TUBERCULOUS MENINGITIS

EARLY DIAGNOSIS, AND A REVIEW OF TREATMENT WITH STREPTOMYCIN

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At a unit at Highgate Hospital, established under the auspices of the Medical Research Council, 67 cases of tuberculous meningitis were admitted during the period July, 1947, to August, 1948. We have analysed the clinical and pathological findings in these cases and in a further 9 patients who recovered without streptomycin.

For the purpose of assessing the results of streptomycin treatment the analysis is confined to 54 cases (Table I) admitted during the period July, 1947, to May, 1948, giving a minimum observation period of 231 days (8 months).* Of these cases 23 were included in the Medical Research Council Report (1948).

Diagnosis

History of Contact.—A history of contact was established in 23 of 67 cases (34%). Patients under 3 years of age differed from older patients as shown in Table II.

TABLE II

	Total No.	No. giving History of Contact
Patients under 3 years of age ..	21	12 (57%)
Patients over 3 ,, ,, ..	46	11 (24%)
	67	23 (34%)

$\chi^2 = 5{\cdot}7$. $P < 0{\cdot}02$.

Three of the nine patients who recovered without streptomycin treatment gave a history of contact with tuberculosis.

Clinical Findings

Table III summarizes the main clinical findings and illustrates the interval between the first appearance of signs and symptoms and the day of diagnosis—the latter being the day on which the decision was made to start streptomycin treatment.

In this series of 67 cases the basic pattern of the disease was remarkably constant. Tuberculous meningitis has a prodromal period, characterized by irritability, listlessness, and fatigue, and failure to gain (or actual loss of) weight. It is not possible to know how long this stage lasts in any given case; it may be a few days or as long as three months. The child may appear to recover temporarily, or may pass directly into the next stage, characterized by headache, vomiting, anorexia, constipation, and fever (in that order of frequency of occurrence). Table III shows that diagnosis was most commonly made eight to fifteen days after the beginning of this second stage. Drowsiness, squint, photophobia, and neck rigidity came later, preceding diagnosis by one to five days.

Twenty-one of our patients were under 3 years of age. In this age group some of the signs and symptoms described above are not easily discernible or are impossible to elicit because such patients are often unable to convey complaints.

*Cases admitted after May, 1948, form part of a series alternate members of which received intrathecal "sulphetrone" in addition to streptomycin; we hope to report on this series later.

TABLE III.—*The Interval between the First Appearance of Signs and Symptoms and the Day of Diagnosis*

	Days before Diagnosis									
	0–3	4–7	8–11	12–15	16–20	21–30	31–40	41–50	51–60	61–70
Headache ..	2	3	12	10	2	6	1	0	1	1
Vomiting ..	4	10	16	5	2	4	0	0	0	0
Anorexia ..	1	2	5	7	3	3	2	0	0	0
Constipation ..	0	5	5	3	0	0	2	0	0	0
Irritability ..	2	2	4	4	2	1	2	1	0	0
Fatigue	0	3	2	2	3	1	1	1	0	0
Wasting	0	0	0	2	1	1	0	1	1	0
Drowsiness ..	6	8	6	3	1	0	0	0	0	1
Squint	3	1	0	0	0	0	0	0	0	0
Fever	1	2	6	3	1	2	0	0	0	0
Neck rigidity ..	21	7	2	0	0	0	0	0	0	0
Paralysis ..	0	0	1	1	0	0	0	0	0	0
Fits	4	0	1	0	0	1	0	0	0	0
Delirium ..	1	2	0	0	0	0	0	0	0	0
Coma	6	0	0	0	0	0	0	0	0	0
Abdominal pain	0	1	0	1	0	0	0	0	0	0
Diarrhoea ..	0	1	0	2	0	0	0	0	0	0
Photophobia ..	4	0	0	0	0	0	0	0	0	0

The figures in the body of the table indicate the frequencies of occurrence of the intervals.

The prodromal features may be missed in this group; listlessness may be difficult to detect, and minor degrees of irritability may be attributed to teething or feeding difficulties. Such patients may be unable to disclose the presence of headache (the earliest and the commonest event in the next stage), so that vomiting becomes the presenting feature. In very young patients the disease tends to run a more rapid course; the vomiting may rapidly give place to meningism, squint, drowsiness, and soon to coma. Vomiting (rapidly followed by meningism) was the earliest sign in 23 of the 67 patients, and 16 of these 23 were not more than 3 years of age, the oldest of the 23 being 5 years of age.

Apart from the variations in mode of onset due to age, certain less common signs and symptoms may be superimposed on the general pattern, or the presenting features may be notably few in number. Three patients (all under 3 years of age) presented with fever only—followed by neck rigidity within a few days. In three cases diarrhoea accompanied vomiting, giving rise to a misleading picture of gastro-enteritis; in another two cases abdominal pain was prominent. Fits or convulsions occurred in six patients: in one of these the fits preceded all else by ten uneventful days; in another the fit was followed by a hemiplegia which lasted six hours and then disappeared; in the remaining four patients fits were a late feature.

Transient paralysis of arm and leg (lasting 24 hours) occurred in one case 15 days before diagnosis and led to an initial diagnosis of poliomyelitis. Transient loss of speech for a few hours accompanied by a headache (which persisted) was noted in one case 40 days before diagnosis; symptoms of the "middle stage" (see below) followed two weeks later. In two cases whooping-cough, and in one case mumps, occurred a few weeks before the onset of signs and symptoms of tuberculous meningitis.

In three cases the child had sustained a blow on the head before the illness. One of these cases was admitted to a hospital with headache and vomiting following a kick on the head, and was there found to be suffering from tuberculous meningitis (previously the child had apparently been quite well).

On admission to the unit, all cases were classified in the following manner. Early cases (E): fully conscious patients, with no focal signs and little or no meningism, but with pathological cerebrospinal fluid and a characteristic mental picture. Middle cases (M): fully conscious but sometimes drowsy and lethargic, with neck rigidity and perhaps focal signs. Advanced cases (A): unconscious or deeply stuporous patients. The length of the period of illness before admission bore no constant relation to the stage on admission.

