APPENDIX

The Case Reports of twenty-six cases of tuberculous meningitis.

Accompanying each report is a graph to show the week by week alterations in the cerebrospinal fluid. In the successfully treated cases the graph becomes discontinued when the sugar and chloride values have become normal. Owing to limitation of size, the graph is not continued until the cell and protein contents return to normal as this has been found to require a prolonged time, usually long after the case is considered cured.

The outstanding feature of these graphs is that they show the sugar-chloride curves and the cell-protein curves to diverge in the successful cases and to converge in the fatal cases or in those making unsatisfactory progress.

During July, August and September 1950 the laboratory was closed at Southfield Sanatorium, due to the indisposition of the laboratory technician and this has been indicated in the graphs concerned by "laboratory closed". Where readings from other laboratories have been included for this period, specific mention is made of it.
CASE No. 1.

Mrs. M.P., a housewife of 28 years of age, first became unwell in June 1948. She complained of tiredness and listlessness and loss of weight. She felt feverish and had an irritable unproductive cough for 2 weeks. Physical and X-ray examination of the chest was negative and her condition was diagnosed as anaemia for which she received appropriate treatment. Because of a deterioration in her condition four months later, X-ray examination of the chest was repeated and showed diffuse miliary infiltrations of both lungs highly suggestive of tuberculosis. She then revealed that her father had died of tuberculosis and her husband's only sister also died of the disease a year ago and since the latter time she had been attending a Tuberculosis Dispensary.

On the diagnosis of miliary tuberculosis being made, the patient was admitted to Southfield Sanatorium on the 4th October 1948. On examination, she was found to be in poor general condition, thin and emaciated and ill-looking. The temperature was 100°F. The pulse rate varied between 90 and 96 per minute. The chest was poorly covered but there was little in the way of detectable abnormality except generalized weakening of the breath sounds. The heart and central nervous system were normal.

Blood examination showed the haemoglobin to be 65% (Sahli)/
(Sahli) and the total white blood count was 8,500 cells per cubic millimetre, of which 68% were polymorphs, 30% lymphocytes and 2% eosinophils. The urine contained acid-fast bacilli on direct smear, which morphologically were tubercle bacilli. Lumbar puncture was carried out; the cerebro-spinal fluid was normal and no acid-fast bacilli were seen on direct smear. The B.S.R. (Westergren) was 55 millimetres in the first hour. The Mantoux test was positive to 8 millimetres with a 1 in 1,000 dilution of old tuberculin. The X-ray of the lungs showed the picture of miliary tuberculosis. This case of miliary tuberculosis was to be watched carefully in view of the possibility of the development of tuberculous meningitis and this in fact did occur.

**Bacteriology.** Tubercle bacilli, of the human type, were cultured from the urine on several occasions during the 8 months' duration of her illness, in spite of intensive streptomycin therapy. The organism was not found by smear, culture on Löwenstein-Jensen medium, or guinea pig inoculation at the time of the first appearance of meningitis in November 1948, but was isolated on several occasions by direct smear and culture following the relapse of the meningitis in March 1949.

**Treatment.** Streptomycin, by intramuscular injection, was given in the form of the sulphate salt until 16th April 1949, thereafter the calcium chloride/
chloride complex was used. The dose was 2 gm. daily and it was started on the 5th October 1948. A month after the commencement, meningitis supervened, and this course was discontinued on the 6th January 1949. On the 15th March 1949 it was obvious that there was a relapse of the meningeal tuberculosis and intramuscular streptomycin was resumed on that date, 2 gm. daily. There was one short rest period from the 10th - 16th April 1949. This second course was discontinued on the 7th May 1949 because of increasing deafness and blindness - the result of optic atrophy subsequent to optic neuritis. As her condition deteriorated further, a third course of 2 gm. daily was started on the 8th June 1949 but only lasted until the 11th June 1949 as it seemed that streptomycin was aggravating her symptoms. The total amount of streptomycin given by the intramuscular route on 125 days was 250 gm.

It was on the 6th November 1948 that tuberculous meningitis was found to have complicated the miliary disease, and intrathecal streptomycin was first commenced on this date. At first the dose was 50 mg. daily of the calcium chloride complex. Coinciding with the first course of intramuscular therapy, intrathecal streptomycin was given from the 6th - 28th November 1948 and from the 17th - 24th December 1948, i.e. 29 days. Coinciding with the second intramuscular course, intrathecal treatment was resumed on the 15th March 1949, having/
having an eight-day rest period from the 8th - 16th April 1949 and being finally discontinued on the 6th May 1949, i.e. 46 days. On the last 13 days of this second course the daily dosage was raised from 50 mg. to 100 mg. The third and final course was started on the 9th June 1949 and 50 mg. were given intermittently until the time of her death on the 30th June 1949. The total number of days on which intrathecal streptomycin was given was 86 (i.e. 70% of the days on which intramuscular treatment was given) and the amount 5 g.

Progress. During the month of October 1948 the patient made some progress, her general condition improved and she had gained some weight. On the 2nd November, for the first time, the temperature rose to 101°F. and she complained of slight stiffness in the neck and photophobia. The C.S.F. findings were a little suspicious of the earliest stage of onset of tuberculous meningitis, namely the cells rose to 10 per cubic millimetre, the sugar falling to 44 mg. %

On the 6th November 1948 there was definite evidence of meningeal involvement. The temperature had risen to 103°F. She complained of frontal headache, photophobia, stiffness of the neck and periodic vomiting. Examination now revealed neck rigidity and a positive Kernig's sign. All reflexes were normal and there was no lesion of the cranial nerves. The C.S.F. findings confirmed the presence of/
of a tuberculous involvement of the meninges. Intrathecal streptomycin was commenced at once and she made a rapid improvement so that towards the end of the same month all symptoms and all signs of meningitis had disappeared, although the C.S.F. was still far from normal.

At the beginning of January 1949 all treatment was stopped. There were no symptoms or signs of meningitis and X-ray of the lungs showed that the miliary shadows had practically disappeared. The temperature fell to 99°F. (Rectal) and she had put on 16 pounds in weight since admission. The two abnormal features were that the C.S.F. continued to be abnormal in its cellular and biochemical contents and tubercle bacilli could still be found in the urine on direct smear and culture. At the end of January she was allowed up for toilet purposes.

This progress continued until the 9th March 1949 when a sudden and rapid deterioration of her condition occurred. The temperature began to rise and approached 103°F. and she felt ill. There was vomiting and slight diarrhoea. The frontal headache returned, the neck felt stiff and she became drowsy, but there were no signs of meningism. However a rise in the white cell content of the C.S.F. and a marked fall of the sugar content to 38 mg.% supported the view that a relapse of the meningitis had occurred. Streptomycin therapy was resumed on the 15th March 1949 and on that day tubercle bacilli were found in the/
the C.S. F. on direct smear. Two days later she was seriously ill and showed mental confusion and disorientation and was incontinent of urine, and signs of meningism appeared. At the beginning of April 1949 there was some improvement in her condition and the temperature was settling but additional features were the complaint of slight haziness of vision and the appearance of weakness of the right internal rectus muscle, a marked right ptosis and inequality of the pupils. By the 1st May 1949 there was improvement in all the symptoms and signs of this relapse - by now the only positive neurological signs were inequality of the pupils, a slight degree of ptosis of the right eyelid and slight bilateral spasm of the hamstring muscles. The C.S.F. was still grossly abnormal. This patient had an old chronic suppurative otitis media of the left ear and slight deafness was appearing in the sound ear. The dimness of vision was increasing. It was for these two reasons that it was felt necessary to discontinue all streptomycin therapy. As the weeks went by she became mentally confused at times, at other times she was noisy and very talkative. The failure of vision increased until perception of light was only possible, while the deafness had almost disappeared. At the end of May 1949 the ophthalmologist, reporting on this patient's condition, stated that there was a considerable degree of bilateral optic atrophy and he considered the condition/
markedly cyanosed and died.

**Autopsy.** The leptomeninges covering the greater part of the supero-lateral aspects of both cerebral hemispheres were free from exudate, but fairly numerous greyish-white tubercles were scattered throughout the subarachnoid space and lay in relation to vessels. A very extensive exudate was present in the leptomeninges covering the base of the brain in the region of the interpeduncular fossa, brain-stem and adjoining parts of the antero-inferior aspect of the cerebellum. This exudate almost completely obscured the vessels, nerves and other structures in these situations at the base of the brain and appeared to be causing considerable compression and atrophy of the optic chiasma and nerves. There was an extension of the exudate into the stems of both lateral fissures. The convolutions of both hemispheres were very markedly flattened and pale in colour.

Section of the brain revealed moderate dilatation of lateral, third and fourth ventricles with thickening of ependyma in most parts of the ventricular system, associated with which were scattered small ependymal tubercles. There was no obstruction at the foramen of Monro but the ependyma lining the aqueduct was very swollen and oedematous, and post mortem showed that its lumen was quite obliterated by the ependymal oedema. Situated in the right temporal lobe was a tuberculoma which measured/
measured 1.5 cm. in its long axis and which had burst into the stem of the lateral fissure.

Microscopically the tuberculoma had the appearance of being a recent and an acute one. There was an extensive area of central caseation and it was bounded externally by copious tuberculous exudate which filled the subarachnoid space. The copious exudate at the base of the brain was typically chronic tuberculous in nature. There was mild fibroblastic activity in the cellular parts of the exudate, but the chronicity of the lesion was emphasised by the marked vascular lesions involving not only the small vessels but the larger cortical arteries. These vessels were infiltrated with similar chronic inflammatory cells and showed striking periarteritis and endarteritis. The underlying nervous tissue was oedematous and showed secondary toxic degenerative changes.

There was an acute tuberculosis of the right kidney and bladder and evidence of healed generalised miliary tuberculosis of lungs, liver and spleen.

Summary. This patient was admitted to the Sanatorium as a case of miliary tuberculosis without meningeal involvement. One month after admission (during which time she was receiving intramuscular streptomycin) or 14 weeks after the commencement of her illness she developed clinical tuberculous meningitis/
meningitis. Two months later she had made excellent progress but urine cultures persistently gave a positive culture of human type tubercle bacilli, and 2 months later still she relapsed and became blind and thereafter followed a downhill course. Total intramuscular streptomycin given during the 9-months' course of her illness was 250 gm.; and the intrathecal total was 5 gm. Post-mortem findings included the presence of a fairly recent and acute tuberculoma in the right temporal lobe and an extensive chronic tuberculous exudate at the base of the brain.
CASE No. 2.

Mrs. S.G., aged 22 years, was admitted to the City Hospital, Edinburgh on the 9th January, 1948, when she gave a history of a productive cough since September 1947. During the latter month she had a small haemoptysis on two occasions. She complained of feeling easily tired, of poor appetite and slight dyspnoea on exertion. She also had vague abdominal pains and a feeling of nausea with occasional sickness. Her last menstrual period was in August 1947. On examination she was pale and thin. The temperature was 98.6°F. and the pulse rate 92 per minute. Over the right upper lobe there was an impaired percussion note, bronchial breathing and medium and coarse crepitations. The fundus uteri was one finger’s breadth below the umbilicus. Her B.S.R. was 30 mm. in the first hour (Westergren). The sputum was negative for tubercle bacilli on admission but became positive in February 1948.

A right artificial pneumothorax was induced on the 2nd February 1948. On the 21st February she spontaneously delivered herself of a dead anencephalic foetus. She developed a post-partem haemorrhage and the lochia persisted for longer than usual. Thoracoscopy and adhesion section were carried out on the 22nd April 1948 and the right upper lobe, previously held out by adhesions, was now densely collapsed. In July 1948 she developed a small right-sided pleural effusion and this required/
required repeated aspiration, the last occasion being September 1948.

On 19th October 1948 her condition deteriorated and she felt tired and ill. Her temperature rose to 102°F., but there was no deterioration of the signs in the lungs. On 25th October the temperature remained high, she was definitely cyanosed and was slightly dyspnoeic. The lungs now showed the presence of profuse fine and medium crepitations over the left upper lobe, the signs on the right being those of an artificial pneumothorax. X-ray examination showed the development of a cavity in the partially collapsed right upper lobe and fine shadowing throughout the whole of the left lung like that of miliary disease, but there was no evidence of miliary shadowing in the partially collapsed right lung. It was on this film that a diagnosis of miliary tuberculosis was made and she was transferred to the Streptomycin Unit at Southfield Sanatorium on 30th October 1948.

On admission to Southfield Sanatorium she was found to be febrile (100°F.) and very weak. Her weight was 6 st. 6 lbs. She was coughing up a large quantity of muco-purulent sputum. The liver was enlarged three inches below the costal margin. She was having troublesome diarrhoea, the bowels moving 3 to 4 times in the 24 hours, the movements being associated with abdominal pain. The diarrhoea had started about two months before her transference. There/
There was a recent history of pyelitis with B. Coli in the urine but there was now no albuminuria or pyuria. There were no abnormalities in the central nervous system. In the left optic fundus was seen a small round pale area with central black pigmentation, having the appearance of a healing choroidal tubercle. The B.S.R. was 10 mm. in the first hour (Westergren) and she was Mantoux positive to 0.1 ml. of 1 in 10,000 old tuberculin.

**Bacteriology.** Tuberculous meningitis was diagnosed on 11th January 1949 and a specimen of C.S.F. at that time was negative on culture and guineapig inoculation. However a human type tubercle bacillus was grown on culture from a specimen of C.S.F. on 24th January 1949. Thereafter C.S.F. cultures were negative. The sputum was repeatedly positive for tubercle bacilli.

**Treatment.** Streptomycin was begun on the day of admission in a dose of 2 gm. daily by intra-muscular injection. Prior to 24th March 1949 streptomycin sulphate was used, thereafter it was the calcium chloride complex. On the fifth day of treatment it was decided to reduce the dose to 1 gm. daily, and this was continued for 10 weeks when tuberculous meningitis developed to complicate the miliary tuberculosis. Thereafter the dosage was increased to 2 gm. daily for the next 14 weeks, to be discontinued on 16th April 1949. Because of a rapid deterioration in her condition a 2 gm. daily dose/
dose was resumed on 15th May 1949 but was discontinued 3 days later as she was deteriorating so very rapidly. The total amount of streptomycin given by the intramuscular route on 166 days was 262 gm.

Intrathecal treatment was begun on 12th January 1949 with the diagnosis of tuberculous meningitis being made. 50 mg. were given on 59 consecutive days. A second series of injections of 50 mg. each was begun on 8th April 1949 and given for 29 consecutive days. There were five isolated injections of 50 mg. each in addition. The total amount given intrathecally on 93 days (i.e. on 56% of the days on which intramuscular streptomycin was given) was 4.5 gm.

Progress. On 9th November 1948 a lumbar puncture was done for the first time - C.S.F. contaminated with blood was obtained but there was no increase in the relative number of the white cells. The glucose content was 41 mg.% On 10th November a second choroidal tubercle, in an early stage of development, was discovered in the left optic fundus. The B.S.R. was now 74 mm. in the first hour. Lumbar puncture was repeated on 7th December and the great majority of the C.S.F. cells were red cells - it was noted at the time that "contamination" was not understood. No pressure could be recorded. There was no response to jugular compression, and the glucose level was 46 mg.% A fourth choroidal tubercle had appeared in the left eye. In other ways/
ways she showed slight improvement; her cough was now less, the quantity of sputum was reduced, X-ray showed some clearing of the miliary shadows and the diarrhoea and colic had ceased.

At the beginning of January 1949 she was still far from well. She now developed headache, two further choroidal tubercles were noted in the left eye (now 6 in all) and a small one appeared in the right optic fundus. A week later her condition was deteriorating and she felt very exhausted, the headache continued and she now had a definite Kernig's sign. On lumbar puncture the C.S.F. contained 25 white cells per c. mm. (none on 28.12.48) and the glucose level had fallen to 35 mg. % On the following day the cells had increased to 110 per c.mm. There was now little doubt that she had developed tuberculous meningitis, though the tubercle bacillus was not isolated, and this had occurred approximately 12 weeks after the first symptoms of miliary tuberculosis had developed. On the 13th January slight neck rigidity had appeared and the Kernig sign was marked. Two further choroidal tubercles had appeared in the right fundus. Drowsiness was noted at times during February and early bilateral papilloedema had appeared.

At the end of March 1949, almost 3 months after the treatment of the meningitis had begun, she was/
The patient gradually became weaker, more emaciated and comatose, and died on 25th May 1949.

Autopsy. The leptomeninges covering the base of the brain in the region of the interpeduncular fossa were thickened and opaque, due to grey-coloured exudate. There was an extension of this exudate into both sylvian fissures and over the inferior surface of the pons. Generalised gyral flattening was present throughout all parts of the cerebrum. Discrete tubercles were not found in the leptomeninges.

Coronal sections revealed marked dilatation of all parts of the lateral ventricles and of the third ventricle. The ependyma was swollen and showed eruption of clusters of small miliary tubercles.

Microscopically the leptomeninges showed extensive tuberculous meningitis of fairly acute character. Extensive mononuclear infiltration of the adventitia of most of the meningeal vessels was a marked feature but there was little or no evidence of any endarteritis obliterans. There was no evidence of fibrous tissue proliferation and numerous acid fast bacilli were found in the exudate. In many sub-ependymal areas the underlying brain tissue was softened and oedematous, showing infiltration by histiocytes and proliferation of astrocytes.
A chronic cavity was found in the upper lobe of the right lung, and numerous acute miliary tubercles were found elsewhere, principally in the liver and kidneys.

**Summary.** The case of a young woman who developed pulmonary tuberculosis of the right upper lobe. She was treated with a right artificial pneumothorax. Ten months after the original diagnosis she developed signs of an acute miliary tuberculosis and was admitted to Southfield Sanatorium for streptomycin treatment. Six weeks after admission she developed tuberculous meningitis and the human type tubercle bacillus was isolated from the cerebro-spinal fluid. There was only a slight clinical response to streptomycin, 262 gm. intramuscularly and 4.5 gm. intrathecally, but she quickly became worse again and died 7 months after commencing treatment of a progressive meningitis and hydrocephalus.
CASE No. 3.

Mrs. H.T., aged 29 years, became unwell at the end of October 1948. She complained of headache, throbbing in character and situated over both temporal regions. Occasionally she had shooting pains in her neck and back. These symptoms were associated with occasional vomiting, constipation and general malaise. At the beginning of November she developed photophobia and the headaches became worse. She also had an unproductive cough and had lost weight since the beginning of her illness. There was nothing of importance to note in her past history. There was no family history of tuberculosis and no history of contact with a case. On admission to Southfield Sanatorium on 16th November 1948 she was an ill-looking, thin and sallow-coloured woman. The temperature was 101° - 102°F. She lay curled up in bed with her head beneath the sheets on account of photophobia. She resented interference, felt very cold and complained bitterly of her headache. She was mentally clear but very unco-operative and irritable. There was marked neck rigidity and Kernig's sign was positive. There was an increased lumbar lordosis due to spasm of the spinal muscles. There was no loss of power or abnormality of sensation. All reflexes were present and equal. The plantar responses were flexor. There were no lesions of the cranial nerves, no papilloedema and no /
no choroidal tubercles were seen. The cardiovascular system was normal apart from bradycardia. No abnormality was found on physical examination of the chest. The alimentary and renal tracts were normal. On admission, the B.S.R. was 11 mm. in the first hour (Westergren). She gave a positive Mantoux test of 8 mm. to 1 in 10,000 old tuberculin. Radiological examination of the lungs showed light ill-defined tuberculous infiltration of both apices.

The initial examination of the C.S.F. by lumbar puncture was as follows:- pressure 260 mm. water, cells 842 per cubic millimetre of which 90% were lymphocytes, the protein content 225 mg.%, sugar 23 mg.% and chloride 690 mg.%

**Bacteriology.** Tubercle bacilli were not found on examination of a direct smear from the C.S.F. but a human type tubercle bacillus was obtained by culture and guineapig inoculation from the fluid obtained on admission.

**Treatment.** Streptomycin sulphate was started on the day of admission. 2 gm. were given daily by intramuscular injection throughout the course of her illness until her death on 29th March 1949. The dosage given by this route on a total of 122 days was thus 244 gm.

The intrathecal dose used on all occasions was 50 mg. It was commenced on the day of admission but was omitted on the 1st December for 2 days because it was thought that the drug was the cause/
cause, at least in part, of recent severe headaches, sometimes associated with nausea and vomiting, and this appeared to be substantiated by the rapidly rising C.S.F. cell count. This in fact did alleviate the symptoms but there was no appreciable fall in the C.S.F. cells. The first course of 23 days was completed on the 8th December. On 17th December she received a further eight intrathecal injections of 50 mg. During January and the first week of February 1949 she received a once-weekly booster intrathecal injection in addition to the intramuscular streptomycin. In view of a clinical deterioration of her condition on 5th February, a further course of daily intrathecal therapy was begun, lasting for another 23 days until 28th February. A 2-day rest period followed because during the previous few days she had severe pain on lumbar puncture. A further five injections completed the course on 7th March 1949. The total amount of intrathecal streptomycin given on 66 days (i.e. on 54% of the days on which intramuscular treatment was given) was 3.5 gm.

Progress. At the beginning of January 1949, 8 weeks after admission, improvement was noted in her condition. She felt better in every way and she was obviously putting on weight. She was rarely sick and had virtually no headache. She occasionally felt a little dizzy and had slight tinnitus. Her appetite was fair but the constipation continued/
continued to be extremely obstinate. The temperature remained elevated, ranging between 100° - 101°F. At that time neck rigidity had gone and Kernig's sign was no longer positive. There was no evidence of cranial nerve involvement, the retinae were normal, and no abnormality of motor or sensory functions was detected. All the reflexes were present and equal. Apart from the chloride content of the C.S.F. the fluid remained grossly abnormal in other respects.

This improvement did not last for long. At the beginning of February 1949 periodic vomiting returned and she had frontal headache some days. Kernig's sign became positive again. Intrathecal therapy was now re-started. At the beginning of March she was far from well; she became drowsy, delirious and disorientated and slight neck rigidity appeared. At the same time an amber-coloured fluid was obtained on lumbar puncture and was under low pressure with a negative Queckenstedt test, while cisternal puncture yielded a clear and colourless fluid - this indicated the development of a spinal block. After 10 days, on 17th March 1949, a positive Queckenstedt's test was obtained on lumbar puncture, indicating that the spinal block had resolved. However her clinical condition was markedly deteriorating and all streptomycin treatment was discontinued.

On 28th March 1949 she went into a semi-comatose condition, yet there were only slight signs of/
of meningism and no other neurological findings though the C.S.F. showed gross abnormality. She became unconscious on 29th March 1949 and died that evening.

**Autopsy.** In the region of the inter-peduncular fossa the leptomeninges showed a typical greyish-yellow exudate, obscuring vessels and nerves in this region. It extended into the stem of the lateral fissure on both sides and downwards onto the upper aspect of the pons. Four tubercles were seen on the supero-lateral aspect of the cerebral hemispheres. There was marked dilatation of the lateral ventricles and also of the 3rd ventricle while many parts of the ependyma showed numerous small raised tubercles. There was also dilatation of the 4th ventricle. There was no abnormality of the spinal cord.

Microscopically, a typical acute tuberculous meningitis was present in the leptomeninges of the mid-brain. Many meningeal vessels showed moderate intimal hyperplasia. The adjacent brain tissue was degenerated. Tubercle bacilli were present, but scanty. There was no evidence of fibrosis. The wall of the lateral ventricle showed well-formed sub-ependymal tubercles and gliosis. Examination of the lumbar cord showed a diffuse and fairly heavy infiltration of the surrounding leptomeninges by lymphocytes and mononuclear cells but no true pattern of tuberculous meningitis. The picture in the lumbar subarachnoid space suggested a reactionary infiltration.
infiltration to a meningitis higher up in the subarachnoid space but not a true meningitis in the lumbar region per se.

**Summary.** A case of tuberculous meningitis and tuberculous infiltration at both lung apices due to a human type tubercle bacillus. She was treated by intramuscular (total 244 gm.) and intrathecal (total 3.5 gm.) streptomycin and at first responded quite well to therapy. Latterly however she became mentally confused and she never recovered from this state. The C.S.F. was always markedly abnormal but in the terminal stages the picture was not that of an active and progressive meningitis, and at post-mortem a marked internal hydrocephalus, in addition to tuberculous meningitis, was found.
CASE No. 4.

C.L., a girl of 18 years of age, gave a history of 2 weeks' illness before admission to Southfield Sanatorium on 24th December 1948. She had been running a slight temperature during this time and had vomited repeatedly and effortlessly. A few days before admission she became constipated, developed frontal headache and photophobia and had become mentally confused. She had lost weight in recent weeks and had had an unproductive cough for several months.

