or at necropsy. In 5 other cases (all fatal) acid-fast bacilli were seen in films of the deposit at some stage; diagnosis was confirmed post mortem. In 6 cases (all fatal) no bacteriological confirmation was obtained at any time.

TABLE VIII—RESULTS OF CULTURE OF C.S.F. FOR TUBERCLE BACILLI IN 23 SATISFACTORY CASES COMPARED WITH THOSE IN FIRST 23 FATAL CASES SURVIVING A MONTH OR MORE

Week	In 23 satisfactory cases		In 23 fatal cases	
	Total cultures	Positive	Total cultures	Positive
1	43	10	58	29
2	46	1	35	10
3	47	3	37	12
4	28	2	20	1
5	29	3	24	3
6	20	0	17	3
7	22	1	13	0
8	17	0	16	1

In every case many samples of C.S.F. were cultured for tubercle bacilli during the course of treatment. Many positive results were obtained, but the frequency of positive cultures was much lower among the group of 23 patients making good progress than among those who died. In the group doing well 16 gave positive cultures at some stage during treatment, but in 12 it was only one isolated positive out of many samples during the whole course; of the remaining 4, 2 deteriorated during the first six weeks of treatment, and each had three positive cultures between the 2nd and 16th days, after which all cultures were negative; 1 patient, who was on intramuscular therapy only for 90 days and began to deterio-

rate clinically after the 70th day, improving again only after intrathecal treatment was started, had positive cultures on the 4th and 67th days; the 4th case had positive cultures on the 18th and 29th days. By contrast, 34 of the 40 fatal cases surviving for over a month had positive cultures at some time during treatment, and of these 16 had at least three and many had a very large number of positive cultures. There is a definite difference in the first three weeks; this is shown in table VIII and fig. 2, where the number of positive cultures obtained per week of treatment from the 23 satisfactory cases has been compared with those from the first 23 fatal cases who survived for a month or more. If the figures for the first three weeks are added together, from the satisfactory cases 10% of all cultures are positive in contrast to 39% of positive cultures among the fatal cases. Considering fatal cases only, during this period 1 case had eleven positive cultures, 2 cases had ten, 1 had six, 2 had five, 1 had four, and 2 had three such cultures.

Though in cases on intramuscular therapy alone the streptomycin level in the C.S.F. is relatively low, there is no evidence that in these cases tubercle bacilli are isolated more easily from the C.S.F. In fact all those cases showing very large numbers of positive cultures were having intrathecal injections; but, against this, fewer samples were tested from cases on intramuscular treatment alone.

While it is true that in patients who initially or subsequently responded badly tubercle bacilli were often isolated in the first weeks, it is also true that in a majority of all cases surviving more than three weeks the C.S.F. became free from tubercle bacilli for long periods. The action of streptomycin on the tuberculous infection was in this respect striking, leading to the conclusion that other factors, such as hydrocephalus and arterial damage, were at least partly responsible for subsequent deterioration.

STREPTOMYCIN SENSITIVITY

As many strains as possible were tested for sensitivity to streptomycin, both initially and during the course of treatment. The method used consisted of serial twofold dilutions in Dubos' Tween albumin liquid medium (Dubos and Davis 1946). The inoculum used was usually 0·02 ml. of a 7–10 day culture (in Dubos medium) per 3 ml. of medium. Strains isolated by culture from the C.S.F. taken from 57 patients before treatment, as well as first positive cultures from 9 further cases, were all shown to have a sensitivity to streptomycin similar to that of the standard culture, H37Rv (0·25–0·5 μg./ml.).

Tubercle bacilli were isolated from the C.S.F. taken from 32 patients after the 28th day of treatment. From 22 of these patients strains isolated between the 29th and 136th days of treatment were tested; and from 19 of the 22 patients strains were found to be as sensitive to streptomycin as the initially isolated strains; in 12 of the 19 patients strains were isolated after the end of the second month of treatment.

Resistant strains were isolated from 3 of the 22 patients. One patient yielded a culture on the 87th day which showed a tenfold increase in resistance and on the 109th day one which showed a twentyfold increase. From 2 cases cultures isolated from specimens taken on the 45th and 90th days were not inhibited by 1000 μg./ml. of streptomycin. All these 3 patients died and all had miliary tuberculosis of the lungs as well as meningitis.

