FACTORS INFLUENCING THE PROGNOSIS IN TUBERCULOUS MENINGITIS TREATED WITH STREPTOMYCIN.

C O N T E N T S.

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INTRODUCTION.

In 1768, Robert Whytt, during the period when he occupied the Chair of Medicine at Edinburgh University, gave the first account of the clinical course of the syndrome now recognised to be that of tuberculous meningitis, in a paper entitled "Observations on the Dropsy of the Brain." His efforts to treat the condition were singularly unavailing: he himself admitted, "I freely own that I have never been so lucky as to cure one patient who had the symptoms which with certainty denote this disease", and he added "I suspect that those who imagine they have been more successful have mistaken another distemper for this". For close on two centuries, his experience was confirmed by practically every physician who endeavoured to treat the malady, described by Trousseau (1867) as "this cruel and inexorable complaint." It is true that a few authenticated cases of spontaneous recovery were reported from time to time, but so exceedingly rare were such cases that nearly every textbook describing the condition in the pre-streptomycin era stated that it was "invariably fatal". Death usually ensued within two to three weeks of the onset of the meningitic illness. Levinson and his associates (1950) reported that 97% of the deaths occurred within 30 days of onset, and the longest survival period was 49 days.

In 1944, Waksman and his associates announced the discovery of streptomycin, and thus gave to physicians the first weapon ever known to have affected the course of this tragic disease. Its use in tuberculous meningitis was first reported/

reported by Cooke, Dunphy and Blake in 1946, in a paper describing successful treatment of a girl aged 1 year admitted with convulsions to New Haven Hospital on 12th May, 1945. Although the patient ultimately became mentally retarded and probably deaf, she had obviously benefited from the treatment. It soon became evident as more and more cases were treated, that the new drug would completely revolutionize the outlook in a once uniformly fatal condition. The succeeding years have seen the flooding of the medical press in all parts of the world with papers on the treatment of tuberculous meningitis. For several years, streptomycin itself was the sheet anchor of treatment, and even now, while successes have been claimed with isoniazid alone, the majority of writers recommend the continued use of streptomycin in addition. Adjuvant therapy, for example, sulphetrone, para-aminosalicylic acid (P.A.S.) streptokinase, intra-thecal tuberculin, has no doubt contributed to the satisfactory results obtained, but of all the drugs used, streptomycin and isoniazid are the only effective anti-tuberculous weapons so far discovered.

In streptomycin-treated cases, however, and even when isoniazid is added to the armamentarium, the proportion of recoveries from tuberculous meningitis falls considerably short of 100%, and a varying percentage of survivors are left with mental or physical disabilities of greater or lesser degree. These facts raise very pertinent questions to which it is the aim of this thesis to endeavour to find an answer.

Why do patients die at all from the disease despite effective antibacterial agents?

What factors might possibly indicate the likelihood of survival?

Can/

Can the illness reach a stage from which the chances of recovery are remote?

Are there any features of the initial illness - clinical or laboratory - from a consideration of which a prognosis can be made with any degree of certainty?

What regime of treatment is most effective?

Can the type of response to treatment be correlated with the end-result?

Are complications arising in the course of treatment likely to affect the ultimate outcome?

What factors, if any, determine the incidence of such complications, and of sequelae?

One of the most disappointing features of cases treated with streptomycin is the liability to relapse. Is this a grave omen, and is it possible to determine beforehand, from the type of patient, the features of the initial illness, or the response to treatment, which patients will be more liable to relapse, and so be able to forecast with greater confidence that recovery will be permanent in any given case?

The literature on the treatment of tuberculous meningitis is vast. In the course of preparation of this thesis, over one hundred and fifty papers from many countries and all continents have been perused, as well as many annotations and letters. It is obviously impossible to refer to all of these in detail. The relevant literature will be considered in connection with each particular section, but a few general observations at this juncture might not be out of place. Various factors affecting the prognosis are mentioned by many/

many writers, but there does not seem to be a consensus of opinion as to their import. Cohen (1952) for example, suggested that the following factors are important:

(1) Duration of illness prior to institution of treatment;

(2) Presence or absence of tuberculomata in the brain - these being more common in adults than in children;

(3) Presence or absence of miliary tuberculosis;

(4) Age of patient, and

(5) Adequacy of treatment.

In an interim report in 1949, of the Department of Health for Scotland, the following factors were stated to be of significance:

(1) Age - A poor prognosis was to be expected in patients under 4 and over 17.

(2) Stage of disease.

(3) Snowstorm appearances in the chest X-Ray.

(4) Presence of choroidal tubercles.