On admission this girl was thin and very ill and lay in a stuporose condition from which she was roused with difficulty. When roused, she understood what was said to her and she could answer simple questions but her speech was slurred. The temperature was 100°F. and the pulse rapid and of poor quality. Examination of the nervous system showed a right facial weakness. There was an early papilloedema of the left optic disc and venous congestion in both optic fundi. There was a moderate degree of neck rigidity and Kernig's sign was present. All abdominal and limb reflexes were present and equal. There was no disturbance of motor or sensory functions of the limbs. On lumbar puncture the cerebro-spinal fluid was opalescent and had a slight yellow tinge. It was under a pressure of 300 mm. water and the response to jugular compression was normal. The total number of white cells/
cells was 110 per c.mm. of which 65% were lymphocytes. There were 960 red cells per c.mm. It was an atraumatic puncture. The glucose content was 4.4 mg.% and the chloride 67.48 mg.% There were signs of bilateral lung tuberculosis, more extensive in the left lung. Over the heart there was a soft systolic apical murmur. The abdomen was scaphoid but no other abnormality was detected. The haemoglobin was 90% (Sahl) and the white blood count 15,000 per c.mm. The E.S.R. was 4 mm. in the first hour (Westergren) and the Mantoux test was negative to a 1 in 1,000 dilution of old tuberculin.

**Bacteriology.** The C.S.F. on admission was plated on Löwenstein-Jensen medium and a human-type tubercle bacillus was isolated. A guinea-pig inoculated from the same specimen of C.S.F. showed extensive generalised tuberculosis.

**Treatment.** Streptomycin sulphate was commenced on 26th December 1948. The total daily dose was 2 gm. by intramuscular injection. All treatment was stopped on 6th January 1949 as there was no response whatsoever to this therapy. The total intramuscular dosage was 24 gm. and the intrathecal total was 0.6 gm.

**Progress.** Two days after admission the right facial weakness was more marked and there was a slight deviation of the tongue to the right when it was protruded. The pupils were now unequal in size, the right being smaller than the left but both responded/
responded normally to light and accommodation. She became incontinent of urine and delirious. Vomiting increased and she retained little fluid by mouth. On 27th December 1948 spinal block was confirmed and only a very small amount of blood-stained C.S.F. was obtained but when cisternal puncture was performed clear C.S.F. under very high pressure was obtained and the intrathecal streptomycin was now given by this route.

At the end of the month some improvement was noted. She became clearer mentally, the vomiting became infrequent and the right facial weakness disappeared, although the inequality of the pupils persisted. She had by now developed a coarse nystagmus to the right and a rotatory nystagmus to the right on upward deviation of the eyes. There was slight nystagmus to the left.

By 4th January 1949 her condition was worse than it was on admission. She was ill, drowsy and mentally confused. There was now a slight left ptosis. Lumbar puncture showed that the spinal block had now recanalised. A marked deterioration followed, she became unconscious and died on 9th January 1949.

Autopsy. There was an extensive, grey, gelatinous, tuberculous exudate within the subarachnoid space over the base of the brain, concealing the structures in the interpeduncular fossa, covering pons and extending laterally into the stems of the lateral sulci. Numerous miliary tubercles were/
were seen along the line of the vessels over the vertex. The cerebral hemispheres were swollen and the gyri flattened.

Coronal sections of the cerebrum showed quite a large irregular area in the lower half of the left insula, of yellow caseating tuberculous exudate, filling the subarachnoid space but involving the surrounding grey matter and extending almost to the underlying white matter. The grey matter surrounding the lesion was deeply congested and oedematous and contained several miliary tubercles around the advancing edge of the lesion. The whole of the left hemisphere was more swollen than the right and this had caused considerable shift of mid-line structures to the opposite side with distortion of the ventricles. Scattered throughout both white and grey matter were many miliary tubercles which were most often found either protruding into the subarachnoid space, or into the underlying white matter. Two larger foci, though not as large as that found in the insula, were seen in the left occipital lobe, lying partly in the grey matter and partly in the white. The entire ventricular system was moderately distended. Microscopically the leptomeninges throughout brain and cord were intensely congested and infiltrated with a typical caseating tuberculous exudate. Dense perivascular collections of cells were seen in many of the sections, but only in those of the left insula and sylvian fissure was there a pronounced/
pronounced subintimal proliferation. Indeed it was so marked in the former, some of the vessels being completely obstructed by endarteritis, as to suggest that this was the original (Rich) focus from which infection of the leptomeninges occurred. In the sylvian fissure the lumen of one small artery was blocked by caseating tuberculous exudate. Extension of the exudate into the underlying nervous tissue was seen in several sections, either directly with destruction and caseation of the superficial cortical tissue, or along the perivascular spaces accompanied by non-specific toxic changes in the nerve cells. In the left insula the vascular changes had produced extensive softening of the subcortical white matter which was beginning to disintegrate and was heavily infiltrated with reacting neuroglia. The meningeal reaction in the lumbar cord was minimal yet quite typically tuberculous in nature. In a chance section taken at the upper lumbar level of the cord a small tubercle was seen and this showed central caseation. It lay partially in the right posterior horn and partially in the column of Burdach upon the right side.

A section from the left insula showed the presence of numerous acid-fast bacilli in the exudate.

The lungs showed evidence of miliary tuberculosis and in the left upper lobe was found a Ghon focus. Numerous tubercles were also found in the/
the spleen and a few in the thyroid and liver. There were numerous tuberculous ulcerations of the small intestine, especially in the terminal ileum.

Summary. The case of a young girl, admitted with pulmonary tuberculosis and tuberculous meningitis in a fairly advanced stage. Human type tubercle bacilli were isolated from the C.S.F. She died eighteen days later without showing any response to a brief course of intramuscular and intrathecal streptomycin. Postmortem examination revealed a Rich focus in the left insula in addition to miliary tuberculosis of the brain and cord. Miliary tubercles were found in most other organs.
CASE No. 5.

A.L., a girl of 9½ years, developed a vague illness in November 1948. While at school she was seen to be easily tired and listless; her appetite became poor and she lost weight. At the beginning of December she complained of slight headache with vomiting periodically. She was then put to bed and while there developed a short dry cough. A 2 weeks' course of sulphamezathine was ineffectual. There was no family history of tuberculosis and no history of contact with a case of the disease. This child was admitted to the Royal Hospital for Sick Children, Edinburgh on 26th December 1948 and upon making a diagnosis of miliary tuberculosis she was transferred to Southfield Sanatorium two days later.

When she was admitted to Southfield Sanatorium her general condition was poor. She was weak and listless. She was slightly emaciated, the skin was dry and the muscle tone poor. She was highly fevered with a temperature swinging from 99° F. to over 102° F. and the pulse rate ranged between 110 and 124 per minute. She had a slight cough but no sputum. The chest was shrunken as part of the general emaciation. The right sterno-mastoid muscle was in spasm but no abnormal findings were detected on auscultation. There was no abnormality of the heart or alimentary tract. The haemoglobin was 70% (Gower) and white blood count 14,000 cells per cubic millimetre of which 68% were neutrophils, 20% lymphocytes/
lymphocytes, 10% monocytes and 2% eosinophils. There was no neck rigidity or Kernig's sign, no disturbance of motor or sensory functions and all the reflexes were present and equal. The cerebrospinal fluid was normal apart from the low glucose content - cells 1 per cubic millimetre, glucose 46 mg./%, chloride 804 mg./%. The optic fundi however revealed the presence of choroidal tubercles. There were 3 in the right eye and 4 in the left eye. All were small pale yellow fluffy patches of recent origin with the exception of one in the left eye which was well defined. The urine was normal apart from a few red blood cells and an occasional white cell. The B.S.R. was 15 mm. in the first hour (Westergren) and the Mantoux test was positive to 1:1,000 old tuberculin.

An X-ray film of the chest on admission showed diffuse fine miliary tuberculous shadows involving the whole of each lung but very sparse in the apices. There were big glands in both lung roots.

**Bacteriology.** This patient had no sputum but tubercle bacilli were cultured from a gastric lavage performed on 6th January 1949. On admission the C.S.F. was normal and no tubercle bacilli were isolated either by culture or by animal inoculation. However after tuberculous meningitis had complicated the miliary disease process, tubercle bacilli were isolated from the C.S.F. by guineapig inoculation on 19th March 1949 and by culture on Löwenstein-Jensen medium/
lymphocytes, 10% monocytes and 2% eosinophils. There was no neck rigidity or Kernig's sign, no disturbance of motor or sensory functions and all the reflexes were present and equal. The cerebrospinal fluid was normal apart from the low glucose content - cells 1 per cubic millimetre, glucose 46 mg.%, chloride 80.4 mg.%. The optic fundi however revealed the presence of choroidal tubercles. There were 3 in the right eye and 4 in the left eye. All were small pale yellow fluffy patches of recent origin with the exception of one in the left eye which was well defined. The urine was normal apart from a few red blood cells and an occasional white cell. The B.S.R. was 15 mm. in the first hour (Westergren) and the Mantoux test was positive to 1:1,000 old tuberculin. An X-ray film of the chest on admission showed diffuse fine miliary tuberculous shadows involving the whole of each lung but very sparse in the apices. There were big glands in both lung roots.

**Bacteriology.** This patient had no sputum but tubercle bacilli were cultured from a gastric lavage performed on 6th January 1949. On admission the C.S.F. was normal and no tubercle bacilli were isolated either by culture or by animal inoculation. However after tuberculous meningitis had complicated the miliary disease process, tubercle bacilli were isolated from the C.S.F. by guineapig inoculation on 19th March 1949 and by culture on Löwenstein-Jensen medium/
medium on five subsequent occasions prior to her death in July 1949.

**Treatment.** Streptomycin was given daily by intramuscular injection from the day of admission until 17th May 1949. An interval of 3 weeks elapsed before a second course, lasting for 15 days, was started on 6th June 1949 and discontinued on 20th June 1949. A third course was commenced on 27th June 1949 but was not continued after 1st July 1949. The daily dose on all occasions was 1 gm. and the total amount of intramuscular streptomycin given on 160 days was 160 gm.

Intrathecal treatment with streptomycin was first commenced on 19th March 1949, at the time that meningitis first manifested itself. It was then given continuously for 22 days, discontinued for one week and resumed on 15th April 1949 for a further 33 days, to be finally discontinued on 17th May 1949, at the same time as the first intramuscular course. A second course of 2 weeks’ duration was commenced on 7th June 1949 and discontinued on 20th June 1949. A third, and last, short course was started on 23rd June 1949 and was discontinued at the same time as the third intramuscular course on 30th June 1949. The daily dose was 50 mg. and the total dosage given by the intrathecal route on 73 days (i.e. on 46% of those days on which intramuscular treatment was given) was 3.5 gm.

**Progress.** There was little change in her condition/
condition until the middle of March, by which time certain ominous features made their appearance. She became more apathetic than usual and slept for a considerable part of the day, though becoming brighter in the evening. She tended to have occasional headaches and vomiting and became more constipated. By now the temperature was not so hectic though it still ranged between 99° and 102°F. She was of better colour and nutrition. There was a slight degree of Kernig's sign and for the first time the disc margins were less clear and suggestive of early papilloedema. Also two further choroidal tubercles, not noted on previous occasions, were detected in the right fundus. The changes in the C.S.F. confirmed the development of a tuberculous meningitis; there was a marked increase in the number of the cells from 3 per cubic millimetre on 14th February to 210 on 18th March, while on the respective dates the glucose level fell from 56 mg.% to 43 mg.%. At this same time radiologically there was a marked clearing of the miliary shadowing of the lungs. Intrathecal streptomycin treatment for meningitis was now started.

By the middle of May 1949, two months after the onset of meningitis, her condition had altered little. She was bright and alert and felt well. The temperature seldom fell below 100°F. morning or evening. She frequently had attacks of frontal headache. There was no change in the neurological picture/
picture, the only signs, that of a positive Kernig's sign and papilloedema, persisting. There was no improvement in the C.S.F. and the most ominous feature was the progressive diminution of the glucose level from 43 mg.% to 37 mg.% A radiograph of the lungs showed that the miliary shadows had completely disappeared.

On 14th June 1949 it was noted on lumbar puncture that there was a high C.S.F. pressure before and after removal of a large quantity of fluid but practically no response to Queckenstedt's test. A cisternal puncture was carried out at the same time and the pressure, cellular and biochemical content of the cisternal fluid were similar to that of the lumbar fluid. This confirmed the block to be above the foramen magnum, probably a tentorial block. The 20th June 1949 was the first occasion on which the intrathecal streptomycin was given by the cisternal route. During the injection she complained that the back of the head and neck were "red hot" and she vomited and complained of generalised headache shortly afterwards. At the same time it was found that there was a commencing atrophy of the right optic disc and the papilloedema was present now only in the left eye.

At the beginning of July 1949 a noticeable deterioration in her condition set in. She had more headache and was becoming drowsy. Definite neck rigidity/
rigidity appeared, there was a positive Kernig's sign and early spastic signs in the lower limbs. She slept most of the day, covering her eyes from the daylight. Her intake of fluid and food were becoming very poor. Intrathecal streptomycin was stopped. Lumbar puncture now yielded a "dry tap" and cisternal puncture was done daily for relief of symptoms. As this spinal block developed it was noted that the tentorial block was disappearing. The cisternal pressure was high, there was a response to jugular compression and after removal of 20 ml. of C.S.F. the pressure had fallen considerably. The tubercle bacillus from the C.S.F. was now found to be resistant to streptomycin in a concentration of at least 10 ug./ml., and sensitive to 50 ug./ml. (at least 20 times more resistant than control culture H37/RV). During the next two or three weeks she steadily lost ground. Her general condition weakened and drowsiness deepened, passing at times into a light coma, and meningism increased. The temperature and pulse rate were increased. She developed a tremor of the hands together with picking and rolling movements of the fingers. The lower limbs were both spastic and there was bilateral ankle clonus. In the left fundus there was a true optic neuritis. On 19th July 1949 she went into a deep coma from which she could not be roused and on cisternal puncture the fluid was found to be at a pressure of 300 mm. water. She became weak and emaciated, both plantar responses/
responses became extensor in type and she developed spasmodic clonic movements of the upper limbs associated with a brief cry of distress and sometimes with incontinence of urine. The downhill course continued and ended with her death on 31st July 1949.

Summary. A case of a young girl admitted with miliary tuberculosis including choroidal tubercles. 11 weeks after admission, during which time she received daily intramuscular streptomycin, she developed tuberculous meningitis. The latter responded to intrathecal streptomycin poorly and the C.S.F. always remained abnormal. Subsequently she developed first a tentorial block then a spinal block and finally died from an acute meningitis and hydrocephalus. The total intramuscular dosage of streptomycin was 160 gm. and intrathecally 3.5 gm.
CASE No. 6.

C.B., a dairymaid of 17 years of age, first became unwell in the middle of December 1948 when she developed attacks of pain in the right loin, radiating downwards, and associated with frequency of micturition, but no dysuria. She was treated for pyelitis but the pain never disappeared. At the beginning of February 1949 she began to suffer from headaches and tiredness, with occasional nausea and vomiting, and a feeling of feverishness. On 7th February 1949 this girl was admitted to Edinburgh Royal Infirmary on account of a severe attack of pain in the right loin and frequency. Cystoscopic examination and retrograde pyelography were carried out and failed to reveal disease or abnormality. A few days later she developed headache, gradually became drowsy and showed signs of meningism. A lumbar puncture was performed which showed a C.S.F. pressure of 450 mm. water. The fluid was slightly cloudy and contained a cobweb clot after standing. The cell count was 500 per c.mm., and the predominant type - 85% - was lymphocytes. On the diagnosis of tuberculous meningitis being made, the patient was transferred to Southfield Sanatorium on 12th February 1949.

On admission to Southfield Sanatorium, she was obviously an ill girl. She was heavily built and her nutrition was good. The temperature was 102°F. /
102° F. but the pulse rate was only 58 per minute. She was drowsy and had some difficulty in keeping to the point while giving her history. There was no abnormality of the heart or lungs and the only positive abdominal finding was indefinite tenderness in the right loin. There was a trace of albumin in the urine. There was moderate neck rigidity and Kernig's sign was positive. There was no cranial nerve lesion but a bilateral nystagmus was observed. All the reflexes were present and equal though depressed. The plantar response was flexor. There was an early bilateral papilloedema and no choroidal tubercles were seen. On lumbar puncture opalescent fluid was obtained under a pressure of 300 mm. water; the total white cell count was 900 per c.mm., of which 90% were lymphocytes. The glucose level was 38 mg.%, chloride 662 mg.%, and protein 150 mg.%. The Mantoux test was strongly positive to a 1 in 10,000 dilution of old tuberculin.

**Bacteriology.** Culture of the C.S.F. on admission on Löwenstein-Jensen medium produced a very scanty growth of tubercle bacilli. The character of the growth and the period which the culture took to grow (10 weeks) suggested that the organism was of the bovine type. A rabbit was inoculated from this culture and died after 43 days from gross disseminated tuberculosis involving all organs and of miliary type. This confirmed the type of/
of organism which had the cultural characteristics of the bovine type. A guineapig inoculated from the C.S.F. on admission showed tuberculosis of glands and spleen. Subsequent cultures of C.S.F. during treatment all proved negative.

Treatment. Streptomycin treatment was commenced on the day of admission. Prior to 24th March 1949 sulphate streptomycin was used; thereafter the calcium chloride complex. The dose was 2 gm. daily. This was discontinued after 15 weeks on 28th May 1949 because the patient had vomited in the early morning before breakfast and shortly after bed-making on several occasions. It seemed likely that this was due to disturbed vestibular function. The total dosage was reduced to 1 gm. and recommenced on 4th February 1950. From 13th to 20th February it was omitted because of increasing nystagmus. On 27th May 1950 her condition was sufficiently satisfactory to justify cessation of intramuscular streptomycin. Over a period of 208 days this patient received a total of 264 gm. streptomycin.

Streptomycin was given intrathecally in intermittent courses as shown in the graph of this case. The total given on 199 days (i.e. on 96% of the days on which intramuscular injection was given) was 9.5 gm.

Para-aminosalicylic acid, 15 gm. daily, was commenced on 25th December 1949. After 1st February 1950/
1950 10 gm. only were given each day. The course was stopped on 30th May 1950.

**Progress.** Her condition rapidly grew worse. She was very restless the first night and became so violent that sedation was necessary. The following day she became semi-comatose and did not respond to questioning and was incontinent of urine. The meningism and papilloedema had increased, and photophobia appeared. The plantar responses became extensor in type; the abdominal reflexes were now absent while the other limb reflexes were difficult to elicit. She was very constipated. The C.S.F. pressure was over 300 mm. water and she was now lumbar-punctured twice daily in order to reduce the intracranial pressure. 3 days later, on 16th February 1949, her condition began to improve. She regained full consciousness, spoke rationally and was no longer incontinent of urine. She was still drowsy but had no headache and the signs of meningism became less marked. Her improvement on the 17th was such that the second lumbar puncture each day was abandoned and on the 22nd she was bright and alert and all evidence of meningism had disappeared and the C.S.F. pressure fell to 210 mm. The papilloedema was still quite marked. The temperature had now fallen below 100°F. and the bradycardia was replaced by tachycardia.

The lungs were X-rayed for the first time in March.
March 1949. There were big glandular shadows in the lung roots, particularly on the left side. There was no evidence of disease of the lung substance. By the beginning of April she had made further progress and the only positive neurological signs were sluggish knee and ankle jerks and a slight degree of papilloedema. The C.S.F. remained grossly abnormal in all respects. On 24th April 1949 she developed a macular rash on trunk and arms of 24 hours' duration only. A month later nystagmus was noticeable and for a week she vomited each morning after she had been moved for bed-making. As this indicated vestibular disturbance, the first course of intramuscular streptomycin was discontinued, and the nausea and vomiting ceased.

At the beginning of July 1949 she continued to be very well and was bright mentally. The temperature range was between 98°F and 99.5°F. The only abnormal finding in the nervous system was horizontal nystagmus. The papilloedema had now disappeared though there was still the remains of engorgement of the retinal vessels. There was little improvement in the C.S.F. At the end of August 1949 she developed a swelling in the upper part of the right side of the neck. This was a hard tonsillar gland with one or two small glands at its lower pole. The fauces were red but there was no tonsillar enlargement. A gradual improvement in the C.S.F./
C.S.F. was now becoming apparent.

During September 1949 the swelling in the upper part of the right side of the neck had increased and became large, hard, and slightly tender. It extended back under the sterno-mastoid muscle to the region of the mastoid process. There was a small area of superficial softening. On the 19th of the next month 30 ml. of thick pus were aspirated from the neck abscess, which seemed to empty the abscess cavity and a hard underlying glandular mass could be felt. Smears from the pus showed a few acid-fast bacilli but culture and guinea-pig inoculation were negative. Aspiration was carried out on two further occasions, but there was progressive involvement of the skin which finally broke down. In October 1949 an incision was made over the central area of involvement and caseous plugs evacuated. The glandular mass was obviously breaking down and continued to discharge for a long time. There were no other features now apart from the persistence of the nystagmus and the ophthalmologist considered that this might be of little significance as nystagmus-like movements can be induced in normal eyes on extreme eversion. There was further but slow improvement in the C.S.F.

It was on 22nd November 1949 that she again complained of headache. The temperature was not elevated but a slight degree of neck rigidity was present.
The C.S.F. cells showed a sudden rise from 80 per c.mm. on the 21st to 892 per c.mm., of which only 64% were lymphocytes. This episode settled in a few days and by the 9th December the C.S.F. cells had returned to their original level. She was now becoming very fat and her weight was rapidly increasing. There were red lineae distensae on the breasts, arms, hips and abdomen.

During the first 3 months of 1950 the temperature gradually fell to normal and she was without neurological signs apart from nystagmus. The C.S.F. was showing great improvement. On 19th April 1950 a second gland on the right side of the neck was incised and a small amount of tuberculous pus obtained from which the tubercle bacillus was not isolated. At the end of May 1950 she remained without symptoms and all streptomycin was stopped. Calciferol, 50,000 units daily, was commenced on 30th May for the glandular disease of the neck, the sinus of which had now dried up. During the month of June she was allowed up for the first time for toilet purposes and at the end of the month she was allowed to go for short walks.

The patient was discharged home on 23rd August 1950. At that time the sinus on the right side of the neck was healed and there was no evidence of adenitis. Her weight was over 15 stones. The B.S.R. was 10 mm. in the first hour (Westergren).
There were no abnormal signs in the nervous system, though a fine nystagmus was still present. There was no tinnitus, no giddiness or unsteadiness of gait and no deafness.

The patient was seen again in February 1951. The general condition was good and she was without symptoms. The weight was now 14 stones. There were no abnormal physical signs in the central nervous system. The nystagmus had disappeared and there was no ataxia. The hearing was normal. The C.S.F. was clear and colourless, under a pressure of 190 mm. water. The cells numbered 9 per c.mm., the protein 40 mg.%, glucose 70 mg.% and chloride 730 mg.%

**Summary.** A girl of 17 years of age, suffering from tuberculous meningitis in an intermediate stage, who made a slow response to treatment over a period of 15 months. The bovine type of tubercle bacillus was isolated. The amount of streptomycin given was 264 mg. intramuscularly and 9.5 gm. intrathecally. Two years after the diagnosis was made, she had made a complete clinical recovery, though the C.S.F. had not yet returned to normality. Tuberculous cervical adenitis complicated the course but resolved satisfactorily.
CASE No. 7.

M.K., a girl of 3 years and 2 months, became ill on 17th February 1949 when her mother noticed she was drowsy and off her food. She later became feverish, constipated, vomited once and complained of headache. She was restless and irritable. On 22nd February this girl was admitted to the Royal Hospital for Sick Children, Edinburgh, as a case of tuberculous meningitis. There was no family history of tuberculosis and no history of contact with a case.

On 26th February 1949 this girl was admitted to Southfield Sanatorium. She was an ill girl with a temperature of 101°F., fairly well nourished, who lay curled up in bed and had photophobia. She resented interference and was very drowsy although completely conscious. There was moderate neck rigidity and a positive Kernig's sign. All reflexes were present, equal, but difficult to elicit. No abnormality was made out on clinical examination of the lungs and radiologically there was no conclusive evidence of miliary lung disease but the prominent lung detail may have represented an early stage of that condition. There was no abnormality of heart or abdomen. The Mantoux test was positive to 1 in 10,000 dilution of old tuberculin. Lumbar puncture revealed a clear fluid under a pressure of 115 mm. water and containing 130 white cells per/
per c.mm. of which 90% were lymphocytes.

