STUDIES OF THE CEREBROSPINAL FLUID CIRCULATION IN TUBERCULOUS MENINGITIS IN CHILDREN

PART II. A REVIEW OF 100 PNEUMOENCEPHALOGRAMS

BY

JOHN LORBER

From the Department of Child Health, University of Sheffield

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Since the introduction by Dandy of the technique of ventriculography (1918) and encephalography (1919) their use has become an indispensable part of neurological investigations. No mention was made of their use in tuberculous meningitis until 1927 when Eckstein reported on the examination of 20 children suffering from this disease. He found varying degrees of hydrocephalus and presumed that this was inevitable in tuberculous meningitis. His view accorded with the usual necropsy findings and thereafter little further work was carried out until the advent of streptomycin. Since then many references have been made to air studies in this disease. Hydrocephalus was frequently found and its causes were analysed by Cairns (1949). In spite of the extensive work on various aspects of tuberculous meningitis treated with streptomycin, only two detailed reports were found on encephalography in presumably unselected groups of cases (Murano, 1948; Schöenberg, 1950).

Present Investigation

Material. This investigation began in September, 1948. At first air studies were only carried out for special reasons. The investigation was soon extended when increasing experience suggested that the procedures were safe and that more could be learnt by systematic and repeated examinations. Between January, 1949, and August, 1950, at least one pneumoencephalogram* has been performed on all but two patients treated for tuberculous meningitis. The two patients excluded were moribund on admission and died within a few days. No examinations were carried out in four other patients admitted in the latter half of 1948. Three of these died, and one recovered without any complications. With the exception of these six cases, the present series is consecutive and unselected. Five children

treated at the same hospital but not under our own care were also investigated.

This study reports the results of the first 100 examinations† on 58 children aged between 5 months and 12 years. Tuberculous meningitis was bacteriologically confirmed in 57. The exception was a one-year-old tuberculin positive child of tuberculous parents, who showed the radiological appearances of a primary tuberculous lung complex. The cerebrospinal fluid was characteristic and after 22 months was still slightly abnormal, the child having recovered apart from a residual hemiparesis.

Objects of the Investigation. The long term objects of this investigation were: (1) a more complete understanding of the circulation of the cerebrospinal fluid in tuberculous meningitis; (2) the determination of the incidence and the sites of obstruction within the ventricular system and the subarachnoid cisterns; (3) the determination of the incidence, degree, permanency, and causes of hydrocephalus; (4) the establishment of criteria of prognosis on the basis of encephalographic findings; (5) the correlation of encephalographic patterns with subsequent physical and mental development; and (6) possibly the finding of definite criteria for the selection of suitable cases for treatment, and conversely, for the abandonment of treatment on humanitarian grounds.

Methods. All encephalograms were performed under rectal thiopentone anaesthesia (Lorber, 1950a). Air was injected by the lumbar route in all cases, except where spinal block necessitated the cisternal route. Approximately two-thirds to three-quarters of the fluid removed was replaced by air, 20 to 80 ml. being injected while the child was in the sitting position. An attempt was made to introduce air into the ventricles as well as the subarachnoid spaces by appropriate positioning of the head (Brain, 1947).

* This term will be used for both encephalograms and ventriculograms, unless otherwise stated.

† 89 encephalograms and 11 ventriculograms.

FIG. 1.

FIG. 1a.

Much information may be obtained by the injection of as little as 5 to 10 ml. of air, if the films are taken in the erect position. This method was employed by Flesch and Gefferth (1949) on a large number of cases. This volume of air can be injected after a routine therapeutic puncture without any preparation. This method was used only as an intermediate step in the present investigation. Figs. 1 and 1a illustrate the result of one such examination.

Encephalography was preferred to ventriculography because the former will usually, at the same time, outline the ventricular system as well as the subarachnoid space, and it is easier to detect blocks in any situation by that technique (Davidoff and Dyke, 1946a). Ventriculography was done if the ventricles failed to fill due to obstruction of the pathways, or if encephalography was contra-indicated by papilloedema.

The whole procedure was carried out in the x-ray department. Pilot films were taken during the injection of air to guide the positioning of the head and the assessment of the volume of air to be injected. The final radiographs of the skull were taken in four standard positions: antero-posterior and lateral with the patient horizontal and erect

respectively. Additional views were taken if the films suggested special features requiring elucidation.

The radiographs were interpreted by the standards of Caffey (1945) and Davidoff and Dyke (1946). An encephalogram was judged to be normal if the ventricular system filled well, showed no signs of dilatation, and if air was obviously present in the subarachnoid spaces (Figs. 2, 2a, and 3, 3a). Dilatation of the ventricles was diagnosed if the size of the ventricles exceeded the limits given by Davidoff and Dyke.

After-effects. These procedures were found to be safe. With one exception no serious after-effects were noted. One infant had been unconscious for three and a half months before ventriculography which disclosed extreme hydrocephalus (Fig. 4, 4a). He died within 24 hours of the examination. His death may have been accelerated.

