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

CONCLUSION

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 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. There 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 collection 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.
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 pyrogenes, &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 \( \mu g \) of base per mg. of material. All weights of streptomycin given here refer to active base (1 \( \mu g \) 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 streptomycin treatment before Aug. 18, 1947, 67 (64%) were diagnosed at a relatively early stage. 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 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 mortality-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 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 stuporous 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 actually advanced cases. 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%) of 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.
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 tuberculous 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 of high significance as 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 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.

**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 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.

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 15 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**

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

<table>
<thead>
<tr>
<th>C.S.F. findings</th>
<th>Cultures (85 specimens)</th>
<th>Guineapig inoculation (53 specimens)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct examination positive</td>
<td>33</td>
<td>3</td>
</tr>
<tr>
<td>Direct examination negative</td>
<td>24</td>
<td>25</td>
</tr>
<tr>
<td>Total</td>
<td>57</td>
<td>28</td>
</tr>
</tbody>
</table>
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.

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.

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 49% 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 lung. C.S.F.: 75 lymphocytes per c.m.m., 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 intramuscular treatment, meningitis 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. 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 compare the results of the 69 patients who responded to these two methods. 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 shows 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 results 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 meningitis and increased 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 not had intrathecal treatment for some weeks. An C.S.F.-streptomycin level after the third week of treatment. The age-distribution was similar in these two centres, as also was the condition of patients on admission.

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**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 29-0 µg./ml. on the 110th day. 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.

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. 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. 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.
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; \( \frac{1}{2} \text{ of the dose injected} \) 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
second course of intrathecal treatment. Miliary lesions in the lungs cleared radiologically. She too developed improvement or no change.-In 9 cases there was an obvious favourable reaction during a short initial period the first two or three weeks ; his temperature fell rapidly to
muscular treatment alone. - Clinically he was improving for
rapidly downhill and died on the 44th day; intrathecal
treatment initiated on the 30th day had no effect.

venous haemorrhage. A diagnosis of internal hydrocephalus
group in that here the improvement gave good grounds
prognosis in cases responding well is severely limited by
the possibility of such relapses.

had been off all treatment for 16 and 88 days. In 5 of
them the temperature had been within normal limits for
one of them having intrathecal therapy also; the other 2
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 papilloedema, drowsy but cooperative,
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
the 45th day of treatment and then fell progressively. Clinically she
was delirious and had well-marked meningism and a charac-
teristic 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
orientated, and the c.s.F. was normal. She was able to walk,
and the discharge of a labial sinus from the bone lesion. Papill.
cedema 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, appyrexial for the past month. She was still in bed, in a spinal
frame for treatment of her ischial lesion. It was reported that
the c.s.F. was in other respects normal or nearly normal.
On psychometric tests she was of normal intelligence, alert, and cooperative.

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
may have been under observation for miliary tuberculosis at home for a
month; the c.s.F. was characteristic. Within two weeks of
the start of treatment there was a very rapid fall in the c.s.F.
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On psychometric tests she was of normal intelligence, alert, and cooperative.

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
may have been under observation for miliary tuberculosis at home for a
month; the c.s.F. was characteristic. Within two weeks of
the start of treatment there was a very rapid fall in the c.s.F.
level and the discharge of a labial sinus from the bone lesion. Papill.
cedema 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, appyrexial for the past month. She was still in bed, in a spinal
frame for treatment of her ischial lesion. It was reported that
the c.s.F. was in other respects normal or nearly normal.
On psychometric tests she was of normal intelligence, alert, and cooperative.
appearing clinically to be deteriorating for 45, 50, 21, and 42 days.