Bacteriology. Tubercle bacilli were found on direct smear examination of the C.S.F. on 23rd February at the Royal Hospital for Sick Children. A positive culture of the human type of tubercle bacillus was produced from the C.S.F. obtained on admission to Southfield Sanatorium and guinea-pig inoculation also gave a positive result. The organism obtained from culture was sensitive to streptomycin in a concentration of 0.25 microgrammes per ml. (i.e. same sensitivity as control organism H37 RV). Cultures during the period of treatment were negative.

Treatment. Intramuscular and intrathecal streptomycin treatment was continued on her admission to Southfield Sanatorium. The daily dose of intramuscular streptomycin sulphate given was 0.5 gm. The first course lasted from 26th February until 26th April 1949. A second course was started on 6th June 1949 and was discontinued on the 18th of that month as it was felt streptomycin was aggravating her already hopeless condition. The total amount of streptomycin given by the intramuscular route on 75 days was 37.5 gm. Prior to the 24th March 1949 streptomycin sulphate was used and thereafter the calcium complex was used. Intrathecal injection of streptomycin sulphate in a dose of 50 mg., was also commenced on 26th February. It was stopped on 24th March/
March for a week because of the failure of supply of the sulphate salt and resumed on 31st March using the calcium chloride complex. It was then given for a further 26 injections, being stopped on 26th May 1949. A third short course was started on 7th June but discontinued on the 18th because of the hopeless deterioration of her condition. The total amount of intrathecal streptomycin given on 65 days (i.e. on 87% of the days on which intramuscular streptomycin was given) was 3 gm.

**Progress.** At the end of March 1949, 5 weeks after admission, her general condition was much the same as on admission and she remained fevered. She was still drowsy, neck rigidity was less, Kernig's test was now negative but she had developed a slight degree of papilloedema. The C.S.F. showed little change. On three occasions during the month of March when the fluid was examined, it was stated to have been "contaminated" with red blood cells although there was no evidence that a traumatic puncture had been performed. There was a further fall in the glucose level to 36 mg.%, and the chloride level was still below 700 mg.%

On 3rd April 1949 she could only be roused with difficulty to take food. There was frequent incontinence of urine and occasional incontinence of faeces. Periodically there were clonic movements of the jaw, left hand and left leg, accompanied by a/
a distressing cry. On the 8th, Kernig's sign returned again and the musculature of the lower limbs was now hypertonic. Photophobia was marked. Bilateral Babinski responses were first obtained on 15th April, and the temperature was becoming more elevated and irregular. At the end of the same month headaches were troublesome again and it was noted that on lumbar puncture the fluid came away under considerable pressure and after removal of only 1 - 2 ml. fell away to a very slow and low pressure flow, suggestive of a partial block. Queckenstedt's test gave a rise of pressure but no fall occurred on releasing jugular compression. Cisternal puncture was carried out and the C.S.F. flowed in a similar manner which showed the block to be higher than spinal. On 26th April the child developed a spastic paresis of the right upper limb which was held in the position of flexion. Head retraction had become marked. The lower limbs, while not paretic, were in full extension and resistant to passive movement. Kernig's sign was markedly positive. There was now a left facial weakness and trismus was present. The pupils were unequal and papilloedema marked. Streptomycin was now discontinued because of this development of monoplegia and partial block at a level above the cisterna magna. On 2nd May 1949 the spinal block resolved and the Queckenstedt test was positive again but she continued to complain.
complain of severe headaches. There was no clinical or C.S.F. improvement by 12th May and on that date bilateral ankle clonus developed. By now she was very fretful and would grind her teeth constantly. Lumbar puncture was being performed twice daily since the beginning of this month, as it relieved her headache and made her less irritable. From time to time she would throw her head violently from side to side. There were signs that she was losing weight and it was becoming more difficult to get her to take fluids and solids. She was distressed and restless especially at night and required syrup of chloral for sedation.

Because of the unsatisfactory nature of her condition, streptomycin was resumed on 6th June 1949. The neurological and C.S.F. findings were unchanged, only a slight fluctuation for improvement or deterioration being noted week by week. Her general condition remained unaltered and the temperature always ranged between 101°F. and 102°F. Again on the 15th a partial spinal block was suggested by the absence of response to jugular compression, the C.S.F. showing xanthochromia and a fine turbidity. On 17th June opisthotonus appeared and, in addition to the spasticity of the right arm and leg, she also had spasticity but no paresis of the left arm and leg. Streptomycin was again stopped and a temporary clinical improvement occurred for a few days.

On/
On 21st June she had a mild convulsion in which there was marked head retraction, opisthotonous, respiratory embarrassment and restlessness. It lasted for half an hour. On the 22nd the child was periodically thrown into the opisthotonic position by spasms of hyperextension of head and trunk. Lumbar puncture produced very little C.S.F. and on cisternal puncture the flow of C.S.F. stopped after 3 ml. had been withdrawn and no C.S.F. was obtained at all when it was repeated in the evening. This proved that the block, which previously was partial and above the level of the cisterna magna, was this time complete. Signs of a progressive hydrocephalus followed, the temperature rose to over 106°F. on the 26th and the patient died on the morning of 27th June.

**Summary.** A young girl, admitted with symptoms and signs of tuberculous meningitis. The human type of tubercle bacillus was isolated from the C.S.F. She never showed any definite signs of clinical improvement with treatment. She developed a paresis of the right arm and spasticity of the other limbs. She died 4 months after admission with signs of a progressive hydrocephalus. The total amount of intramuscular streptomycin given was 57.5 gm. and the intrathecal amount was 3 gm. Permission for postmortem was refused.
CASE No. 8.

A.S., a girl of 2½ years, was first noted by her parents to be in poor health about the second week of January 1949. She went off her food and was miserable and irritable. She was not sleeping well and was frequently feverish at night. Purgatives were required for increasing constipation. Towards the end of the month the child had lain in bed taking very little interest though she recognised her parents. She now vomited at least once daily and complained of severe headache above the eyes. This girl had never been in contact with a case of tuberculosis as far as was known but both paternal grandparents died of tuberculosis, though they were never in contact with the patient.

This girl was admitted to the Royal Hospital for Sick Children, Edinburgh on the 1st March 1949 and transferred to Southfield Sanatorium the following day. She was an ill child lying curled up and obviously photophobie. She was drowsy but conscious and responded to simple questions. She had a temperature of 101.8°F. and the pulse rate was 120 per minute. There was marked neck rigidity and Kernig's test was positive. The reflexes were all present but diminished and there was a flexor plantar response. There were no cranial nerve lesions but there was moderate bilateral papilloedema. No choroidal tubercles were seen. There was no abnormality/
abnormality of heart, lungs or abdomen. Radiologically there was a large glandular mass in the right lung root but no evidence of disease of the lung substance. The Mantoux test was strongly positive to a 1 in 10,000 dilution of old tuberculin. On lumbar puncture the C.S.F. was a clear fluid under a pressure of 250 mm. water, containing 190 cells per c.mm., of which 85% were lymphocytes. The glucose level was 47 mg.%, and chloride 725 mg.%

**Bacteriology.** Tubercle bacilli were found on direct smear from the C.S.F. obtained on admission to the Royal Hospital for Sick Children on 1st March 1949, and a growth of human type tubercle bacilli was obtained on culture after 3 weeks. Before being transferred to Southfield on 2nd March she had received one 50 mg. intrathecal injection of streptomycin and direct smear on that date was negative as was culture on Löwenstein-Jensen medium and guinea-pig inoculation. Subsequent cultures of C.S.F. were also negative.

**Treatment.** Streptomycin was commenced on the day of admission in a dose of 0.5 gm. daily. Prior to 31st March 1949 the sulphate salt was used; thereafter the calcium chloride complex. The first intramuscular course was discontinued after 56 days on 27th April 1949 because of frequent vomiting and listlessness. It was resumed on 5th May for a further 66 days in the same dosage but stopped on 19th/
19th July 1949 because of the development of a coarse nystagmus. The total amount given by the intramuscular route on 122 days was 61 gm.

Intrathecal therapy in a dose of 50 mg. was commenced on 2nd March 1949. It was given continuously for 22 days, and discontinued for one week before commencing with the calcium chloride complex on 31st March 1949. It was then given for a further 27 days until 27th April 1949. During June, July and August she received a once-weekly boosting dose of 50 mg. The total dosage given on a total of 63 days (i.e. on 50% of the days on which intramuscular treatment was given) was 3 gm.

**Progress.** By 14th March 1949 there was definite clinical improvement, but deterioration in the C.S.F. The temperature was slowly falling and she could now sit up in her cot and cry in a loud voice. She remained irritable but not drowsy. There was no neck rigidity, Kernig's or other neurological sign. She was eating and taking fluids remarkably well. At the beginning of April 1949 she was very well clinically and without neurological signs but the ominous feature was the progressive fall of the C.S.F. glucose level from 47 mg.% to 38 mg.%

Things were going very well until 27th April 1949 when she again developed headache and vomited on several occasions and she was now less bright. On this account streptomycin was stopped for a/
a few days' rest period. From this upset she recovered in a few days. The papilloedema had now disappeared. The condition of the C.S.F. remained unsatisfactory.

At the beginning of May 1949 the temperature, which had been gradually falling, was now ranging between 98° and 99.8°F. There were no symptoms but there was little improvement in the C.S.F., and intramuscular streptomycin combined with a once-weekly intrathecal injection was resumed.

At the end of June 1949 improvement was noted in the C.S.F. and she was now almost afebrile. The ophthalmologist saw her for the first time and reported that there was slight optic atrophy in both discs and that the prognosis for vision depended on which fibres were involved. There was also a right concomitant convergent strabismus for which he ordered spectacles. During the middle of the following month she developed a marked horizontal nystagmus and occasional vomiting; on account of this vestibular disturbance the second intramuscular course of streptomycin was stopped. During August and September 1949 there was nothing abnormal to note clinically and the C.S.F. was fast approaching normality. By December 1949 she was allowed up in the ward and on 11th February 1950 she was discharged home. At this time the C.S.F. showed that neither the cells nor the protein content had returned to normal/
normal - the former level was 7 per c.mm. and the latter 62 mg.%

Follow-up. This girl was seen again on 12th July 1950. There were no symptoms and she was in good health. No abnormality was detected on physical examination. Lumbar puncture was carried out and clear C.S.F. obtained. The white cell count was 3 per c.mm. Owing to illness of the laboratory technician at Southfield Sanatorium, the biochemical examination was carried out at another laboratory and the results are therefore not comparable with the figures on discharge.

On 30th November 1950 she was again seen by the ophthalmologist who confirmed the presence of a slight degree of bilateral optic atrophy but found that visual field examination was impossible. This patient was last seen in July 1951. There were no abnormal physical signs, no ataxia and no impairment of hearing. The C.S.F. examination was as follows:- cells 1 per c.mm., glucose 68 mg.%, chloride 73½ mg.% and protein 50 mg.%

Summary. A case of tuberculous meningitis in a young girl, of intermediate severity, due to the human type of tubercle bacillus. The clinical response to streptomycin was rapid and complete and within four weeks all clinical evidence of meningitis had disappeared. However, as usual, the C.S.F. improvement lagged far behind and even at the time of/
of discharge, 11 months after the start of treatment, it had still not returned to normality. The total intramuscular dosage of streptomycin was 61 gm. and that given intrathecally amounted to 3 gm. When last seen 17 months after her discharge home, she was in excellent condition and the C.S.F. was normal apart from slight elevation of the protein content. She is starting school next session.
CASE No. 9.

M.A., a married woman of 28 years of age, had a positive Mass Radiography finding in December 1948. The X-ray film showed clusters of discrete shadows of a blood-borne character in both lungs. She was at this time 5 months pregnant. On 30th April 1949 she became ill and fevered and was admitted to the Royal Infirmary, Edinburgh. She was thought to have miliary tuberculosis of the lungs. There was also slight neck rigidity and a lumbar puncture on 3rd May 1949 showed findings suggestive of tuberculous meningitis. Tubercle bacilli were isolated from the C.S.F. Streptomycin, by intramuscular injection of 2 gm. daily, was now commenced. On 17th May 1949 she gave birth to a live, apparently normal child. She had stood labour comparatively well but during the following 48 hours her condition became very serious. She was therefore transferred to Southfield Sanatorium on 26th May 1949.

On the latter date she was found to be lethargic and drowsy, but could be roused to answer questions intelligently. The temperature was 100°F. She was very emaciated and weak. The only abnormality found in the lungs was diffuse crepitations. There was marked neck rigidity and a positive Kernig's sign. The superficial and deep reflexes were present and equal. The Babinski sign was present on the left side. The cranial nerves were intact. Lumbar puncture/
puncture was carried out and xanthochromic fluid was obtained under a pressure of 150 mm. of water. The response to the Queckenstedt test was poor. The C.S.F. contained 68 cells per c.mm., all of which were lymphocytes. The protein content was 400 mg.%, the glucose content 37 mg.% and the chloride 667 mg.%. The B.S.R. (Westergren) was 25 mm. in the first hour and the Mantoux test was positive to a 1 in 10,000 dilution of old tuberculin.

**Bacteriology.** Tubercle bacilli of the human type were isolated from the C.S.F. after 4 weeks' growth on Löwenstein-Jensen medium and extensive tuberculosis was found following guinea-pig inoculation.

**Treatment.** The calcium chloride complex of streptomycin was used. Prior to admission to Southfield Sanatorium this patient had received 44 gm. of intramuscular streptomycin. On 26th May 1949 it was continued, in a dose of 2 gm. daily, for a month and at the beginning of July 1949 a further 4 days' treatment was given. The total amount of streptomycin given on a total of 56 days was thus 112 gm.

Between 26th May and 7th July 1949 a total of 3\(\frac{1}{4}\) intrathecal injections of 50 mg. each were given. The total amount of intrathecal streptomycin given on a total of 3\(\frac{1}{4}\) days (i.e. on 60% of the days on which intramuscular streptomycin was given) was 2/
Para-aminosalicylic acid was commenced on 15th June in a dose of 15 gm. daily and was given continuously until 4th July 1949. The patient could no longer swallow it.

Progress. There was little change in her condition during the last few days of May 1949. On lumbar puncture the response to jugular compression was either very poor or absent, indicating a partial spinal block.

At the beginning of June 1949 she remained weak and easily exhausted. She had become more drowsy and there were now bilateral extensor plantar responses. It was difficult to maintain an adequate fluid intake as she complained of difficulty of swallowing and the fluid intake was supplemented by a rectal drip. By the middle of the month she had made no progress. A bilateral horizontal nystagmus was now present. On 16th June and on other days a cisternal and a lumbar puncture were done on the same day and in both situations the initial pressure was low, little response was obtained to jugular compression and the pressure fell away sharply after very little fluid had been withdrawn. There was such a slight difference in the character of the two fluids that it seemed more probable that the partial block was above the level of the cisterna magna than spinal. In both, the cellular and biochemical constituents/
constituents remained abnormal. There was no papilloedema. At the end of the month there was no improvement in her general condition, signs of meningism were more marked; there was still evidence of a supra-cisternal block and the C.S.F. showed no improvement. The temperature remained below the level of 100°F.

At the beginning of July 1949 she became semi-comatose. She developed a right facial palsy and spasticity of the left arm and leg, and later a spastic monoplegia of the left arm. Later in the month she became weaker with increased signs of meningism and became more comatose. Signs of respiratory embarrassment appeared and she died on 26th July 1949.

**Autopsy.** The convolutions of both cerebral hemispheres showed flattening with some slight congestion. At the base of the brain in relation to the optic chiasma, there was definite tuberculous granulation tissue. This enveloped both optic nerves and the chiasma. The meninges at the base were thickened and pin-point tubercles were seen, and these extended into both the lateral fissures. Coronal sections revealed marked dilatation of the lateral and third ventricles. The ependymal lining was considerably swollen and in practically every part there was an eruption of innumerable small pin-point tubercles. No evidence of a Rich focus was found.
The aqueduct and fourth ventricle were also considerably dilated.

Microscopically the picture was that of a very cellular tuberculous exudate in the subarachnoid space. Many small areas of caseation were found, and more especially in the section from the medulla a marked degree of fibrosis was occurring. The meningeal vessels were congested, showed perivascular cuffing with round cells and often a striking fibrous periarteritis and endarteritis. Extension of the caseating process had taken place in many instances a short way into the adjacent nervous tissue, which was, besides congested, oedematous and showed perivascular cuffing with round cells and an early gliosis. A section from the sylvian fissure showed similar changes but in addition there were small areas of softening in the underlying cortex, presumably the result of vascular occlusion. In these there was loss of cellular architecture, necrosis and heavy infiltrations of cerebral histiocytes. The ependyma had, in many parts, vanished and the wall of the ventricle was now lined by subependymal white matter showing a reactive gliosis.

**Summary.** A woman of 28 years of age, diagnosed at the fifth month of pregnancy as having bilateral pulmonary tuberculosis. Five months later she developed meningitis and radiologically was thought/
thought to have miliary tuberculosis. Her condition worsened after the birth of a normal child 2 weeks later. She died after 2 months of treatment to which she showed no response. The total amount of intramuscular streptomycin was 112 gm. and the intrathecal amount was 2 gm. The postmortem findings were those of chronic tuberculous meningitis and subacute pulmonary tuberculosis without evidence of miliary disease.
CASE No. 10.

N.F., aged 7 years, was admitted to the City Fever Hospital, Edinburgh on 11th July 1949. This girl had complained of a sore throat, backache, some headache and stiffness of the legs two days previously and she was admitted for observation as a possible case of poliomyelitis. By 16th July 1949 a diagnosis of tuberculous meningitis was made by clinical signs and C.S.F. examination and she was transferred to Southfield Sanatorium. Further questioning elicited the fact that the girl and her sister lived in overcrowded conditions at home and shared the same bed. Over a period of 3 years, a 22-year old girl, a case of open pulmonary tuberculosis, first diagnosed in September 1949, visited them at the weekends and shared the same bed as this patient and her sister. (The latter was also admitted to this sanatorium in January 1950 as a case of tuberculous meningitis. Case no. 17) The patient had been under observation for the past year following a primary tuberculous pleurisy, and it is also stated that she was thought to have had erythema nodosum 2 months before this present illness began.

On admission to Southfield Sanatorium on 16th July 1949 she was irritable and drowsy and lay curled up resenting any interference. She showed slight photophobia. There had been fairly frequent vomiting and she was very constipated. She was thin/
thin, flushed and ill-looking. She could be roused sufficiently to answer questions intelligently.

Examination of the central nervous system showed definite neck rigidity and a slight degree of bilateral Kernig's sign. The pupils were equal, there was no external ophthalmoplegia and no choroidal tubercles were seen. Cranial nerves were intact. There was no spasticity of limbs and the reflexes were brisk but equal. The plantar responses were flexor in type.

The Mantoux test with 0.1 ml. of 1 in 10,000 old tuberculin gave a positive result of 10 mm. Lumbar puncture was carried out the next day. After 2 ml. of xanthochromic fluid had been withdrawn the flow stopped altogether. The flow was unaffected by jugular compression. The fluid contained 310 cells per cubic millimetre, the majority of which were lymphocytes, with a protein content of 450 mg.% glucose 39 mg.%, and chloride 596 mg.%. A spinal block was thus found to be present.

**Bacteriology.** The tubercle bacillus was not isolated after several cultures of C.S.F. on Löwenstein-Jensen medium or by inoculation of a guinea-pig.

**Treatment.** Streptomycin was given intramuscularly in intermittent courses for a total of 101 days during the period of treatment which lasted for 25 weeks from 16th July 1949 to 6th January 1950.
1950. The total amount of streptomycin given by this route was 135 gm. The scheme of intramuscular dosage was rather irregular and of a shorter total duration than desirable on account of the reaction of the patient to the injections. In the first course from 16th July to 18th August 1949 the calcium chloride complex was used by intramuscular injection into the gluteal region; the patient found the injection of this salt extremely painful and the legs became stiff and painful though no nodules formed at the site of injection. A small supply of dihydrostreptomycin sulphate was obtained on 11th August 1949 and these injections resulted in less discomfort. The dosage during this first period was 2 gm. daily. On 29th August a second course was started using 1 gm. daily of the dihydrostreptomycin. Our supply of this salt was finished on 3rd September 1949, so a return was made to the calcium chloride complex. However this second course had to be terminated on 10th September 1949 as her hips and back became extremely painful. It was noted that she was an extremely unstable type of girl and this had much to do with her reaction to the injections. A third course of 1 gm. of the calcium chloride complex lasted from 21st September to 2nd October but again had to be prematurely terminated on account of severe local pain. A further supply of dihydrostreptomycin was obtained and a fourth course of/
of 1 gm. daily was given with much less discomfort from 26th November 1949 until 6th January 1950 when all treatment was stopped.

The administration of streptomycin by the intrathecal route also presented difficulties as the patient was most unco-operative and complained of a great deal of discomfort. Since an obstruction to the flow of the cerebrospinal fluid was found at the original lumbar puncture, the cisternal route was used for the injection of intrathecal streptomycin. On all days on which it was given intrathecally the dose was 50 mg. of the calcium chloride complex. On 19th July 1949 administration of this dose was commenced by daily cisternal puncture because of the spinal block found at the initial lumbar puncture. By 25th July jugular compression revealed that the spinal block had opened up and the lumbar route for therapy was now used. But only 2 days later the block re-appeared and for the next 8 days the cisternal route was used again. With the final clearing of the spinal block on 4th August 1949 the lumbar route was thereafter used. Intrathecal streptomycin was given on 95 days (i.e. on 94% of the days on which intramuscular treatment was given), the total being 4.5 gm. The amount given does not conform to any definite scheme because on some days lumbar puncture was impossible. Some days she became quite hysterical and could not keep her back still, rotating it and flexing it from side/
side to side while at other times she would complain of severe pain of root distribution. She was repeatedly sedated for this procedure, requiring as much as 1 gr. phenobarbitone and 3 gr. sodium amytal.

Para-aminosalicylic acid, 5 gm. daily, was commenced on 30th November 1949; the dosage being gradually increased until 10 gm. daily were being taken by 14th December 1949. It was discontinued at the end of February 1950.

Progress. During the first few days of treatment there was considerable headache associated with nausea and vomiting. The cisternal injections, given because of the presence of a spinal block, caused acute pain in the occipital region at the time of the injection. At the same time a gradual weakness in the motor power of the left leg appeared but there was no alteration in the state of the reflexes. Signs of meningism and irritability continued unabated. The intramuscular injections of streptomycin had caused acute tenderness of the buttocks at the site of injection but without the formation of nodules, and movement of the hip joints resulted in considerable pain. The temperature continued to swing between 100° and 102°F. On 25th July 1949 a slow flow of C.S.F. was obtained by the lumbar route and the fluid was xanthochromic. Jugular compression showed the flow to be a free one but this result was reversed two days/
days later and a resort was made to the cisternal route for the administration of the intrathecal streptomycin. Though her clinical condition remained unaltered, a considerable clearing of the spinal block had occurred, and on 4th August 1949 a good flow of clear fluid was obtained. No further spinal blockage occurred during the course of her treatment and subsequently the lumbar route could be used for treatment.

On 8th August 1949 improvement in her condition had occurred after 3 weeks' treatment. She was bright and communicative and the signs of meningitis were minimal—slight neck rigidity and positivity of Kernig's sign on the right side. There were no cranial nerve palsies and the left lower limb was now functioning normally. The C.S.F. however showed little improvement apart from a reduction in the number of the white cells. The temperature was running at a lower level although the child was still fevered. Headache was only slight and occasional. This improvement was not maintained and on 18th August 1949 she developed signs of acute hydrocephalus with marked head retraction and neck rigidity, a marked bilateral Kernig's sign and some degree of opisthotonus. There was headache and vomiting. However by 23rd August her condition had returned to the state where it was on 8th August and there was now an improvement in both/
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<td>Intramuscular Streptomycin</td>
<td>2 Gms</td>
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<td>50 mg. 25-25-50 mg. 50 mg. 50-20-50 mg. 50-</td>
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<th>C.S.F. Pressure (mm H2O)</th>
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<td>Intrathecal Cisternal</td>
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both cellular and biochemical constituents of the C.S.F.

By the end of September 1949 all symptoms and signs of meningitis had gone but the C.S.F. was still abnormal in all its respects. On 6th January 1950 nystagmus, to left and right, was noted and all treatment ceased. Her recovery was continuing and she was without any clinical feature of meningitis but the C.S.F. remained abnormal though the cell count and the protein level were falling and the glucose and chloride levels were rising. The first X-ray of the chest was taken at this time and showed broadening of the upper mediastinal shadow due to glandular enlargement, and an area of lung collapse in the apex of the lower lobe on the right side. A film in June 1950 showed this area of collapse to have re-expanded.