Pneumoencephalography was well tolerated by most children, especially if they spent three hours in an oxygen tent following the examination. This procedure has been shown to hasten the absorption of the injected air (Fine, Frehling, and Starr, 1935; Kornreich, 1948; Schwab, Fine, and Mixter, 1937). The children had often no memory of the examination and were found sitting up and playing six or seven hours after it. Moderate headache and some vomiting for 24 hours was, however, fairly frequent. Air must be removed if symptoms of excessive pressure should supervene. The after-effects were proportionately milder when the volume of injected air was less. This was also noted by Davidoff and Dyke (1946b).

It has been suggested that pneumoencephalography may precipitate a relapse of the meningitis (MacCarthy and Mann, 1950). The probable fallacy of this statement was pointed out elsewhere (Lorber, 1950b). In none of the present series was there clinical or other evidence of relapse within two months of the examination. It is as well to remember, however, that the introduction of air may provoke a considerable cellular reaction even in patients whose cerebrospinal fluid was normal at the beginning of the injection. This pleocytosis may occasionally reach several thousand cells but will usually subside within eight days (Cestan and Riser, 1924; Eley and Vogt, 1932; Hermann, 1922; Kryspin-Exner, 1932; Merritt and Fremont-Smith, 1937; Schwab and von Storch, 1937; Thurzó and Nagy, 1923; and Tschugunoff, 1929). The increase in the cell count starts immediately after the injection of air. In one of the present series of cases separate examination of each 5 ml. specimen of fluid during the course of an encephalogram showed a tenfold increase in the cell count. A mere rise in cell count following pneumoencephalography should not be

FIG. 2.

FIGS. 2 and 2a.—Normal encephalogram from a case of tuberculous meningitis 32 weeks after the beginning of treatment showing normal sized lateral ventricles (1), air in the subarachnoid space (6), and the sella (13).

FIG. 2a.

FIG. 3.

FIGS. 3 and 3a.—Normal encephalogram (AP) from a case of tuberculous meningitis after 22 weeks of treatment, showing normal sized lateral (1), and third ventricles (3), and air in the subarachnoid space (6).

FIG. 3a.

FIG. 4.

FIGS. 4 and 4a.—Ventriculogram showing extreme dilatation of the lateral ventricles (1), gross widening of the sutures (11), and air trapped in the basal cisterns (7), behind the sella (13), and in the posterior fossa (9). The child died within 24 hours of the examination.

FIG. 4a.

FIG. 5.

FIG. 5a.

FIGS. 5 and 5a.—Encephalogram showing block at the tentorial opening. The lateral ventricles (1) are dilated, there is air in the third ventricle (3), and a large collection of air in the distended basal cisterns (7) behind the sella (13). No subarachnoid air.

FIGS. 6 and 6a.—Lateral view of FIGS. 12 and 12a, showing dilatation of all parts of the ventricular system: the lateral ventricles (1), foramen of Monro (2), third ventricles (3), Sylvian aqueduct (4), and fourth ventricle (5). The sutures are widened (11) and there is no subarachnoid air. Air distends the cisterna magna (9), but there is no bubble of air behind the sella (13), indicating obstruction in the basal cisterns.

FIG. 6.

FIG. 6a.

FIG. 7.

FIG. 7a.

FIGS. 7 and 7a.—Encephalogram (AP) showing probable block at the tentorial opening. The lateral ventricles (1) are grossly dilated, the suture lines (11) are widened. Subdural air is seen under the tentorium (8) and along the falx (10). No subarachnoid air.

taken therefore as an indication of relapse in the absence of other evidence.

Results. The results of the present investigation are discussed in two groups according to the radiological findings. In the first group are those children in whom the examination disclosed normal conditions, and in the second those in whom the appearances were abnormal. As six of a consecutive series of 64 cases were not investigated, the proportion of normal to abnormal findings is probably slightly distorted, because in five of the six omitted cases, the appearances would probably have been abnormal.

Group I: Children with Normal Radiological Appearances

Twenty-eight, or nearly half the children belonged to Group I. In 11 of them only one examination was carried out, and in eight of these was performed either late in the course of treatment or after treatment had been concluded, at an average of 33 weeks after the first streptomycin injection. All these children were in good clinical condition at that time.

The examinations were repeated two to four times in 17 of the 28 children whose initial encephalogram was normal. In 15 of these 17 the initial examination was carried out at an average of 2·3 weeks after the start of treatment when streptomycin had already had an opportunity to effect some improvement.

The subsequent examinations were carried out either for clinical reasons (unfavourable progress, convulsions, relapse) or to assess the condition

FIG. 8.

FIG. 8a.

FIGS. 8 and 8a.—Encephalogram showing block at Sylvian aqueduct. The fourth ventricle (5) is dilated but no air penetrated beyond the beginning of the aqueduct. The suture lines are widened (11) suggesting hydrocephalus. Tentorial block is also present, because air is held up in the basal cisterns (7) behind the sella (13) and in the cisterna magna (9). There is no air in the subarachnoid spaces.

FIG. 9.

FIG. 9a.

FIGS. 9 and 9a.—Encephalogram showing block at foramina in the roof of the fourth ventricle. Air distends the basal cisterns (7) behind the sella (13), and the cisterna magna (9), but none penetrated into the ventricles or to the subarachnoid space.

towards the end of the proposed course of treatment. In 11 children the appearances remained normal after an average interval of 18 weeks between the first and last examinations. In six other children pathological changes appeared at the second or a later examination. This leaves altogether 22 children with normal encephalographic appearances, in 18 of whom they were found between four and 14 months after the beginning of treatment. Hydrocephalus is thus by no means an essential pathological feature of tuberculous meningitis.