Mental Picture on Admission.—The mental picture was that of apathy, with poverty of speech and movement even in fully conscious patients—often accompanied by resentment of even the slightest interference. We have come to the conclusion that this mental attitude is the most valuable single criterion in the differential diagnosis from other forms of meningitis. The apathy may later give place to a state of confusion, in which the patient lies quietly in bed; interrogation will reveal varying degrees of withdrawal from the environment. Occasionally noisy confused behaviour alternates with the apathy. This mental picture is of course recognized as indicative of raised intracranial pressure.

Eyes.—Papilloedema is a common finding in middle or advanced cases. Choroidal tubercles were seen in 5 cases in association with miliary tuberculosis of the lungs accompanying the tuberculous meningitis.

Diagnostic Investigations

(i) *Mantoux Test.*—This was completed in 51 cases; 16 patients lived only a few days after admission. The reactions are shown in Table IV.

TABLE IV

	E Cases	M Cases	A Cases	Total Cases
Positive at 1 in 10,000	17	13	4	34
,, ,, 1 in 1,000	6	3	3	12
,, ,, 1 in 100	0	3	1	4
Negative in all three dilutions ..	0	1	0	1

A positive reaction was defined as an area of oedema measuring at least 8 mm. in diameter.

(ii) *Chest Radiograph.*—Definite abnormalities in the chest *x*-ray film were seen in 50 of 66 cases (one patient died before radiographs could be taken). They comprised: (*a*) *A primary complex* (usually hilar adenitis, sometimes accompanied by indications of pulmonary collapse) in 35 cases. (*b*) *Miliary disease of the lungs in 13 cases.* (A further 6 cases proved at necropsy to have miliary disease of the lungs, although there was no radiological evidence of this during life.) (*c*) *Phthisis,* present in two adults. In the remaining 16 cases no abnormality was seen.

(iii) *Cerebrospinal Fluid.*—The following investigations were carried out:

Cell Count.—The cell count ranged between 30 and 1,000 cells per c.mm. The figure bore no relation to the stage of the disease on admission. The picture was predominantly lymphocytic in all but two cases.

Protein Content.—All cases (with one exception) showed increased protein at the initial lumbar puncture: the figures ranged from 35 mg. to 3.5 g. per 100 ml., and bore no relation to the stage of the disease, except that grossly raised protein levels were usually associated with spinal loculation due to spread of the disease down the theca.

Chlorides.—It is generally appreciated that though a falling chloride level in the C.S.F. is often found the level is not usually of great help in diagnosis, because in early cases it may be quite normal or only slightly reduced. Our figures confirm this view.

Sugar.—C.S.F. sugar levels were not accurately estimated in the early period of our work, as it was not appreciated that diagnostic information would be obtained. When later such estimations were performed approximately 1 ml. of C.S.F. was collected in a separate bijou bottle containing an appropriate amount of sodium fluoride. The sugar levels at initial lumbar puncture are summarized in Table V. It will be seen that in no case was the level above 45 mg. per 100 ml. The significance of these figures is discussed later.

Direct Examination of C.S.F. for Acid-fast Bacilli.—Prior to and within 48 hours of admission, acid-fast bacilli were seen in the centrifuged deposit of the C.S.F. in 39 of 67 cases (58%).

TABLE V

C.S.F. Sugar mg./100 ml.	No. of Cases	C.S.F. Sugar mg./100 ml.	No. of Cases
5+	2	30+	1
10+	4	35+	5
15+	6	40+	2
20+	4	45+	—
25+	4	50+	—

Five further cases first showed acid-fast bacilli at later dates. The organisms were often very scanty in number.

Culture and Guinea-pig Inoculation.—Culture of the C.S.F. was made on Löwenstein medium in every case and a guinea-pig inoculation was carried out. The results* are summarized as follows: total cases, 67; positive by culture and/or guinea-pig, 58 (87%). Nineteen cases whose C.S.F. was negative by direct examination for acid-fast bacilli were verified bacteriologically by culture and/or guinea-pig inoculation. Four cases were diagnosed by microscopical examination of the C.S.F. but failed to yield positive cultures or inoculations. (The diagnosis in these cases was verified at necropsy.) If these are added to the positive cultures and inoculations the total number of cases diagnosed bacteriologically (otherwise than by post-mortem examination) is 62 (92%). Varying numbers of strains from 43 patients have shown no significant streptomycin resistance.

Differential Diagnosis

Nine patients admitted to the unit as cases of tuberculous meningitis were not treated with streptomycin. Meningitis was present in all. Their ages and the findings in the C.S.F. are given in Table VI.

TABLE VI

Case No.	Age (Years)	C.S.F. Findings				Remarks
		Cells	Protein	Chlorides	Sugar	
68	4½	193 (L. 95%)	160	710	—	N. in 19 days
69	8/12	Blood-stained fluid with excess W.B.C.			—	N. ,, 9 ,,
70	6	520 (L. 65%)	35	740	—	N. ,, 20 ,,
71	1½	56 (L. 100%)	20	740	50	N. ,, 14 ,,
72	10½	60 (L. 95%)	20	750	—	N. ,, 7 ,,
73	4½	34 (L. 80%)	40	695	—	N. ,, 3 ,,
74	8½	95 (L. 15% P. 85%)	60	700	60	N. ,, 9 ,,
75	5¼	18 (L. 100%)	20	760	—	N. ,, 10 ,,
76	5¾	85 (L. 25% P. 75%)	35	705	67	N. ,, 23 ,,

N. = Normal. L. = Lymphocytes. P. = Polymorphs.

Case 68.—Mantoux-negative. Chest radiograph, negative. History of contact, negative. Meningism, slight. No focal signs. Mentally alert. The meningism disappeared within 48 hours of admission. C.S.F. normal in 19 days; subsequent history uneventful.

Case 69.—Mantoux-negative. Chest radiograph, negative. No history of contact. The infant was unable to sit up, but seemed mentally alert. Full recovery with normal C.S.F. in 9 days.

Case 70.—Mantoux-negative. Chest radiograph, negative. History of contact, *positive.* Meningism slight. No focal signs. Patient mentally alert. Meningism disappeared within 48 hours of admission.

Case 71.—Mantoux-negative. Chest radiograph, negative. History of contact, *positive.* Definite meningism, with right sixth nerve paralysis. Patient mentally alert. This case caused us considerable anxiety at the time of admission. The picture was suggestive—but the mental condition (and the high sugar content in the C.S.F.) led us to withhold treatment. The child was much better within 48 hours—all meningism disappeared and the patient stood up at the foot of the cot and played happily. The C.S.F. was normal in 14 days. Subsequent history uneventful. Very slight right sixth nerve weakness persists.