The patient from whom a slightly streptomycin-resistant strain was isolated yielded ten positive cultures from the C.S.F. in the first 17 days of treatment, then between the 18th and 86th days all cultures were negative. Throughout these three months the patient improved steadily. At the beginning of the fourth month the child relapsed, and five specimens of C.S.F. taken on the 87th, 92nd, 109th, 117th, and 118th days all yielded positive cultures. One of the two patients with grossly resistant strains died after three and a half months' treatment, and tubercle bacilli were isolated post mortem from a miliary lesion of lung, a caseous gland, spleen, liver, kidney, and epididymis. All these cultures showed a similar increase in resistance to streptomycin.

Necropsy Findings

Necropsies were made in 53 cases: 13 of the patients had died within a week of starting treatment, and 7 more before the end of four weeks; 14 had died between the 28th and 56th days, 11 during the third and fourth months, and 8 after more than four months.

CENTRAL NERVOUS SYSTEM

In patients dying early in the disease the usual widespread tuberculous meningitis affecting the base of the brain and the spinal cord was seen. All cases showed evidence of basal meningitis most pronounced in the region of the interpeduncular fossa. In most cases the posterior portion of the basal cistern appeared relatively free from exudate, so it seems probable that the blockage of the anterior half or two-thirds of the basal cistern by inflammatory exudate was largely responsible for the hydrocephalus, often extreme, present in nearly all cases surviving for more than a week. The hydrocephalus was in most cases of the communicating type. The pathology of the arteritis seen was essentially similar to that seen in untreated cases, though the degree of occlusion was extreme in some patients who had survived for a few months.

The trial brought to the notice of pathologists some less familiar features of the disease, which in any case were rendered more striking since, owing to prolongation of life, many of the tuberculous processes were seen in a chronic and unusual form. One such lesion was gross thickening of the spinal leptomeninges by tuberculous granulation tissue. Acid-fast bacilli were not always sought in films; but where they were the number found ranged from none to enormous numbers, the number apparently bearing no relationship to the duration of treatment.

The 13 cases which were fatal within a week of starting treatment all had the characteristic lesions of acute tuberculous meningitis; 7 showed evidence of hydrocephalus.

The 7 cases in which death occurred between one and four weeks after onset of treatment showed on the whole a similar picture, but all had hydrocephalus; and in case 26 (death on the 12th day), though sections showed a caseating proliferative tuberculous cellular reaction in the meninges, the acute exudative lesion of the classical cases was absent, and there was no arteritis.

A feature of the 14 cases dying between the 28th and 56th days was the degree of hydrocephalus, all but 2 showing considerable dilatation of the ventricles. All had evidence of active tuberculous meningitis, and only in case 65, where the patient died in the 8th week, was there any histological evidence of healing in the central nervous system. This case had "firm white granulations in the interpeduncular fossa," and sections showed "ischæmic softening in the brain, active tuberculous ependymitis, healed and active tuberculous arteritis throughout the subarachnoid space, and a slight and patchy but definite tuberculous leptomeningitis of the base of brain and spinal cord." In case 79, where the patient also died in the 8th week, granulation tissue reaching a thickness of 5 mm. or more was present over the lower part of the spinal cord.

All 11 cases in which death occurred during the third and fourth months of treatment had hydrocephalus, and in many it was exceedingly severe. The degree of active infection present and the number of acid-fast bacilli seen in the lesions varied very much. Case 4, dying after thirteen weeks' treatment, showed granulations localised to the interpeduncular fossa, and caseous necrosis in the region of the tuber cinereum, teeming with acid-fast bacilli; the basilar arteries showed a striking occlusive fibroblastic intimal proliferation. In

case 67 there was little evidence of active tuberculosis in the central nervous system, but there were perivascular fibrosis and endarteritis.

Of the 8 cases dying after more than four months, 7 had a considerable degree of hydrocephalus, and in 3 cases it was extreme.