The report indicated that rapid fall in temperature, pulse-rate or erythrocyte sedimentation rate (E.S.R.) was not significant, but that a persistently low cerebrospinal fluid (C.S.F.) sugar was ominous and a distinct rise in the sugar level was favourable. In a subsequent report (Dunlop et al, 1953) based on a larger series of patients, the earlier impression of the significance of miliary mottling in the Chest X-Ray was corrected: the finding seemed to be 'of little prognostic value'. MacCarthy and Mann (1950) stated that the "initial response to treatment depends on a combination of several factors besides streptomycin - age, mechanical obstruction of the cerebrospinal pathways, early diagnosis, innate resistance to tuberculosis and perhaps virulence/

virulence of the tubercle bacilli." They felt that the survival rate was not affected so much by the particular rhythm of treatment as by the number of initially responsive cases. On the other hand, Robertson and Gairdner (1952), in a review of 146 cases treated in the Newcastle area, could find no significant effect on survival rate of age, existing miliary tuberculosis, length of history, development of meningitis during treatment of miliary tuberculosis with streptomycin, choroidal tubercles or papilloedema. The only prognostic guide on admission was the clinical picture based on a combination of psychological and physical findings. Lorber (1954c) too, in a study of 549 cases from 5 different centres in England, found few factors of prognostic import and, indeed, felt that the only one of real value was the state of consciousness. 80% of patients who were conscious on admission could be saved with combined intramuscular and intrathecal streptomycin using P.A.S. as a routine and intrathecal tuberculin as an adjuvant in selected cases. This opinion concurs with the view of Smith and Vollum (1950) who stated that the only findings of prognostic value at the beginning of treatment were the state of consciousness and the presence of neurological signs.

MATERIAL.

The present investigation commenced with the introduction of streptomycin to Ayrshire, Scotland, in the early summer of 1948, when a special supply was obtained from America for a boy of five years admitted to Ayrshire Central Hospital (A.C.H.) Irvine, in June, 1948, suffering from tuberculous meningitis. Thereafter, when supplies became freely available for/

for the treatment of this disease, further 25 cases of tuberculous meningitis were admitted to A.C.H. between June 1948 and October 1949, received streptomycin treatment and are included in this series. These patients were completely unselected: all cases of tuberculous meningitis in Ayrshire were admitted to this unit and in none was treatment refused, however far advanced the disease appeared to be. The remaining 76 patients in this series were treated in Belvidere Hospital, Glasgow, where there was a certain degree of selection enforced by the arrangement in Glasgow that all female patients and children under five years of age notified as suffering from "meningitis" were admitted to another unit (in Ruchill Hospital) only males over 5 years being treated in Belvidere. A number of females and of children under 5 are, however, included in this part of the series, mainly because patients belonging to these groups notified as having "pyrexia of unknown origin" were admitted to Belvidere Hospital. A proportion of these were proved to be suffering from tuberculous meningitis, and were retained and treated. Other cases of tuberculous meningitis were admitted to hospital as cases of "pneumonia" or with other diagnostic labels, and still others developed tuberculous meningitis while under treatment for some other condition, e.g. whooping cough or measles, or in the course of treatment of miliary tuberculosis. For these reasons, the 76 patients treated at Belvidere included 16 females and 15 children under five years of age. Otherwise these 76 patients were also unselected. Throughout the period from June 1948 to December 1951, during which these patients were all admitted to hospital, treatment was not withheld on any occasion even when the patient's condition seemed desperate and the outlook hopeless./

hopeless. All except eleven of the 102 patients were under my personal care and supervision throughout the course of their treatment and stay in hospital. Of the eleven exceptions, one was initially treated by me at A.C.H., relapsed after having had a full 6 months' course of streptomycin, and died after a further 9 months, during the last 4 of which he was under the care of my successor. Four of the eleven had commenced treatment in the three months before I was transferred to Belvidere Hospital in March 1950, and thereafter continued and completed their course of treatment under my supervision. The remaining six patients had already been treated by my predecessor at Belvidere, but are included in this series because they subsequently relapsed and required another course (or courses) of treatment while I was there.

Since the results obtained in this series of patients were collected and tabulated, there has been one further death - in one of the six patients last mentioned in the above paragraph. This is not included in the tables presented nor taken into account in the conclusions drawn from the series. Death occurred five years after admission to hospital and more than three years after complete clinical recovery and restoration of C.S.F. to normal. The patient had extensive bilateral tuberculosis which was the cause of death: the C.S.F. remained normal and there was no recurrence of meningitis. It seemed justifiable to retain this patient among the "survivors".