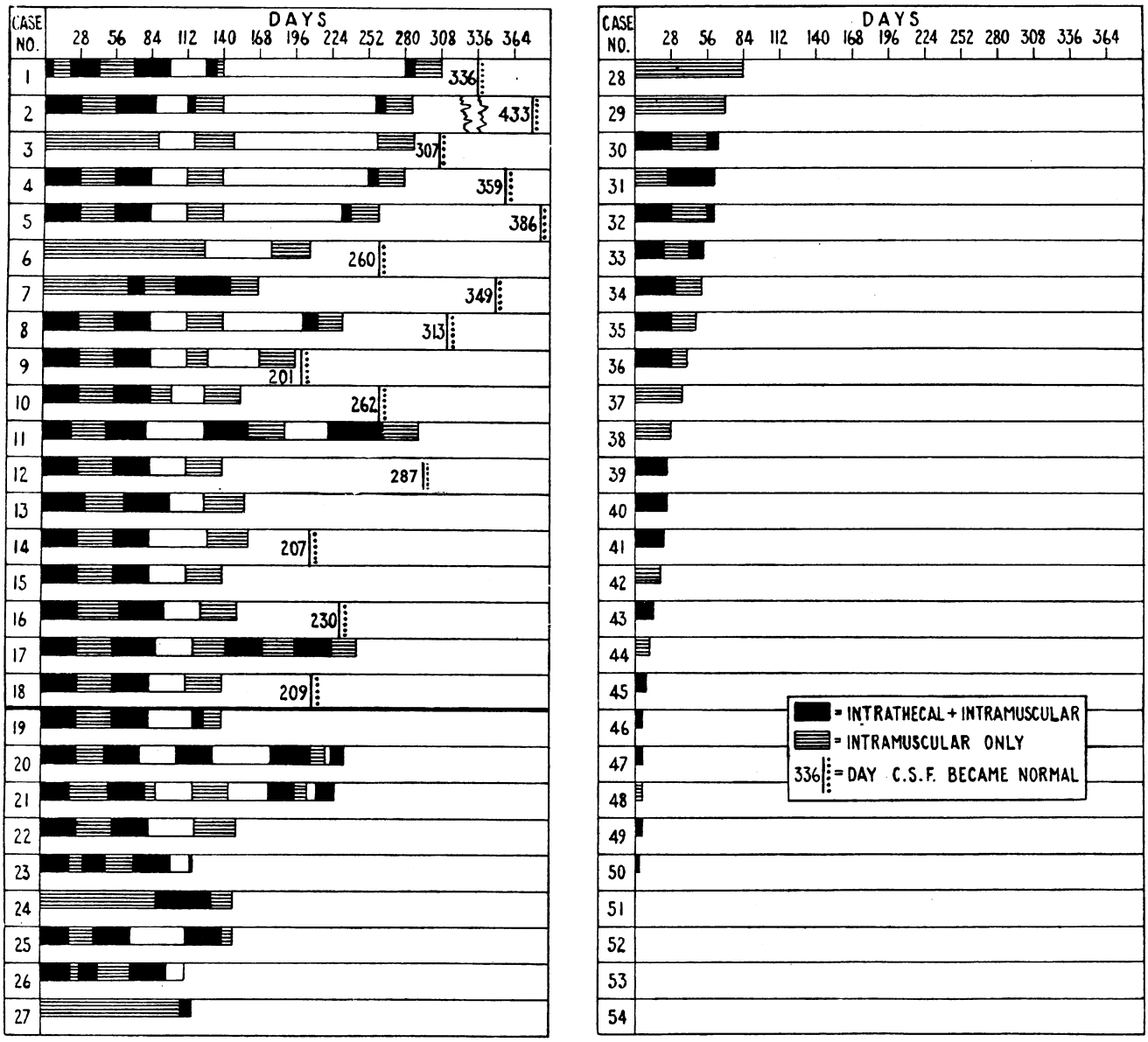
In the four above cases a diagnosis was never established. It is possible that they were cases of polio-encephalitis. It is also possible that Case 71 was in fact an abortive case

*These results do not allow comparison to be made between Löwenstein culture and guinea-pig inoculation, as the number of specimens cultured is greater than the number inoculated into guinea-pigs.