Case 15 showed no hydrocephalus. This was a girl of 4 years who made a clinical recovery during the first four months of treatment and had only one positive tubercle-bacillus culture from the C.S.F. in this period; she later relapsed, and died seven months after starting treatment. At necropsy the cerebral lesions were all of an acute type; numerous small tuberculomata were present in the brain, and many were very active in appearance and communicated with the meninges; there was also an active primary complex in the lungs, caseous glands in the abdomen, and miliary tubercles throughout both lungs and in the liver, spleen, and kidneys.

Case 27.—In contrast to case 15, this child, aged $2^1/_2$ years, who died after 120 days' treatment, showed only slight evidence of any active infection in the C.N.S.; there was gross distension of all ventricles, and the interpeduncular fossa contained scar tissue 0·25 cm. thick; the arachnoid over the rest of the brain was slightly opaque, and the dorsal surface of the spinal cord was covered with a gelatinous exudate. Histological sections showed persistent tuberculous meningitis at the base of the brain and of the spinal cord. During treatment in this child the C.S.F. elements, except for protein level which remained high, returned to normal, and on no occasion after starting treatment were tubercle bacilli isolated.

The other cases in this group all showed active tuberculous meningitis, but there was evidence in several cases of this becoming chronic. Case 82 showed an extreme degree of hydrocephalus and only a small amount of caseating exudate in the basal cistern; yet this exudate contained vast numbers of acid-fast bacilli, and histological sections showed extensive tuberculous meningitis.

OTHER ORGANS

A description of the other lesions found at necropsy must be left for report elsewhere, as must also the more detailed analysis of lesions in the central nervous system. A few outstanding features may, however, be given here.

The state of the lesions in the central nervous system, showing only in rare cases any evidence of healing, must be contrasted with the state of miliary lesions found in other parts of the body. Miliary lesions in the lungs were present in 18 of the 51 cases on which a full examination was made; many showed definite evidence of healing, and this is in concordance with the radiological clearing of pulmonary miliary lesions observed in these cases during life. Similar fibrosing tubercles were found in other organs, particularly in cases which had been treated for several months. The healed lesions were similar to those found in chronic miliary tuberculosis and showed all stages of healing. They were all non-caseous and contained few or no tubercle bacilli. Some consisted of masses of epithelioid cells separated by reticulin. In others, presumably older, the reticulin was giving way to collagen fibres and the epithelioid cells were disappearing. Finally there were foci of hyalinised fibrosis recognisable as tubercles only because of their shape and because transitional forms were present.

It is interesting to note, however, that alongside these fibrosing lesions were found in some cases also active tubercles of obviously recent formation. In addition—and this is perhaps one of the most important findings—an active primary complex, with caseous pulmonary and glandular lesions, was found in 38 of the 51 cases; 2 more had caseous bronchopulmonary glands without a visible lung focus; and 2 had a mass of caseous glands in the abdomen. These lesions had apparently been unaffected by streptomycin treatment even over long periods.

Discussion

The streptomycin treatment of tuberculous meningitis, prolonging the course of the disease in most cases, producing considerable improvement in many and possibly clinical cure in a few, represents an outstanding advance. The problem of improving the results so far achieved raises numerous questions, many of which still remain unanswered.

DIAGNOSIS

An important finding is that the prospects of a favourable response are greatest in early cases and very poor in patients admitted comatose or with established gross pareses.

The findings render imperative a close observation of tuberculous patients, particularly of children with diagnosed miliary or primary tuberculosis, for signs of incipient meningitis. In these circumstances, where a very early diagnosis may be made, what abnormal C.S.F. findings may be considered diagnostic? Doubts have been raised about the validity of the diagnosis in certain cases with minimal findings which Lincoln (1947) terms "tuberculous serous meningitis." The condition she describes is probably exceptional (one such case was seen in a M.R.C. centre), and for the present it is justifiable to suggest that any patient with diagnosed tuberculosis and a lymphocytic reaction in the C.S.F. should be treated as a case of tuberculous meningitis unless an alternative diagnosis is clearly demonstrated. A reduced C.S.F.-chloride level should not be considered indispensable for the diagnosis.