**Case 41.**—A girl of 31/2 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.m.m., 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.m.m., 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.m.m., 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 semicomatose, 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

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Age (yrs.)</th>
<th>Duration of c.s.f.</th>
<th>Treatment status</th>
<th>General condition</th>
<th>Temperature</th>
<th>Date</th>
<th>Cells per c.m.m.</th>
<th>Chlorides (mg. per 100 ml.)</th>
<th>Protein (mg. per 100 ml.)</th>
<th>Sugar (mg. per 100 ml.)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>7</td>
<td>206</td>
<td>Nil for 171 days</td>
<td>Good</td>
<td>Normal</td>
<td>Sept. 4, 1947</td>
<td>15</td>
<td>760</td>
<td>100</td>
<td></td>
<td>.</td>
</tr>
<tr>
<td>8</td>
<td>3</td>
<td>302</td>
<td>&quot;</td>
<td>Good</td>
<td>Normal</td>
<td>Aug. 8, 1947</td>
<td>2</td>
<td>780</td>
<td>30</td>
<td></td>
<td>.</td>
</tr>
<tr>
<td>11</td>
<td>6</td>
<td>259</td>
<td>&quot;</td>
<td>Good</td>
<td>Normal</td>
<td>Nov. 15, 1947</td>
<td>80</td>
<td>724</td>
<td>112</td>
<td></td>
<td>.</td>
</tr>
<tr>
<td>23</td>
<td>3</td>
<td>252</td>
<td>&quot;</td>
<td>Good</td>
<td>Normal</td>
<td>Nov. 17, 1947</td>
<td>13</td>
<td>745</td>
<td>40</td>
<td></td>
<td>.</td>
</tr>
<tr>
<td>30</td>
<td>8</td>
<td>231</td>
<td>&quot;</td>
<td>Good</td>
<td>Normal</td>
<td>Jan. 1, 1948</td>
<td>12</td>
<td>740</td>
<td>60</td>
<td>50</td>
<td>.</td>
</tr>
<tr>
<td>31</td>
<td>5</td>
<td>221</td>
<td>&quot;</td>
<td>Good</td>
<td>Normal</td>
<td>Sept. 24, 1947</td>
<td>.</td>
<td>.</td>
<td>720</td>
<td>90</td>
<td>.</td>
</tr>
<tr>
<td>36</td>
<td>7</td>
<td>206</td>
<td>&quot;</td>
<td>Good</td>
<td>Normal</td>
<td>Aug. 28, 1947</td>
<td>28</td>
<td>627</td>
<td>5830</td>
<td></td>
<td>.</td>
</tr>
<tr>
<td>38</td>
<td>2</td>
<td>198</td>
<td>&quot;</td>
<td>Good</td>
<td>Occasional 90°</td>
<td>Oct. 19, 1947</td>
<td>90</td>
<td>740</td>
<td>60</td>
<td></td>
<td>.</td>
</tr>
<tr>
<td>41</td>
<td>3</td>
<td>195</td>
<td>&quot;</td>
<td>Good</td>
<td>Normal</td>
<td>Dec. 9, 1947</td>
<td>9</td>
<td>750</td>
<td>20</td>
<td></td>
<td>.</td>
</tr>
<tr>
<td>48</td>
<td>3</td>
<td>172</td>
<td>&quot;</td>
<td>Good</td>
<td>Normal</td>
<td>Nov. 22, 1947</td>
<td>55</td>
<td>729</td>
<td>73</td>
<td></td>
<td>.</td>
</tr>
<tr>
<td>50</td>
<td>2</td>
<td>161</td>
<td>&quot;</td>
<td>Good</td>
<td>Normal</td>
<td>Dec. 16, 1947</td>
<td>6</td>
<td>710</td>
<td>40</td>
<td></td>
<td>.</td>
</tr>
<tr>
<td>58</td>
<td>7</td>
<td>156</td>
<td>&quot;</td>
<td>Good</td>
<td>Still pyrexial</td>
<td>Dec. 1, 1947</td>
<td>400</td>
<td>645</td>
<td>500</td>
<td></td>
<td>.</td>
</tr>
<tr>
<td>69</td>
<td>5</td>
<td>141</td>
<td>&quot;</td>
<td>Good</td>
<td>Normal</td>
<td>Dec. 15, 1947</td>
<td>12</td>
<td>692</td>
<td>68</td>
<td></td>
<td>.</td>
</tr>
<tr>
<td>73</td>
<td>8</td>
<td>140</td>
<td>&quot;</td>
<td>Good</td>
<td>Normal</td>
<td>Dec. 22, 1947</td>
<td>8</td>
<td>735</td>
<td>60</td>
<td></td>
<td>.</td>
</tr>
<tr>
<td>74</td>
<td>7</td>
<td>140</td>
<td>&quot;</td>
<td>Good</td>
<td>Low pyrexia</td>
<td>Dec. 18, 1947</td>
<td>7</td>
<td>716</td>
<td>30</td>
<td></td>
<td>.</td>
</tr>
<tr>
<td>78</td>
<td>7</td>
<td>138</td>
<td>&quot;</td>
<td>Good</td>
<td>Normal</td>
<td>Dec. 15, 1947</td>
<td>26</td>
<td>750</td>
<td>30</td>
<td></td>
<td>.</td>
</tr>
<tr>
<td>81</td>
<td>4</td>
<td>135</td>
<td>&quot;</td>
<td>Fair</td>
<td>Still pyrexial</td>
<td>Dec. 23, 1947</td>
<td>.</td>
<td>670</td>
<td>692</td>
<td></td>
<td>.</td>
</tr>
<tr>
<td>91</td>
<td>6</td>
<td>120</td>
<td>&quot;</td>
<td>Good</td>
<td>Normal</td>
<td>Dec. 30, 1947</td>
<td>94</td>
<td>735</td>
<td>80</td>
<td></td>
<td>.</td>
</tr>
</tbody>
</table>
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 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 not used.