TABLE I.—*Details of the 54 Cases dealt with in Section on Treatment*

	Case No.	Age	Days History Before Diag.	Stage on Admission	Direct Exam. of C.S.F. for Tb.	Culture of C.S.F. for Tb.	Gu. Pig. Inoc. of C.S.F.	Chest X Ray etc.	History of Contact	No. of Days Observed	Method of Treatment	Result
SURVIVING CASES	1	4 6/12	10	E	+	+	+	P.C. Mil.	+	560	I.T. + I.M.	C.S.F. normal; deaf; slight ataxia
	2	4 7/12	31	M	O	+	O	Mil.	O	547	I.T. + I.M.	C.S.F. normal; slight ataxia
	3	8 8/12	3	E	+	+	+	P.C.	+	536	I.M.	C.S.F. normal; full recovery
	4	6 1/12	8	M	+	+	O	Knee P.C.	O	533	I.T. + I.M.	C.S.F. normal; full recovery
	5	**6 6/12**	8	**E**	**+**	**+**	**+**	**O**	**+**	**517**	**I.T. + I.M.**	**C.S.F. normal; full recovery**
	6	3 4/12	5	E	O	+	O	P.C.	O	490	I.M.	C.S.F. normal; full recovery
	7	12 11/12	12	M	+	O	+	Spine O	O	485	I.M.→I.T.	C.S.F. normal; full recovery
	8	15 6/12	8	E	+	+	+	Mil.	O	481	I.T. + I.M.	C.S.F. normal; full recovery
	9	10/12	12	M	+	+	+	Perit. P.C.	O	425	I.T. + I.M.	C.S.F. normal; full recovery
	10	10 4/12	30	A	+	+	+	O	O	363	I.T. + I.M.	C.S.F. normal; full recovery
	11	11	10	E	+	+	+	Mil.	O	290	I.T. + I.M.	Relapsed twice; doing well; C.S.F. almost normal
	12	17 8/12	28	E	O	+	O	O	O	287	I.T. + I.M.	C.S.F. normal; full clinical recovery
	13	10	10	M	+	+	+	O	O	282	I.T. + I.M.	C.S.F. almost normal; full clinical recovery
	14	6	13	M	O	+	O	P.C.	O	279	I.T. + I.M.	C.S.F. normal; right hemiplegia; great improvement; up and about
	15	5 6/12	10	E	+	+	+	Mil.	O	262	I.T. + I.M.	C.S.F. almost normal; full clinical recovery
	16	10 3/12	28	E	O	O	O	Mil.	O	246	I.T. + I.M.	C.S.F. normal; full recovery
	17	5 1/12	10	M	+	+	+	P.C.	+	238	I.T. + I.M.	Relapsed; responding again
	18	4 11/12	10	E	+	+	+	P.C.	O	231	I.T. + I.M.	C.S.F. normal; full recovery
	19	7 2/12	17	M	O	O	+	O	O	270	I.T. + I.M.	Late relapse; was never well
	20	5 2/12	42	E	+	+	O	P.C.	+	241	I.T. + I.M.	Late relapse; was never well
	21	15 7/12	12	M	+	+	+	O	O	237	I.T. + I.M.	Late relapse after initial improvement; late surgical intervention
	22	20	4	E	+	+	+	Pthisis	O	217	I.T. + I.M.	Initial response; sudden late deterioration
	23	10 5/12	70	A	+	+	+	O	O	195	I.T. + I.M.	Slight initial response; became chronic; never looked like recovering
	24	4 3/12	28	E	+	+	O	P.C.	+	181	I.M.→I.T.	Initial promising response, especially when given I.T. treatment
	25	11 6/12	11	M	+	+	+	O	O	149	I.T. + I.M.	Late relapse; surgical intervention and further streptomycin prolonged life
	26	19	15	M	+	+	+	Pthisis	O	120	I.T. + I.M.	Rapid deterioration; became chronic after surgical intervention
	27	9 10/12	13	E	+	+	O	P.C.	O	104	I.M.→I.T.	Initial promising response; life prolonged
	28	4	17	M	+	+	+	Mil.* P.C.	+	103	I.M.	Very slight initial response; slow deterioration
	29	4 11/12	15	M	+	O	O	Mil.	O	69	I.M.	Slight initial response, then slow deterioration
	30	11/12	19	E	+	O	O	O	+	67	I.T. + I.M.	Surgical intervention too late
	31	5 11/12	30	M	+	+	+	P.C.	O	63	I.M.→I.T.	Initial improvement; life prolonged
	32	17	12	M	+	+	+	O	O	63	I.T. + I.M.	Promising initial response; relapse; surgical intervention; vascular accident, due to arteritis
	33	3 2/12	16	M	O	+	+	P.C.	O	55	I.T. + I.M.	Surgical intervention too late
	34	4 9/12	14	A	O	+	+	P.C.	O	52	I.T. + I.M.	Initial response; life prolonged
	35	2 10/12	23	A	O	O	O	P.C. Mil.*	O	51	I.T. + I.M.	Initial response; life prolonged
	36	2 9/12	21	E	O	O	O	O	O	45	I.T. + I.M.	Steady deterioration; no response
	37	2 11/12	60	M	+	+	O	Mil.	+	37	I.M.	Initial response; life prolonged
	38	1 5/12	9	A	O	+	+	P.C. Mil.*	+	29	I.M.	Slight response
	39	1 9/12	14	E	+	+	O	O	+	27	I.T. + I.M.	No response
	40	2 9/12	43	M	+	+	O	P.C.	+	25	I.T. + I.M.	Rapid deterioration
	41	5 1/12	9	M	+	+	+	P.C. Mil.*	O	23	I.T. + I.M.	Rapid deterioration
	42	5 9/12	10	M	+	O	O	P.C.	+	19	I.M.	Rapid deterioration
	43	1 8/12	9	A	+	+	+	O	O	12	I.T. + I.M.	Admitted hopelessly ill
	44	2 11/12	12	A	O	+	+	P.C.	+	11	I.M.	Admitted hopelessly ill
	45	27	56	E	+	+	+	Spine Mil.	O	8	I.T. + I.M.	Died of renal failure; Tb. kidneys; cachexia
	46	1 7/12	15	A	+	O	+	P.C.	O	7	I.T. + I.M.	Admitted hopelessly ill
	47	1	15	M	+	O	O	O	+	7	I.T. + I.M.	Admitted hopelessly ill
	48	2 2/12	6	A	O	+	+	Mil.	+	6	I.M.	Admitted hopelessly ill
	49	6/12	16	A	+	+	+	P.C.	O	6	I.T. + I.M.	Admitted hopelessly ill
	50	8 11/12	36	A	O	O	+	P.C.	O	5	I.T. + I.M.	Admitted hopelessly ill
	51	6 10/12	16	M	+	+	O	P.C.	O	4	I.T. + I.M.	Admitted hopelessly ill
	52	1 4/12	6	A	O	O	O	P.C.	+	3	I.M.	Admitted hopelessly ill
	53	2 6/12	9	A	+	+	+	P.C. Mil.*	+	3	I.T. + I.M.	Admitted hopelessly ill
	54	2 1/12	10	A	O	+	O	P.C. Mil.*	O	2	I.T. + I.M.	Admitted hopelessly ill

E = Early case. M = Middle case. A = Advanced case. P.C. = Primary complex. Mil. = Miliary disease of lungs. Mil.* = Miliary found P.M.
I.T. + I.M. = Intrathecal + intramuscular. I.M. = Intramuscular. I.M.→I.T. = Intramuscular going on to intrathecal.



Charts of the 54 cases detailed in Table I

of tuberculous meningitis, although this seems unlikely. We favour the diagnosis of polio-encephalitis here too.

Case 72.—This patient was in hospital following a pleural effusion, and was awaiting transfer to a pleural-effusion unit as a case of primary tuberculosis. Mantoux-positive. He developed a fever accompanied by headache and vomiting. The C.S.F. was pathological (see Table VI), but this child in particular was alert and happy. The C.S.F. was normal in 7 days.