The certain diagnosis of tuberculous meningitis is clearly dependent on the isolation of viable tubercle bacilli from the C.S.F. It is obvious, however, that treatment must be instituted in every case before the results of/

of guinea-pig inoculation or Loewenstein culture of the C.S.F. are available in confirmation (or otherwise) of the diagnosis, and in many cases in the absence of positive finding of acid and alcohol-fast bacilli in direct films of the C.S.F. The clinical and cyto-chemical changes in the C.S.F. - in particular, the reduction of the sugar content of the latter - are the criteria on which the decision is taken to institute streptomycin therapy, since delay in commencing treatment may be costly. It is therefore not surprising that very few of the series of cases reported in the literature show 100% bacteriological confirmation. Even cases confirmed histologically at autopsy have been negative bacteriologically during life and even after death. Thus in an early report by the Medical Research Council in 1948, 6 out of the series of 92 cases did not have bacteriological confirmation, but were proven histologically post-mortem; guinea-pig inoculation and culture were negative in 5 other patients whose C.S.F. showed tubercle bacilli on direct examination; and 3 survivors, who were believed to be suffering from tuberculous meningitis were excluded from the series because of lack of bacteriological proof. It is to be expected, therefore, that confirmation will be lacking in a proportion of survivors, despite the assertion by Debré and his associates (1947) that "it is possible to determine the exact nature of the disease with absolute certainty from the results of cultures of the C.S.F. on Loewenstein's medium, a test which practically never fails."

The proportion of cases confirmed bacteriologically, varies from series/

series to series, usually from 80% to 100% as shown in the following figures abstracted from the literature:

Authors	Year	No.of Cases	Number Confirmed bacterio-logically	Per-centage confirm-ation.	Remarks.
Medical Research Council	1948	92	86	93	6 others confirmed histologically.
Smith et al	1948	18	15	83	1 proved P.M. 2 survivors unconfirmed.
Lincoln et al	1948	7	5	71	
Mann	1948	33	32	97	
Dept.of Health (Scotland)	1949	81	75	93	2 others confirmed P.M.
Rubie & Mohun	1949	67	62	92	4 of the confirmed cases - on direct film only.
MacCarthy and Mann	1950	43	40	93	1 other confirmed P.M.
Cathie and MacFarlane	1950	60	60	100	
Cairns et al	1950	93	92	99	
Brainerd and Eagle	1950	27	23	85	
Calnan et al	1951	48	47	98	
Illingworth and Lorber	1951	82	73	89	4 others confirmed P.M.
High	1951	22	19	86	
Lassen and Neukirch	1951	44	39	89	3 others confirmed P.M.
Finberg	1951	35	32	91	Figures include cases only confirmed P.M.
Ruziczka	1952	60	54	90	

Jamieson/

Authors	Year	No.of Cases	Number Confirmed bacterio-logically	Per-centage confirm-ation.	Remarks.
Jamieson	1952	35	30	86	1 other confirmed P.M.
Harvey	1952	150	138	92	3 others confirmed P.M.
Cohen	1952	17	10	59	
Ravreby et al	1952	40	24	60	
Perry	1952	26	25	96	
Riley	1953	60	52	87	
Lorber	1954c	549	513	93	15 others confirmed P.M.
Present Series		102	84	82	3 others confirmed P.M.

It is evident, therefore, that while the isolation of M. tuberculosis from the C.S.F. is desirable for establishing the diagnosis, it should not be taken as indispensable for this purpose. Indeed Choremis and his fellow workers (1948) have shown that "the finding of tubercle bacilli in the cerebrospinal fluid is not inevitably followed by tuberculous meningitis." They isolated tubercle bacilli from the C.S.F. of cases of meningism associated with primary tuberculosis in children who did not develop meningitis and who recovered in a few days without specific treatment. Moreover, they showed that the presence of M. tuberculosis in the C.S.F. of patients treated with streptomycin for tuberculous meningitis and fully recovered is not in itself significant; such patients had remained well and did not relapse.

It is certainly unjustifiable, as emphasised by Smith et al (1948) to withhold streptomycin until bacteriological proof has been obtained even/

even though some cases are never verified. In the present series, M. tuberculosis was isolated from the C.S.F. of 84 cases (82%) - in the majority of these, by guinea-pig inoculation; in a few, only by direct examination of a film of the C.S.F. Unfortunately, the C.S.F. of 9 of the 18 unconfirmed cases was not submitted for culture or guinea-pig inoculation prior to the institution of treatment. In 7 of these, treatment had been commenced before my transfer to Belvidere Hospital, at a time when inoculation of guinea-pigs with C.S.F. of cases of suspected tuberculous meningitis was not carried out routinely; the other 2 were transferred to the meningitis ward from another ward where treatment was commenced without submitting specimens of C.S.F. for bacteriological examination. Throughout the remainder of the series, 2 specimens of C.S.F. were routinely sent to the laboratory for guinea-pig inoculation. In one patient, however, only one such specimen was sent, and the inoculated guinea-pig died of intercurrent disease. Thus, in 10 of the 18 unconfirmed cases, there was virtually no prior bacteriological examination of the C.S.F. 91% of the 92 cases examined proved to be positive bacteriologically either in life or after death.