Group II: Children with Abnormal Radiological Appearances

There were 36 children in Group II, including the six in whom the first examination was normal, but in whom abnormalities were detected later. Three main abnormalities were seen: (1) the presence of one or more blocks in the cerebrospinal pathways; (2) absence of air in the subarachnoid space; and (3) hydrocephalus of various degrees. As the last two features are usually the result of the first, all three were often found together. In addition, some less common features (cyst formation, subdural air) were also noted.

Blocks. Blocks other than those within the spinal theca were seen in 30 of the 36 children and in two others their presence was not definitely excluded by ventriculography. In five children blocks were demonstrated at two sites, but in every one of the 30 cases with blocks one of these was situated either at the tentorial opening or in the basal cisterns. A block at the tentorial opening can be recognized in the lateral film by the collection of air in the distended cisterns behind the sella together with the absence of subarachnoid air (Smith, Vollum, and Cairns, 1948) and often by the collection of air under the tentorium (Figs. 5 and 5a). The encephalogram is similar when the block occludes the basal cisterns, except that the air is held further back, in the cisterna magna (Figs. 6 and 6a). In the anteroposterior film the normal filling of the lateral ventricles, with the absence of subarachnoid air and often the presence of a large collection of subdural air under the tentorium, is strong indirect evidence of a block at these sites, especially if the ventricles are already dilated (Figs. 7 and 7a.) The presence of air in the sulci over the hemispheres excludes the possibility of a block at the tentorial opening, irrespective of other suggestive features.

In two children the block occluded the Sylvian aqueduct. This is a rare condition in tuberculous meningitis. It was demonstrated by the failure of the ascending air to outline the ventricular system above the level of the distal end of the Sylvian

aqueduct (Figs. 8 and 8a). At necropsy these blocks were verified by the finding of a small tuberculoma completely obstructing the aqueduct in each case. In three other cases the foramina in the roof of the fourth ventricle were obliterated, as shown by air distending the basal cisterns, but failing to enter the ventricles (Figs. 9 and 9a) having been injected by the lumbar route. These blocks were also verified at necropsy.

It is of great practical interest to know the time of onset of these blocks. Although it was found that they may occur at any stage of the disease and during treatment, it seems likely that in the large majority they were already present before treatment had started. As no encephalograms were performed in any of these children before treatment, this cannot be stated with certainty. In 17 of the 30 patients with blocks, however, the examination was carried out within a fortnight, and in 22 within five weeks of the beginning of the treatment, and the blocks were already present. In only six children was the appearance of blocks observed during the course of the treatment after a previously normal encephalogram. These were demonstrated between six and 53 weeks after intrathecal treatment had started and active infection was still present in all. When such a block appears it can often be recognized by the rapid deterioration in the child's condition.

CASE 1. A girl of 4½ years had been treated for tuberculous meningitis and her clinical condition had been favourable for eight months although the cerebrospinal fluid remained grossly abnormal and tubercle bacilli were found from time to time. Her progress was followed at intervals by repeated encephalograms, and three of these all showed normal appearances. She was bright, active, and interested during this time, playing like a normal child. In the thirty-sixth week she started vomiting, complained of headache, became drowsy, and within a week became unconscious. An air encephalogram now showed a block at the basal foramina, and penicillin assay (Lorber and Stewart, 1950) confirmed this finding. In spite of ventricular punctures she died within a fortnight. Necropsy confirmed the diagnosis.

Absence of Air in the Subarachnoid Space. Absence of air in the subarachnoid space was the second main abnormality noted. This may occasionally occur in normal persons without an obvious reason, but in this series good filling of the subarachnoid space was seen with remarkable regularity in children with otherwise normal encephalograms and its absence was regularly connected with or followed by other abnormalities. In three children the absence of subarachnoid air was the first abnormality noted and preceded the development of hydrocephalus. There were only four children in whom hydrocephalus was demonstrated in spite of the presence

of some subarachnoid air, and in one of them the hydrocephalus was unilateral.

Occasionally air may find its way into the subdural space after lumbar injection. Subdural air is not necessarily pathological, and its importance lies in the possibility of confusing it with air in the subarachnoid space. If mistaken for the latter, cortical atrophy or the absence of tentorial block may be incorrectly inferred. Subdural air does not occupy the sulci but occupies the whole surface of the brain and it is mobile, as shown when films are taken in various positions of the head (Figs. 10 and

10a, 11 and 11a). In anteroposterior projections taken in the upright position it may outline the longitudinal sinus (Figs. 11 and 11a), and often occupies the space along the falx and the under surface of the tentorium (Figs. 7 and 7a). More detailed observations regarding subdural air may be found in a study by Smith and Crothers (1950).