Case 73.—After two months' history of listlessness, anorexia, and abdominal pain this patient had a fit and was admitted to a hospital in an unconscious state. He recovered consciousness but was mentally unstable; a week later he had a series of fits, after which his reflexes were absent and his plantar responses extensor. At this time the Mantoux reaction was very strongly positive at 1 in 10,000. He was transferred to our unit with the provisional diagnosis of tuberculoma of the brain. He had no further fits. His C.S.F. became normal in 3 days, and clinically he recovered completely. We had the advantage of seeing him late in the illness, when he was recovering and was mentally and clinically normal.

Case 74.—This patient was in a sanatorium for treatment of a large primary complex. His chest radiograph showed right hilar adenitis with pneumonic changes in the upper lobe. He had displayed meningism. On admission to the unit he was mentally alert, and showed some slight neck rigidity but no focal signs. The C.S.F. became normal in 9 days.

Case 75.—This child had pulmonary tuberculosis with a pleural effusion. She became febrile again, vomited, and was less playful. Neck rigidity and drowsiness were noted. She was admitted with a C.S.F. picture as shown in Table VI. Clinical examination on admission (11 days after the onset of these symptoms) was negative. Her C.S.F. became normal in 10 days.

Case 76.—A boy aged 5¼ years was admitted from a sanatorium where he had been under observation for primary tuberculosis of the right lung with a pleural effusion. He complained of headache and was febrile. Table VI shows the C.S.F. findings at the initial lumbar puncture at the sanatorium. He was admitted to the unit, and 48 hours after the initial lumbar puncture the C.S.F. showed: W.B.C., 316 per c.mm. (lymphocytes 100%); protein, 25 mg. per 100 ml.; chlorides, 725 mg. per 100 ml.; sugar, 37 mg. per 100 ml. In spite of this suggestive finding he was mentally alert, and he had no meningism or focal signs. The C.S.F. the next day showed: W.B.C., 184 per c.mm. (lymphocytes 100%); protein, 25 mg.; chlorides, 710 mg.; sugar, 55 mg. He remained well, was not treated with streptomycin, and the C.S.F. became normal in 23 days.

Cases 72–76, it will be noted, showed evidence of existing tuberculous infection, with a positive Mantoux reaction or an abnormal chest radiograph. (In this respect they differ from the first four cases described above.) It seems possible that they were examples of serous tuberculous meningitis (Lincoln, 1947).

In cases of miliary disease of the lungs receiving intramuscular streptomycin we have observed transient meningeal reactions, lasting 7–10 days and characterized by C.S.F. pleocytosis, raised protein, *but normal sugar.*

It is difficult to give precise reasons for the decision not to begin treatment with streptomycin in the nine cases summarized above: undoubtedly the mental condition of the patients was a factor. The contrast between this comparative alertness and the apathetic detachment of cases of tuberculous meningitis is an extremely useful guide to diagnosis. Perhaps a mother's statement that her child is "not himself" is in reality the earliest possible detection of this sign. Professor Craig (1948) stresses the early stage of this withdrawal from contact with others and gives a very full account of the subtle mental changes often noticed first by the mother.

In regard to the findings in the C.S.F., these are incomplete in respect of sugar estimations, as six of the above nine cases were admitted before our realization that such estimations might be valuable. In Cases 71 and 74 the C.S.F. sugar content was a factor in the decision not to treat with streptomycin. We agree with Lincoln (1947) that the low sugar content may be the earliest informative change in the C.S.F. in tuberculous meningitis, but it may not be evident when other symptoms are already suggestive, as the following case shows.

Case 18.—This is a proved case of tuberculous meningitis and is now doing well under treatment. The disease started with a convulsion. C.S.F. examination showed no abnormality: W.B.C., 4 per c.mm.; protein, 15 mg. per 100 ml.; sugar, 82 mg. per 100 ml.; chlorides, 770 mg. per 100 ml. Eight days later the C.S.F. showed: W.B.C., 500 per c.mm., mainly lymphocytes; protein, 60 mg.; chlorides, 730 mg. The child had suffered from erythema nodosum five months previously; chest radiographs showed a well-marked primary focus. She was admitted to the unit, and the C.S.F. findings were: W.B.C., 603 per c.mm., mainly lymphocytes; protein, 140 mg.; sugar, 40 mg.; chlorides, 690 mg. Three days later the findings were: W.B.C., 193 per c.mm.; protein, 160 mg.; sugar, 22 mg.; chlorides, 700 mg. Acid-fast bacilli were seen.

This case shows that in the earliest stages the C.S.F. may be normal. This point was also illustrated in Case 9, in which a normal C.S.F. was found at initial lumbar puncture and in which the C.S.F. became abnormal five days after the onset of symptoms. Case 36 showed a normal C.S.F. 11 days after the first symptoms. The first pathological C.S.F. was found 15 days after the onset of symptoms.

The causes of a lymphocytic cell increase in the C.S.F. may be summarized as follows: (1) Tuberculous meningitis, and serous tuberculous meningitis; (2) polio-encephalitis and poliomyelitis; (3) benign lymphocytic choriomeningitis; (4) glandular fever (infectious mononucleosis); (5) mumps encephalitis; (6) spirochaetal infections (syphilis, leptospiral diseases, relapsing fever); (7) infective hepatitis; (8) atypical pneumonia; (9) herpes zoster; (10) psittacosis; (11) trypanosomiasis; (12) yeast meningitis.

Summary and Conclusions in Regard to Diagnosis

Chest radiography, lumbar puncture, and the injection of 0.1 ml. of 1 in 1,000* Mantoux reagent should all be performed within 48 hours and not be spread over several days.

We had hoped to be able to discover at least one diagnostically helpful feature in the C.S.F. But it is now clear that such a hope did not take into account the urgent necessity for earlier diagnosis. It is true that *when the disease has reached the stage indicated in the cases reviewed in this report* the most useful findings in the C.S.F. (if acid-fast bacilli are very scanty or absent) are the low sugar content, the raised protein, and the increased (lymphocytic) cell count—in that order of importance.

There is a high correlation between the speed of diagnosis and success in treatment.