Of the 18 unconfirmed cases, 6 died and 12 survived. Permission for post-mortem examination was refused in 3 of the former, but in the other 3 - cases 31, 49, 72 - autopsy confirmed histologically the diagnosis of tuberculous meningitis. (In case 49, the evidence of meningitis was very slight: the patient, who died one day after the commencement of treatment, had widespread miliary tuberculosis and early meningitis: C.S.F. changes were typical.)

The diagnosis was never in doubt in the 3 patients (cases 7, 10, 54) for whom autopsy permission was not granted. All had a positive Mantoux reaction and evidence of an active primary complex in the chest; in addition X-Ray of one (54) showed miliary mottling throughout the lung fields. Each gave a history of a meningitic illness, had some degree of meningism and typical C.S.F. changes - with persistently low sugar level.

8 of the 12 survivors (28, 29, 32, 33, 35, 36, 85, 87) did not have adequate pre-treatment bacteriological examination of the C.S.F.; in another (50), 2 specimens of C.S.F. were submitted for guinea-pig inoculation, but one of the guinea-pigs inoculated died of intercurrent disease. Review of all these cases revealed that the diagnosis was in doubt in only 3 of them. All had evidence of present or previous tuberculous infection - lung primary in 5, pleurisy in 2, adult pulmonary in 2, miliary in 2, and bone disease in 1 - and the Mantoux was +ve in all except in the cases known to have had adult pulmonary and bone tuberculosis, in whom it was not carried out. All had a meningitic illness of varying severity except one (85) in whom the meningeal inflammation was discovered on routine C.S.F. examination in the course of treatment of miliary tuberculosis. The C.S.F. was typical in all except two (70, 85). In one of these (70), the illness was at an early stage on admission, but he did have severe headache and other typical features of tuberculous meningitis; C.S.F. examination showed a raised cell-count and protein content and the chloride level was reduced; C.S.F. response to streptomycin was typical, as described by Smith and Vollum (1950). The only feature that raised doubt was a persistently normal C.S.F. sugar level. It will be seen later, however, that this has been observed in many cases/

cases in this and other series in whom the diagnosis has been confirmed. Two Consultants who examined this patient had no doubt about the validity of the diagnosis. Case 85, as already stated, was found on routine C.S.F. examination in the course of treatment of miliary tuberculosis, to have a pleocytosis; unfortunately intrathecal treatment was commenced in another ward without prior bacteriological examination of the C.S.F. It is conceivable that this was a case of tuberculous serous meningitis, described by Lincoln (1947). At the time of diagnosis, the only abnormal C.S.F. constituent was the cell-count which was 85 per c.mm. Within 4 days, however, this had risen to 280 per c.mm. and the protein content was 90 mg. per 100 ml; and the sugar level fell to 43.4 mg. per 100 ml. after a month. This patient has therefore been regarded as a case of tuberculous meningitis. The only other case whose diagnosis was at all in doubt was a child of 5 (17) with a previous history of primary tuberculosis treated in hospital, who developed a mild meningitic illness. The C.S.F., though examined, was never positive for M. tuberculosis and the chloride content was normal, falling to below 700 mg. per 100 ml. on only 3 occasions - never below 685 mg. per 100 ml. The C.S.F. sugar level, however, was 35 mg. per 100 ml. on admission and remained low for nearly 6 months. This would appear sufficient evidence on which to base a diagnosis of tuberculous meningitis. Thus, although bacteriological proof was lacking in 18 of the 102 patients in this series, it is highly probable that the diagnosis in all of these was correct.

All 102 patients were treated with streptomycin prior to the introduction of isoniazid. While the latter is now an integral part of the therapy for tuberculous/

tuberculous meningitis and the use of streptomycin alone has thus been superceded, it seems useful to examine in retrospect the results of pre-isoniazid treatment as it is not unreasonable to suppose that such an investigation may provide information of value in the study of the effects of more potent drugs such as isoniazid on tuberculous meningitis. As stated by the M.R.C. (1948) in reporting an early series before the discovery of isoniazid "it is possible that whatever emerges from this study may apply also to other more potent chemotherapeutic agents that may be discovered in the future." The results here presented may thus serve as a yardstick for comparing the results of new regimes of treatment. A series of 102 patients admittedly is, comparatively speaking, almost minute and insignificant; not too small, however, to justify limited conclusions. Moreover, in studying a disease such a tuberculous meningitis with its prolonged course of treatment and liability to fatal relapses after as much as $3\frac{1}{2}$ years of good health (Russell and MacArthur, 1953) or even 5 years after the onset of the initial illness (Oldham et al, 1954), a long period of observation and follow-up is highly desirable if not essential. In this series, the minimum period of follow-up was five years.