The main problem is that of securing earlier diagnosis in patients not previously known to be tuberculous. Both before and after the admission to hospital of a patient with suspected meningitis much can be achieved by a systematic search for collateral evidence of tuberculosis; such evidence was elicited in the great majority of cases reported here. The importance of a history of contact, and of the Mantoux test, particularly in children, is worth emphasis: 72 of 73 patients in whom the test was completed were positive. The urgency of establishing the diagnosis justifies the use of O.T. 1/1000 as first test instead of a weaker dilution; if the child is not tuberculous, no harm can result; if tuberculous, the questionable risk of a focal reaction is amply offset by the advantage of early diagnosis.

TREATMENT

Analysis of cases which responded well to streptomycin has shown that modes of treatment differing considerably in rhythm and duration were apparently equally successful; it is therefore impossible at present to draw hard and fast conclusions about optimal methods.

That intrathecal treatment is practically indispensable is one of the few definite findings. Why this should be so is still conjectural. In many cases intramuscular therapy controlled the general infection for several weeks; this would account for the initial good general response. But apparently the meningeal infection was controlled only at borderline level, with the patient in a precarious state sometimes for months before finally succumbing. The streptomycin concentration in the C.S.F. reached by intramuscular injection alone was one which might be considered a satisfactory bacteriostatic level. Were the levels reached by intrathecal injection bactericidal? The bactericidal action of streptomycin has been emphasised by Garrod (1948). Is there in some cases a frequent discharge of tubercle bacilli into the C.S.F. from cerebral lesions which, as pathological findings suggest (Baggenstoss et al. 1947), are untouched by streptomycin?

Until it is understood why intrathecal treatment is necessary, it is obviously impossible to say at what intervals and for how long the dosage should be continued. Continental workers, such as Debré et al. (1947), favour a short intensive intrathecal course not repeated later except in the event of relapse; in this country and in the U.S.A. longer courses are favoured, though it is acknowledged that protracted courses may be harmful.

It is too early to compare results on this basis. The high C.S.F.-streptomycin level should perhaps be maintained for longer than is possible with intrathecal injections only once a day. Possibly the surgical procedures suggested in the Oxford report should be adopted more often. Probably patients diagnosed only at a late stage require highly intensive treatment if they are to respond at all; probably where tubercle bacilli are found repeatedly in the C.S.F. during the first three weeks more prolonged and intensive intrathecal treatment is called for; it is likely that intrathecal treatment should be resumed at the first sign of relapse. An interesting feature in patients on intramuscular therapy only has been a rising C.S.F.-streptomycin level before clinical signs of deterioration appear; possibly a rising level, even in the absence of known signs of relapse, should be an indication for the resumption of intrathecal treatment.

Intramuscular therapy is indispensable, and should probably be given continuously for three months at least; but whether it should be continued much longer without interruption, or whether periods of total rest from treatment are desirable, followed by repeated courses, it is impossible to say. No relapse that occurred in this series could be clearly attributed to premature suspension of treatment; indeed, some patients improved remarkably during periods when all treatment was suspended.

The evidence suggests that patients with miliary tuberculosis detected in the lungs, or with active primary tuberculosis, should have long courses of intramuscular treatment; the large caseous glands found in some patients treated for many weeks are evidence that, though the general infection may be controlled with streptomycin, in some patients the primary source of tubercle bacilli remains a danger. Possibly, however, this danger is no greater than in the average primary infection, and streptomycin is effective in controlling degrees of infection that are uncontrollable by natural defence mechanisms.

Should treatment be undertaken in patients diagnosed at an advanced stage? At present, when limitations in both streptomycin supplies and beds in treatment centres necessitate the selection of cases most likely to respond, the answer can only be that such patients should not be accepted for treatment. Later, if supplies and beds are available, but if the prognosis for advanced cases remains as severe as before, the problem will be a moral one very difficult to resolve. When, if at all, should treatment be stopped in patients deteriorating? Judging from the course of the illness in this series, it seems that where there is progressive severe deterioration throughout two months of treatment it is justifiable to cease treatment at the end of that period to avoid the miserable deferment of an inevitably fatal outcome.