Reference to the nine cases reviewed under "Differential Diagnosis" shows that patients may present themselves with a history of contact with tuberculosis, with evidence of extrameningeal tuberculosis, and with abnormal C.S.F. and yet may not develop what is ordinarily regarded as tuberculous meningitis. Our experience suggests that the crucial feature in diagnosis is the clinical picture—in particular the mental state of the patient. By this criterion we have (apparently successfully) distinguished the cases referred to above.

Lincoln (1947) and Choremis and Vrachnos (1948) have described cases displaying acid-fast bacilli in the C.S.F. but not developing tuberculous meningitis. On the other hand, three of our cases (9, 18, and 36) which in spite of suggestive clinical features initially showed a normal C.S.F. subsequently developed typical tuberculous meningitis.

Review of Treatment with Streptomycin

The scheme of streptomycin treatment we follow is: intrathecal and intramuscular, 28 days; intramuscular, 28 days; intrathecal and intramuscular, 28 days; rest period, 28 days; intramuscular only, 28 days. The intramuscular dose is 0.02 g. per lb. (0.45 kg.) body weight in 24 hours, given six-hourly. The intrathecal dose is 0.1 g. in 10 ml. normal saline daily. Further treatment is given subsequently if indicated.

On this scheme we have cultured tubercle bacilli from the C.S.F. in cases (which have since recovered) as follows: in 3 cases, 21 days after the beginning of treatment; in 1 case 53 days after; in 1 case 56 days after.

We feel, therefore, that there is no case for lessening the intensity or duration of the initial attack and are inclined to favour the suggestion of Dubois *et al.* (1947) and the practice of Smith, Vollum, and Cairns (1948) that 45 days or more initial intrathecal therapy should be given. This is, however, difficult because of the chemical meningitis and the general ordeal of treatment. One or two days' rest during intrathecal treatment allows the chemical meningitis to abate.

It is possible to effect a cure with intramuscular streptomycin, but we agree with the conclusions reported by the Medical Research Council (1948) that combined therapy gives better results, though there may be a misleading initial response.

During streptomycin treatment patients show to a varying degree fever, loss of weight, anorexia, vomiting, and skin rashes. With the exception of the last-named, these features, if severe and prolonged, are due to the disease rather than the drug. Chemical meningitis varies in intensity. The urticarial rashes respond to "benadryl" and those of the exfoliative dermatitis type to local application of cod-liver oil. Towards the end of the intrathecal course patients complain of severe pains in the legs, probably due to nerve-root irritation. A soft growth of hair on the body

*Omission of the 1 in 10,000 dilution is considered justifiable: 48 hours may be saved, and the risk of troublesome local reaction is small.

(chiefly back, limbs, and neck) is common. Eyelashes become very long ; scalp hair often falls out.

Most of the signs and symptoms seen before and during treatment are due to increased intracranial pressure, at first probably a diffuse swelling of the brain, but sooner or later hydrocephalus. Vascular lesions cause paralysis and occasionally death, and the exudate may be responsible for cranial-nerve abnormalities, especially of the third, sixth, and seventh nerves.

Drowsiness, voracious appetite (somewhat resembling the Kleine-Levin syndrome), facial flushing, glycosuria, hyperthermia, hyperalgesia, and emotional instability may be due to the hydrocephalus and its effect upon the midbrain, thalamic, and hypothalamic regions ; or, on the other hand, the dominant lesion may be a tuberculous arteritis depriving these centres of their blood supply (Smith, Vollum, and Cairns, 1948).

We consider that carpo-pedal spasm and main d'accoucheur, resembling tetany, are manifestations of tonic fits (Ford, 1946). They do not respond to calcium.

C.S.F. during Treatment

Intrathecal, but not intramuscular, streptomycin causes a pleocytosis. A steadily rising protein level is usually of bad omen, indicating an extension of disease down the spinal theca. We have, however, seen complete recovery after the lumbar C.S.F. protein had reached 11 g. per 100 ml. Table VII shows the streptomycin levels in a case on

TABLE VII

Time	Streptomycin Content (Micrograms per ml.)	
	Lumbar C.S.F.	Cisternal C.S.F.
12 noon. Before treatment (0.1 g. streptomycin given intrathecally by lumbar route)	0	0
1 p.m.	4,400	174
4 p.m.	1,000	—
12 midnight	40	—
12 noon (24 hours after injection) ..	10	3·3

intrathecal therapy. Tests on another patient (24 hours after lumbar injection of 0.1 g.) showed a ventricular level of 2.7 micrograms per ml.

Return to Normal.—So long as intrathecal streptomycin is continued the C.S.F. remains abnormal in cell content. It gradually becomes more normal when streptomycin is stopped, and in the absence of relapse complete return to normal has been noted at approximately 200 days from the beginning of treatment on the lines described. However, cases have been observed in which, in spite of apparent clinical recovery, the C.S.F. cell count remained slightly raised. A further month's course of streptomycin was given to these cases, but the abnormality persisted and the C.S.F. did not return to normal till seven months after the cessation of all treatment and approximately a year after admission. Of the 18 cases which have survived for more than 230 days, 14 have a normal C.S.F. No case in which the C.S.F. has become normal has relapsed.

Chest Lesions.—Streptomycin does not seem to affect the process of healing of the tuberculous adenitis which accompanies the primary infection. Miliary tuberculosis of the lungs, however, clears radiologically in from 8 to 12 weeks. Such clearance occurred in one case in which nevertheless death resulted from tuberculous meningitis.

Eighth-nerve Lesions.—Audiogram tests were carried out in 8 cases. One child (Case 1) is very deaf and slightly ataxic ; it is difficult to decide whether this is due to the streptomycin or to the disease. We believe it is due to the tuberculous meningitis. Audiograms on the other children showed a loss of hearing of 10–20 decibels at all frequencies, but it requires this special test to detect the abnormality. A second child (Case 2) is very slightly ataxic, but the disability is improving rapidly and is hardly discernible. An older case (No. 12) was ataxic—in particular in the dark of the cinema ; but with special exercises at King's College Hospital he too has improved.

Surgical Intervention

Ten cases have been operated on with the object of relieving hydrocephalus. The operations tried included the placing of a plastic tube 1 mm. in diameter in the lateral ventricle through a burr-hole. The hydrocephalus is of the communicating type, and, whereas in chronic hydrocephalus this operation is disappointing, in this acute condition (especially as the cause has been shown by Sir Hugh Cairns and others to be pressure of the brain back against the free margin of the tentorium) we felt it should be tried. We hoped that by relieving the intracranial tension we could break the vicious circle by relaxing the brain away from the tentorium and at the same time allow the drug to circulate. The approach is either by the anterior or by the posterior route.