METHODS.

Routine examination on admission of the patients in this series included complete clinical examination, Mantoux testing (except in patients known to have or to have had tuberculosis), chest radiography (in all but 1 patient), ophthalmoscopic examination to detect the presence of papilloedema and/or choroidal tubercles (in 92 patients), erythrocyte sedimentation/

sedimentation rate - E.S.R. (in 78 patients) and C.S.F. examination (cell, protein and sugar content in all cases, and chloride content in 90 cases; and bacteriological examination by guinea-pig inoculation as already indicated; culture on Loewenstein's medium was also carried out in some of the earlier cases in the series). To facilitate subsequent review of the features, special stencilled sheets were completed for each patient on admission. On each were entered the name, age and address of the patient; the dates of admission to hospital and of commencement of treatment for meningitis; the duration and severity of the illness; the presence and duration of individual symptoms and signs; any history of previous tuberculous illness or of contacts (family or other) with tuberculosis; temperature, pulse and respiration rates; degree of meningeal signs; the state of reflexes and presence of cranial or spinal nerve palsies; results of ophthalmoscopic examination; X-Ray appearances and Mantoux state; E.S.R.; C.S.F. appearances and pressure and the isolation of tubercle bacilli. Further stencilled sheets were used to indicate treatment given and progress made. In these, entries were made, at weekly intervals throughout the stay in hospital, of the dosage of intramuscular and intrathecal streptomycin being administered; general condition; presence and severity of headache, vomiting, anorexia, constipation, meningeal signs, drowsiness and irritability; temperature; weight (when considered fit enough for this to be measured) and level of C.S.F. constituents. E.S.R. was estimated at monthly intervals and recorded in the sheet. Tables were compiled with the aid of statistical cards with punch-holes, specially/

specially prepared for the purpose.

Every patient in the series was treated with streptomycin (or dihydrostreptomycin) by both intramuecular and intrathecal routes. With the exception of six patients who were given an initial course lasting $3\frac{1}{2}$ months and who came under my care when they subsequently relapsed, the routine duration of treatment was 6 months; this was maintained even when recovery appeared to have taken place by a much earlier date. In a few who showed deterioration in the latter half of this period, the treatment was continued for longer than 6 months. On the occurrence of relapse, a full 6 months' course was repeated. The different patterns of treatment adopted will be described later in considering the effect of the treatment regime on prognosis.

Para-amino-salicylic acid (P.A.S.) was introduced into the treatment, in the dosage shown in Table 33, early in 1950. Consequently the first 26 patients did not receive any of this drug; cases 27-32 received it only when they relapsed; and cases 33-37 commenced treatment with streptomycin alone, P.A.S. being introduced later. Apart from mild goitre in 2 patients, no toxic effects of this therapy were observed. One patient (33) was given sulphetrone until the completion of the streptomycin course. The initial doze of 0.25g. twice daily by mouth was gradually increased over a period of 3 months to 1 g. three times daily, the haemoglobin level being recorded at weekly intervals till treatment was discontinued. No complications of this treatment were observed except slight cyanosis.

Streptokinase/

Streptokinase and tuberculin (P.P.D.) were used in a proportion of cases; their use and effect will be described later.

Accessory treatment included transfusions of blood, plasma and glucose saline in some very ill and comatose patients. In one comatose patient, feeding by stomach tube was necessary for the first week or two. Vitamins were administered routinely, and iron when necessary.

At first, patients were nursed in bed throughout the 6 months of treatment and thereafter gradually up-graded. It was soon realized that, despite physiotherapy, the danger of stiffness and deformities increased with prolonged bed-rest, and so, subsequently, patients were allowed up after 3 months if they were making satisfactory progress and there were no contraindications. Passive and active exercises were given from the outset in all cases, under the direction of a trained physiotherapist, and the patients were encouraged to move about and frequently change their positions in bed. There is no doubt that efficient nursing care and attention during the acute illness plays a very great part, which cannot be measured, in the speedy rehabilitation of patients and that the morale of the patients, of so great importance in such a severe illness with prolonged treatment, is dependent in large measure, on the encouragement of nursing staff and other attendants.