Hydrocephalus. Hydrocephalus is the third common abnormality (Figs. 6 and 6a, 12 and 12a). Its presence was demonstrated in 34 of the 36 children in this second group. In the other two ventricular filling was not obtained by encephalograms

TABLE I
CLINICAL AND ENCEPHALOGRAPHIC FEATURES IN SIX CHILDREN WITH HYDROCEPHALUS

Case No.	Age on Admission (Years)	Sex	Condition at Beginning of Treatment	Pneumoencephalogram (weeks after beginning treatment)	Condition at Time of Encephalography	Result of Examination	Length of Follow-up (months)	Condition* on 30.9.50.
2	1½	M.	Coma	First: 7 Second: 22	Coma Recovered	Considerable hydrocephalus No change	26	Physically well. C.S.F. normal. Retarded (I.Q. = 53).
3	5	F.	Coma	First: 2 Second: 7 Third: 17	Coma Coma, spinal block Fully conscious Doing well, spinal block resolved	Moderate hydrocephalus (Fig. 13) Increased hydrocephalus Cyst right frontal lobe (Fig. 14.) Same (Fig. 15.)	17	Very well. C.S.F. normal. Optic atrophy. Vision (6/12:6/24). Fields restricted. (I.Q. = 101.)
4	1½	M.	Drowsy, apathetic	First: 5 Second: 21	Drowsy, irritable, wasting Much brighter, recovering	Slight hydrocephalus Gross hydrocephalus. Cyst right frontal lobe	17	Well, C.S.F. normal. Hemiplegic, deaf, and grossly retarded. (I.Q. = below 30).
5	3½	F.	Coma, hemiplegia	First: ½ Second: 5 Third: 7 Fourth: 17	Coma, hemiplegia Drowsy, irritable, hemiplegia Same Very well, hemiplegia	Slightly dilated ventricles No block Increased hydrocephalus tentorial block Considerable hydrocephalus Same	12	Very well. C.S.F. normal. Residual hemiplegia. (I.Q. = 77.)
6	5	F.	Acutely ill, fully conscious	First: 1 Second: 22	Extremely ill, bulbar palsy Recovering, satisfactory progress	Moderate hydrocephalus Much increased hydrocephalus	8½	Very well. C.S.F. slightly abnormal. Still treated. (I.Q. = 100+.)
7	2½	M.	Coma	First: ½ Second: 9 Third: 27	Coma Conscious but blind Recovered, and has good vision	Moderate hydrocephalus Gross hydrocephalus, especially of posterior horns Regression of hydrocephalus to original size	8½	Well. C.S.F. normal. Rapid mental improvement continuing. (I.Q. = 61.)

* All children alive on 20.1.51. Minimum follow-up 12 months.

FIGS. 10 and 10a.—Lateral view taken with brow up, showing lateral ventricles (1), the sella (13), and a pocket of subdural air (10) covering the frontal cortex.

FIG. 11.

FIG. 11a.

FIGS. 11 and 11a.—Antero-posterior view, showing the lateral ventricles (1), air in the subdural space (10) outlining the superior longitudinal sinus (12). The shaded area is the surface of the brain. There is no air in the subarachnoid space.

FIG. 12.

FIG. 12a.

FIGS. 12 and 12a.—Antero-posterior view of Fig. 6. There is considerable dilatation of the lateral (1) and third ventricles (3), absence of air in the subarachnoid space and widening of the sutures.

FIG. 13.

FIG. 13a.

FIGS. 13 and 13a.—First encephalogram (Case 3) two weeks after beginning of treatment showing moderate dilatation of the lateral ventricles (1) but not of the fourth ventricle (5). Air is held up under the tentorium (8) and there is none in the subarachnoid spaces. The sella is shown (13).

FIG. 14.

FIGS. 14 and 14a.—Ventriculogram (Case 3) seven weeks after beginning of treatment, showing gross increase in the size of the lateral ventricles (1) since the previous examination. Air is still held up under the tentorium (8) and also in the basal cisterns (7) behind the sella (13). There is a large cyst (14) in the right frontal lobe, communicating with the ventricle.

FIG. 14a.

FIG. 15.

FIG. 15a.

FIGS. 15 and 15a.—Final encephalogram (recumbent position) 17 weeks after admission of Case 3 showing at least as great dilatation of the lateral ventricles (1) as before. The foramen of Monro (2) and the third ventricle (3) are also demonstrated. Air is still present under the tentorium (8) and in the basal cisterns (7) behind the sella (13). The right frontal lobe cyst (14) is still present. There is no air in the subarachnoid space.

FIGS. 16 and 16a.—Encephalogram of Case 7, at the time of blindness showing gross dilatation of the lateral ventricles (1) but especially that of the posterior horns. Air is collecting under the tentorium (8) and in the cisterna magna, but none behind the sella (13). There is no air in the subarachnoid space.

FIGS. 17 and 17a.—Traumatic cyst at the site of a ventricular puncture track (14). There is considerable dilatation of the lateral ventricles (1), and air collects under the tentorium (8). There is no air in the subarachnoid space.

FIGS. 18 and 18a.—Asymmetrical hydrocephalus and traumatic cyst (14) in the left hemisphere following ventricular puncture. The right lateral ventricle (1) is larger. Hemiplegia was present on the opposite side. There is subdural air under the tentorium (8).

due to blocking of the foramina in the roof of the fourth ventricle. Ventriculography was not performed, but at necropsy ventricular dilatation was found in both cases and the site of the block was confirmed.