A child aged 1½ years (admitted later than May, 1948) was treated by intrathecal and intramuscular streptomycin for a month, but a week after intrathecal therapy was stopped he vomited and cried and developed increasing meningism. A plastic tube was inserted into the right lateral ventricle through a frontal burr-hole and left *in situ* for six weeks. A Bateman needle occluded the end, and the stylet was removed every six hours to allow the C.S.F. to drain. (The lumbar C.S.F. protein rises while this is being done.) The tube has now been out for four months and the child appears to be responding. It seems that this operation relieved the acute hydrocephalus. This child is the only survivor of the 10 cases surgically treated.

In another infant Mr. Dickson Wright placed a fine tube into the third ventricle and ran the other end over the cortex backwards. In this case the child was too ill for the operation to have a chance.

A girl of 15 relapsed after seven months—a situation in which we have found that the mere placing of a tube into the lateral ventricle does no good. Mr. Dickson Wright raised a frontal flap, and in addition to the ventricular tube a second tube was placed at the site of the disease, in front of the optic chiasma, and streptomycin was given through it. She improved and life was certainly prolonged, but ultimately she died. Necropsy showed an extensive tuberculous exudate at the base of the brain.

To summarize, while surgical intervention seems to offer a logical approach to the relief of the hydrocephalus, our results have been disappointing. Only one of the ten cases thus treated survives, but in other cases life was certainly prolonged. Operation is useless in advanced cases. The difficulty is to formulate the indications for surgical intervention, which will probably need to be early to be successful. Further work on this problem is essential.

Other Factors in Treatment.—Many of these cases were admitted to the unit in a dehydrated condition, but it is remarkable how even the most drowsy will take fluid by mouth in automatic fashion. If this is not possible then rectal or intravenous fluid should be given. Chloral and barbiturates are used when indicated for restlessness or insomnia.

Nursing

The nursing of the cases presents a special problem. The patients are often irritable, unreasonable, and confused. They may be incontinent and wasted, and may vomit frequently. They sometimes refuse food, or are too ill to eat and have to be fed. By pushing food and fluid the

nursing staff can do much to improve the general condition of the patients, which otherwise becomes very poor. Bedsores develop easily, and very special attention must be given to the way in which a semiconscious or drowsy child lies. The constant crying out and the cephalic cry can be very disturbing. We attach importance to the frequent change of posture of these patients and feel that they should be sat up as soon as possible. If this is impossible they should be nursed prone for periods—with the object of preventing the exudate from settling heavily on the under surface of the cerebellum and round the foramina. Young infants who lie supine show this localization of exudate markedly, and it may yet be another factor in the bad prognosis of infants under 3 years of age.

It is our practice to give patients massage and passive exercises after eight weeks and to get them up after three months. Close co-operation with the physiotherapists will prevent much pain and delay in ultimately walking again.

In this unit we do all the lumbar punctures on a high narrow table, not in the bed. No local analgesic is used. Very difficult cases are premedicated with tab. " seconal," in dose according to age. The skin is sterilized with ether, spirit, and iodine ; and thin, sharp lumbar-puncture needles are used (Howard Jones type). The latter are of various lengths from 2–3 in. (5–7.5 cm.), and are sterilized in packets in the autoclave in the operating theatre. After adequate scrubbing-up by the operator the punctures are performed without touching the shaft of the needle. No collodion or dressing is applied, but the skin is moved to break the track. A minimum of trauma and the avoidance of " bloody taps " are extremely important, especially in young infants. Patients need to be kept in hospital for five to six months and should then go to a suitable convalescent home for six months, but should still have cerebrospinal fluid examinations, probably fortnightly, for control.

Mention must be made of the problems which arise in regard to the relatives of the patients. These people are under great emotional stress, and this persists for several months in a way not commonly met with in other circumstances. The greatest tact and understanding are required from the nursing staff and others in dealing with these unfortunate people.

Results of Treatment

Table I details the cases admitted before May 28, 1948 (minimum observation period of surviving cases, 231 days). We hesitate to regard any case as certainly cured. Our longest-surviving case has been under observation for 560 days (18 months). The 36 patients who died include 9 who lived for seven days or less after admission. Of the 18 surviving cases 14 have a normal C.S.F. (Cases 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14, 16, and 18). All have been bacteriologically proved except Case 16. The remaining 4 survivors show the following features:

Case 15.—Clinically recovered. C.S.F. normal except for low sugar. (Further observation is required to estimate the significance of delayed return to normal of the sugar level.)

Case 13.—Clinically recovered. C.S.F. shows slight pleocytosis and slightly increased protein.

Case 11.—This case has relapsed twice, and, although there was apparent response to further treatment, has a C.S.F. which is abnormal in respect of protein (55 mg. per 100 ml.).

Case 17.—Has relapsed once. Otherwise resembles Case 11.

When clinical suspicion of relapse is aroused a fall in the C.S.F. sugar should be regarded as confirmation.

The poor prognosis in patients under 3 years of age is largely due to the rapidity with which they reach the advanced state of the disease, as is shown in Table VIII.

TABLE VIII.—*Cases under 3 Years*

Stage on Admission	No.	Survivors
Early	3	0
Middle	4	1
Advanced	10	0
Total	17	1

Table IX summarizes the results with reference to stage on admission, and distinguishes the 40 cases which had the standard course* of treatment from the remainder (admitted in the earlier part of our work before the superiority of " combined " treatment was established).

TABLE IX

Course of Treatment	Stage	Cases	No. Surviving
Intramuscular only	E	2	2
	M	4	0
	A	4	0
Total		10	2
Intramuscular, followed by intrathecal	E	2	0
	M	2	1
	A	0	0
Total		4	1
Combined I.T. and I.M. course (with minor variations shown in Table I)	E	14	8 (57%)
	M	16	6 (37%)
	A	10	1 (10%)
Total		40	15 (37%)
Overall totals		54	18 (33%)

These results emphasize the importance of the earliest possible diagnosis of tuberculous meningitis. Apart from streptomycin, the most important single factor in such success as we have had is to be found in the quality of the nursing. At Highgate Hospital Sister S. E. Robinson and the nursing staff have maintained the highest standard in this respect.