Can the prognosis be improved by association of streptomycin with another chemotherapeutic agent? Experimental work by Smith et al. (1946) and clinical results reported by Cocchi and Pasquinucci (1947) and Lincoln et al. (1948) indicate that streptomycin associated with a sulphone may give better results than streptomycin alone; possibly much further progress will be made along these lines.

RELAPSES

Prognosis in patients responding well to streptomycin treatment is clouded by the possibility of late relapses, the causes of which are still obscure. Late thrombosis of cerebral vessels may have been the dominant feature in one or two cases but was certainly not the major cause of most relapses. Were they caused by the multiplication of tubercle bacilli resistant to streptomycin? The evidence is against such an explanation. Strains isolated from 19 of 22 patients after several weeks or months of treatment were as sensitive to streptomycin as strains isolated before treatment was started. As was suggested above, these sensitive bacilli may have come from foci in the brain not reached by streptomycin given systemically.

The persistence and breakdown of foci of infection inaccessible to circulating streptomycin may well be an important factor in the relapses observed. In some, however, the impression was that renewed spread of tuberculous infection was not alone responsible. This applies to patients in whom the clinical character of the relapse pointed rather to progressive or acute hydrocephalus as the dominant feature; it also applies to some patients who continued to deteriorate from the date of admission to death many months later, though the clinical picture indicated that the infection was under control. Coupled with these observations, the frequent post-mortem finding of obstruction at the base of the brain, particularly in the interpeduncular fossa, and the gross internal hydrocephalus present in so many cases, indicate that mechanical factors of obstruction due to organisation of tuberculous exudate were at least partly responsible for the clinical deterioration.

Was this to be expected as a feature of the normal healing process in an intracranial tuberculous infection that had been arrested? Or was continued production of exudate from a persistent infection responsible? Or were infection and obstructive organisation of exudate mutually reinforced, in that colonies of tubercle bacilli flourished in fibrin-walled pockets inaccessible to streptomycin from the thecal space or from the systemic circulation? The pathological features of cases in which death took place after many months indicate that both factors are responsible for many of the relapses seen, though their relative places in the sequence of pathological events remain obscure.

It is now a commonly expressed view that the prevention of fibrinous organisation of exudate at the base of the brain would considerably reduce the number of late relapses. Possibilities of such prevention are being investigated,§ in particular by the prophylactic use of heparin, but the work is still at an experimental stage.

Recommended Procedures

DIAGNOSIS

Early diagnosis has become of prime importance. In the great majority of cases the diagnostic problem presents in one of two ways:

(1) A patient has a history and clinical signs suggesting meningitis. Confirmation of meningitis and evidence of its tuberculous nature are required. Apart from full clinical examination, the following are indispensable procedures, to be carried out within 24 hours of admission to hospital:

(*a*) Full inquiry about tuberculosis contact.

(*b*) Mantoux test, with 0·1 ml. of old tuberculin 1/1000. If negative after 48 hours, repeat with O.T. 1/100.

(*c*) Chest radiogram.

(*d*) Examination of fundi for choroidal tubercles.

(*e*) Lumbar puncture. Examination of C.S.F. for levels of protein, sugar, and chlorides; cell-count (with differential); and isolation of tubercle bacillus. At least two adequate samples of C.S.F. should be examined before starting treatment. Both should be centrifuged; from part of the deposit a thick film should be made, and the rest should be cultured and injected into guineapigs. For the latter it is best to emulsify the deposit in 1–2 ml. of the supernatant fluid. Strains isolated should be tested for sensitivity.

(2) In a patient with diagnosed tuberculosis slight character changes (irritability, drowsiness), vomiting, and a rise in temperature should arouse suspicion of meningitis. Lumbar puncture is imperative for confirmation.

TREATMENT

Treatment must be started without delay when there is definite or strong presumptive evidence of tuberculous

§ In centres under the Ministry of Health scheme.

meningitis. Bacteriological confirmation must not be considered a prerequisite to starting treatment.