As far as possible, patients remained in hospital till 3 months after the course of treatment was completed; in a few of the later patients, part of this period was spent in a convalescent home. Following discharge from/

from hospital, they were asked to report back at gradually increasing intervals, and nearly all were very happy to do so and be reassured from time to time. The C.S.F. was examined at weekly intervals throughout the streptomycin course; thereafter the interval between lumbar (or, in some cases, cisternal) punctures was gradually extended. On discharge, patients (or their relatives) were warned of the possibility of relapse, and encouraged to report to hospital should any abnormal symptoms develop. As a general rule, this advice was carefully heeded.

RESULTS.

The considerable variation in results in published series of streptomycin-treated cases of tuberculous meningitis has already been noted. The survival rate varies from as little as 0% to as high as 80%. As is to expected, the series showing these extremes are comparatively small, and the average recovery rate seems to be between 40% and 60% as shown in the following samples of published results:-

Country	Year	Authors	No. of Cases	No.and Percentage of survivors.	Minimum Period of observation.	Remarks.
Great Britain	1948	Medical Research Council.	105	34 (32.4%)	7 months	
	1949	Dept.of Health (Scotland)	81	36 (44.4%)	4 months	5 survivors in unsatisfactory condition.
	1949	Cairns and Taylor	48	28 (58.3%)	?	
	1950	Cathie and MacFarlane	60	28 (46.7%)	6 months	

1950/

Country.	Year	Authors	No. of Cases	No. and Percentage of survivors.	Minimum Period of observation.	Remarks.
Great Britain	1950	MacCarthy and Mann	43	13 (30.2%)	16 months	All children under 7 except two aged 8. 6 treated with I.M. streptomycin only. - All died.
	1951	Calnan et al	54	16 (29.6%)	$2\frac{1}{2}$ years	
	1951	Calnan	114	53 (46.5%)	1 year	
	1951	Illingworth and Lorber	82	36 (43.9%)	1 year	
	1953	Ministry of Health	371	102 (27.6%)	$2\frac{10}{12}$ years	
	1952	Jamieson	35	28 (80%)	1 year	
	1952	Robertson and Gairdner	146	69 (47.3%)	2 years	
	1952	Somner	26	14 (54%)	9 months	
	1953	Russell and MacArthur	33	12 (36.4%)	49 months	All children, 3 grossly disabled.
	1953	Dunlop et al	266	125 (47%)	$2\frac{3}{12}$ years	20 in unsatisfactory condition.
	1954a	Lorber	38	28 (73.7%)	2 years	Children treated from Aug. 1950 to March 1952.
	1954c	Lorber	549	253 (46.1%)	2 years	Survey of results in 5 centres. 4 further deaths in 3rd year and 2 in 4th year.
		Present Series	102	66 (64.7%)	5 years.	

Ireland/

Country	Year	Authors	No. of Cases	No.and Percentage of survivors.	Minimum Period of observation.	Remarks
Ireland	1950	McSweeney	94	19 (20%)	4 months	
U.S.A.	1950a	Bunn	78	21 (26.9%)	?	2 survivors moribund.
	1950	Levinson et al	38	7 (18.4%)	1 year	Children
	1951	Lincoln and Wilking	39	28 (71.8%)	6 months	Treated from 1946-1951.
	1952	Ravreby et al	40	30 (75%)	20 more than 1 year) 3 less than 6 months.)	Children treated 1947-1951.
	1952	Perry	26	7 (26.9%)	?	Infants and children.
	1953	Riley	60	4 (6.7%)	2 years	Ages 15-76 1946-1951. 7 treated without I.T.streptomycin and 1 without I.M.streptomycin.
	1954	Spies et al	61	11 (18%)	?	12 had no I.T. streptomycin.
	1954	Spies et al	38	9 (23.6%)	?	Included in above series. All had I.T. streptomycin.
Australia	1952	Beveridge	52	16 (30.8%)	?	Total series 57 - 5 not treated.
	1952	Williams	40	9 (22.5%)	?	
France	1947	Debré et al	118	46 (39%)	2 months	
	1952b	Debré	262	127 (48.5%)	15 months.	

Greece/

Country	Year	Authors	No. of Cases	No.and Percentage of survivors.	Minimum Period of observation.	Remarks
Greece	1948	Choremis et al	63	29 (46%)	?	3 still under treatment.
	1951	do.	132	87 (65.9%)	?	All survivors discharged well.
Austria	1952	Ruziczka	114	60 (52.6%)	1 year	
Denmark	1951	Lassen and Neukirch	44	13 (29.5%)	?	I.M.streptomycin only except in 13 cases.
Italy	1950	Flori	265	152 (57.4%)	?	104 cases regarded as cured
Finland	1951	Wasz-Hockert	60	30 (50%)	?	Mainly children under 7.
Holland	1951	Hooft and Deneve	143	63 (44.1%)		
Algiers	1950	Sarrouy et al	30	0		No trace found of 4. Presumed dead.