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 was stopped and the child 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 hemiplegia and meningitis. The c.s.F. 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; there was typical cerebellar ataxia, and optic disc swelling. After the end of the 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 cheerful. From the 105th 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 2 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 (guinea-pig 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 complained of cough 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 2½ 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; meningeval signs had then disappeared, and he was bright, cooperative, 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 98°F, from the 90th day. Treatment was stopped on the 100th day, and the child improved 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 (83% lymphocytes) per c.mm., protein 136 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 had been raised for 2½ months, with mild meningism, no pareses, and full consciousness. She responded well to treatment 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 examination of the deposit and in culture. Intramuscular injections were continued, without additional intrathecal therapy. Clinically the child continued to be very well, without signs of meningitis; she became mildly less irritable and gained weight, but 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 remained stationary at 40 per c.mm., protein 100 mg. per 100 ml., and sugar 200 mg. per 100 ml.; the protein level rose slowly. On the 90th day of meningitis she was still gaining weight and was afebrile; the
c.s.f. contained 60 cells (94% lymphocytes) per c.mm., protein 120 mg. per 100 ml., chlorides 790 mg. per 100 ml., and sugar 10 mg. per 100 ml. She was still having intravenous 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 progressing 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.

In 7 cases streptomycin was administered by the external 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. 16; 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 1 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

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.

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 in 23 satisfactory cases compared with those in first 23 fatal cases surviving a month or more.

### 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

<table>
<thead>
<tr>
<th>Week</th>
<th>In 23 satisfactory cases</th>
<th>In 23 fatal cases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total cultures</td>
<td>Positive</td>
</tr>
<tr>
<td>1</td>
<td>43</td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td>46</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>47</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>28</td>
<td>2</td>
</tr>
<tr>
<td>5</td>
<td>29</td>
<td>3</td>
</tr>
<tr>
<td>6</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>22</td>
<td>1</td>
</tr>
<tr>
<td>8</td>
<td>17</td>
<td>0</td>
</tr>
</tbody>
</table>

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 in 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, 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 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 subsided from bacillary meningitis the bacilli were 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 80th days were not inhibited by 1000 µg./ml. of streptomycin, and in 1 of the 19 patients strains were isolated 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 11 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 arteries 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 9 (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 "ischemic 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, for example, 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.
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 several 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 2½ 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 all stages of healing. They were all non-caseous and those found in chronic miliary tuberculosis and showed only in rare cases any evidence of healing, must be contrasted with the state of miliary lesions 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. Others, presumably older, the reticulin was giving way to collagen fibres and the epithelioid cells were disappearing. Finally there were foci of hyalineised 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 contrast to the cerebral lesions—the diagnosis of 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, produced 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 equally successful—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 border-line 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 focal reaction in the spinal cord? It is therefore impossible at present to draw hard and fast conclusions about optimal methods.