(1) *Intramuscular therapy:* the daily dose should be not more than 0·02 g. per lb. of body-weight; it may be given in divided doses—four 6-hourly, or two 12-hourly, doses. It should be continued uninterruptedly for three months at least. Further treatment beyond that period is probably necessary, even in cases responding very well. Long treatment is recommended particularly for patients with miliary or recent primary tuberculosis.

(2) *Intrathecal therapy* must be considered indispensable pending further information about the occasional type of case that may not require it. The dose now recommended is 0·05–0·1 g. per day in one dose. The optimal intrathecal treatment for the first three months will probably be found to be either a short intensive course (with possibly injections twice a day) or two courses interrupted by a rest period, or treatment only every two or every three days for two to three months. When intramuscular treatment is given 12-hourly, the intrathecal injection should be given six hours after the last intramuscular injection.

(3) *Relapse and spinal block:* a patient who, after responding well to treatment for some weeks, begins to vomit and becomes slightly irritable and drowsy must be considered as in danger of relapse. Important clinical features which may precede or follow the first appearance of these symptoms are an increasing lymphocyte-count in the C.S.F., a falling C.S.F.-sugar level, and a rising C.S.F.-streptomycin level (when the patient is off intrathecal treatment). Diagnosis of impending relapse makes imperative immediate resumption of combined therapy.

When complete spinal block develops at an early stage of treatment, streptomycin should be administered by the cisternal or ventricular route instead of by the lumbar route. At a late stage of treatment, particularly if the intrathecal course has been completed, in the absence of clinical evidence of increasing infection it is probably unnecessary to attempt to administer streptomycin by other than the intramuscular route. Evidence of increasing intracranial pressure, with probable progressive hydrocephalus, calls for relief of the pressure by ventricular tap or repeated lumbar puncture.

Work on the prevention of organisation of exudate is still at an experimental stage. Present lines of investigation include the use of heparin to prevent fibrin formation, and routine surgical drainage to the base of the brain (see Oxford report).

(4) *Convalescence:* the time of discharge will depend on local hospital facilities, and in most cases it will be impracticable to retain the patient in the original streptomycin centre until the C.S.F. is normal. In all cases, the patient should go from hospital to a convalescent institution or a sanatorium where general care is particularly good and expert medical supervision is possible. He should be re-examined at, say, three-monthly intervals for two years by the doctor originally in charge of him. The convalescent patient should be considered primarily as a tuberculous patient recovering from a severe form of the disease, and cared for as such for at least two years after leaving hospital. Psychometric examination should be made at the earliest opportunity.

ROUTINE RE-EXAMINATIONS OF C.S.F.

Levels of protein, sugar, and chlorides, and cell-counts with differential counts should be estimated once weekly during treatment, and after treatment has stopped fortnightly for three months. If at the end of three months the C.S.F. elements have not returned to normal, lumbar puncture should be repeated at monthly intervals until normal. If there is a rising lymphocyte-count, or a falling sugar level, the need for further intrathecal treatment should promptly be considered.

Isolation of tubercle bacillus: frequent examinations by film and culture are recommended during the first few weeks of treatment, since they may be a valuable guide to prognosis. Thereafter culture (and film examination if time allows) of the C.S.F. once a week is probably adequate. Any specimens of C.S.F. taken after treatment ceases should be cultured, and a film should be examined if the cell-count has increased.

Sensitivity tests: all positive cultures isolated after a month or more of treatment should be tested for their sensitivity to streptomycin.

Streptomycin assays: in a case of spinal block, if cisternal or ventricular specimens are taken, they should be tested for streptomycin level. When the patient is on intramuscular treatment only, assays should be done once a week; a rising C.S.F.-streptomycin concentration may be the first indication of increasing infection, and resumption of intrathecal treatment should then be considered.

Specimens for assay must not be passed through a Seitz filter, since this removes much of the streptomycin.