The hydrocephalus was symmetrical in all but three cases although slight differences in size between the two lateral ventricles were frequently seen. A slight tilt or rotation of the head was enough to cause such apparent asymmetry. In three children, however, one lateral ventricle was definitely larger than the other (Fig. 18 and 18a): all had hemiplegia on the opposite side of the body.

The degree of hydrocephalus varied from slight (Figs. 11 and 11a) to extreme (Figs. 4 and 4a), according to the timing of the examination. The examination was not repeated in nine children whose clinical progress was poor and in whom considerable hydrocephalus was demonstrated on the first occasion. It is likely that hydrocephalus increased further in size up to the time of their death. This belief is based on the observation of 13 other children who are either dead or whose condition makes recovery extremely unlikely and in whom repeated examinations showed a progressive increase in the degree of hydrocephalus.

It is of particular importance to observe the progress of hydrocephalus in those children who made an apparent recovery or are making such good progress that their recovery is likely. There are six such children in this series whose progress was watched by repeated air studies. Details are presented in Table 1, but some addition is necessary in two cases.

CASE 3. The spontaneous formation of a cerebral cyst in the right frontal lobe communicating with the lateral ventricle was demonstrated at the second examination, when the first ventricular puncture was performed. The cyst was in front of the needle's track (Fig. 14 and 14a). Soon after this examination the child's sensorium began to clear and some four weeks later she was fully conscious. Since then her progress has been excellent and she was very well when the last encephalogram was performed. Further examinations were not justifiable and therefore the present size of her ventricles is not known with certainty, but it seems that in spite of considerable hydrocephalus she is a bright, intelligent girl. Her I.Q. is 101, and she has a good memory for past and recent events, except for a period of amnesia during her illness. She has a normal personality and excellent physique. Unfortunately she has bilateral optic atrophy and restricted visual fields, although her vision is good. Her pupils are dilated and fail to react to light.

CASE 7. This boy was found to be totally blind when he regained consciousness, and he remained blind for two months. His slight papilloedema did not appear to be the cause of the blindness. The second encephalogram

taken during this time, however, showed considerable increase of the hydrocephalus which especially affected the posterior horns of the lateral ventricles (Figs. 16 and 16a). It was thought that the blindness was probably due either to the destruction or compression of the fibres of the optic radiation. His vision slowly returned and at present it appears to be normal. The child made a remarkable recovery and his mental development rapidly approached normal. Just before treatment was concluded a third encephalogram was performed. The appearances were strikingly better, the size of the ventricles being much less, similar to that shown on Fig. 14. The posterior horns of the lateral ventricles showed the greatest regression in size. This is the only case in which regression of the hydrocephalus was observed.

In addition to the hydrocephalus the spontaneous formation of a cyst was demonstrated within the substance of the frontal lobes in two cases (Nos. 3 and 4). The formation of a cyst in a parietal lobe was demonstrated in a 5-months-old infant two weeks after a ventricular puncture. This cyst was exactly at the site of the track of the needle (Figs. 17, 17a, and 18, 18a).

Correlation of Encephalographic Findings with Clinical Progress

After this survey of the cardinal findings it is interesting to compare the fate of the children in the two groups. For this purpose only those 44 patients will be considered who on September 30, 1950, have been observed for more than seven months from the beginning of treatment. Twenty-four (54%) of those 44 survived (Table 2).

TABLE 2
FOLLOW-UP PERIOD OF SURVIVORS ON 30.9.50*

Months	Number
7-9	4
9-12	3
12-15	4
15-18	5
18-24	4
24-31	4
7-31	24

* All survivors were alive on 20.1.51, a minimum of 11 months after the beginning of treatment.

Of the 18 children in whom the findings were consistently normal only two died, and only one of them from meningitis (Table 3). This boy was in a severely anergic phase and had practically normal

TABLE 3
CONDITION* OF CHILDREN WITH NORMAL AND ABNORMAL PNEUMOENCEPHALOGRAMS

Condition on September 30, 1950				Pneumoencephalogram	
				Normal	Abnormal
Alive	Recovered	Mentally normal	No neurological disability	13	—
			Optic atrophy	—	1
			Hemiplegia	—	1
	Retarded		No neurological disability	—	2
			Deafness	1	—
			Hemiplegia	—	2
			Hemiplegia and deafness	—	1
Still under treatment		2	1		
Total alive		16	8		
Dead		2	18		
Total		18	26		

* Minimum follow-up of seven months. All alive on 20.1.51.

cerebrospinal fluid throughout his illness except that a heavy growth of tubercle bacilli was obtained from almost all specimens of fluid examined. At necropsy there was but slight exudate and the ventricles were little larger than normal. This enlargement took place after the encephalogram was performed.

The second child was being treated for miliary tuberculosis at the time when meningitis developed. She responded well to treatment, and was discharged with a normal cerebrospinal fluid and radiographically and clinically normal lungs. Two months later she returned with fulminating phthisis and there was no response to further streptomycin treatment. At necropsy the meninges and the ventricular system were normal, but there were several small encapsulated subcortical tuberculomata.