Clearly, several factors may be responsible for this remarkable variation in results, apart altogether from the treatment regime employed and, indeed, the types of patients treated. Increasing experience would be expected to lower the mortality rate in later series reported. This is well demonstrated in Lorber's review (1954c) of the results of treatment of 549 cases of tuberculous meningitis in 5 different centres in London, Oxford, Newcastle and Sheffield. Particularly bad results were obtained in 1947 when the recovery rate was 31.6% compared with 49.3% in succeeding years. In 1951, (when P.A.S. was introduced) 64% of 89 patients survived, compared with 52% in/

in the years 1948-50. Calnan's series (1951) of 140 cases (114 with 1 year's observation) showed a progressive increase in recovery rate in successive groups of 25 cases from 24% to 68%. Flori also (1950) traced a progressive fall in mortality from 77% in the first half of 1947 to 15% in the last half of 1948.

Another important factor is the period of observation. While it is true that the majority of patients who die, do so within 6 months, a proportion of cases die during the second 6 months, and a smaller proportion in the second year. Thus, in Lorber's series of 549 cases already quoted, 266 (48.4%) survived 1 year; 253 (46.1%) survived 2 years; while 4 more patients died in the third year and 2 in the fourth. In the Ministry of Health report on 371 patients (1951), it was stated that in all clinical groups the mortality was heaviest in the first 3 months and continued to be fairly high for 6 months; thereafter it slackened and ceased after 18 months in cases of meningitis alone, 13 months in cases of miliary tuberculosis with coincident meningitis; and 9 months in cases of miliary tuberculosis developing meningitis. Finberg (1951) in a review of 30 cases of tuberculous meningitis treated between September 1946 and November 1950, presented this declining mortality in diagrammatic form. The diagram, in which data are presented as though patients were started on treatment simultaneously, showed that most of the mortality occurred in the first year of therapy; and that after eighteen months, additional mortality was not appreciable./

appreciable. Figure 1 (with table 4) is an application of this mode of presentation to the cases in this series and shows similar features.

Table 1 shows that 66 (64.7%) of the 102 patients comprising this series survived for at least 5 years. (One of these actually died of pulmonary tuberculosis at the end of 5 years as already indicated.) The first 26 of these, treated at Ayrshire Central Hospital, showed a 50% mortality compared with 30.3% of the succeeding 76 patients treated at Belvidere; but the higher mortality in the former series may well be attributed, at least in part, to other factors such as the higher proportion of younger children included in the series for reasons already stated. 3 of 9 patients (33.3%) admitted in 1948 died, compared with 11 of 26 patients (42.3%) admitted in 1949, 14 of 35 patients (40%) admitted in 1950, and 8 of 32 patients (25%) admitted in 1951. Thus there is no definite trend in this series which could not be attributed to chance variation. Table 4 and Figure 1, showing the duration of life in fatal cases, demonstrate that five-twelfths of deaths occurred within the first month, over half within 2 months, and two-thirds within 3 months. Only 6 of the 36 fatal cases survived longer than 6 months and only 3 were still alive at the end of a year; one of these lived for over 2 years.

When allowance is made for these considerations, there are still obvious discrepancies between results obtained by different workers during the same time-period and with uniform follow-up. It is the object of this investigation to assess the factors that may have been responsible for the diversity of results in this series. I propose to consider the subject in the/

the following sections:-

A. Influence on the prognosis of the type of patient, and his/her condition at the time of commencing treatment.

B. Influence of different treatment regimes employed on the survival rate.

C. Type of response to treatment and its effect on the outcome.

D. Incidence of complications, especially spinal block, and assessment of their effect on prognosis.

E. Incidence of relapse and its effect on the ultimate outcome.

F. Factors affecting the incidence of sequelae; in particular, deafness.

A. ASSESSMENT OF PROGNOSTIC FACTORS AT THE COMMENCEMENT OF TREATMENT.

It was by means easy in pre-isoniazid days - well nigh impossible, indeed - to make a confident prognosis when confronted with a patient known to have tuberculous meningitis. The writer's experience on occasions has no doubt been shared by most other physicians who have treated the disease, namely that patients, who appeared to have an excellent prospect of uncomplicated recovery, have failed to respond to treatment, while others, who seemed almost moribund on admission and were only given treatment because it was considered wrong to withhold it, survived without sequelae. Nevertheless such cases are the exception rather than the rule, and several factors are generally recognized to be fairly reliable prognostic guides.