Addendum

On March 15, 1948—i.e., after a minimal period of seven months' observation of all survivors—amended figures for tables I and VI are as follows:

	No. of cases admitted before Aug. 18, 1947	Condition on March 15, 1948			
		Good	Stationary or relapsed	Deteriorating	Dead
Table I	105 (*100%*)	27 (*26%*)	6 (*6%*)	1 (*1%*)	71 (*67%*)
Table VI	48 (*100%*)	19 (*40%*)	3 (*6%*)	0	26 (*54%*)

Three patients who were making good progress in December relapsed and died in the subsequent three months: (1) case 81, a child who responded well to intrathecal streptomycin after being on intramuscular therapy alone; (2) case 37, an advanced case on admission; (3) a patient at Oxford, not reported in detail in this paper. The 27 other patients doing well in December have continued to improve; in several cases the C.S.F. has become normal.

Summary

This report analyses the results on Dec. 15, 1947—i.e., after a minimum of 120 days' observation of survivors—in 105 cases of tuberculous meningitis admitted to M.R.C. centres before Aug. 18, 1947, and treated with streptomycin.

All the cases were proved by culture, by guineapig inoculation, or by post-mortem histology. Collateral evidence of tuberculosis was found in a high proportion of cases.

Of the 33 children under 3 years, 27 (82%) had died and 4 (12%) were making good progress in December. Of the 72 older children and adults, 40 (56%) had died and 26 (36%) were making good progress.

Of the patients admitted at an early stage of the disease, 42% were making good progress in December, compared with 26% of those at a medium stage, and 7% of those at an advanced stage on admission.

Of the patients who received only intramuscular streptomycin, 11% made good progress, compared with 35% of those receiving streptomycin by both intramuscular and intrathecal routes. 50% of cases, age 3 years and over, admitted at early or medium stages, and receiving combined therapy, made good progress.

The streptomycin levels in the cerebrospinal fluid during intramuscular treatment alone ranged usually between 3 and 16 μg. per ml. In patients recovering, the range was lower; in some patients deteriorating the level rose as the meningitis progressed.

Case-records representative of the various types of clinical response to streptomycin treatment are given. The condition of 23 patients making good progress in December, 1947, is described. The main features of the 17 cases of clinical relapse are given.

In patients who ultimately fared badly tubercle bacilli were isolated from the cerebrospinal fluid much more frequently during the first three weeks than in patients who made good progress.

Strains isolated from 22 patients between the 29th and 136th days of treatment were tested for sensitivity; only 3 of these were resistant to streptomycin.

Necropsy findings are discussed. Communicating hydrocephalus was found in most cases.

An addendum brings the main results up to March 15, 1948, when 27 cases were still doing well.

The clinical work in these trials was coördinated by Dr. Marc Daniels (scientific staff, M.R.C.), who also prepared this report for the committee, with assistance from Dr. Mary Barber (Hammersmith Hospital) in the analysis of the pathological data.

The opinions expressed in the report represent a consensus of the opinions of the majority of clinicians and pathologists concerned in the trials, of whom those principally involved are named below. The committee is indebted to them for their constant coöperation and for the detailed investigations undertaken.

Centre	*Clinicians*	*Pathologists*
Hammersmith Hospital (L.C.C.)	Dr. D. MacCarthy Dr. T. P. Mann	Dr. Mary Barber Dr. I. Doniach
Royal Hospital for Sick Children, Glasgow	Prof. G. B. Fleming Prof. Stanley Graham Dr. P. McArthur	Dr. G. L. Montgomery
Alder Hey Children's Hospital, Liverpool	Prof. N. B. Capon Dr. R. M. Todd	Prof. A. W. Downie Dr. H. Lederer
The Hospital for Sick Children	Dr. P. M. Ransford Dr. B. J. Hussey	Dr. I. A. B. Cathie Dr. J. C. W. MacFarlane
The National Hospital for Nervous Diseases	Dr. E. A. Carmichael Dr. A. P. Morley	Dr. J. N. Cumings Dr. R. E. Kelly
Guy's Hospital	Dr. P. R. Evans Dr. C. W. Kesson	Dr. F. L. Jackson Prof. G. Payling Wright
Highgate Hospital (L.C.C.)	Dr. A. L. Jacobs Dr. J. Rubie	Dr. J. M. Alston Dr. A. Mohun
Radcliffe Infirmary, Oxford	Sir Hugh Cairns Dr. Honor Smith	Dr. R. L. Vollum Dr. P. D. Daniel

The clinical pathologists met on several occasions, under the chairmanship of Dr. Robert Cruickshank, to discuss technique and the many other problems arising. A group of morbid anatomists were responsible for a memorandum on necropsy procedure.