By June 1950 she had made a complete clinical recovery and the C.S.F. had almost reached the state of normality. She was being allowed up for short periods each day and she put on several pounds in weight during convalescence. Her behaviour was that of a normal child. There were no residual changes in the central nervous system apart from the following observations: -

(1) There was a slight but definite nystagmus to left and right. Optic fundi were normal.

(2) Since November 1949 a slight degree of bilateral nerve/
nerve deafness had become manifest as a result of the streptomycin therapy. By August 1950 she was only just able to hear the whispered voice in the left ear, while in the right only a conversational voice could be heard.

In August 1950 the patient was transferred to Loanhead Children's Hospital for convalescence. She returned to Southfield Sanatorium on 23rd October 1950 for re-assessment. She was extremely well and the nystagmus and nerve deafness noted above had persisted. Examination of the cerebrospinal fluid was as follows:— cells 9 per c.mm., protein 70 mg.% glucose 68 mg.%, chloride 740 mg.%. When last seen in June 1951 she was looking extremely well. The nystagmus still persisted. There was no ataxia, but she was found to sway slightly when walking along a straight line. The state of hearing was virtually unaltered. There was no other after-effect of the disease. The cerebrospinal fluid examination was as follows:— cells 4 per c.mm., protein 60 mg.%, glucose 6½ mg.%, chloride 736 mg.%

The girl is now living an ordinary life at home but is prevented from attending normal school by her hearing impairment.

Summary. The case of a girl of 8½ years suffering from tuberculous meningitis in an intermediate stage. A history of repeated contact with a case of open pulmonary tuberculosis was given but the tubercle/
tubercle bacillus was never isolated from the C.S.F. of this case. The total amount of systemic streptomycin given was 135 gm., and the intrathecal amount was 4.5 gm. Recovery has been complete, though the C.S.F. has not yet completely returned to normal. Slight impairment of hearing prevents her attendance at a normal school.
CASE No. 11.

A.L., a girl of 8½ years, was admitted to the sanatorium on 19th July 1949. Her history began at the age of 2 years when she developed tuberculosis of the upper dorsal region of the spine. At the age of 7 years the spinal condition was regarded as inactive and immobilization was discontinued. A follow-up examination was carried out every three months and in June 1949 the X-ray examination of the affected region was satisfactory. During the summer of 1949 she attended school for the first time. A week prior to admission she became unwell with headache, drowsiness, irritability and periodic vomiting. She was admitted to the Royal Infirmary, Edinburgh on 17th July 1949. A diagnosis of tuberculosis meningitis was made. X-ray examination showed healing Pott's disease in the upper dorsal spine; there were calcified masses in both lung roots but no evidence of pulmonary tuberculosis.

On admission to Southfield Sanatorium the child looked ill and was extremely irritable and drowsy. The temperature was 100.5°F. and the pulse rate 60 per minute. She was resentful of examination and exhibited photophobia. Her nutrition and development were fairly good. There was a small knuckle gibbus over the second dorsal spine. She showed a moderate degree of neck rigidity and a positive Kernig's sign. The pupils were equal and reacted/
reacted to light and there was no external ophthalmoplegia. A right lower facial weakness was present. There was no spasticity of the limbs and the reflexes were present and equal. The plantar response was equivocal. The optic discs were normal and no choroidal tubercles were seen.

On lumbar puncture the C.S.F. was clear and contained 50 cells per c.mm., all of which were lymphocytes. Protein was 40 mg.%, glucose 76 mg.%, and chloride 662 mg.%. The B.S.R. was 23 mm. in the first hour. The Mantoux test was positive to a 1 in 10,000 dilution old tuberculin.

Bacteriology. Tubercle bacilli were not obtained from the C.S.F. on admission either by guinea-pig inoculation or by culture on Löwenstein-Jensen medium. A sparse growth of tubercle bacilli was obtained for the first time, and the only time, from C.S.F. obtained on 22nd April 1950. The growth had the characteristics of a human type.

Treatment. Streptomycin, intramuscularly, was given in the form of the calcium chloride complex. The graph of this case shows that a total of 195.5 gm. was given for a total of 169 days during the period of treatment which lasted for 38 weeks from 20th July 1949 to 12th April 1950. During the first five weeks the daily dose was 2 gm.; during the remainder of the period it was 1 gm. with the exception of the last course when it was 0.5 gm. daily.
daily. The intermittency of the intramuscular dosage was necessitated by signs of probable toxicity and by the need to institute short rest periods.

Streptomycin was also given intrathecally; it was given by the lumbar route, but on the first five days spinal block necessitated the use of the cisternal route. The accompanying graph shows that 50 mg. (25 mg. only during the last course) daily were given for 131 days (i.e. on 78% of the days on which intramuscular treatment was given) during the 38-week period of treatment, the total amount being 6.5 gm.

During the period 30th November 1949 to 10th February 1950 para-aminosalicylic acid - 7.5 gm. daily - was given.

**Progress.** Treatment was started the day after admission on 20th July 1949. However, administration of the intrathecal streptomycin by the lumbar route was not possible since there was evidence of a partial spinal block. For the first five days the cisternal route was used for this purpose. The block in the flow of the cerebrospinal fluid within the spinal meninges persisted for five days. On the 6th day a flow of cerebrospinal fluid by lumbar puncture indicated that the spinal block had been transitory. During the remainder of the course of treatment the lumbar route was always used.

During the first five days her condition quickly/
quickly deteriorated. She became more drowsy and irritable and more photophobic. Marked retraction of the head developed with spinal spasm and opisthotonos and complete extensor spasm of the legs with an extensor plantar response on the right side.

By 8th August 1949 an obvious improvement occurred. She was now bright and alert and took an interest in her surroundings. The temperature ranged about 99°F. The signs of meningism were less though there was still a definite degree of neck rigidity and spasm of the hamstring muscles. The right facial weakness was still present but the spasm of the spine and the extensor spasm of the legs had disappeared. In the period so far considered there had been little alteration in the cellular and biochemical contents of the cerebrospinal fluid.

On 23rd August horizontal nystagmus was noted for the first time, and all streptomycin was stopped for one week. Then occurred an attack of acute tonsillitis which was treated with sulphonamide and which lasted for five days. From a throat swab streptococcus viridans was isolated.

At the beginning of September 1949 the signs of meningism were minimal. The legs were no longer spastic, the reflexes were normal, and the plantar responses flexor. The right facial weakness persisted. The cerebrospinal fluid however showed no improvement so far.

During/
During October and November 1949 there was little to note either way in her condition. By the middle of December 1949 there were no symptoms, she was behaving like a normal child and there were no physical signs whatsoever, and a slow improvement in the cerebrospinal fluid was occurring. The improvement was so encouraging that intrathecal streptomycin was discontinued on 3rd January 1950 and intramuscular streptomycin on 3rd February.

Towards the end of February 1950 she complained of pain on movement in the lower cervical and upper dorsal region of the spine. The spinous processes were tender on pressure, most marked over the gibbus in the upper thoracic region. The reflexes of the limbs were normal. Since the features were suggestive of re-activation of the spinal lesion she was placed in a spinal plaster shell. In the middle of March 1950 a slow deterioration in her condition was noticed. The first symptoms in the subsequent downhill course were obstinate constipation and frequent vomiting; she retained very little food. Later she became slightly drowsy and the temperature began to rise again to 100°F. or thereabouts. Slight neck rigidity and hamstring spasm became manifest again. The fluid loss became so severe that it was necessary to give fluids per rectum. A fall in the glucose and chloride level of the cerebrospinal fluid was commencing/
WEEK BEGINNING:  

INTRAMUSCULAR  

STREPTOMYCIN  

INTRATHECAL  

2000 800 800 80  

104° 1750 700 700 70  

103° 1500 600 600 60  

102° 1250 500 500 50  

101° 1000 400 40  

100° 750 300 30  

99° 500 200 20  

98° 250 100 10  

97° 0 0 0  

C.S.F. PRESSURE, mm H₂O  

150. 150. 100. 90. 100. 80. 145. 135.  

1949  

18 JULY 25 JUL 8 AUG 15 AUG 22 AUG 29 AUG 5 SEPT  

2 Gm.  

50 mm.  

1 Gm.  

50 mm.
commencing. By 21st March her condition necessitated her removal from the plaster shell. A further course of intramuscular and intrathecal streptomycin was commenced the same day. On 23rd March 1950 there was a marked increase in the symptoms and meningism was marked. The reflexes were sluggish and the plantar responses extensor. She was incontinent of urine and became very drowsy, and lay with the knees flexed onto the abdomen. She periodically uttered a loud cry.

At the beginning of April her condition was deteriorating fast. She lay motionless in bed in the early stage of coma. Oral feeding was becoming impossible due to spasm of the muscles of mastication and she was becoming very emaciated. There was gross head retraction, opisthotonos, flexion of all limbs and a bilateral extensor plantar response. It was almost impossible to extend the legs. There was a continuous tremor of the mouth and upper limbs. An early bilateral papilloedema appeared. All treatment with streptomycin was discontinued on 12th April 1950.

This slow deterioration lasted for another six weeks with the intracranial pressure and signs of meningism steadily increasing and the coma deepening. She died on 12th May 1950.

Autopsy Report. Examination of the brain showed marked flattening of the convolutions throughout/
throughout both cerebral hemispheres. The sulci were obliterated. The interpeduncular fossa was covered by a thick gelatinous exudate. Numerous miliary tubercles could be seen, particularly in relation to both lateral sulci. Pin point tubercles could also be seen in relation to the interpeduncular fossa. In error a small incision was made over the surface of one of the hemispheres and a considerable quantity of slightly opalescent cerebrospinal fluid poured forth - the brain seemed as if it suddenly became "deflated" and it collapsed down into a soft flabby mass. Section of the brain revealed a gross degree of internal hydrocephalus and both lateral ventricles showed marked dilatation. Each extended half an inch from the frontal pole to half an inch from the occipital pole. So great had this pressure been that the convolutions of the hemispheres were represented only as a thin layer of brain tissue surrounding grossly dilated lateral ventricles. The ependyma was covered with a yellowish shaggy exudate and both it and the choroid plexuses were covered with numerous miliary tubercles.

**Summary.** This is a case of tuberculous meningitis occurring in a girl already the subject of destructive tuberculous disease of the spine. A combined course of intramuscular (total 195.5 gm.) and intrathecal streptomycin of 28 weeks' duration resulted/
resulted in what was thought to be an apparent cure. A relapse subsequently occurred, only a small second course of streptomycin was given, and she died shortly afterwards.
CASE No. 12.

A.S., a young girl of 11 years of age, was first taken to the Out-patient Department of the Royal Hospital for Sick Children, Edinburgh on 8th August 1949. Her mother then stated that six days previously the child complained of frontal headache and had complained frequently of it since then. She had had these headaches before but not so severely. She seemed feverish and her appetite was poor, but she remained ambulant. On 5th August she had a bile-stained vomit and was complaining of pain and tiredness in the legs which had also been a common complaint from the child. There was no tuberculosis in the family and no known exposure. She had been a frequent attender at that hospital from 1940 to 1947, when the complaints were enuresis, tracheitis, extreme shyness, multiple tics, pains in the limbs and halitosis. On examination at that time it was remarked that she was a pale, asthenic child, sobbing and hanging her head; she appeared to be very sorry for herself and the elderly mother was markedly over-solicitous. Clinically no abnormality was detected but the radiologist reported that the lung appearances were suggestive of a resolving pneumonia in the middle lobe or right lower lobe.

During the 3 days following this visit she became increasingly drowsy and irritable, and developed severe frontal and occipital headache.

Further/
Further vomiting occurred. She was admitted to the City Hospital on 11th August 1949 where tuberculous meningitis was diagnosed and she was transferred to Southfield Sanatorium the next day.

On 12th August 1949 she was found to be an ill girl, although her general nutrition was good. She was markedly photophobic, drowsy and irritable although she could be roused to answer questions in an intelligent way. She cried periodically. The temperature was 101°F. and the pulse rate 118 per minute. There was no abnormality of the heart or abdomen. The breath sounds over the lower half of the right lung in front were weak and a few accompanying rales were heard. There was marked neck rigidity and a mild degree of Kernig's sign on both sides. A paralysis of the right external rectus muscle of the eye was noted. She had an albinoid type of fundus which was poorly pigmented. Even allowing for the albinoid type of fundus, the ophthalmologist considered that the right optic disc was rather pale, suggesting a right temporal optic atrophy. There was no papilloedema and no choroidal tubercles were seen. There were no objective motor or sensory disturbances. The abdominal reflexes were brisk and the knee and ankle jerks were present but depressed. The plantar responses were flexor. The Mantoux test was positive to a 1 in 10,000 dilution of old tuberculin. A lumbar puncture was performed and opalescent C.S.F., not under increased pressure, was/
was obtained. It contained 78 cells per c.mm., most of which were lymphocytes. The protein content was \(10^4\) mg.%, glucose \(43\) mg.% and chloride \(664\) mg.%

X-ray examination of the lungs showed a small triangular shadow bulging from the centre of the right lung root which possibly represented a collapsed middle lobe.

**Bacteriology.** Examination of the C.S.F. obtained on admission showed acid-fast bacilli morphologically like tubercle bacilli. A culture yielded a growth of human type tubercle bacilli after 5 weeks, and guinea-pig inoculation was also positive, numerous tubercle bacilli being found in the smears from the inguinal and lumbar glands.

**Treatment.** The calcium chloride complex was used throughout and treatment was commenced on 12th August 1949 with an intramuscular dosage of 2 gm. daily. On the 21st of that month she developed a maculo-papular rash, a marked rise of temperature, headache and anorexia. At first this was considered to be entirely a sensitization reaction to streptomycin and it was therefore stopped. In the course of a week it became obvious that the acute fever and upset of the previous week were probably not altogether due to sensitivity to streptomycin and it was therefore resumed in a dose of 1 gm. daily on 31st August. A rest period was started on 17th September, and on the 26th of the same month a further fortnight of intramuscular streptomycin was given.
given. After another rest period from 10th to 20th October the drug was again given, 1 gm. daily, until 1st November, and also from 15th to 22nd November. The two final courses of 1 gm. daily were given from 26th November to 6th January 1950 and, after a week's rest, from 13th January to 11th February 1950. The total amount of streptomycin given by the intramuscular route on 130 days was then 138 gm.

The streptomycin was given intrathecally in a dose of 50 mg. It was commenced on the day of admission and given continuously for 37 days. Then followed an 8-day rest period. On 26th October a fortnight's course followed by a week's rest was instituted and repeated twice. A weekly course, followed by a week's interval, was commenced on 2nd December 1949 and repeated twice, and after a four-week rest period, a two-week period of injections completed the treatment. Intrathecal streptomycin was thus given on 112 days (i.e. on 86% of the days on which intramuscular treatment was given) and the total amount was 5.5 gm.

Para-aminosalicylic acid, 5 gm. daily, was commenced on 22nd August 1949 and was increased to 10 gm. daily on 24th August. Because of vomiting it was discontinued 3 days later. It was restarted on 30th November in a dose of 5 gm. daily and on 5th December increased to 7.5 gm. daily; by the 14th the dose was 10 gm. daily, but had to be stopped on 5th January 1950 because of a recurrence of vomiting.
From 13th January to 7th March 1950 a course of para-aminosalicylic acid was given in a dose of 5 gm. daily.

**Progress.** On 14th August 1949 she was less drowsy and was taking fluids and some solid food fairly well. She complained practically all day of frontal headache and vomited on two occasions. During the evening of the 17th the temperature rose suddenly to 103°F. The white blood cell count was now 10,400 per c.mm. During the next 2 days she felt a little better again but on the evening of the 19th the temperature began to rise again to 103°F; the frontal headache returned, there was indefinite pain in the back and legs, but there was no other change in the neurological picture. It was on the following day that the temperature rose to 104°F and a faint itchy maculo-papular rash appeared, most marked on the trunk and proximal part of the limbs. At the time this was considered to be a sensitization reaction to streptomycin, the drug was stopped and the rash disappeared in 24 - 36 hours. At this time she was still drowsy but intelligent and friendly. There was now marked neck rigidity and a positive Kernig's sign. The knee jerks were equal but the ankle jerks were not now obtained. A week later, on 27th August, she had not improved, but the ankle jerks were again obtainable. It now became reasonably certain that this upset was not entirely due to streptomycin and it was resumed on 31st August.
WEEK BEGINNINGS:

INTRAMUSCULAR.

STREPTOMYCIN.

INTRATHecal.

2000 800 800 80

104° 1750 700 700 70

103° 1500 600 600 60

102° 1250 500 500 50

101° 1000 400 40

100° 750 300 30

99° 500 200 20

98° 250 100 10

97° 0 0 0

C.S.F. PRESSURE. mm H2O. 80. 130. 45. 185. 150. 150. 210. 130.
10th September there was little progress to report - the meningeal signs were minimal, but she was still drowsy and listless and continued to show a swinging temperature. Again, a similar itchy rash appeared on the trunk, neck and front of both thighs. Both eyelids also were reddened and swollen. On account of this rash Anthisan, 0.1 gm. thrice daily, was started and it gradually faded, but reappeared transitorily during the following week.

It was at the beginning of October 1949 that clinical improvement was noticeable. There was no evidence of meningism, all reflexes were present and equal and the right 6th nerve palsy had improved. The temperature too was settling below the level of 100°F. and she was bright and cheerful. As regards the C.S.F., there was little material change since the day of admission. At the end of November 1949 the only positive signs were the slight right optic atrophy and slight weakness of the right lateral rectus muscle. The C.S.F. however showed only moderate improvement. The temperature was becoming normal.

During the first three months of 1950 the clinical improvement was maintained, and the weakness of the right lateral rectus muscle was no longer visible. The C.S.F. findings were becoming very satisfactory. By July she was allowed up for the first time and on 16th August 1950 she was sent home. At the time of discharge she was a perfectly normal, intelligent/
intelligent child. There were no abnormal neurological signs. The C.S.F. was within normal limits apart from the protein level which was 71 mg.%

**Summary.** A case of tuberculous meningitis in a girl of 11 years from which the human type of tubercle bacillus was isolated. Clinical improvement of the meningitis to streptomycin treatment was slow and the C.S.F. improvement lagged many weeks behind the clinical improvement. She was discharged home 6 months after the cessation of all treatment with a normal C.S.F. apart from a slightly raised protein level. The total intramuscular dosage of streptomycin was 138 gm. and the intrathecal amount was 5.5 gm.

This girl was seen again in February 1951. She was without symptoms and in excellent condition. There was no nystagmus and no ataxia. Hearing was normal. There were no abnormal physical signs in the central nervous system. The cerebrospinal fluid examination was as follows: cells 1 per c.mm., protein 50 mg.%, glucose 68 mg.%, chloride 730 mg.%. The child was mentally normal and was due to start school in the coming session.
CASE No. 11.

J.W., a boy aged 5 years and 4 months, developed a feverish illness on 23rd February 1949 which was diagnosed as influenza. Three days later he developed frontal headache and this gradually became worse and more constant; he also began to vomit two or three times daily. He was eating very little and he was losing weight. At the same time he also developed photophobia and a non-productive cough. His bowels only moved with the aid of an aperient. His family were all healthy and there was no known tubercle contact.

The boy was admitted to the Royal Hospital for Sick Children, Edinburgh on 2nd March 1949. He was not pyrexial at this time and the pulse rate was 108 per minute. He was irritable, drowsy and photophobic. There was moderate neck rigidity and a doubtful Kernig's sign. There was a slight degree of bilateral papilloedema. All reflexes were present and equal. There was no abnormality of heart, lungs or abdomen. The urine contained a trace of albumin. The Mantoux test was positive to a dilution of 1 in 1,000 old tuberculin and the B.S.R. 6 mm. in the first hour (Westergren). The white blood count was 11,800 per c.mm., of which 74% were polymorphs. Lumbar puncture was performed and a clear fluid under a pressure of over 300 mm. water was obtained. There was no evidence of spinal block. On standing a coagulum formed. The protein content was 180 mg%, chloride/
chloride 670 mg.% and glucose 25 mg.%. There was no X-ray evidence of lung disease.

**Bacteriology.** A diagnosis of tuberculous meningitis was confirmed by the finding of tubercle bacilli on direct smear examination of the C.S.F. Tubercle bacilli having the cultural characteristics of the human type were grown on Löwenstein-Jensen medium from the C.S.F. on admission.

**Treatment** at the Royal Hospital for Sick Children was commenced on 3rd March 1949. The intramuscular dosage was 400 mg. twice daily. This was given in a continuous course until 2nd July 1949. Following a recrudescence early in August of the same year, treatment was re-started on the 10th of that month and was continued after the patient was transferred to Southfield Sanatorium on 16th August 1949. The total intramuscular amount given at this hospital over a period of 130 days was thus 99.5 gm.

**Intrathecal therapy** was also commenced on 3rd March 1949 in a daily dose of 50 mg. It was given continuously for 21 days. After a rest period of 2 weeks it was recommenced for a period of 2 weeks, finishing on 21st April 1949. Between 17th May and 30th June 1949 this boy received a 50 mg. intrathecal injection twice weekly. Following the recrudescence a further course was commenced on 10th August 1949, lasting only for 7 days as the patient was then transferred to Southfield Sanatorium. The total number of days on which intrathecal treatment was given/
given was 44 (i.e. on 33% of the days on which intramuscular streptomycin was given) and the total amount was 2 gm.

Progress at Royal Hospital for Sick Children. During the first week the temperature ranged between 99°F. and 102°F. On 10th March 1949 he developed a left facial palsy and on the 11th a right lateral rectus palsy of the eye. On the latter date he developed measles and was transferred to the City Fever Hospital where the continuous intramuscular and intrathecal streptomycin treatment was carried on. On his return on 22nd March he was lethargic but not drowsy. Neck rigidity was minimal. The same degree of papilloedema was still present. The two previously noted palsies were still evident.

The child was very slow to show any improvement but by the middle of June 1949 he was able to sit up unaided, was eating well but continued to have obstinate constipation. In spite of the clinical improvement, the C.S.F. cells and biochemistry remained grossly abnormal with the cell count in the region of 200 per c.mm., the glucose content varying between 20 and 38 mg.%, the chloride level always below 700 mg.% and the protein varying between 200 and 300 mg.%. Acid-fast bacilli were still found in the fluid on 8th May. By the end of July the cranial nerve palsies had disappeared and he did not appear either deaf or ataxic.

At/
At the beginning of August 1949 the temperature started to climb again and acid-fast bacilli were isolated from the C.S.F. which had never shown any real improvement since the day of admission. Later, frontal headache, restlessness and irritability occurred and it was now obvious that a recrudescence had set in. Treatment was recommenced at once and he was transferred to Southfield Sanatorium on 16th August 1949.

Examination at Southfield Sanatorium found this boy to be thin and sallow and slightly drowsy. The temperature was 100°F. There was a slight degree of neck rigidity and a positive Kernig's sign. The limbs were weak and thin but there was no paresis and the reflexes were present though depressed. No cranial nerve palsies were visible. There was marked bilateral papilloedema, engorged veins and oedema of the surrounding retina. He took very little interest in his surroundings but was able to feed himself. Clear C.S.F. was obtained under a pressure of 230 mm. water. The cells numbered 88 per c.mm., most of which were lymphocytes. The protein content was 219 mg.% glucose 42 mg.% and chloride 682 mg.%

Bacteriology. As was to be expected, tubercle bacilli were not now isolated either by smear, culture or guinea-pig inoculation.

Treatment. On 17th August 1949 streptomycin treatment/
treatment was continued at Southfield Sanatorium, but with some alteration in the dosage. The daily intramuscular dose was 1 gm. The calcium chloride complex was used. On 22nd August 1949 the dose was reduced to 0.5 gm. daily, but was stopped on 9th September due to persistent vomiting. Streptomycin was resumed on 21st September in a dose of 1 gm. daily and this course was stopped on 25th October. The amount of streptomycin given at Southfield Sanatorium over a period of 60 days was 50.5 gm. At the Royal Hospital for Sick Children 99.5 gm. were given over a period of 130 days, giving a total of 150 gm.

Intrathecal therapy was recommenced on 17th August with a dose of 50 mg. 24 daily injections were then given until 9th September. A further 14 intrathecal injections were given from 22nd September to 5th October, and 9 more from 16th to 20th October. A fourth course was started on 6th November, but only three injections were given before the patient's condition deteriorated so quickly that it was discontinued.

The total amount of intrathecal streptomycin given on 50 days (i.e. on 83% of the days on which intramuscular streptomycin was given) was 2.5 gm. 2 gm. of intrathecal streptomycin were given at the Royal Hospital for Sick Children over a period of 44 days. Thus the total amount of streptomycin given intrathecally in this case was 4.5 gm. This was given/
given in 50 mg. doses on 44% of the days on which intramuscular streptomycin was given.