Excluding two children still on treatment, 13 of the 16 survivors in the first group are physically and mentally normal. One acquired deafness during treatment before she could speak and consequently she is dumb as well. These handicaps obviously retarded her mental development, although there is reason to believe that she is retarded even beyond that.

Of the 26 patients with abnormal encephalograms 18 (69%) died, all of them of meningitis. Excluding one child (Case 6) who is still on treatment, there are seven survivors in this second group. All of them have hydrocephalus. There is not one among them without some residual neurological or mental lesion. Only one child in this group has so far escaped death or major disability (Case 3). Three

other children will probably be able to lead a useful, if restricted, life, in spite of their disabilities. The remaining three are so severely retarded that they are never likely to be able to fend for themselves.

This apparent close correlation between the encephalographic findings and the fate of the children must be assessed with regard to the severity of their disease at the beginning of the treatment. All cases were classified on admission into one of three groups, according to the criteria of the Medical Research Council (1948). This classification was used in the assessment of the results (Table 4).

Of the 44 children who have been followed for a minimum of seven months, 11 were classified as 'early,' 18 as 'intermediate,' and 15 as 'advanced' cases. It is well established that most early cases will recover if adequately treated, but only a few in the advanced state will be saved. The prognosis is very doubtful in cases of intermediate severity.

In this series the initial encephalogram was within normal limits in all children in the early stage of the disease, but subsequently it became abnormal in one of them. This child and another died (of phthisis), but the remaining nine survived. Thus encephalography confirmed the good prognosis of this group.

Of the 15 advanced cases 13 had initially and permanently abnormal encephalograms. In only two was the first encephalogram normal and in one of these it became abnormal later. This last child and four others survived with the various disabilities which have been described, and ten died. Thus encephalography stressed the poor prognosis

TABLE 4

PROGNOSIS OF CHILDREN WITH TUBERCULOUS MENINGITIS CORRELATED WITH STAGE OF DISEASE AT BEGINNING OF TREATMENT AND ENCEPHALOGRAPHIC FINDINGS

Clinical Stage	Encephalograms		Number of Cases	Survivors (%)
	Initial	Final		
Early	Normal	Normal	10	9
	Normal	Abnormal	1	—
	Abnormal	Abnormal	—	—
Intermediate	Normal	Normal	7	7
	Normal	Abnormal	2	—
	Abnormal	Abnormal	9	3
Advanced	Normal	Normal	1	—
	Normal	Abnormal	1	1
	Abnormal	Abnormal	13	4
Total	Normal	Normal	18	16
	Normal	Abnormal	4	1
	Abnormal	Abnormal	22	7

of this group, both as regards chances of survival and the likelihood of residual defects.

The group between these two extremes is the most important because it is the largest and because of the uncertainty of the prognosis as judged by existing clinical criteria. At the best about half of them may recover but it is not possible to say which half. Of the 18 children in this group nine had initially normal encephalograms: seven recovered (78%) and the encephalograms became abnormal later in the two fatal cases. Of the nine with initially abnormal encephalograms only three are alive (33%) and one of them is an idiot. With the help of encephalography this group could be divided into two halves, one with a good and one with a bad prognosis (Table 4).

The last feature investigated was the prognosis of nine relapsed* cases of meningitis in relation to the pneumoencephalographic findings. The examinations were performed soon after the relapse. In five of them the appearances were normal and they survived. In the other four the appearances were abnormal. These are all dead.

Discussion

Certain objects of this investigation were set out

* 'Relapse' is used in a broad sense to denote the condition of children who were clinically well and whose cerebrospinal fluid was either normal (two cases) or approaching normal (seven cases), but were not necessarily off intramuscular treatment at the time.

at the beginning of this study and these will be examined in the light of the results presented.

(1) Over 100 reports on the treatment of tuberculous meningitis commented on the frequency of hydrocephalus. Many of them illustrated this by pneumoencephalograms or pathological specimens. Very few reports, however, mention that hydrocephalus is not an invariable finding. The reason for this is that pneumoencephalograms were usually performed in *selected* cases, either because some abnormality was expected or because the patient's clinical condition was unsatisfactory and surgical intervention was contemplated. This led to the belief that at least some degree of hydrocephalus is inevitable in all cases and this view was supported by Cairns (1949). Janbon, Bertrand, Salvaing, and Vernhet (1949), however, report that only 63% of their 55 patients had hydrocephalus, but no further details were given. Only two encephalographic studies reported the result in small series of unselected cases. Murano (1948) found normal ventricles in two out of 19 cases. Unfortunately the reproductions of his radiographs do not allow their critical assessment, but Schöenberg (1950) reproduced two encephalograms which appear to be normal and there were other similar cases in his series of 26.

It is because of this background, that the most

unexpected outcome of the planned investigation of this virtually unselected group of children was the frequency with which perfectly normal conditions were discovered. Yet there is no theoretical reason why ventricular dilatation should occur in the early stages of tuberculous meningitis before obstruction of the pathways has had time to develop. Nor does such an obstruction necessarily develop if treatment is promptly instituted. This was conclusively demonstrated in the early and some of the intermediate cases of meningitis of this series, where repeated examinations were performed. In approximately 40% of all cases no abnormal findings were present at any time.