Summary

Diagnosis

The clinical and laboratory findings in 76 admissions are analysed. A diagnosis of tuberculous meningitis was made in 67 cases. The remaining 9 included five examples of a meningeal reaction in tuberculous subjects which may have been cases of serous tuberculous meningitis.

The problems of early diagnosis are discussed in relation to these cases. Mental apathy is an important early diagnostic feature. In 3 cases of tuberculous meningitis the C.S.F. was normal in the earliest stage in spite of clinically suggestive features. Diagnostically important C.S.F. changes are fall in sugar, rise in protein, and pleocytosis.

Prior to and within 48 hours of admission acid-fast bacilli were seen in the C.S.F. in 39 cases (58%). *M. tuberculosis* was recovered by culture and/or guinea-pig inoculation in 58 cases (87%). Diagnosis by one or both of these criteria was established in 62 cases (92%).

A positive history of contact with tuberculosis was obtained in 12 of 21 patients (57%) under 3 years of age, and in 11 of 46 patients (24%) over 3 years of age.

The commonest interval between the first appearance of signs or symptoms and the day of diagnosis was 8–15 days.

The Mantoux reaction was positive in 50 of 51 cases.

Abnormalities in the chest radiograph were seen in 50 of 66 cases.

Treatment

Cases were classified on admission as " early," " middle," or " advanced." Of these, 54 are considered, with a minimum observation period of 231 days (8 months). Forty cases received combined intrathecal and intramuscular streptomycin: of these, 15 (37%) survive—comprising 8 of 14 early cases

*With minor variations shown in Table I.

(57%), 6 of 16 middle cases (37%), and 1 of 10 advanced cases (10%).

Ten cases received intramuscular therapy only (in the early part of our work), and two survive. Four cases received intramuscular therapy followed by combined therapy: one of these survives.

Important factors operating against success are vascular changes in the brain and hydrocephalus. Further work is essential to assess the value of surgical intervention to combat the hydrocephalus.

Strains of *M. tuberculosis* isolated from 43 patients have not shown resistance to streptomycin.

Eighteen cases (33%) survive, and of these 16 show full clinical recovery—14 having entirely normal C.S.F. and 2 showing slight abnormalities. Two survivors have a history of relapse and show definitely abnormal C.S.F. The diagnosis has been confirmed bacteriologically in all except one of the survivors.

Apart from streptomycin, the most important aids to successful treatment are the rapidity of diagnosis and the quality of the nursing.

The value of intrathecal sulphetrone in addition to streptomycin is now being investigated.

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NASAL CARRIERS AND STREPTOCOCCAL TONSILLITIS

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In discussing the possible sources of streptococcal infection in puerperal fever Colebrook (1933) considered that the nasal carrier might prove of greater danger than the throat carrier. Hamburger (1944), in a study of the transmission of streptococcal infection in Army hospital wards, showed that the incidence of cross-infections did not necessarily show a close correlation with the throat-carrier rate and suggested that some carriers were more likely to spread infection than others. Further studies by Hamburger and his associates demonstrated not only that many more streptococci were expelled into the environment by nasal carriers than by throat carriers (Hamburger *et al.*, 1945a), but also that the majority of hospital cross-infections studied could be traced to heavy nasal carriers (Hamburger *et al.*, 1945b). Their findings led to an investigation of the relative importance of nose-blowing, sneezing, and coughing by nasal carriers in the dissemination of streptococci; it was shown that blowing the nose expelled the largest numbers of organisms and also resulted in sudden and heavy contamination of the hands (Hamburger and Green, 1946). These workers concluded that in certain situations, such as hospital wards, Army barracks, and boarding-schools, nasal carriers were of more importance in the spread of streptococcal disease than throat carriers because they caused a greater degree of environmental contamination. In such communities secondary reservoirs of infection—e.g., dust and bedding—are probably of special significance, and the part played by dormitories in the spread of scarlet fever, diphtheria, and streptococcal tonsillitis has been demonstrated (Dudley, 1923, 1926; Hamburger *et al.*, 1945b).

The outbreak of tonsillitis to be described illustrates the importance of both the nasal streptococcal carrier and the dormitory in the spread of infection in a residential school over a period of two terms. Symptoms were mild, complications few, and there were no rashes. Recovery was rapid and boys were usually discharged from the sanatorium in five to seven days.

The Outbreak

The school of 340 boys is housed in five separate buildings, which will be referred to as houses A–E. Each house has its own sleeping accommodation and common-rooms. D house has its own dining-room, but the boys from all other houses feed in the dining-room of A house, though each house has its own table. The classrooms are in a separate building and are shared by all the boys. Thirty-two of the 57 cases occurred in A house, where the sleeping accommodation consists of six dormitories holding 48 boys and 85 single rooms, the latter chiefly occupied by older boys. The boys of this house, whether sleeping in dormitories or in single rooms, mix freely with each other in the common-room and to some extent with the members of B, C, and E houses at meal-times. All boys meet other members of the school during classes, games, chapel, etc.

Epidemiology

The first case, H., occurred in A house on Feb. 16, 1948, and was admitted to the sanatorium with a sore throat and fever. A throat swab examined by another laboratory showed the presence of haemolytic streptococci, but these were not typed at that time, though later swabs grew haemolytic streptococci type 12. This boy returned to the school on Feb. 26; two days later a fresh case was reported, and further cases continued to occur almost daily till the end of the term on March 25. Cases of streptococcal tonsillitis due to the epidemic type were again observed within a few days of the beginning of the summer term, and 20 further cases among the boys occurred during this term, eight of them within the first two weeks. The last of these became ill on July 3. The accompanying Chart shows the daily incidence of cases of tonsillitis among dormitory and single-room boys of A house and the rest of the school. The overall pattern suggested an initial spread through A house, boys in dormitories especially being attacked, with a gradual extension to other houses towards the end of the Easter term. This general spread was continued during the following term until all houses had at least one case.

In all, 57 boys were attacked with acute tonsillitis—37 in the Easter and 20 in the summer term. Of the 37 cases in the first term 29 were in A house. The incidence of disease among boys in A house and the rest of the school for each term is shown in the Table, A house being divided