**Progress.** During the remainder of the month of August he became alert and bright and was taking his food well, but there was no change in the neurological signs or in the C.S.F. At the beginning of September 1949 nystagmus appeared for the first time and the degree of papilloedema was decreasing. He started to vomit again and intramuscular streptomycin was thus stopped. On the 17th of that month meningeal signs were minimal, and vomiting had ceased. The right optic disc was now normal, while on the left side there was still a slight degree of papilloedema. The C.S.F. pressure was now normal. On the 28th it was confirmed that papilloedema had reappeared on the right side and at this time the C.S.F. pressure had risen to over 250 mm. water.

During October his condition deteriorated. The temperature became more elevated and there was fairly frequent vomiting. There was increasing papilloedema and the right plantar response was now extensor. The C.S.F. findings were also deteriorating and the pressure was rising. At the beginning of November 1949 the tempo of the deterioration increased rapidly. The temperature was still more elevated and he was frequently restless. He was flushed and becoming emaciated. On the 2nd he was found to have a left-sided facial palsy.
palsy. Both plantar responses were now of the extensor type. On the 7th he had advanced to the stage of opisthotonos with tetanic spasms of the wrists and hands. He was extremely drowsy and no longer spoke even to his mother. He had become incontinent of urine. There was a further rise in the pressure of the C.S.F. On the 9th he had become unconscious, the corneal reflex was absent, the limbs were flaccid and all tendon reflexes absent, the skin was cold and the pulse almost imperceptible. The boy was still unconscious on the 10th, both pupils were pin-point and the bilateral papilloedema was marked. All the retinal vessels were narrow and empty. There was now no neck rigidity but Kernig's sign was very definite on both sides.

The cells in the C.S.F. had fallen from 328 to 50 per c.mm. in the last 14 days. He died the following day.

Summary. A boy of 5 years admitted to the Royal Hospital for Sick Children with tuberculous meningitis in an intermediate stage, from which the human type of tubercle bacillus was isolated. Treatment with streptomycin was commenced there and clinical improvement was excellent but no improvement occurred in the constituents of the C.S.F. Streptomycin was however stopped and in a few weeks a recrudescence occurred. Treatment was re-started and he was transferred to Southfield Sanatorium. No striking clinical improvement now occurred and the C.S.F./
C.S.F. showed gradual deterioration. 10 days before his death, after an illness lasting 9 months, he developed the signs of a progressive hydrocephalus.

The total amount of intramuscular streptomycin given was 150 gm. and the total intrathecal amount was 4.5 gm., which was given on 44% of the days on which intramuscular streptomycin was given.
CASE No. 14.

A.S., a boy of 2 years, became unwell at the end of July 1949. His chief symptoms were vomiting, malaise and constipation. He had also become lethargic and irritable. On 6th August he was admitted to the Sick Children's Hospital, Edinburgh and a diagnosis of tuberculous meningitis was made. Intramuscular and intrathecal streptomycin was begun. He was transferred to Southfield Sanatorium on 16th August 1949.

On examination this baby was found to be fairly well nourished but was semi-comatose and very irritable. The whole body and the limbs were held rigidly when he was moved. He responded to sensory stimuli. On examination of the nervous system, the pupils were dilated, fixed and equal. There was marked neck rigidity and the muscle tonus in all limbs was increased. There was a definite Kernig's sign on both sides. All the joints of the upper limbs were in full flexion. The plantar responses were flexor and all the reflexes exaggerated. On lumbar puncture the C.S.F. was clear and had a free circulation but a low pressure. The white cells numbered 60 per c.mm., of which the majority were lymphocytes, the glucose 37 mg., and the chloride 598 mg. The Mantoux test was positive to 1 in 1,000 old tuberculin.

Bacteriology. A guinea-pig, inoculated from the C.S.F. on admission, showed enlargement of inguinal/
inguinal and lumbar glands and contained caseous material from which smears showed numerous acid-fast bacilli resembling tubercle bacilli. Culture on Löwenstein-Jensen medium was also positive, a growth of the human type of tubercle bacilli being obtained.

**Treatment.** From the day of admission streptomycin was commenced in a dosage of 0.5 gm. daily and 50 mg. were given intrathecally.

**Progress.** It was impossible to feed him orally in his semi-comatose condition and 4-hourly feeds by intra-gastric tube were required. On 18th August, a poor response to jugular compression was obtained on lumbar puncture, indicating a partial spinal block at a high spinal or intercerebral level. On 19th August he was unconscious, there was a strabismus of the right eye and a ptosis of the left eye. Both arms were in extensor spasm with pronounced internal rotation and flexor spasm of the wrist and fingers. The legs were flaccid but went into tense extensor and adductor spasm when handled. Both plantar reflexes were extensor. There was a bilateral papilloedema with engorgement of vessels. Two days later he had developed marked head retraction, gross opisthotonus and breathing of Cheyne-Stokes type. Within a period of 3 hours his temperature rose from 100°F. to 105°F. On 22nd August he developed respiratory embarrassment and cisternal puncture was carried out but it did not relieve/
relieve his symptoms. This specimen of C.S.F. contained 36 cells per c.mm., protein 120 mg.\%, glucose 35 mg.\%, and chloride 682 mg.\%. The pressure was not raised. Two hours later the child died from central respiratory failure.

**Summary.** A case of tuberculous meningitis, from which tubercle bacilli were isolated from the C.S.F., admitted in an advanced stage. There was no response to streptomycin treatment. He developed signs of acute hydrocephalus and died from respiratory failure 7 days after admission. Permission for autopsy was refused.
CASE No. 15.

B.A., a boy of 7 years of age, was perfectly well until the middle of August 1949. His mother states she then noticed he was ailing. He often felt tired and sleepy and he lost his appetite. He had a slight cough and had lost some weight. He did not improve after a ten days' holiday at the coast. He was admitted to the Royal Infirmary on 10th September 1949 where the diagnosis of miliary tuberculosis was made.

On admission to Southfield Sanatorium on 14th September 1949 he was found to be in good general condition. He was flushed and the temperature was 100°F. There was no detectable abnormality on clinical examination of the lungs, but radiographically there were calcified glands in the right lung root and very fine miliary tuberculous shadowing of both lungs. He was constipated and there was no abnormality in the abdomen. There was no evidence of meningism and no abnormalities of the nervous system. Examination of the optic fundi revealed the presence of numerous choroidal tubercles, 13 in the right eye and 7 in the left eye. All, with the exception of one which was pigmented, had the appearance of being of recent origin. The B.S.R. (Westergren) was 9 mm. in the first hour and the Mantoux test was positive to a 1 in 10,000 dilution of old tuberculin. Lumbar puncture was carried out and /
and the C.S.F. was under a pressure of 95 mm. of water. It contained one or two lymphocytes per cubic millimetre. The protein level was 60 mg.%, glucose 47 mg.% and chloride 728 mg.%

**Bacteriology.** Tubercle bacilli of the human type were first isolated from the C.S.F. on culture and guinea-pig inoculation on 2nd May 1950, at the time of recrudescence of meningitis which subsequently developed.

**Treatment.** The calcium chloride complex of streptomycin was commenced by intramuscular injection in a dose of 1 gm. daily on 14th September 1949. On 2nd October 1949 it was discontinued for a period of 10 days and recommenced with the daily dose reduced to 0.5 gm. Nystagmus appeared by the 9th January 1950 and the drug was stopped. It was re-started again on 20th January for a further 8 weeks. By 14th March he had had six months' almost continuous treatment and intramuscular streptomycin was therefore stopped. A tuberculous meningitis developed in October 1949 and by March 1950 appeared to have been arrested. However on 1st May 1950 there was a marked increase in the cellular content of the C.S.F. and intramuscular streptomycin was resumed. The dosage this time was 1.5 gm. and on 20th May he was not at all well; though there were no clinical signs of meningitis he was pale and exhausted and was vomiting. Streptomycin was omitted for 4 days and/
and he certainly looked and felt better and the vomiting ceased. It was then resumed in the reduced dose of 1 gm. daily for 28 weeks (during first 4 weeks the calcium chloride complex was used, there- after it was dihydrostreptomycin), to be finally discontinued on 8th December 1950 because he was without symptoms or signs of meningitis although the C.S.F. continued to deteriorate. The total amount of intramuscular streptomycin given on 379 days was 316.5 gm. (of which 171 gm. were dihydro- streptomycin).

Intrathecal therapy was first commenced on 22nd October 1949 because changes in the C.S.F. suggested that infection of the meninges had occurred while the patient was under treatment with intramuscular streptomycin. The dose on each occasion was 50 mg. It was first given continuously for 32 days, and for the next 6 weeks it was given on alternate weeks. It was thereafter discontinued because of the development of nystagmus, and though the C.S.F. was not normal it had not become any more abnormal during this period of treatment. A very definite deterioration however did occur on 1st May 1950 and for this reason intrathecal therapy was resumed in the increased dosage of 100 mg. It was stopped again after 19 continuous injections because of his poor general condition and when it was resumed on 25th May it was at the reduced dosage of 50 mg.
28 consecutive injections were given and a one-week rest period followed. For the next four weeks it was given on alternate weeks. This scheme of intrathecal injections was repeated twice. This interrupted course was commenced for a fourth time on 27th November 1950 but after 13 consecutive injections he was still without symptoms or signs of meningitis, and although the C.S.F. was deteriorating, it was decided to stop all treatment and await events. A change over from the calcium chloride complex to dihydrostreptomycin was made after the first 28 consecutive injections on 26th June 1950. The total amount of intrathecal streptomycin given on a total of 208 days (i.e. on 55% of the days on which intramuscular streptomycin was given) was 11.5 gm. (of which 3 gm. were in the form of dihydrostreptomycin).

Para-aminosalicylic acid was given orally as follows:

<table>
<thead>
<tr>
<th>Date</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>28th November 1949</td>
<td>2.5 gm. daily commenced.</td>
</tr>
<tr>
<td>5th December</td>
<td>increased to 7.5 gm. daily</td>
</tr>
<tr>
<td>14th December</td>
<td>increased to 10 gm. daily</td>
</tr>
<tr>
<td>8th January 1950</td>
<td>reduced to 7.5 gm. daily</td>
</tr>
<tr>
<td>4th February</td>
<td>increased to 10 gm. daily</td>
</tr>
<tr>
<td>4th March</td>
<td>treatment stopped</td>
</tr>
<tr>
<td>3rd May</td>
<td>recommenced 7.5 gm. daily</td>
</tr>
<tr>
<td>6th May</td>
<td>stopped</td>
</tr>
<tr>
<td>27th May</td>
<td>resumed at 5 gm. daily</td>
</tr>
<tr>
<td>12th July 1950</td>
<td>stopped finally</td>
</tr>
</tbody>
</table>

Progress /
Progress. It was on 17th October 1949, two months after the commencement of his illness and four weeks after the commencement of intramuscular streptomycin, that the C.S.F. white cells increased to 12 lymphocytes per c.mm., and on 21st October had risen to 39 per c.mm. The glucose content remained normal. This was extremely suggestive of an onset of tuberculous meningitis though there were no clinical signs and intrathecal therapy was commenced forthwith. Tubercle bacilli were not isolated from the C.S.F. By 27th October the first clinical sign appeared in the form of a positive Kernig's test and this sign persisted for a fortnight only. No further choroidal tubercles had appeared but those that were already present showed their golden yellow centres to be brighter in colour and the oedematous look of the retina overlying the tubercles had now disappeared. Most were better defined than when first seen and pigmentation was occurring around many of them. There was no papilloedema.

During November 1949 the temperature continued to show a diurnal range of 100° - 102° F. and his general condition continued to be fairly good. There were still no abnormal physical signs in the chest and radiologically the miliary shadows were quite unchanged and there was gross glandular enlargement in each lung root and in the mediastinum. Kernig remained the only neurological sign. There was no further change in the C.S.F. and the glucose content remained/
remained normal. The choroidal tubercles now appeared perfectly flat and a fine dust-like pigmentation was occurring in and around all the tubercles.

At the beginning of December the temperature slowly began to fall below 100°F. and this coincided with the commencement of P.A.S. There was still no sputum, and the breath sounds were now broncho-vesicular in all areas without crepitations. Clubbing of the fingers and toes was now present. Kernig's sign had disappeared and there was no clinical evidence of meningitis. He was bright and lively. During this month there were still no significant changes in the C.S.F. apart from the rise in the cell and protein content.

On 6th January 1950 a few patches of urticarial erythema developed on the trunk, and on the 9th nystagmus appeared. All streptomycin treatment was now stopped. The latter sign disappeared quickly and intramuscular streptomycin was resumed on the 18th. His condition was otherwise satisfactory from the clinical viewpoint.

All treatment was stopped by the middle of March 1950, six months after its commencement. His general condition was now very good. The temperature was normal. An X-ray of the lungs showed the miliary shadowing almost to have disappeared. There were no neurological signs and the choroidal tubercles/
tubercles were unchanged and no fresh lesions had appeared. There was an improvement in all the constituents of the C.S.F.

On 1st May 1950 however the boy was not so well. The temperature remained elevated in the region of 100°F. and he had developed a slight headache and had vomited twice in the morning. There were no neurological signs but he was slightly drowsy and lay curled up in bed. On lumber puncture the C.S.F. cells numbered 144 per c.mm., the protein had risen to 123 mg.% and the chloride had fallen below 700 mg.% From this fluid tubercle bacilli of human type were isolated on culture and by guinea-pig inoculation. Streptomycin treatment was recommenced forthwith. During the next 3 weeks the temperature remained elevated, and he was pale and lethargic. He vomited practically every day. No signs of meningitis were evident. Since it was considered that this state might be in part accounted for by streptomycin and P.A.S., these drugs were omitted from 21st to 23rd May and there was definite improvement in the symptoms noted previously. He was again bright and alert. The C.S.F. however had further deteriorated in all respects.

During June 1950 the temperature continued to swing, but his general condition remained fair. The C.S.F. was now definitely xanthochromic and more abnormal with the glucose level reduced to 38 mg. % and/
and the cell count and protein level rising. During July 1950 it was obvious that he was making no improvement from renewed treatment. He was becoming thinner, he felt tired and his appetite was poor. The temperature was continuously elevated between 100° and 101°F. He was very constipated. Still there were no positive signs in the nervous system apart from the worsening condition of the C.S.F.

Similar absence of physical signs (apart from continuous pyrexia) and deterioration of the C.S.F. persisted during August, September and October white treatment continued. During September the appearance of the C.S.F. varied between a xanthochromic turbid fluid to a brownish or at times brightly red coloured fluid from its content of blood, yet there was no evidence to suggest trauma as the cause. The staining of the fluid was uniform during its flow from the spinal needle.

By November 1950 he was gradually losing a little more ground. He was not always the pleasant co-operative boy that he was formerly. He had lately shown a slight change in his behaviour. He was a little cantankerous and would fly into a temper over trivial things and burst into tears. He was thin and the skin was dry and inelastic. His appetite was poor. The temperature was now normal. However there were no symptoms or signs of meningitis apart from his behaviour change; the white and red cell content of the C.S.F. remained greatly increased while/
while the glucose level was showing a progressive and steady fall to a level of 24 mg.% The chloride content was normal. There were no abnormal physical signs in the chest and radiographically the miliary shadowing had completely disappeared and the root glandular shadows were less. There was however a very big right upper mediastinal bulge.

It was on 8th December 1950 that all streptomycin treatment was stopped as he was without clinical signs of meningitis, yet the C.S.F. remained in its grossly abnormal state. Since the recrudescence of the meningitis in May 1950 he had had a second course of treatment lasting 7 months yet the C.S.F. showed no response whatsoever to treatment.

At the beginning of May 1951, in the absence of specific treatment, the striking feature about this boy's case was the all-round improvement he was showing. His general clinical condition was satisfactory and there continued to be no physical signs of meningitis. In the last 5 months there had been a quite unexpected improvement in the C.S.F. The cells had fallen to below 10 per c.mm., the chloride was normal and the glucose level had risen from 24 mg.% to 47 mg.% There was by now a slight degree of impairment of hearing. Shortly afterwards, a recrudescence of the meningitis occurred for the second time. It was ushered in by a gradual rise of temperature and a complaint of tiredness and headache. Physical/
Physical signs were completely absent. A third course of streptomycin (calcium chloride complex) was commenced, and this was followed by deterioration. After 5 weeks he had become completely deaf in both ears, and an all-round deterioration of the C.S.F. was occurring. Yet at all times physical signs of meningitis remained absent. The C.S.F. on 9th July 1951 contained 392 cells per c.mm., 38 mg.% glucose, and 672 mg.% chloride. Treatment is being continued.

**Summary.** A boy of 7 years of age admitted with miliary tuberculosis. A month later there was evidence in the C.S.F. to indicate that meningitis had supervened. Energetic streptomycin was instituted and 2 years later he was still not cured. In the interval a recrudescence of the disease had occurred on two occasions and he is at present undergoing a third course of treatment. He is now completely deaf and has received a total of over 400 gm. of streptomycin by intramuscular and intrathecal routes.
CASE No. 16.

W.M., a boy of 14 years of age, was confined to bed for 4½ weeks with pain and stiffness in the knees and elbows and returned to school on 14th October 1949. The following day headache started with fever and shivering attacks. On the 18th he vomited and this had persisted. He had been very constipated for the past two weeks. A year ago, he was stated to have had "catarrh of the ears" and from each there has been a periodic purulent discharge. There was no evidence of deafness and no discharge at the time of admission. There was a large chronic perforation of the right drum and a posterior perforation of the left drum with cholesteatoma formation.

He was admitted to Southfield Sanatorium on 26th October 1949. This boy was resentful of examination, lying curled up in bed. He was complaining of headache and was confused in thought. His general condition was quite good. The temperature was 102.4°F and the pulse rate 70 per minute. Neck rigidity and Kernig's sign were present. All reflexes, superficial and deep, were present and equal, and the plantar responses were flexor. There was no muscular weakness or inco-ordination. There was an early papilloedema of both optic discs and a palsy of the left trochlear nerve. No choroidal tubercles were seen. A right facial palsy was also present. On lumbar puncture the/
the C.S.F. was slightly turbid. The total white cell count was 651 per c.mm., most of which were lymphocytes. The glucose content was 36 mg.%, chloride 688 mg.% and protein 142 mg.%. The B.S.R. was 5 mm. in the first hour (Westergren) and the Mantoux test was positive to a 1 in 10,000 dilution of old tuberculin. A radiograph of the lungs showed no evidence of an active primary complex or of active lung disease.

Bacteriology. No acid-fast bacilli were seen in direct smear of the C.S.F. on admission. A growth of human type tubercle bacilli was obtained on culture on Lowenstein-Jensen medium. This strain was sensitive to 2 microgrammes of streptomycin (twice as resistant as control culture H 37 RV). Guinea-pig inoculation was also positive for tuberculosis.

Treatment. On 26th October 1949 intramuscular streptomycin 1 gm. daily was commenced. The calcium chloride complex was used. This was given continuously for 6 months and all treatment was discontinued on 25th April 1950. However a deterioration in the C.S.F. occurred on 1st May 1950 and the intramuscular dosage was recommenced on 2nd May in a dosage of 2 gm. a day. An acute vestibular disturbance occurred on 9th May and the streptomycin was stopped until the 13th when it was resumed in a dosage of 0.5 gm. daily for the next 16 weeks. All treatment was finally discontinued on 5th September 1950.
1950. A change over from the calcium chloride complex to dihydrostreptomycin was made on 13th June. A total of 255 gm. of streptomycin (of which 48 gm. were dihydrostreptomycin) was given on 366 days of treatment.

Intrathecal therapy was commenced, using the calcium chloride complex, on 26th October 1949. It was given continuously for 32 injections, the first eight of which were of 25 mg. and the remainder of 50 mg. After 7 days' rest it was given on alternate weeks in a dose of 50 mg. until 2nd April 1950. Recommencing on 10th April 1950 the drug was given continuously for 38 days - after the first 21 injections of 50 mg. each had been given the relapse occurred on 1st May and the dose was increased to 100 mg. However the acute vestibular upset on 9th May necessitated it being omitted on the 10th and 11th and when it was resumed on 12th May it was at the reduced dosage of 25 mg. daily. By 16th May it was increased again to 50 mg. daily until 21st May, when a rest period followed. The 50 mg. daily dose was next given from 29th May for 7 days. On 19th June a change was made to dihydrostreptomycin and from then until 27th August 48 injections of 50 mg. were given. All intrathecal therapy was now finally discontinued. The total amount of intrathecal streptomycin given on 188 days (i.e. on 61% of the days on which intramuscular streptomycin was given) was 9.5 gm. (of which 2.5 gm. were dihydrostreptomycin).
Para-aminosalicylic acid was given as follows:

<table>
<thead>
<tr>
<th>Date</th>
<th>Dose</th>
</tr>
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<tbody>
<tr>
<td>9th November 1949</td>
<td>5 gm. daily</td>
</tr>
<tr>
<td>14th November 1949</td>
<td>increased to 10 gm. daily</td>
</tr>
<tr>
<td>22nd November 1949</td>
<td>P.A.S. discontinued</td>
</tr>
<tr>
<td>11th December 1949</td>
<td>P.A.S. resumed 5 gm. daily</td>
</tr>
<tr>
<td>17th December 1949</td>
<td>increased to 10 gm. daily</td>
</tr>
<tr>
<td>27th March 1950</td>
<td>increased to 15 gm. daily</td>
</tr>
<tr>
<td>26th June 1950</td>
<td>P.A.S. discontinued</td>
</tr>
</tbody>
</table>

**Progress.** A month after admission, his general condition had improved. He was clear mentally and behaving normally. The hectic fever was persisting. Neck rigidity had disappeared though Kernig's sign was still present on both sides. The palsies of the 4th and 6th cranial nerves on the right side had cleared up. The papilloedema remained unaltered. The C.S.F. was under a pressure of about 300 mm. water with a white cell count over 700 per c.mm. The glucose level was below 40 mg.% and that of the chloride below 700 mg.%

At the beginning of December 1949 he was subjectively better but the high temperature persisted. Neck rigidity returned again, otherwise there was no alteration in the neurological picture. There was an increase in the sugar level of the C.S.F. but otherwise it was still highly abnormal.

The temperature range at the beginning of January 1950 was 100° - 101°F. and during the month a/
a gradual fall occurred, but it was still not normal at the end of the month. His general condition was now fairly good and by the end of the month the neck rigidity had disappeared again and the degree of Kernig's sign was lessening. The papilloedema, though less, was still present. There were no other neurological changes.

For the first time the morning temperature was normal at the beginning of February though the evening level was in the region of 100°F. He was looking and feeling much better. Kernig's sign was still present and the papilloedema remained unaltered. Little improvement was yet noted in the C.S.F. At the end of the month the temperature was almost normal, the papilloedema had now disappeared and definite improvement was noted in the C.S.F.; the white cells had fallen below 100 per c.mm., the glucose level had risen above 40 mg., and the chloride level was above 700 mg. All signs of meningism had disappeared at the beginning of March 1950 and the improvement in the C.S.F. was being maintained. The temperature was in the region of 99°F. At the end of April 1950 he had completed his six months of treatment and the meningitis appeared to have been arrested.

However on 1st May 1950 lumbar puncture showed that there was a slight deterioration in the cerebrospinal fluid. The white cells had risen from 24 to 97 per c.mm., the glucose level fell from/
WEEK BEGINNING:
INTRAMUSCULAR STREPTOMYCIN

INTRATHecal

<table>
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<th>1949</th>
<th>1950</th>
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<tbody>
<tr>
<td>26 OCT</td>
<td>31 OCT</td>
</tr>
<tr>
<td>50 mgm</td>
<td>50 mgm</td>
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</tbody>
</table>

Graph showing changes over time.
from 50 mg.% to 47 mg.% and the chloride level was 696 mg.% No physical signs were found to indicate a relapse of his condition and he felt perfectly well. Culture of the C.S.F. produced no growth. It was felt wise however to resume streptomycin in an increased dosage - 2 gm. intramuscularly and 100 mg. intrathecally; the latter produced a slight elevation of temperature but this had been noted previously to a slight extent even with the 50 mg. dose. On 9th May he developed a dizzy turn associated with diplopia and marked nystagmus, and this vestibular disturbance was presumably due to the larger dose of streptomycin. This vestibular disturbance settled on 13th May and streptomycin was resumed in reduced dosage. At this time a slight degree of optic atrophy was noted in the temporal margin of the right disc. A very definite improvement in the C.S.F. had occurred by the end of the month and his clinical condition was satisfactory. He had by now gained a great deal of weight and red lineae distensae were observed on the shoulders and buttocks.

There was no change in his condition during June, July and August 1950. A slight degree of optic atrophy was now observed in both temporal margins, but by rough and ready tests the fields of vision were normal. A slight nystagmus in both directions had developed. The temperature and pulse rates had been normal since the vestibular upset in May.