The necropsy findings of streptomycin-treated cases of tuberculous meningitis are only of limited value as these cannot represent the conditions in the survivors. The findings in untreated cases are nearer to the conditions obtained in the living. Although most textbooks consider hydrocephalus as one of the characteristic features of the disease, some support for the observations of the present investigation may be found in the monograph on the pathology of hydrocephalus by Russell (1949a). She found only slight degrees of hydrocephalus in some cases of tuberculous meningitis, and in others there was none.

Lincoln (1947) was struck by the infrequency of hydrocephalus in cases where the duration of illness to death was less than three weeks (nine out of 40 cases, 22.5%). In cases of longer duration the incidence rose to 63.6% (14 out of 22). Perry (1950) reports a 31% incidence of hydrocephalus in his 80 cases. It is therefore reasonable to expect that these proportions need not be exceeded if effective treatment is given early in the disease.

(2) Obstructions were observed in more than half of the cases, either within the ventricular system, or, much more frequently, at the tentorial opening and in the subarachnoid cisterns. In this respect the present investigation fully confirms the encephalographic findings of Cairns (1949), Feld (1949), Janbon *et al.* (1949), and Smith *et al.* (1948). In pyogenic meningitis blockage of the Sylvian aqueduct or the foramina of Magendie and Luschka may occur, due to deposition of inspissated pus (Cairns, 1949), but obstruction at these sites was rarely found in this series, because of the clear nature of the fluid in tuberculous meningitis.

Great importance is attached to the absence of subarachnoid air as a sign of blockage at the tentorial opening. Feld (1949) also drew attention to this sign which he considered an indication for surgical intervention before hydrocephalus has time to develop. In the three cases of the present series where subarachnoid air was absent but with initially

normal-sized ventricles, hydrocephalus developed in all. Whether any operative procedures would have been of value is unlikely in view of the published evidence (Feld, 1949).

(3) The incidence of hydrocephalus was almost the same as the incidence of obstructive lesions, and occurred in the same patients. This observation is in full accord with that of Russell (1949b) that an obstructive lesion can be found in at least 99% of cases of internal hydrocephalus. Nevertheless in four cases a moderate degree of hydrocephalus was observed in the presence of subarachnoid air and the absence of demonstrable obstruction, and such a case has also been illustrated by Feld (1949). This hydrocephalus is probably of the passive type and the ventricles merely enlarge to occupy the space left by the shrunken brain substance, due possibly to loss of nerve tissue as a direct result of coincident encephalitis or infarction. It is possible that this latter mechanism does play some part in the other much larger group of cases of hydrocephalus with a known obstructive element. Support for this suggestion may be found in the observation that appreciable enlargement of the head was rare even when the ventricles were of extreme size. There is no doubt, however, that obstruction is the dominant element in the production of hydrocephalus.

In only six cases of the present series did hydrocephalus develop in the course of treatment when normal encephalograms had been previously obtained, showing that early diagnosis may avert this frequent complication. Conversely, hydrocephalus, or the obstruction leading to it, was probably already present before treatment was begun in the large majority of the more advanced cases. This latter observation was more definitely established by Schöenberg (1950) who performed encephalograms on 26 patients before therapy. These facts strengthen the belief that intrathecal streptomycin plays no part in the causation of hydrocephalus, but merely renders it more obvious by prolonging the patient's survival (De, 1949).

One of the most important problems is the permanency of hydrocephalus in surviving patients. It is well established that even a considerable degree of hydrocephalus may regress if the obstruction giving rise to it is removed in time. Instances of this have been recorded by Fincher, Strewler, and Swanson (1948), Swanson and Perrett (1950), Torkildsen (1948), and Walker and Hopple (1949) in cases of cerebral tumour or stenosis of the Sylvian aqueduct, but regression of the hydrocephalus in tuberculous meningitis has not been previously described in the available literature. Of the six surviving cases of hydrocephalus repeated encephalograms showed no decrease in its degree

in two, and a substantial increase in three, in spite of considerable clinical improvement or indeed recovery of physical and mental health when the last encephalogram was performed. Cairns and Taylor (1949) had a similar experience with an adult patient. In one child in this series definite regression of the hydrocephalus was noted (Case 7), and consequently this may have occurred in others after the last encephalogram was performed. This problem is the subject of further investigations.

The aetiology of the spontaneous formation of a cyst in the brain substance in two cases is not quite certain. They may represent porencephalic cavities due to arteritis and infarction. Arteritis is a frequent pathological feature of tuberculous meningitis (Daniel, 1949; Doniach, 1949; Hektoen, 1896; Rigdon and Lefebvre, 1950; Smith and Daniel, 1947; Winter, 1950), but there has been no description of arteritis leading to the formation of large cerebral cysts. Torkildsen's (1948) explanation is more likely. He reported on the spontaneous rupture of the ventricular ependyma in five cases of hydrocephalus due to cerebral tumour. This rupture was thought to have been caused by the difference between the high intraventricular and the low subarachnoid pressure and was followed by cyst formation. Cerebral cyst formations have been described in hydrocephalus of various aetiologies (Childe and McNaughton, 1942; de Lange, 1929; Penfield, 1929; Pennybacker and Russell, 1943; and Sweet, 1940) including one in an untreated case of tuberculous meningitis (Russell, 1949c). Torkildsen (1948) writes:

Occasionally hydrocephalic patients give a history of sudden subsidence of the signs of increased intracranial tension which conceivably may be due to ventricular rupture with formation of a short circuit giving the cerebrospinal fluid direct access to the subarachnoid space.