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It is too early to compare results on this basis. The high CSF-streptomycin level should perhaps be maintained 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; possibly where tubercle bacilli are found repeatedly in the CSF, 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. Continuing treatment in patients on intramuscular therapy only has been a rising CSF-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 defense 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 Cecchi 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 some 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, particularly 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) 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.

2. Lumbar puncture. Examination of CSF for levels of protein, sugar, and leucocytes; and isolation of tubercle bacilli. At least two adequate samples of CSF 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 guinea-pigs. Key to the latter is it 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 tuberculous meningitis, to be started without delay when there is definite or strong presumptive evidence of tuberculous meningitis. Lumbar puncture is imperative for confirmation.

**TREATMENT**

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

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.

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:

<table>
<thead>
<tr>
<th>No. of cases admitted before Aug. 18, 1947</th>
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<td></td>
<td>Good</td>
</tr>
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<td>------------------------------------------</td>
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<td><strong>Table I</strong></td>
<td>153</td>
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<tr>
<td><strong>Table VI</strong></td>
<td>48 (100%)</td>
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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.

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 the condition of the patient suggests that 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 puncture should be considered.

Isolation of tubercle bacilli: 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. should be done at monthly intervals. Any positive specimen 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 from hospital to a convalescent institution or a sanatorium until the C.S.F. is normal. In all cases the patient should go as an inpatient for at least three months. When intramuscular treatment is given 12-hourly, the intrathecal injection should be given six hours after the last intramuscular injection. 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 the end 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 intrathecal route. Evidence of increasing intracranial pressure, with progressive headaches or 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).

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 much for at least two years after leaving hospital. Psychometric examination should be made at the earliest opportunity.

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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-reports 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 in 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 coordinated 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 cooperation and for the detailed investigations undertaken.

Centre
- Hammersmith Hospital: Dr. D. MacCarthy, Dr. Mary Barber
- Royal Hospital for Sick: Prof. G. B. Fleming
- Children: Glasgow: Prof. Stanley Graham
- Alder Hey Children's Hospital, Liverpool: Dr. R. M. Todd, Dr. D. MacCarthy
- The Hospital for Sick: Dr. P. M. Ransford, Dr. D. MacFarlane
- The National Hospital, London: Dr. A. P. Morley, Dr. R. E. Kelly
- Guy's Hospital: Dr. F. R. Evans, Dr. C. W. Kessiss, Dr. G. L. MacFarlane
- Hichinbro' Hospital: Dr. J. Ruhi, Dr. A. L. Jacobs
- Radcliffe Infirmary, Oxford: Dr. D. MacFarlane
- 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 morphid anatomists were responsible for a memorandum on necropsy procedure.

REFERENCES

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 hypoglycaemia were present. The distribution of different blood-sugar levels was as follows:

<table>
<thead>
<tr>
<th>Blood-sugar (mg. per 100 ml.)</th>
<th>No. of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Below 80</td>
<td>62</td>
</tr>
<tr>
<td>80-120</td>
<td>99</td>
</tr>
<tr>
<td>120-180</td>
<td>34-7</td>
</tr>
<tr>
<td>Above 180</td>
<td>6-2%</td>
</tr>
</tbody>
</table>

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:

<table>
<thead>
<tr>
<th>Blood-sugar (mg. per 100 ml.)</th>
<th>No. of cases</th>
<th>Average</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Below 40</td>
<td>40</td>
<td>40</td>
<td>30-60</td>
</tr>
<tr>
<td>Above 40</td>
<td>5-6%</td>
<td>90-5%</td>
<td></td>
</tr>
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</table>

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 hypoglycaemic symptoms, but their general condition was low, with extreme emaciation and prostration. They could hardly speak distinctly. They were full conscious and eager to live. One patient had a blood sugar level of 17-6 mg. per 100 ml, but he also had cancerous carcinoma of the brain 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, giving 50 g. of glucose by mouth. A representative