During
During this 3-month period there had been fluctuations in the white cell level of the C.S.F., but the biochemical constituents had shown very definite improvement and all treatment was stopped on 5th September 1950.

At the beginning of December 1950 he was allowed out of bed for toilet purposes. His condition was very satisfactory and he was without symptoms or signs, apart from slight ataxia and a slight degree of pallor of the temporal margins of the optic discs. On 18th April 1951 he was discharged home.

This patient was last seen in August 1951. His general condition was very satisfactory and he was without symptoms apart from ataxia. This caused him difficulty when walking on rough ground; twice he had fallen from a bicycle, once from a step-ladder and once down the stairs. A slight degree of nystagmus was persisting. There were no other abnormal signs in the central nervous system. The C.S.F. was entirely normal in all respects. His weight was now over 11 stones. The mental behaviour was normal.

Summary. A case of a young boy admitted with tuberculous meningitis in an intermediate stage. The human tubercle bacillus was isolated from the C.S.F. Response to treatment was slow, a total of 11 months being required. A complete recovery has now occurred. He is at home at present and is shortly to commence training at a rehabilitation
CASE No. 17.

J.F., a girl of 10 years of age, was first examined in May 1949 on account of her sister having developed a primary tuberculous pleurisy, and was found to be Mantoux positive to a 1 in 1,000 dilution of old tuberculin. (The latter subsequently developed tuberculous meningitis and is described as Case 10) These sisters shared a bed at home, and over a period of 3 years a 22-year old girl, a case of open pulmonary tuberculosis, first diagnosed in September 1949, visited them at weekends and all three shared the same bed. J.F. remained well until 23rd December 1949 when she complained of headache and was generally unwell. A week later she started to vomit and went off her food. The patient was admitted to the City Hospital, Edinburgh on 30th December 1949, when she was found to be drowsy, had neck stiffness and a right facial paralysis, and examination of the C.S.F. showed the typical picture of tuberculous meningitis.

The patient was transferred to Southfield Sanatorium on 3rd January 1950. She was fevered with a temperature of 101°F. and she was drowsy. The pupils were equal and reacted to light and there was a concomitant convergent strabismus associated with hypermetropia but no paresis of eye movements. The optic fundi were normal. There was a facial palsy on the right side affecting the lower part/
part of the face. Neck and spinal rigidity were present. The knee and ankle jerks were difficult to elicit, and the plantar responses were flexor. There was no paresis of the limbs. There was no abnormality of heart, lungs or abdomen. The Mantoux test was strongly positive to a 1 in 1,000 dilution. The E.S.R. was 14 mm. in the first hour (Westergren). A radiograph of the lungs showed the root shadows to be prominent but there was no evidence of lung disease. On lumbar puncture the C.S.F. was opalescent and the flow was free. The pressure was 185 mm. water. The total cell count was 363 per c.mm., of which 50% were lymphocytes and 50% polymorphs. The glucose content was 40 mg.%, the chloride 676 mg.% and the protein 86 mg.%

**Bacteriology.** Guinea-pig inoculation and culture of the C.S.F. on Löwenstein-Jensen medium on admission were negative and tubercle bacilli were not found on direct smear.

**Treatment.** The calcium chloride complex of streptomycin was used at first. The first course was commenced on 3rd January 1950 and the daily dose was 1 gm. On 18th January the dose was reduced to 0.5 gm. daily and this course was discontinued on 12th April 1950 because she had developed a marked nystagmus and it was felt wise to introduce a rest period. On 11th May 1950 a second course was started, in spite of the fact that the nystagmus persisted, because of a rise in the cell count of the/
the C.S.F. though the other constituents showed no
deterioration. Again the dosage was 0.5 gm. On
19th June 1950 a change was made to the dihydro-
streptomycin but the dosage was unaltered. This
second course was completed on 12th October 1950.
Over a period of 241 days the total amount of
streptomycin given by the intramuscular route was
128 gm. (of which 56 gm. were in the form of the
dihydrostreptomycin).

The duration of the interrupted courses of
intrathecal streptomycin is shown in the
accompanying graph of this case. A definite
schedule was not adhered to for reasons discussed
under the progress of this case. The number of days
on which intrathecal streptomycin was given was
185 (i.e. on 77% of the days on which intramuscular
streptomycin was given) and the total dosage was
7.5 gm. (of which 4 gm. were in the form of the
dihydrostreptomycin).

On 4th January 1950 para-aminosalicylic acid
was commenced in a dosage of 10 gm. daily and this
was given until 24th May 1950.

Progress. Within a few days of commencing
treatment, the headaches had disappeared, the right
facial palsy was no longer noticed and the drowsiness
had gone, and there was a definite improvement in
her condition. On 19th January nystagmus appeared,
and it was present to right and left a week later.
At the end of January there was no evidence of
meningism/
meningism, all reflexes were easily elicited, the
temperature was settling and she was bright and
co-operative. During February she seemed to be
making progress, but it was noted that a coarse
nystagmus persisted and that during the week in
which intrathecal streptomycin was being given the
temperature was generally more elevated than during
the week when it was not being given.

During March there was no clinical evidence
of tuberculous meningitis and there was improvement
in the C.S.F.; the cells were falling and the
chloride and glucose contents were rising. The
nystagmus now showed a change in its character - it
was of a rotatory type on lateral movement of the
eyes to the left and horizontal to the right. During
April and May there were still no physical signs
apart from the persistence of the nystagmus and some
pyrexia and the C.S.F. was showing further improve-
ment.

However on the evening of 31st May she
had a slight set-back. She complained of headache
and pain in the legs. She was drowsy. The
temperature rose to 103°F. There were no physical
signs of meningitis but the upper nasal quadrants
of both optic discs were hazy and suggested the
presence of an early papilloedema. On lumbar
puncture the C.S.F. was slightly turbid, the cells
had risen to 410 per c.mm. while the glucose and
chloride levels had fallen. The nystagmus was still
present/
<table>
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<td></td>
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<tr>
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<th>103°</th>
<th>102°</th>
<th>101°</th>
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<th>99°</th>
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*C.S.F. Pressure*: mm Hg

*Temperature*: °C

*Pressure*: mm Hg
present. Treatment was continued but on June 15th the intrathecal injection was interrupted for a few days because the patient experienced acute pain in the lumbar region on the introduction of the spinal needle - this was believed due to a chemical inflammation of the tissues, the result of C.S.F. tracking back along the needle track following the injection of streptomycin. She recovered from this setback quite quickly but at the beginning of July there was still slight papilloedema of both discs and for the first time early optic atrophy was noted in the temporal margin of the right optic disc though there was no impairment of the visual fields. On 31st July an isolated finding was the rise of the C.S.F. cells to 919 per c.mm. yet clinically she was well and without physical signs, though nystagmus persisted. During August and September treatment was continued in the absence of physical signs of meningitis, although the temperature was constantly elevated. It was in October 1950 that all treatment was discontinued and the temperature now settled to a lower level than it had ever done while she was having treatment, even though it was still not always normal. The association of elevated temperature and administration of streptomycin had always been noted in this patient. It was also at this time that a slight degree of nerve deafness became apparent in both ears. The optic atrophy of the temporal half of the right/
right disc was now definite.

By December 1950 there was little change to note. The nystagmus was now almost away and could only be obtained on full lateral eversion of the eyes. A degree of nerve deafness was such that the whispered voice could be heard at 3 feet in the right ear and only at the level of the ear on the left side. The C.S.F. was now approaching normal limits – the fluid was clear and contained 8 cells per c.mm., the protein level was 80 mg., chloride 744 mg.\% and the glucose 60 mg.\%. There were no abnormal signs in the nervous system. On 18th December 1950 she was transferred to Loanhead Hospital for convalescence. A lumbar puncture was done on 11th January 1951 and there was a free flow of the C.S.F. which was under a pressure of 180 mm. water. The fluid was examined in Southfield Sanatorium laboratory and it contained 11 white cells per c.mm., 60 mg.\% protein, 746 mg.\% chloride and 60 mg.\% glucose.

**Summary.** A case of tuberculous meningitis, whose sister was admitted 5 months earlier with the same disease. Both had slept in the same bed as a case of infectious lung tuberculosis. The patient made a rapid response initially to streptomycin treatment, had an exacerbation of the condition 5 months after admission and the disease was finally arrested after 10 months' treatment. A total of 128 gm. of intramuscular streptomycin was given and 7.5/
7.5 gm. were given intrathecally. She has now been observed for 3 months, she is well and without physical signs though the C.S.F. cell and protein contents have not yet returned to normal.

This girl was last seen on 12th July 1951. The general condition was satisfactory but an otherwise excellent result was spoiled by a marked increase of deafness since she was last seen. She was almost totally deaf in both ears. A slight degree of nystagmus persisted and though she was not ataxic she was unable to walk along a straight line. There were no abnormal physical signs in the central nervous system apart from slight pallor of the right optic disc. The C.S.F. examination was as follows:— cells 1 per c.mm., protein 50 mg.%, glucose 62 mg.% and chloride 73½ mg.% This girl is at present at home and special arrangements will be required for her education on account of the deafness.
CASE No. 18.

W.B., a girl of 7½ years of age, was well until Christmas 1949 when she became feverish and developed a slight cough. She had become paler than usual and was losing weight. The appetite had become very poor. There was no history of tuberculosis in the family and there was no history of contact. She was admitted to the Western General Hospital, Edinburgh on 16th January 1950 and found to have miliary tuberculosis and a pleural effusion on the left side. Cultures of three specimens of sputum were positive for the human type tubercle bacillus. The Mantoux test was strongly positive to a 1 in 1,000 dilution of old tuberculin. The B.S.R. (Westergren) was 98 mm. in the first hour. Two choroidal tubercles were noted in the left optic fundus. Lumbar puncture was performed and the C.S.F. was clear and contained seven lymphocytes per cubic millimetre with a normal biochemistry. On 17th February 1950 the C.S.F. was again examined and found to contain 25 lymphocytes per c.mm. On 22nd February 1950 she was seen by Professor Cameron who considered that she was an early case of meningitis and she was admitted to Southfield Sanatorium on 23rd February 1950.

On examination she was a thin, flushed, fevered child with a slight cyanotic tinge of the lips. The skin was dry and scaly. The temperature was just over 100°F. and the pulse rate 130 per minute./
minute. The left side of the chest was flatter than the right but there were no conclusively abnormal signs. The spleen was slightly enlarged. There were no clinical signs of meningitis. The presence of choroidal tubercles in the left fundus was confirmed. A radiograph of the lungs showed a big ill-defined mass projecting from the upper part of the right lung root and fine miliary shadows throughout the lungs. The left pleural effusion had largely cleared up. Lumbar puncture revealed a clear cerebrospinal fluid under a normal pressure. The white cells numbered 28 per c.mm. of which 94% were lymphocytes. The chloride level was 732 mg.% and the glucose was 46 mg.% At this time the B.S.R. (Wester gren) had fallen to 5 mm. in the first hour and the Mantoux test was strongly positive to a 1 in 10,000 dilution of old tuberculin.

Bacteriology. Tubercle bacilli of the human type were isolated by culture from the sputum on 3 occasions. They were never isolated from the C.S.F.

Treatment. Intramuscular streptomycin treatment was commenced at the Western General Hospital on 18th January 1950. The calcium chloride complex was used and the daily dose was 1 gm. It was continued on her admission to Southfield Sanatorium but on 13th March 1950 the dose was reduced to 0.5 gm. daily. This dosage was then given continuously for 213 days until all treatment was/
was finally discontinued on 12th October 1950. On 12th June 1950 a change was made to the dihydrostreptomycin. The total amount of intramuscular streptomycin given on a total of 262 days was 155.5 gm. (of which 61 gm. were dihydrostreptomycin).

Though there was no clinical evidence of tuberculous meningitis, the C.S.F. showed sufficient abnormality to necessitate intrathecal therapy being given. The calcium chloride complex was given and was started on 20th April 1950. After no reaction had been observed to the first four injections of 25 mg. each, the dose was increased to 50 mg. daily and given up to a total of 28 days. After a week's rest, it was resumed on alternate weeks for the next four weeks. From 26th June 1950 28 continuous injections were given. Commencing on 16th August 1950 the 6 weeks' interrupted course given at the beginning was repeated. The total amount of intrathecal streptomycin given on a total of 112 days (i.e. on 43% of the days on which intramuscular streptomycin was given) was 5.5 gm. (of which 4 gm. were in the form of dihydrostreptomycin).

Para-aminosalicylic acid was commenced at the Western General Hospital on 4th February 1950 in a dose of 5 gm. daily. It was continued at Southfield Sanatorium and finally discontinued on 9th June 1950.

Progress. The slight increase in the cells of/
of the C.S.F. was found on lumbar puncture each week during the months of March and April 1950. There were no clinical signs of meningitis. The temperature was about 99°F., occasionally rising to 100°F. Otherwise there was no change in her condition. In view of the C.S.F. changes, it was decided to commence intrathecal streptomycin in addition to the intramuscular therapy. During the first four weeks of intrathecal injections it was noted that the C.S.F. cells increased considerably, while the other constituents remained unaltered, and the temperature range was increased and most evenings it was over 100°F. However, this finding was not constant, though the highest C.S.F. counts and the highest temperatures were always recorded during intrathecal courses. These findings seemed quite independent and could not be correlated with any change in her clinical condition.

A radiograph of the lungs in July 1950 showed the miliary shadows to have disappeared. The pleurisy had also disappeared but there was still a very prominent shadow in the right lung root. During the summer months her clinical condition was becoming increasingly satisfactory and she had put on a considerable amount of weight.

On 6th October 1950 all treatment was stopped because her general condition was good and there were no signs of meningitis. The slight pyrexia and raised cell count of the C.S.F. persisted.
Week: Beginning:

1950
27 Feb. 6 Mar. 13 Mar. 20 Mar. 27 Mar. 3 Apr. 10 Apr. 17 Apr. 24 Apr. 1 May. 8 May. 15 May.

Intramuscular Streptomycin

0.04 2000 800 800 80

0.02 1500 600 600 60

0.01 1250 500 500 50

0.00 1000 400 40

99° 750 300 30

98° 500 200 20

97° 250 100 10

96° 0 0 0 0

CSF Pressure: mm. H₂O

110. 110. 40. 130. 110. 90. 80. 65. 8
persisted. These two abnormalities had actually got worse during the period of treatment and when this was stopped they were at the same levels as when intrathecal therapy was first commenced. The choroidal tubercles in the left eye were less conspicuous and pigmentation was advancing.

Within a few weeks of stopping treatment the C.S.F. cells began a steady fall from 38 per c.mm. on 6th October 1950 to 4 per c.mm. at the end of January 1951. The glucose and chloride contents were already normal and there was occasional slight elevation of the protein. Since stopping treatment the temperature had shown a gradual fall and by the end of 1950 it was normal, apart from an occasional evening rise to 100°F. This girl has never complained of deafness but on testing her hearing it was discovered that she could not hear clearly the whispered voice in the right ear. Hearing in the left ear remained normal.

Examination of the optic fundi provided much interest. As already stated, two choroidal tubercles were present in the left eye on admission on 23rd February 1950. Examinations were made weekly but it was not until November 1950 that a tubercle, already showing considerable pigmentation, was found in the region of the left macula. Again in April 1951, 3 choroidal tubercles not previously seen were found. These were lying further away from the disc than the others.
in May 1951, yet another was found in the same fundus lying even further out from the disc than any of the others. They were never found in the right fundus. All the tubercles found on later occasions did not have the appearance of being recently formed.

On 6th August 1951 this girl was transferred to Loanhead Hospital. When last seen on 27th August 1951 she was in good clinical condition and had gained a considerable amount in weight. There were no abnormal physical signs in the central nervous system apart from slight impairment of hearing in the right ear. She had no ataxia and there was no nystagmus. The C.S.F. had returned to normal though an occasional slight elevation of the protein still occurred. An X-ray of the lungs showed calcification in both lung roots and the lung fields were now normal.

**Summary.** A girl of 7½ years who developed a pleocytosis of the C.S.F. shortly after she had developed miliary tuberculosis. Though tubercle bacilli were never isolated from the C.S.F., she was regarded and treated as a case of meningitis. A satisfactory response occurred to intramuscular (155 gm.) and intrathecal (5.5 gm.) streptomycin and she is at present convalescing before going home. Two choroidal tubercles were present at the time of diagnosis but before her discharge a further five tubercles were discovered.
CASE No. 19.

J. T., an apprentice joiner of 16 years of age, developed headache on 12th May 1950 for which he required to take aspirin. Two days later while playing football he was struck on the head by the ball. He felt a little dazed for a few minutes. This incident made the headache worse and it persisted until the time of admission. He had been vomiting daily for the past six days. The bowels had been very constipated. Radiological examination of the family at this time revealed a pulmonary tuberculous lesion in an elder brother aged 19. The patient and this brother had always lived at home.

On admission to Southfield Sanatorium on 22nd May 1950 he was found to have miliary and meningeal tuberculosis. He was very ill and flushed, lying curled up in bed. There was periodic vomiting of small amounts of bile-stained vomit. He was very thin and emaciated. The temperature was 102°F. and the pulse rate 98 per minute. There was a marked degree of drowsiness and he did not answer simple questions. Neck rigidity and head retraction were marked and a bilateral Kernig's sign was present. Flexion of the spine was very painful. There was no motor weakness or inco-ordination. The knee and ankle jerks were absent, the abdominal reflexes present and the plantar responses flexor in type. No cranial nerve palsy was observed. There was a slight degree of bilateral papilloedema and no choroidal/
choroidal tubercles were visible. The heart was not enlarged and there was a soft systolic murmur at the apex. No abnormality was detected on examination of the lungs. The abdomen was scaphoid but otherwise normal. On lumbar puncture the C.S.F. was slightly turbid and had a yellow tinge. It was under a pressure of 210 mm. of water and the flow was slow. The white cell count was 68 per c.mm.; 20% of which were lymphocytes. The protein level was 85 mg.% glucose 32 mg.% and chloride 660 mg.%. A radiograph of the lungs showed diffuse fine miliary shadows throughout both lungs with prominent shadows in the lung roots and a moderately dense ill-defined focus in the left mid-zone. The B.S.R. (Westergren) was 8 mm. in the first hour and the Mantoux test was weakly positive to a 1 in 1,000 dilution of old tuberculin.

**Bacteriology.** Tubercle bacilli were not found on direct smear examination of the C.S.F. on admission. After four weeks' growth on Löwenstein-Jensen medium, a growth of human type tubercle bacilli was obtained and guinea-pig inoculation was also positive. No further positive results were obtained on periodic cultures during the course of treatment.

**Treatment.** Dihydrostreptomycin was used throughout. The intramuscular daily dose was 2 gm. and this was commenced on 23rd May 1950. The dose was reduced to 1.5 gm. daily on 6th June because of the development of a blotchy erythematous rash, vomiting/
vomiting and increased signs of meningism. On 27th June it was further reduced to 1 gm. daily because of the advent of slight headache, dizziness and a recurrence of the rash. During October deafness developed and it was necessary to discontinue treatment on 7th November 1950. The total amount of dihydrostreptomycin given on 168 days was 189.5 gm.

Intrathecal therapy with dihydrostreptomycin was commenced on 22nd May 1950. On the first day 25 mg. were given, on the second and third days 50 mg. and thereafter 100 mg. were given in a total of 28 days' continuous treatment. After a week's rest period it was given in a 100 mg. dose on alternate weeks for the next four weeks. Then followed another week's rest period. This scheme was repeated twice. On 27th November a further 22 injections were given, the last half of this number being reduced to a 50 mg. dose. The total amount of intrathecal dihydrostreptomycin given on a total of 148 days (i.e. on 88% of the days on which intramuscular streptomycin was given) was 14 gm.

Para-aminosalicylic acid was commenced, 10 gm. daily, on 4th July 1950 but discontinued after 2 weeks because of repeated vomiting. It was resumed on 26th July and a month later was increased to 15 gm. daily. It was finally discontinued on 20th December 1950.
Progress. There was no change in his condition until 3rd June 1950 when it appeared to be worse. There was head retraction and an increase in the neck rigidity. The periodic vomiting persisted and he could retain nothing except fluids. A blotchy pale erythematous rash had developed on the trunk. On this account the intramuscular dosage of streptomycin was reduced to 1.5 gm. daily. The rash disappeared in 48 hours.

On 14th June a gradual but definite clinical improvement was occurring. The temperature, which had been hectic, was now settling below 100°F. He was brighter and the vomiting had ceased. The head retraction had disappeared, the neck rigidity had diminished and Kernig's sign was less. All reflexes, including the abdominal, were absent. He remained very constipated and the abdomen was distended with flatus. On 28th June the rash reappeared and he again had slight headache and dizziness. The intramuscular dose was further reduced to 1 gm. daily and the rash disappeared in a few days. One choroidal tubercle was discovered in the right fundus on 29th June; already it showed early evidence of pigmentation so that it must have been present for some time before it was discovered. A slight degree of papilloedema persisted.

About the middle of July further improvement was noted. Neck rigidity had disappeared, but Kernig's sign was still present. The knee, ankle and/
WEEK BEGINNING:

STREPTOMYCIN.

INTRAMUSCULAR.

INTRATHECAL.

1950

22 MAY, 29 MAY, 5 JUNE, 12 JUNE, 19 JUNE, 26 JUNE, 3 JULY, 10 JULY, 17 JULY, 24 JULY, 31 JULY, 7 AUG., 14 AUG.

26 Gm., 1.5 Gm.

25.50 mgm., 100 mgm., 100 mgm., 100 mgm., 100 mgm.

LABORATORY.

CSF PRESSURE, mm. H₂O.

210, 75, 105, 100, 65, 57, 75, 113, 130, 105, 165, 80.
and abdominal reflexes had returned and the papilloedema had disappeared. He was bright and taking an interest in his surroundings.

On 1st August 1950 he again complained of headache and said that his whole body felt stiff. The temperature and pulse rate showed no elevation. He was found to have a return of neck rigidity, an increase of Kernig's sign, the abdominal and knee reflexes were again absent and the ankle jerks were just present and no more. There was no papilloedema. A week later he had improved again and the neck rigidity had disappeared but the other neurological signs were unaltered. Definite nystagmus had now appeared. At the end of the same month temperature and pulse rates had returned to normal and he felt very well. The nystagmus had disappeared. A slight degree of Kernig's sign still persisted, the knee jerks and the abdominal reflexes had returned. All the reflexes were present, including those of the upper limbs for the first time. Steady progress continued until by October he was without clinical signs of meningitis. A steady improvement had been noted in the C.S.F. However at this time he began to develop increasing deafness in both ears associated with tinnitus, and for this reason intramuscular streptomycin was stopped on 7th November 1950. A radiograph of the lungs showed that the miliary shadowing had disappeared.

On 22nd December 1950 the bilateral nerve deafness/
deafness had increased to the extent that he could no longer hear the whispered voice in either ear and the improvement in the C.S.F. was such that it was considered necessary to discontinue the intrathecal therapy as well. The white cells numbered 25 per c.mm., the glucose 52 mg.%, the chloride 720 mg.% and the protein 100 mg.%

At the beginning of 1951 he was a healthy-looking boy without clinical signs of meningitis and with an improving C.S.F. There was slight further pigmentation of the choroidal tubercle which has been the only one noted. There was no improvement in the deafness which was now so bad that he could only hear the loudest voice close to the ear.

During the next eight months he remained well and showed no residual effects of meningitis apart from the nerve deafness which had now become complete. There was no response to the cold caloric test which indicated complete abolition of function of the vestibular apparatus. There was no nystagmus and no clinical evidence of ataxia. The last C.S.F. examination before he was discharged home on 17th August 1951 was as follows:—cells 4 per c.mm., protein 80 mg.%, glucose 58 mg.% and chloride 730 mg.%

Summary. A boy of 16 years of age admitted with miliary and meningeal tuberculosis. Tubercle bacilli of the human type were isolated from the C.S.F. He made satisfactory clinical response and the/
the C.S. F. has shown a slow but gradual improvement. He was treated with dihydrostreptomycin alone, and developed a total bilateral nerve deafness. The total amount of intramuscular streptomycin given was 189.5 gm. and the intrathecal amount was 14 gm.
CASE NO. 20

J.C., a robust young man of 27 years of age, was in good health until May 1950. About the middle of that month he was put to bed and treated for influenza. He did not respond to a full course of sulphatriad. He became increasingly breathless and developed an irritating non-productive cough. The appetite became very poor and he became depressed and worried because he was not getting any better. On 29th May 1950 this patient was admitted to Edinburgh Royal Infirmary. During routine investigation there an X-ray film showed lung shadows which were reported to be those of miliary tuberculosis. On 31st May he was transferred to Southfield Sanatorium.