It may be more than coincidence that the appearance of the cysts in the patients of the present series more or less coincided with a striking clinical improvement although actual communication with the subarachnoid space was not demonstrated.

Another case in this series supports the second theory. This infant had gross hydrocephalus, and at necropsy several ruptures were found in the ependyma of both lateral ventricles (Fig. 19), very similar to those of the case of Pennybacker and Russell (1943). It is assumed that there had been no time for cysts to develop.

(4) The correlation between the encephalographic findings, the stage of the disease, and the prognosis have already been analysed in detail (Tables 3 and 4). It is beyond the scope of this paper to correlate the encephalographic findings with all other factors

which are generally thought to be of prognostic significance, e.g., age, coexisting miliary and other forms of tuberculosis, and the length of delay before treatment is instituted (Lorber, 1950c). In this series, however, encephalography was a very reliable single prognostic criterion. If taken together with all the other known factors, a correct prognosis may be given in almost all cases.

(5) Amatruda (1942) and Casamajor, Laidlaw, and Kozinn (1949) have pointed out that there is no definite correlation between encephalographic appearances and various degrees of mental development and that encephalography does not picture the functional capacity of the cerebrum. Amatruda noted that children with even gross communicating hydrocephalus may do particularly well from the standpoint of development. The observations of these authors apply to a large extent to the survivors of tuberculous meningitis in this series, but with certain reservations. Using the methods described elsewhere (Lorber, 1949) no apparent deterioration was detected in the intellectual capacity of 15 of the 16 survivors with normal encephalograms, but three of the eight survivors with variable degrees of hydrocephalus are severely retarded. It is interesting, however, that two children with considerable hydrocephalus have I.Q.s above 100. Although the numbers in this hydrocephalic group are small, it seems that mental deterioration is more frequent when ventricular dilatation is present.

(6) The most difficult problem is whether selection of cases for treatment and the abandonment of treatment on humanitarian grounds is justifiable or not. Many children live a vegetative existence for months, and streptomycin may not only unnecessarily prolong their suffering, but, worse still, may

FIG. 19.—Spontaneous rupture of the ventricular ependyma in a case of tuberculous meningitis with gross hydrocephalus.

cure them of their infection and thus create serious social and moral problems. It would be of great practical advantage if one could recognize these cases early. Criteria are needed to define certain cases as untreatable, just as there are criteria for judging certain cancers inoperable. The observations in the present series suggest that encephalography may substantially contribute to the fulfilment of this need, but much more experience is necessary before any firm rules may be formulated. It is, however, probably advisable to interrupt treatment early where really gross hydrocephalus (Fig. 4) exists.

Summary

One hundred pneumoencephalograms were performed on 58 children suffering from tuberculous meningitis. With the possible exception of one case, no serious after-effects were noted. No relapse of the meningitis followed within two months of any examination.

In 18 children normal conditions existed four to 14 months after beginning the treatment.

Abnormalities were found in 36 children. In six of these a previous pneumoencephalogram had been normal. Three main abnormalities were detected.

(1) One or more blocks other than spinal ones were found in 30 cases. In all of these there was a block at the tentorial opening or in the basal cisterns. In two cases there was an additional block at the Sylvian aqueduct, and in three others in the foramina of the fourth ventricle. These blocks were usually present at or soon after the beginning of treatment.

(2) In no case of tentorial or basal cisternal block was there subarachnoid air. This sign preceded the hydrocephalus in three cases. In only four children was any degree of hydrocephalus seen when subarachnoid air was present. Subarachnoid air must be distinguished from subdural air which may occur in any encephalogram.

(3) Hydrocephalus of varying degrees was found in 34 cases. Clinical recovery was almost complete in eight of these children. Repeated pneumoencephalograms in six of them showed an increase in the degree of the hydrocephalus in three, no change in two, and a decrease in one.

In three hydrocephalic children cerebral cysts developed; in two cases spontaneously and in the other following a ventricular puncture. The aetiology of the cysts is discussed.

A close correlation was found between encephalographic appearances and prognosis. After a minimum follow-up period of eleven months 16 of 18 children with normal encephalograms were alive and only one of the survivors was left with serious

neurological sequelae. One of the deaths was not due to meningitis.

Of 26 children with abnormal encephalograms only eight were alive after the same period of observation. They all have neurological or mental residual lesions, and these are serious in five.

Of nine cases of meningitis which relapsed, five had normal encephalograms and survived. The four others died.

No absolute dividing line was found regarding mental development following recovery from tuberculous meningitis in children with normal and abnormal encephalograms, but only one child out of 16 became retarded where the final encephalogram was normal, and three of eight children who survived with hydrocephalus are grossly retarded. In two cases considerable hydrocephalus was compatible with good intelligence.

It is suggested that further experience may well show that encephalography supplies criteria for the selection of cases for treatment and for the abandonment of treatment.

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