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BLOOD-SUGAR LEVELS IN SLOW STARVATION

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SUGAR is so stable a constituent of the blood that if the level falls from 80 to 75 mg. per 100 ml. symptoms of hypoglycæmia may develop. Nevertheless in some cases the level has fallen to 30 mg. per 100 ml. or less before any symptom could be detected (Wright 1942). Conn (1940) reported cases in which symptoms did not appear until the level reached 21–37 mg. per 100 ml. These were cases in which the usual level was normal. But where the usual level is below normal, symptoms develop only when the level is further reduced. The reason for this is not known. Harris (1924) suggested hyperinsulinism. Wilder and his associates (1927) corroborated him. Conn (1940) classified the cases into two broad groups, functional and organic. He reported cases in which symptoms of hypoglycæmia appeared when the blood-sugar level fell to 14–18 mg. per 100 ml.

Harris also studied blood-sugar levels in starvation and found that in rabbits the lethal level was 40 mg. per 100 ml. In three patients who could not eat anything owing to obstruction of the œsophagus by malignant growth he obtained blood-sugar levels of 90, 84, and 90 mg. per 100 ml.

I have studied blood-sugar levels in 407 cases of pure malnutrition due not to disease but to the Bengal famine of 1943–45. These patients were not usually hypoglycæmic, because when they recovered their blood-sugar levels were normal. They were all free from any disease as determined clinically or by laboratory examination.

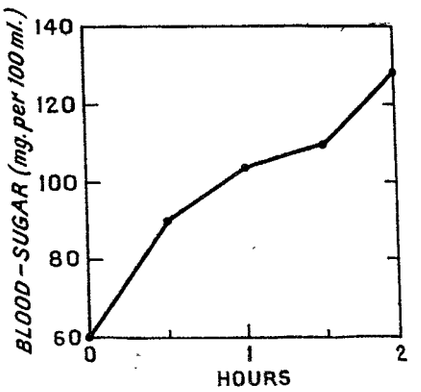

Fig. 1—Glucose-tolerance test in fairly advanced stage of starvation (50 g. of glucose given by mouth).

METHODS

Blood was drawn with a hypodermic syringe from the antecubital vein in the morning before the patient had any food or intravenous medication. Neutral potassium oxalate 2 mg. per ml. of blood was added as anticoagulant. Folin and Wu's method was used in the estimation and a Klett colorimeter in the colour comparisons. All estimations were done in natural light in the hospital laboratory. In no case did more than 15 min. elapse between collection and examination of the sample.

RESULTS

About 60% of cases showed a blood-sugar level below 80 mg. per 100 ml., but no symptoms of hypoglycæmia were present. The distribution of different blood-sugar levels was as follows:

Blood-sugar (mg. per 100 ml.)

Below 80	*80–120*	*Above 120*
59·1%	34·7%	6·2%

Below 40	*40*	*Above 40*
5·6%	3·9%	90·5%

It will be seen that, though most cases showed a low blood-sugar level, a few gave figures above normal. However, when cases with a low blood-sugar level were further scrutinised, 5·6% showed a blood-sugar level below 40 mg. per 100 ml.

The average and the range of the blood-sugar values were as follows:

Blood-sugar (mg. 100 per ml.)

No. of cases	*Average*	*Range*
407	76·7	19·2–307·6

The lowest value for blood-sugar was 19·2 mg. per 100 ml. This was found in only one case, which proved fatal, but another patient with a level of 20 mg. per 100 ml. survived. As already stated these patients did not show hypoglycæmic symptoms, but their general condition was low, with extreme emaciation and prostration. They could hardly speak distinctly. They were fully conscious and eager to live. One patient had a blood-sugar level of 17·6 mg. per 100 ml., but he also had cancrum oris and died; this case is not included in this review but was published elsewhere (Chakrabarty 1944).

A sugar-tolerance test was done on many of them by giving 50 g. of glucose by mouth. A representativ