On admission to Southfield Sanatorium this man had a livid complexion, suffused conjunctivae, a dry furred tongue, dry lips and sordes on his teeth. He was mentally confused and his speech was slurred and obviously that of an ill man who found difficulty in concentrating his thoughts. There was a moderate degree of dyspnoea and cyanosis. There had obviously been no loss of weight over this short period. The temperature was 105°F. but the pulse rate only 98 per minute. There were signs of a coarse diffuse bronchitic character throughout both lungs. There was no distension of the abdomen and the viscera were not palpable. There was no abnormality of the central nervous system. The optic/
optic discs were normal and no choroidal tubercles were seen. The Mantoux test was negative to a 1 in 1,000 dilution of old tuberculin. Lumbar puncture was carried out and the cerebrospinal fluid was normal. The B.S.R. was 7 mm. in the first hour (Westergren). The white blood count was 7,600 per c.mm. with a normal differential count. The urine contained albumen but no cells. Blood was withdrawn for culture and agglutination tests.

On 1st June his condition was unchanged. He was perspiring freely and was slightly restless. Intramuscular streptomycin in a dose of 2 gm. daily was commenced. On the 2nd he remained very ill - the lungs still showed signs of diffuse bronchitis with numerous rhonchi and crepitations, he was cyanosed and definitely dyspnoeic. The tongue was as dry as a board in spite of an intake of over 100 ounces daily and an output of 63 ounces of urine. Penicillin, 200,000 units twice daily, was commenced on the 3rd because of the uncertainty of the diagnosis. On 6th June his condition was unchanged. The mental confusion and prostration were marked, he had no headache but said he could not think properly as there was a cloud over his brain. The abdomen was becoming slightly distended and he was constipated. On the evening of 14th June the results of the Widal Reaction were obtained from the laboratory. It was stated that there was agglutination in very high dilutions for B. Abortus and/
Melitensis, the highest titre being 1 in 15,000 which was very significant. There was also agglutination with 'H' agglutinin of B. Para-
typhosus "A" in a dilution of 1 in 120, which in view of T.A.B. inoculation during Army service was of little significance. Serum agglutination tests for Psittacosis and "Q" fever were negative. No organisms of the Enteric group were isolated from blood culture. In view of this very definite finding, Aureomycin Hydrochloride was obtained and, in case of any reaction of intolerance shown by some cases of Brucellosis, he was started on 250 mg. six-
hourly. Streptomycin and penicillin were now stopped. On the following day he felt a little better. The temperature had fallen to 102°F. and the pulse rate was 72 per minute. The mental confusion was lessening and he felt that he could think and speak more clearly. The dyspnoea was less and the cyanosis had gone. The abdomen was more distended. The chest signs were unchanged. On 6th June the laboratory telephoned to say that a mistake had been made with the serum and it was not J.C.'s serum which had given this agglutination to B. Abortus and B. Melitensis. Aureomycin was now stopped (total 1.5 gm.) and streptomycin and penicillin resumed in the previous dosage. The temperature had now fallen to 101°F. but there was no other change to note.

On/
On 8th June the temperature was rising again and by the evening was 104.5°F. The bronchitic signs in the chest were lessening and the breath sounds at the left base were broncho-vesicular in type, accompanied by crepitations, but above the left costal margin superficial pleural friction was heard for the first time. His drowsy apathetic condition continued and on the following day he complained of pain in the region of the left nipple. He was without sputum, but the irritating cough continued. A gastric lavage was performed on the 10th and the gastric washings contained several flecks of brightly blood-stained mucoid material which was believed to be secretion from the lungs. No tubercle bacilli were found on direct smear. During that night he had a drenching sweat and the temperature the following morning was 99°F and the pulse rate 76 per minute, but there was no improvement in his general condition. Penicillin was discontinued now and aureomycin 500 mg. six-hourly resumed. On the same evening the temperature had risen to 105°F. He seemed to be deteriorating on 14th June. The temperature was 103.5°F, the face was covered in perspiration, the cheeks were sunken and there was a pallid look about the face. The pulse was weak and the extremities were cyanosed. There were now signs of a coarse pleurisy over most of the left lung, completely masking the breath sounds. A Mantoux test, using a/
a 1 in 100 dilution, was negative. In view of the gravity of his condition, the diagnosis of which was still in doubt, and since chemotherapy was quite ineffective, streptomycin and aureomycin were stopped and one pint of group O Rh-negative blood was transfused. This had a distinctly beneficial effect. A further one-pint of blood was given two days later. A radiograph of the lungs showed relative opacity of both lower lobes, more extensive in the left - the shadowing in this lobe, despite the intensity of the physical signs, was not like that of tuberculosis.

On 19th June, over a month after the beginning of this "pyrexia of uncertain origin", he was a weary, exhausted man. The face was shrunken and of a grey colour. The temperature was climbing again and was nearly 104°F. while the pulse rate varied between 90 and 100 per minute. Over the left lung the coarse pleural friction rub had disappeared but a superficial fine rub remained; the breath sounds were weak and pulmonary consolidation was present though there was no evidence of fluid. At the right base the same features as appeared at the left base were commencing and there was definitely a pleurisy present on this side as well. For the sake of not being able to give anything better, aureomycin 750 mg. six-hourly was commenced for the third time.

By 22nd June it was noted that over the previous few days there had been a gradual step-ladder/
ladder rise of temperature and it was now 105°F. again. His condition was poor and the signs at the right base had advanced to those of consolidation and coarse pleurisy. He developed a thrombosis of the right internal saphenous vein. On this same date another lumbar puncture was performed. The C.S.F. was clear and under a pressure of 120 mm. of water. The cells numbered 52 per c.mm. of which 80% were lymphocytes, no clot appearing on standing. The protein content was 89%, glucose 44 mg.%, and chloride 666 mg.% No organisms were seen on direct smear. These findings were most suggestive of tuberculous meningitis and the appropriate treatment with streptomycin was started. There were however no clinical features of meningitis until 26th June when neck rigidity and a positive Kernig's sign were obtained, and at the same time choroidal tubercles were discovered to substantiate the diagnosis of miliary and meningeal tuberculosis.

**Bacteriology.** Tubercle bacilli have never been isolated from the cerebrospinal fluid, either by culture or guinea-pig inoculation. However a guinea-pig inoculated with urine on 6th June 1950 showed a strongly positive tuberculin test and extensive generalised tuberculosis. Through a technical error this was not successfully cultured.

**Treatment.** Intramuscular dihydro-streptomycin was given in a dose of 2 gm. daily for 12 days prior to the diagnosis of tuberculosis being made.
made. On 22nd June 1950 dihydrostreptomycin was resumed in the same dosage for 9 days and on 1st July the daily intramuscular dose was reduced to 1 gm. It was then given continuously for 15 weeks and, because of increasing deafness, was discontinued on 14th October 1950. After a rest period of three weeks, there was no improvement in his hearing and since the C.S.F. continued to be grossly abnormal, it was felt necessary to recommence the 1 gm. intramuscular daily dose on 6th November. This was given for a further 8 weeks and all treatment was finally stopped on 2nd January 1951 because his deafness had reached the stage where he could only hear a loud voice at the ear's level and because the C.S.F. had shown a definite improvement. Dihydrostreptomycin was used throughout. The total amount of intramuscular dihydrostreptomycin given on a total of 183 days was 204 gm.

Intrathecal dihydrostreptomycin was commenced on 22nd June 1950. The daily dose was 100 mg. It was given continuously for 25 days, on four days of which it was given by the cisternal route on account of a partial spinal block. Each cisternal injection produced very coarse nystagmus which lessened but did not completely disappear as the day went on, only to be greatly increased again by the injection on the following day. On 26th July a 10-day course was given, and starting on 7th August a 7-day course was commenced. A 4-week course of
100 mg. daily was started on 21st August, and was followed by a 1-week course on 25th September. Between 8th October and 12th November 25 intrathecal injections were given, and during the latter part of this time the cisternal route was again used because of the re-development of a partial spinal block. In addition to producing nystagmus these injections produced varying subjective sensory disturbances. Two 7-day periods of cisternal injections with the dose reduced to 50 mg. were given between 20th and 27th November and from 4th to 10th December 1950 - after the spinal block had re-canalised on 18th December seven injections were given by the lumbar route and intrathecal therapy was finally discontinued on 23rd December. The total amount of intrathecal dihydrostreptomycin given on a total of 122 days (i.e. on 67% of the days on which intramuscular streptomycin was given) was 11 gm. 21 out of the total of 122 injections were given by cisternal puncture.

Para-aminosalicylic acid, in a dose of 10 gm. daily, was commenced on 26th July 1950 and was increased to 15 gm. daily on 26th August. It was given in this dosage until all treatment was finally stopped on 2nd January 1951.

Progress. (from the time of diagnosis of tuberculous meningitis). It was on 26th June that the first clinical manifestations of meningitis appeared. Neck rigidity and Kernig's sign were present/
present; the knee and ankle jerks and the abdominal reflexes were absent.

Confirmation of the diagnosis of miliary tuberculosis occurred on 24th June when choroidal tubercles were discovered - there were four in the right eye and one in the left and all had the appearance of being of recent origin. All were small, irregular or circular pale yellow patches of a few millimetres diameter with a fluffy edge, the larger ones appearing raised above the surface, and none showing evidence of pigmentation. There was no papilloedema. His general condition was by now deteriorating. He was not actually drowsy but mentally very confused and at times there was a muttering delirium. The temperature at times was over 105°F. He had developed a venous thrombosis of the internal saphenous vein of the right leg and for 4 days received 10,000 units heparin thrice daily. The left side of the chest showed a recurrence of the signs of diffuse bronchitis in addition to signs of patchy consolidation at the base. The right lung now showed signs of a very coarse pleurisy, just as the left base had done earlier. He was extremely restless and delirious at night which was only controlled by intramuscular paraldehyde.

On 29th June signs of consolidation appeared at the right base as well, but still there was no sputum. There was now a fine nystagmus present/
present and the knee and ankle jerks had returned. A slight degree of bilateral papilloedema had appeared. A "dry tap" was found on lumbar puncture on 30th June and a cisternal puncture was performed. For the next 3 days the dihydrostreptomycin was given by this route in the usual dosage of 100 mg. About 15 minutes after the injection had been given he developed an extremely coarse horizontal nystagmus which did not require lateral movement of the eyes to show its presence but was present with the eye looking straight ahead. At times it was so coarse that it jolted the right upper eyelid with each rhythmic movement. Nystagmus diminished as the day went on, and on the following morning before the next cisternal injection was given it was just present and no more. The temperature at this time was becoming hectic with a diurnal range of 98° to 104°F. On 3rd July he first complained of headache accompanied by dizziness. Signs of meningism remained marked and once more knee and ankle jerks were absent. A coarse pleurisy had reappeared at the left base and there were now signs of a small pleural effusion at the right base. Lumbar puncture on 5th July showed the partial spinal block was no longer present. There was now a right extensor plantar response.

By 16th July he began to feel better and he was less confused mentally. The hectic temperature was also lessening. The C.S.F. was now definitely xanthochromic/
xanthochromic and contained numerous blood cells every day. The lumbar punctures were atraumatic. On the 20th neck rigidity had disappeared. The signs of pleurisy and consolidation at both bases were slowly resolving. At the beginning of August his condition remained poor and temperature was still elevated. There was now no papilloedema and no neck rigidity but a marked Kernig's sign. All reflexes were absent, apart from the knee jerks which were elicited with reinforcement. There were bilateral extensor plantar responses. There was a free C.S.F. flow but this fluid was yellow and contained many red cells and its biochemistry was unsatisfactory.

It was in the middle of August 1950 that he first seemed to be gaining some ground and clinical improvement was becoming noticeable. The temperature range was 100° to 101°F. There was no neck rigidity and the marked degree of hamstring muscle spasm seemed out of all proportion to his clinical condition. The state of the reflexes was as follows: knee jerks present, ankle jerks absent, both plantar responses extensor in type, cremasteric reflex present, the upper abdominal reflexes present but quickly exhausted, the lower abdominal reflexes absent and all upper limb reflexes absent. There was no nystagmus, no papilloedema and no cranial nerve lesions. Clinical examination of the chest revealed that the pleural effusion at the right base was lessening and broncho-vesicular breath sounds/
Sounds were more clearly audible. There was still bronchial breathing at the left base accompanied by fine crepitations and a few sonorous rhonchi. There were no respiratory symptoms. A radiograph at this time showed an ill-defined opacity above the right diaphragm and some ill-defined shadowing in the left lower lobe, the appearances being more suggestive of pleural shadowing than shadowing of lung disease. The miliary shadows seen on admission had disappeared.

It was on 22nd August 1950 that he first complained of slight deafness in the left ear. A slight degree of horizontal nystagmus was present again. A few days later difficulty was experienced again in the flow of C.S.F. On lumbar puncture only a small quantity of orange-yellow turbid C.S.F. could be obtained and this either by continuous jugular or abdominal pressure or by aspiration. With the latter method, using a 2 cc. syringe, subsequent specimens became less and less xanthochromic suggesting that the C.S.F. was stagnating at the distal end of the subarachnoid space of the spinal canal. The C.S.F. had now been yellow-stained with red blood cells for 5 weeks and this was not the result of traumatic punctures.

At the beginning of September he was feeling quite well, his appetite was better and he appeared to be gaining weight. There was no significant change in the neurological signs, and no improvement in the C.S.F., but for the first time the diurnal temperature/
temperature remained below 100°F. By the end of the month there was increasing deafness in the left ear and to a slight extent in the right ear and for this reason intramuscular streptomycin was discontinued for 3 weeks on 14th October 1950.

His only complaint at the beginning of November 1950 was his deafness. No improvement had resulted from interrupting his course of intramuscular streptomycin. Both ear drums were normal, apart from slight injection of the vessels around the handle of malleus which was accounted for by a recent exacerbation of an otitis externa. He could hear a whisper in the right ear but not at all in the left ear. Nystagmus, especially horizontal to the left, was now more marked than previously.

Neurological examination was now as follows - no cranial nerve lesions, no papilloedema, biceps and triceps reflexes were present for the first time, the supinators were absent, abdominal and cremasteric reflexes absent, the knee jerks were now brisk, ankle jerks absent and plantar responses flexor. There was no change in the choroidal tubercles. Apart from signs of pleural thickening at the right base, the lung disease had cleared up. Radiographically all the miliary shadows had disappeared and prominent shadows in the left lung root were all that remained. His general condition was now satisfactory and the temperature was normal. On 8th November it was decided to resume intramuscular/
intramuscular streptomycin in spite of the degree of deafness because there was no improvement in the C.S.F. It continued to be a xanthochromic fluid containing many blood cells, showed definite spider-web clot formation and had a sugar content of 35 mg.% with the chloride below 700 mg.%. The flow of the C.S.F. was poor. Queckenstedt's test was negative but a rise in the pressure was obtained with a cough but no subsequent fall occurred. This showed that a degree of spinal block had again occurred.

From the beginning of November until 18th December the spinal block was present and during this period a lumbar and cisternal puncture were carried out at the same time once weekly, while the intrathecal streptomycin was given by the cisternal route. On three occasions the cisternal fluid was clear and colourless, on two it was colourless and had a fine turbidity present with some clot formation, and on one occasion it was xanthochromic. The lumbar fluid was clear and colourless on two occasions, and xanthochromic and turbid on four occasions. The white cell count in all specimens was low, while the red cell count varied within wide limits on different occasions. On 11th December the cisternal fluid contained 3,457 red cells per c.mm., and the lumbar fluid 2,507 per c.mm. At this stage of his illness the red cell count was the striking feature in the C.S.F. On all occasions the glucose content of the lumbar fluid was a few milligrams lower than that/
that of the cisternal fluid and the same relationship existed in regard to the chloride content. Unfortunately, regular restimation of the protein contents was not possible owing to a defect in the Biochem Absorptiometer. During this period of partial spinal block intra-cisternal dihydrostreptomycin in a dose of 50 mg. was given on 17 occasions. The reactions which occurred with each injection were fairly constant. While the fluid was being injected he experienced a "burning pain" in the region of the ear which sometimes spread over the left half of the skull or sometimes down over the left side of the face to the nose. This subjective symptom passed away shortly after the injection was completed. The nystagmus (which had now been present for some weeks) gradually increased to become extremely coarse about 15 - 30 minutes after each injection. It occurred spontaneously when the patient looked straight ahead, always more marked towards the left side, and was accentuated even more by slight lateral movement of the eyes. At its worst it became vertical when the eyes were turned to the right and horizontal to the left, otherwise it was horizontal to left and right. This would gradually lessen during the day, and by next morning had returned to the degree at which it was before the intra-cisternal injection was given, only to be re-activated by the injection on the following morning/
Week Beginning:

Intrathecal Streptomycin:

105° 2000 800 800 80
104° 1750 700 700 70
103° 1500 600 600 60
102° 1250 500 500 50
101° 1000 400 40
100° 750 300 30
99° 500 200 20
98° 250 100 10
97° 0 0 0

C.S.T. Pressure. mm. H₂O.

65. 120. 133. 70. 105. 60. 50. 50. 50.
morning. During the morning and afternoon on some days he complained that he could not read print clearly and this was due to the vestibular disturbance. At times the nystagmus jolted the upper eyelid by its intensity. It was on 18th December that a positive Queckenstedt's test was obtained on lumbar puncture to indicate an opening up of the partial spinal block.

The last intrathecal injection of streptomycin was given on 23rd December 1950 and at that time the C.S.F. still had a fairly yellow colour with a fine turbidity. On 2nd January 1951 the fluid was clear and colourless on lumbar puncture and the white and red cell counts were the lowest they had ever been. Because of this improvement, which had occurred so soon after stopping intrathecal treatment, and because of complete nerve deafness in the left ear and severe impairment of hearing in the right ear, intramuscular streptomycin was stopped on 2nd January 1951. On this date his general condition was very satisfactory. He was cheerful and had a good appetite. The temperature was normal. Two of the five original choroidal tubercles showed evidence of healing and pigmentation. There were no cranial nerve lesions and no papilloedema. There was a fine sustained nystagmus. There was no neck rigidity but there was a positive Kernig's sign to 50° in both legs - this was probably not entirely the result of meningeal irritation/
irritation but an actual shortening of the hamstring muscles (this feature was also observed in Case no. 11). The state of the reflexes were - triceps, biceps and supinator reflexes present, abdominal reflexes absent, knee jerks very brisk, ankle jerks both absent. The soles of the feet were now so sensitive that attempts to elicit the plantar response produced jerking movements of all toes and a mass withdrawal. The urine was now perfectly normal.

On 22nd January 1951 a sixth choroidal tubercle was found lying far out from the optic disc. It was already pigmented so had obviously been missed on previous examinations. At the beginning of March 1951 he started to get up. The nystagmus persisted and for a time he was so ataxic that he could not walk unaided. Deafness in both ears was now complete.

There was little change to note in the following months. At the beginning of August 1951 he was convalescing at the Royal Victoria Hospital. His general condition was satisfactory. Nystagmus was still present and though the ataxia had shown improvement he still grasped for support when it was readily available. Compensation for a markedly diminished vestibular function was not helped by the severe degree of myopia present. He was totally deaf. There was little change in the choroidal tubercles, though all but two were pigmented. It was/
was not possible to extend the leg with the thigh flexed and this gave the impression of a positive Kernig's sign. It was probably a residual tightening of the hamstring muscles, as a result of their prolonged spasm during the acute stage. The abdominal reflexes and ankle jerks remained absent and the plantar responses were equivocal - this was probably a vascular manifestation of the acute spinal meningitis which had occurred. The last examination of the C.S.F. was as follows:

- cells 12 per c.mm.,
- protein 80 mg.%,
- glucose 58 mg.%,
- chloride 724 mg.%

It has been noticed that the cell content is still excessively elevated considering treatment was stopped 7 months ago, and this will require further observation.

**Summary.** A case of miliary tuberculosis who subsequently developed meningitis. The initial symptoms were those of a severe toxaemia. Clinical signs of meningitis appeared later. Response to streptomycin treatment was satisfactory and treatment was stopped as soon as possible as this patient had become totally deaf. Dihydrostreptomycin alone was used. He is now very well, apart from deafness and vestibular disturbance, but the C.S.F. cell and protein contents continue to remain slightly abnormal. He is up for several hours in the day, and it is hoped that it will not be long before he is discharged home.
CASE No. 21.

D.J., a young boy of 3 years of age, contracted whooping cough followed by German measles. He recovered completely from both, except that his appetite remained rather poor. At the beginning of July 1950 his mother was admitted to hospital with pulmonary tuberculosis and this patient was examined as a contact. He was found to be ill and feverish and an X-ray of the lungs showed enlarged upper mediastinal glands and miliary tuberculosis of both lungs. For two days prior to admission he had complained of some headache and photophobia. He had also become constipated.

He was admitted to Southfield Sanatorium on 20th July 1950. He was a pale, thin child with a temperature of 102.5°F. He was fretful but not drowsy. There was some neck rigidity but no Kernig's sign. Deep and superficial reflexes were all present. There was no papilloedema but two early choroidal tubercles were discovered in the right optic fundus. There were no conclusively abnormal lung signs. The urine contained no albumin, but a number of cellular casts, pus cells and red blood cells were present. The E.S.R. (Westergren) was 38 mm. in the first hour and the Mantoux test was positive to a 1 in 1,000 dilution of old tuberculin. Lumbar puncture was performed and a colourless, slightly turbid fluid was obtained. It contained 308 cells per c.mm., of which 70% were lymphocytes.
The protein content was 70 mg.%, glucose 34 mg.%, and chloride 60+ gm.%

**Bacteriology.** The human type tubercle bacillus was isolated from the cerebrospinal fluid on admission but not during the course of treatment.

**Treatment.** Dihydrostreptomycin was used throughout treatment. The daily intramuscular dose was 1 gm. This was given continuously for 23 weeks, the total amount given being 160 gm.

Intrathecal therapy was commenced on 22nd July 1950. A 50 mg. dose daily was given continuously for 73 days. After a fortnight's interval at the beginning of October 1950 it was given for a further 64 days, to be finally discontinued on 26th December 1950, due to the development of a sudden and complete deafness. The total amount of intrathecal dihydrostreptomycin given on a total of 137 days (i.e. on 85% of the days on which intramuscular streptomycin was given) was 6 gm.

**Progress.** By the end of July he was still an ill boy. The temperature remained elevated in the region of 101°F. The neck rigidity and photophobia present on admission had disappeared, and he was now without physical signs.

During the next three months he showed a gradual improvement in his general condition. The temperature slowly fell and by October 1950 was normal on most days. His appetite was good and he was gaining weight. He was bright and happy. A gradual/
WEEK BEGINNING:
STREPTOMYCIN.

INTRAMUSCULAR:

INTRATHecal:

1950

R.I.E. Readings.

C.S.F. PRESSURE \( \text{mm} \times H_{2}O \)

160. 110. 110. 105. 120. 145.
gradual improvement had been occurring in the C.S.F. all the time. The E.S.R. was normal. On 6th November 1950 there was a steep rise in the C.S.F. cells to 209 per c.mm., but this was an independent finding and bore no relation to his good clinical condition. A radiograph of the lungs at this time showed the mediastinal glandular bulge to be unaltered and in most of the lung fields there were fine shadows suggesting residual miliary deposits. The choroidal tubercles in the right fundus were now showing evidence of healing and early pigmentation.

A few days before Christmas 1950 it was noticed that he sometimes was slow to answer questions or else failed to answer them altogether, and sometimes he would just grin when talked to. On 27th December 1950 his hearing was tried out by various means and it was obvious that he was now totally deaf in both ears. He was always a very good speaker for a boy of his years but a sudden change occurred in his speech. He muttered away frequently but his speech was largely unintelligible. Dihydrostreptomycin was stopped forthwith. By this time the glucose and chloride levels of the C.S.F. were normal while the cells and protein remained elevated.

At the end of January 1951 the C.S.F. had shown a further improvement since treatment was stopped and the number of cells was decreasing. He was in good general condition with a normal temperature. His deafness however remained complete and/
and his speech showed no improvement.

By the beginning of September 1951 the general condition was very satisfactory and the C.S.F. had returned to complete normality. However, the deafness remained complete and at the time of writing he no longer spoke at all. When he wanted something he would just point with his finger, making no effort to speak.

**Summary.** A boy of 3 years, admitted with miliary tuberculosis and very early clinical signs of meningitis. The response to dihydrostreptomycin was satisfactory and complete, but he has become totally deaf. He is at present convalescing and special speech training is being arranged for him.
CASE No. 22.

F.N., an infant of 12 months of age, became unwell shortly after the death of his mother from pulmonary tuberculosis in April 1950. He developed a severe irritating cough and his breathing was wheezy. He was eating and sleeping poorly and the bowels were constipated. He was admitted to the Royal Hospital for Sick Children, Edinburgh on 16th June 1950 as a case of suspected tuberculosis.

Radiographical evidence of miliary tuberculosis and right paratracheal glandular enlargement were found. The Mantoux test was weakly positive to a dilution of 1 in 1,000 old tuberculin. At that time there was no evidence of meningitis and the cerebrospinal fluid was normal. However on 2nd August 1950 a diagnosis of tuberculous meningitis was confirmed by the isolation of the tubercle bacillus from the C.S.F. which was also typical in other respects. This infant was admitted to Southfield Sanatorium on 3rd August 1950. His general condition was quite good and he was not emaciated. He was fretful but not drowsy and there were no clinical signs of meningitis. The temperature was 101°F.

**Bacteriology.** Tubercle bacilli having the cultural characteristics of the human type were isolated from gastric washings in June 1950. The organism was also isolated from the C.S.F. on direct smear, on culture and by guinea-pig inoculation at the/
the time of development of the meningitis.

**Treatment.** Dihydrostreptomycin by the intramuscular route was commenced on 16th June 1950. The daily dose was 0.5 gm. It was given continuously until 27th September 1950. The total amount given was 52 gm. on 104 days. It was discontinued because of the rapid deterioration in his condition at this time.

Intrathecal dihydrostreptomycin was commenced on 4th August 1950 in a dose of 50 mg. 47 injections were given between then and 27th September 1950 when all treatment was discontinued. At this time intrathecal tuberculin was instituted and periodic intrathecal injections of streptomycin followed. The number of the latter given before his death on 21st February 1951 was 49, the dose varying between 25 and 50 mg. The total amount of intrathecal streptomycin given on 96 days was 4 gm. (i.e. on 92% of the days on which intramuscular streptomycin was given).

**Progress.** There was little change in his condition until the end of August 1950 when he began to vomit with increasing frequency, and he was able to retain very little nourishment by mouth. At the beginning of September a marked deterioration in his condition occurred. Neck rigidity appeared for the first time and head retraction soon followed. Vomiting persisted and weakness and emaciation became evident. Soon a tremor of the mouth and eyelids appeared and sometimes a coarse tremor involved the whole/
whole head. There was no papilloedema. By the middle of the same month the deterioration was accelerated and he now showed opisthotonus in addition to marked head retraction and he was becoming weak and wasted. There was now an obvious increase in the size of the head. At the end of September his condition was approaching one of decerebrate rigidity and all streptomycin therapy was now stopped. Within a week there was a noticeable degree of clinical improvement. He became more alert, the degree of meningism decreased and the vomiting ceased. This improvement however was only temporary. Meningism increased again and the C.S.F. became xanthochromic and was under low pressure. The protein content was 3,500 mg.% and a partial spinal block was therefore present.

In view of the hopeless outlook for the child, the use of intrathecal tuberculin was decided upon. At this time the Mantoux test was positive (6 mm.) to a 1 in 1,000 dilution. On 12th October 1950 he was given 1 ml. of 1 in 1,000 dilution of P.P.D. (containing 7.5 ug./ per ml.) by the lumbar route. Gradually increasing doses of tuberculin were given at about 6-day intervals, by which time the reaction to the previous injection would have settled. The reaction commenced about 12 hours after the injection and usually took the form of increased head retraction and opisthotonus; he would be pale, listless and very irritable; there was no rise of temperature but the pulse rate was usually raised/
raised; vomiting often occurred. This exacerbation generally lasted 36 - 48 hours and then subsided for the next 24 - 48 hours. Then followed a secondary exacerbation, less marked than the initial reaction, if the initial reaction had been at all severe. After the primary reaction had passed, small doses of intrathecal streptomycin were given for 2 or 3 days preceding the next tuberculin injection. The C.S.F. reaction to the intrathecal tuberculin was fairly constant. The rise of pressure from outpouring of fluid from the choroid plexuses was always controlled by removal of fluid by the lumbar route. A marked increase of cells occurred, the vast majority being red cells and the protein content was considerably increased. Following the first injection of intrathecal tuberculin, the spinal block appeared to resolve and no further difficulties were encountered during the administration of tuberculin.

Between 12th October 1950 and 7th January 1951 this child received 12 intrathecal injections of tuberculin, the final dose being 0.8 ml. of a 1 in 10 dilution (i.e. 0.6 ug. of tuberculin). During this period, the clinical response was dramatic. He gradually came to behave and play like a normal child, he was bright and cheerful and had a keen appetite. He put on flesh and strength returned to his muscles. Clinical signs of meningitis became minimal and there was only slight evidence of neck rigidity and Kernig’s sign. The sugar content of the C.S.F. had risen from 20 mg.%
20 mg.% to 40 mg.% At the end of this time the Mantoux test was positive (5 mm.) to a 1 in 1,000 dilution.

Unfortunately at the beginning of February 1951 the improvement was no longer maintained. Definite signs of meningism returned, he lost his appetite and began to vomit again. Early papilloedema was detected. Only 1 or 2 ml. of C.S.F. could be obtained by lumbar puncture and by cisternal puncture, and this fluid was xanthochromic. Blockage of the cerebrospinal pathway thus necessitated bilateral frontal burr holes being made into the anterior horns of the lateral ventricles. Considerable dilatation of the lateral ventricles was found and gradual decompression of the hydrocephalus was instituted through a soft rubber catheter in the anterior horn. During the next few days about 200 ml. of slightly blood-stained C.S.F. were drained daily, and there was some improvement in his general condition, while signs of meningism decreased. Further deterioration however set in on 6th February. He developed increased meningism with sudden extensor spasms which produced marked opisthotonus. He was very distressed and restless. On 7th February the dose of the last P.P.D. injection was repeated and injected in the right lateral ventricle. It produced a marked rise of temperature and pulse rate and led to increased meningism. Thereafter his condition/
condition went rapidly downhill. He became semi-comatose and emaciated and vomited frequently. Tremor and purposeless movements of the limbs appeared and signs of meningitis increased. On 21st February circulatory and respiratory failure occurred and he died. His weight at the time of death was only 1½ pounds.

Post-mortem examination was carried out by Dr. Agnes Macgregor of the Royal Hospital for Sick Children, Edinburgh. The sutures of the skull were gaping slightly and the anterior fontanelle was still widely open. The surface of the brain was dry and the convolutions flattened. At the base of the brain, in the interpeduncular fossa and around the mid-brain and medulla, there was a thick layer of hard, opaque, presumably organizing tuberculous exudate. It varied in thickness from 4 - 8 mm. There was a similar exudate lying between the cerebellum and medulla, which filled the cisterna magna and appeared completely to shut off the exit of the C.S.F. from the interior of the brain. The lateral ventricles were distended and the cerebral tissue surrounding them greatly thinned. No caseous nodules were found in the substance of the brain.

Microscopically, the character of the meningeal exudate was found to vary in different areas. Generally, a considerable amount of organization had taken place. This resulted in the replacement/
replacement of the fibrino-cellular tissue by tuberculous granulation tissue, which had become densely fibrous in some areas. However among this tissue were found many typical tubercle follicles, all showing peripheral fibrosis and most being devoid of caseation. Furthermore, in the interpeduncular fossa and cisterna magna fairly large caseous masses had formed, but were surrounded by a fairly thick wall of fibrous or granulation tissue. Amongst the organizing tissue there were areas containing many lymphocytes and histiocytes; there was no fibrin, the cells being supported on a delicate network of fibroblasts. In the cisterna magna, where the organizing exudate was so dense, were spaces which had the appearance of having contained fluid and might have formed communicating channels through which a small amount of C.S.F. could have percolated into the subarachnoid space of the spinal cord.

The meningeal blood vessels showed varying changes. Many remained unaltered even when found to be traversing organizing exudate. Some however had been obliterated by endarteritis; while others showed a reduction in the size of their lumen. Fibrous thickening of the intima was seen in most of the larger arteries, and intimal fibrosis had led to narrowing of the lumen in smaller arteries. The endarteritis appeared to be of long standing.

Thrombosis/
Thrombosis of arteries or veins was not seen.

There was little alteration of the brain substance. Cellular infiltration along the blood vessels entering from the meninges was less than seen in the untreated case.

The spinal cord was covered with tuberculous exudate, most plentiful towards the upper end. This exudate appeared to be more recent than at the base of the brain. The dura was not obviously damaged or thickened at the site of lumbar punctures but in this region there were several small red masses on the posterior aspect of the dura. Microscopical examination showed fibrous thickening and several deposits of haemosiderin and a few small cellular tubercles.

A primary tuberculous focus was found in the lower lobe of the right lung. It had a caseous centre which was partly calcified and surrounded by a thin fibrous membrane. It did not seem to have been healing satisfactorily and very many tubercle bacilli were isolated from it. Throughout both lungs moderate numbers of minute miliary tubercles were present. The glands at the lung root were minute and calcified and hard to find. The microscopical appearance of the very small miliary tubercles was striking. They consisted of foci of endothelioid cells with a variable number of lymphocytes forming an ill-defined outer zone. There was no evidence of caseation/
of caseation and no fibrosis. Giant cells were very occasional. These miliary tubercles appeared to be of relatively recent origin.

Also found in the lungs was a considerable amount of old fibrosis, having a patchy distribution. Its character and distribution suggested that it was the result of healing of former miliary tubercles. If this was the case, it represented a very complete healing of a fairly heavy miliary dissemination.

The liver contained numerous very small miliary tubercles. None were healed. There was no fibrosis or caseation. In place of the usual lymphocytes considerable numbers of polymorphonuclears were present. The spleen also showed numerous very small miliary tubercles, similar to the recent ones found in the lungs. None were healed. Numbers of tubercles were also found in the Peyer's patches of the ileum, resembling those found elsewhere and showing neither caseation nor fibrosis.

Summary. The case of a young child who developed tuberculous meningitis three months after contracting miliary disease. This occurred in spite of the administration of systemic streptomycin. There was an initial response to treatment but a rapid deterioration occurred. The use of intrathecal tuberculin caused dramatic exacerbations of the meningitis but finally led to considerable improvement. This again was not maintained, and in spite of intra-ventricular drainage for increasing hydrocephalus/
hydrocephalus, he went downhill and died. The post-mortem findings indicated considerable healing had taken place while foci of acute tuberculous disease were present in the surrounding areas in most organs.
CASE No. 23.

W. S., aged 13 years, developed frontal headache five days before admission. Vomiting occurred and he lost his appetite. He also became constipated. In December 1950 he was treated for an "atypical pneumonia with effusion". The presence of tuberculous disease in the underlying lung was suspected but was not confirmed. There was no history of contact with tuberculosis.

On admission to Southfield Sanatorium on 5th February 1951 he was drowsy but could answer questions intelligently. The temperature was 101°F. Neck rigidity was moderate and Kernig's sign was marked. There was slight photophobia. Papilloedema was not present. There was a 7th nerve palsy on the left side. The limb reflexes were depressed and the plantar responses were flexor. A radiograph of the lungs showed diffuse irregular opacities throughout both lungs. The Mantoux test was positive to a 1 in 1,000 dilution of old tuberculin. The C.S.F. was under a pressure of 260 mm. water and showed a fine turbidity. The white cells numbered 195 per c.mm., the protein content was 240 mg.%, the glucose 25 mg.%, and the chloride 656 mg.%

Bacteriology. The tubercle bacillus of the human type was isolated from the C.S.F. on Löwenstein-Jensen culture and by guinea-pig inoculation.

Treatment. The calcium chloride complex of streptomycin/
streptomycin was commenced in a daily dose of 1 gm. on the day of admission. It was given continuously and at the time of writing (August 1951) he had already received 175 gm. and, from the progress he was making, it was anticipated that treatment would be stopped in a few weeks' time.

The intrathecal dose of streptomycin used was 50 mg. During the first four weeks he received 21 intrathecal injections, to each of which were added 6 units of streptokinase. After this, he received the standard course of 4 weeks' continuous injections, followed by treatment on alternate weeks for the next four weeks. This course was repeated twice up to the time of writing. Intrathecal streptomycin was given on a total of 128 days (i.e. on 73% of the days on which intramuscular treatment was given) and the total amount to date was 6.5 gm.

The total amount of streptokinase given was 114 units.

**Progress.** The headache and vomiting quickly subsided but he remained lethargic for many weeks. No unusual symptoms occurred as a result of the use of streptokinase. A fortnight after admission he developed a slight ptosis on the right side, and the left plantar response became extensor.

Four weeks after commencing treatment definite clinical improvement occurred. The temperature was settling in the region of 100°F. Meningism was less but the focal signs were unchanged. He became less lethargic/
lethargic. At the beginning of April 1951 further clinical improvement was evident. Lethargy disappeared and he became bright and cheerful once more. The temperature fell below 100°F. The right ptosis was no longer visible and the left facial palsy was less noticeable. Neck rigidity had disappeared and Kernig's sign became less marked. The left plantar response remained extensor and the right one was equivocal. He remained constipated. A gradual but definite improvement was also occurring in the C.S.F.

At the end of May 1951 he was a bright, active boy without symptoms. The temperature was falling to within normal limits. The right ptosis and the left facial palsy had completely cleared up. A slight degree of Kernig's sign persisted. Both plantar responses were now extensor and both ankle jerks were absent.

His satisfactory improvement continued and at the time of writing he is without symptoms and in good general condition. The temperature is normal. At present the only physical signs are the slightest degree of Kernig's sign, persisting bilateral extensor plantar responses and fine nystagmus which appeared 4 weeks ago. All other reflexes are present and equal. The C.S.F. has shown considerable improvement and at present the cells number 9 per c.mm., the protein content is 60 mg.%, the glucose 146 mg.%, and the chloride 740 mg.%. He has now completed 6 months'
months' treatment and treatment will be discontinued when a glucose level of over 50 mg.% has been attained. Hearing has been normal at all times.

Summary. A boy of 13 years suffering from tuberculous meningitis in an intermediate stage. The response to treatment was entirely satisfactory throughout, the C.S.F. and clinical picture showing gradual improvement all the time. The C.S.F. graph shows typically the glucose-chloride curves diverging from the cell-protein curves as improvement occurred.
CASE No. 24.

Mrs. E.W., aged 26 years, complained of an increasingly sore throat and difficulty in swallowing in October 1950. Neck glands showed considerable enlargement. From the ulcers of the throat and pharynx tubercle bacilli were recovered and this was regarded as the primary site of the tuberculous infection. While receiving treatment for this condition in an Edinburgh hospital she developed headaches, sickness and signs of meningeal irritation, and lumbar puncture showed characteristic changes in the C.S.F. Tubercle bacilli were discovered on direct smear examination of the fluid.

Treatment of the meningitis was instituted at the City Hospital, Edinburgh on 24th December 1950. Clinical improvement occurred but the C.S.F. findings remained most unsatisfactory. The patient was then admitted to Southfield Sanatorium on 15th March 1951. She was an anxious, nervous woman without any symptoms of meningitis. The temperature range was between 98.5° and 100°F. She was neither lethargic nor drowsy and was entirely co-operative. She had lost a considerable amount of weight. There was a slight degree of neck rigidity and Kernig's sign was present. The only alteration in the reflexes was an extensor plantar response on the left side and absence of the abdominal reflexes. The optic fundi were normal. No abnormality was seen in the throat and there only remained an odd shotty gland/
gland on the right side of the neck. The lungs were normal. The Mantoux test was positive to a 1 in 1,000 dilution and the B.S.R. was 23 mm. in the first hour (Westergren). The C.S.F. was slightly turbid and was under a pressure of 120 mm. water. It contained 405 cells per c.mm., of which only 32% were lymphocytes. (The high polymorph percentage was due to the intrathecal streptomycin previously administered.)

**Bacteriology.** Tubercle bacilli of the human type were isolated from the C.S.F. when the patient was admitted to Southfield Sanatorium in spite of 3 months' streptomycin treatment.

**Treatment.** The calcium chloride complex was used throughout. While in the City Hospital she received a total of 76 gm. intramuscularly. 1 gm. daily was commenced at Southfield Sanatorium on 15th March 1951 and this was given continuously until 9th July. It was recommenced again on 9th August 1951 as the C.S.F. condition was not yet satisfactory. The total amount of systemic streptomycin given to date (August 1951) was 191 gm.

While at the City Hospital this patient received 40 intrathecal injections of 100 mg. each. At Southfield Sanatorium she received the standard course of 42 injections in 63 days and this course has been repeated twice up to the present. The amount of intrathecal streptomycin given on a total of 127 days (i.e. on 66% of the days on which intramuscular/
intramuscular treatment was given) was 12 gm.

P.A.S. was given for the first three weeks, but as it led to anorexia and nausea, it was not continued.

Progress. There was very little progress to note at first. Symptoms of meningitis were absent from the time she was admitted. At first there was a slow improvement in the C.S.F. but after the first few weeks the improvement ceased and its condition remained stationary. After four weeks' treatment neck rigidity had disappeared and Kernig's sign was less on both sides. Towards the end of April 1951 a fine nystagmus appeared for the first time.

Towards the end of July 1951 there had been definite improvement in her general condition. She was looking well and happier and had gained weight. The temperature had returned to normal, though I.T. therapy always led to a slight elevation. She was entirely without symptoms. Neck rigidity was absent, but a slight degree of Kernig's sign persisted. Nystagmus was now absent and the hearing was entirely normal. The abdominal reflexes remained absent and the plantar responses were now both flexor. All other reflexes were present and equal. Slight improvement was occurring in the C.S.F., but compared to the satisfactory clinical state at the time of writing, its response was disappointing.

Treatment has now been in progress for 7 months and, in spite of the improving clinical condition,
condition, will be continued until a better response has occurred in the C.S.F.

Summary. A woman aged 26 with a primary tuberculous infection of throat and larynx and cervical adenitis who developed clinical meningitis 3 months later. The response to treatment, especially the C.S.F. response, has been slow. Improvement is now occurring after 7 months' treatment and the prognosis seems more favourable.
CASE No. 25.

M. McD., 23 years of age, developed "influenza" seven weeks prior to admission. It was associated with headache and tiredness and pain in the spine and between the shoulder blades. She was confined to bed for a fortnight. She went back to work but never felt really well. Four weeks before admission, she began to vomit and notice photophobia. Later the headache became more severe, and she was sleeping poorly. The back and shoulders were painful and stiff. Weakness of the face caused her to dribble saliva. She lost her appetite and became constipated.

On admission to Southfield Sanatorium on 25th April 1951 she was an ill woman with a temperature of 100°F. She was drowsy but could be roused to answer questions sensibly. There was marked neck rigidity and Kernig's sign. A marked left facial palsy and considerable papilloedema were present. There was a complete left hemiplegia and the reflexes on the left side were brisk. Left ankle clonus was present. The abdominal reflexes were absent and the plantar responses were extensor. There was no evidence of disease elsewhere. The Mantoux test was positive to a 1 in 1,000 dilution of old tuberculin and the B.S.R. was 27 mm. (Westergren). On lumbar puncture the C.S.F. was under a pressure of over 300 mm. water and contained a fine turbidity. The white count was 167 per c.mm., of which 80% were lymphocytes/
lymphocytes. The protein content was 210 mg.%, glucose 33 mg.% and the chloride 630 mg.%. An X-ray of lungs showed ill-defined shadowing of the central area of the right lung.

**Bacteriology.** Tubercle bacilli of the human type were isolated from the C.S.F. on admission by culture and guinea-pig inoculation.

**Treatment.** The calcium chloride complex of streptomycin was used throughout. The intramuscular dose was 1 gm. daily and was commenced on the day of admission. It has been given continuously until the time of writing (July 1951) and the total amount is therefore 98 gm.

The daily intrathecal dose was 100 mg. The usual interrupted course was followed and to date she has received injections on 66 days (i.e. on 67% of the days on which intramuscular treatment was given). The total amount was 6.5 gm.

**Progress.** As this patient is still undergoing treatment and the outcome is most uncertain, the progress notes will be brief.

A considerable degree of power returned to the left arm and left leg a few weeks after the commencement of treatment, but the speed of recovery is at present much slower. Both limbs remain spastic and there is often a coarse tremor of the left hand. The reflexes remain very brisk and ankle clonus has persisted throughout.

Headache/
Week Beginning:
23 Apr. 30 Apr. 7 May. 14 May. 21 May. 28 May. 4 June. 11 June. 18 June. 25 June. 2 July. 9 July. 16 July. 23 July. 30 July. 6 Aug. 13 Aug. 20 Aug. 27 Aug. 3 Sept.

1 Gm.

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### CISTERNAL

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### CHLORIDE

- 100 mgm

### GLUCOSE

- 100 mgm

### TEMPERATURE

- 100 mgm

### PROTEIN

- 100 mgm
Headache was very troublesome for weeks and it was not until July 1951 that it finally cleared up. Neck rigidity is slightly less than at the time of admission but it is still very marked. Kernig's sign is even greater than on admission. Drowsiness quickly left her but she remains rather lethargic and still continues to sleep for a large part of the day. The marked papilloedema did not disappear until 3 months after admission. Thus in spite of over 3 months' treatment, her clinical condition has shown very little improvement.

The same unsatisfactory state of affairs exists in the C.S.F. There has been virtually no improvement from 3 months' treatment. This is shown in the accompanying graph. The glucose value is actually lower now than at the time of admission. A partial spinal block supervened on 28th May 1951 and required the administration of the intrathecal streptomycin by the cisternal route. The usual toxic manifestations of drowsiness, marked nystagmus and blurring of vision occurred. The block cleared in a week's time and once again suggested that the obstruction was partly due to exudate but was accentuated by the administration of streptomycin into the lumbar theca.

One aspect of the intrathecal therapy of this case merits a separate description. After the resolution of the spinal block, a cisternal puncture was/
was performed on two occasions to assess the state of the cisternal C.S.F. On each occasion symptoms of subarachnoid haemorrhage followed and heavily blood-stained C.S.F. was obtained at lumbar puncture the following day. This presumably was due to bleeding from the alanto-occipital membrane which had become unusually vascular as a result of the injection of cisternal streptomycin.

Summary. A patient of 23 years of age admitted in an advanced stage of tuberculous meningitis. A left hemiplegia was present. After 3 months' treatment there has been little clinical response and the C.S.F. remains as unsatisfactory as at the time of admission. The prognosis appears definitely unfavourable in this case. Treatment is at present being continued (July 1951).
CASE No. 26.

M. McC., a girl of 12 years of age, had a non-tuberculous pyelitis in February 1951 and afterwards she just never seemed very well. Two weeks before admission she had become listless and irritable. She lost her appetite and became constipated. Two days before admission she became drowsy and mentally confused. She had been obviously losing weight.

On admission to Southfield Sanatorium on 12th May 1951 she was ill and emaciated. The temperature was 102°F. She was stuporous, failing to answer questions but responding to simple orders. There was grinding of the teeth. There was marked neck rigidity and Kernig's sign was positive. A slight degree of bilateral papilloedema was present. There was absence of the abdominal reflexes, and the plantar responses were extensor. Photophobia was present. There was no evidence of disease elsewhere. The urine was not examined as she was incontinent. The Mantoux test was positive to a 1 in 1,000 dilution old tuberculin. The C.S.F. was under a pressure of 200 mm. water, was faintly yellow in colour and contained a fine turbidity. The cells numbered 508 per c.mm., of which 80% were lymphocytes. The protein content was 730 mg.%, glucose 20 mg.% and the chloride 580 mg.%

**Bacteriology.** The human type tubercle bacillus was isolated from the C.S.F. on admission by/
by culture and guinea-pig inoculation.

Treatment. The calcium chloride complex of streptomycin was given in a daily dosage of 1 gm. daily by the intramuscular route and 50 mg. daily by the intrathecal route.

Progress. During the first few days of treatment there was some improvement in the mental state. 5 days after admission she had two convulsions, one shortly after the other. The pulse quickened and the respirations became irregular and she died shortly afterwards.

Autopsy. The brain showed thick opaque yellow exudate in the interpeduncular fossa, over the pons and around the mid-brain. It had spread to a slight extent along the lateral fissures, but was absent over the hemispheres. The brain was swollen and the convolutions flattened. There was moderate dilatation of the whole ventricular system. Microscopically the exudate had the usual characters of the untreated case of tuberculous meningitis. Apart from slight evidence around the basilar artery, there was no evidence of organization. No vessels showed endarteritis. The exudate, which showed the usual concentration in the perivascular spaces, had invaded the brain substance. The superficial layer of the pons was softened and infiltrated with white cells. A small caseous primary focus was present in the lower lobe of the right lung, and the regional/
regional lymph glands were also caseous. There was no evidence of miliary tuberculosis.

**Summary.** A case of tuberculous meningitis in a girl of 12 years of age, admitted in an advanced stage. There was no response to treatment and she died 5 days after admission.