Tables 5 to 31 have been compiled to show the influence of various factors on the ultimate outcome of the illness in this series. It will be seen later that 4 patients survived the first course of treatment but subsequently relapsed and died. Notwithstanding their initial favourable response, these are classified in these tables with the other patients who died. Further, the survivors include 12 patients who received more than one course of streptomycin therapy before they appeared to be finally "cured". The particular problems raised by all these patients will be considered subsequently in section E. Finally, these tables do not take into account the sequelae; they are concerned with the quantity rather than the quality of results.

AGE/

AGE.

It was early discovered that the prognosis was worse in children under 3 years than in older children and that the disease in adults also carried a high mortality; these findings have been fairly uniformly confirmed in successive series of cases.

In the early trial of the M.R.C. (1948), it was found that the proportion of older children surviving and making good progress after four months was more than three times that in children under 3. Choremis and his associates (1948) found that the average age of 21 patients who recovered was 6 years 11 months whereas that of 26 who died was 4 years 8 months; and in 1951, reporting on a series of 132 cases, they found the mortality rate in 54 patients under 4 years was 40.7%, compared with 24.4% in 78 patients aged 4 years and over. Rubie and Mohun (1949) treated 54 cases, 18 of whom survived; only 1 of the 17 cases under 3 years survived. Calnan (1951) reported a mortality of 73.5% in 34 children under 3 years (25 deaths; but 6 of 13 under 1 year survived); compared with 45% in 80 patients over 3 years. In Lincoln and Wilking's series (1951) of 39 patients, 9 (36%) of 25 patients under 3 years died, compared with only 2 (14.3%) of 14 patients aged 3 years and over. Corresponding percentages in Robertson and Gairdner's series (1952) of 146patients were 68.2% in 44 children under 3; and 53.9% in 102 patients aged three and over; and in Ruziczka's series (1952) of 114 children - 69% of 42 younger children and 34.7% of 72 older children. Debre (1952b) found a mortality of 75% in 16 infants under 1 year; 58% in 118 children between 1 and 6, and 37.52 in 128 between 6 and 20.

On the other hand, some writers have not found results less satisfactory in the younger age-groups. For example, Cairns and Taylor (1949) reporting 48 cases of tuberculous meningitis, stated that infants under 3 years did as well as older children; and in 1950 Cairns, Smith and Vollum wrote that the results were the same in all ages except the extremes. Russell and MacArthur (1950) found no appreciable difference between the mortality in patients under 4 years and that in patients 4 years and over-9 (52.9%) of 17 in the former group died, compared with 9 (56.25%) of 16 in the latter. Perry (1952) reported that 12 (70.6%) of 17 children under 2 years died, compared with 6 (75%) of 8 of 2 years and over. In reviewing the results of treatment of 549 cases, Lorber (1954c) found a significantly higher mortality rate in children under 3, but he attributed this entirely to delayed diagnosis in this group and asserted that, with earlier diagnosis, the prognosis for younger children need not be worse than for other groups. In an earlier paper, in which the effect of delayed diagnosis was stressed, Illingworth/

Illingworth and Lorber (1951) found no significant difference between the results in patients under 3 years and those in patients aged 3 and over.

In the present series, the mortality rate of 60% in 25 children under 5 years of age was significantly higher than in other age-groups (Table 5); Table 6 shows that most of these deaths occurred in the 20 children under 3 years, the mortality here being 65%. It is noteworthy also that only one of the five patients over 30 years of age survived. While the latter numbers are too small to be conclusive, the finding corresponds with results in other series. Riley (1953) attributed the poor results in adults to the frequent association of tuberculous meningitis with actively disseminating widespread haematogenous extrapulmonary tuberculosis. The five adults over 30 in this series all had pulmonary tuberculosis; in at least four of these it was active and only in the one survivor, was control achieved. There seems no doubt that the presence of uncontrolled pulmonary tuberculosis at least contributed to the fatal outcome in the other three patients.

The higher mortality in young children in this series could not be fully accounted for either by increased severity of the illness or delay in making the diagnosis in these age-groups. Neither the severity nor the duration of the illness differed significantly from the corresponding findings in other age groups. Of the 20 children under 3 years 8 (40%) were severely ill on admission, 11 (55%) moderately ill and 1 (5%) mildly ill compared with 31.9%, 57.3% and 11% respectively in other age-groups.
($\chi^2 = 0.953$ with $n = 2$; $P = 0.7 - 0.5$). 7(35%) of the 20 children had been ill for less than a week; 6 (30%) for 1 to 2 weeks; and 3 (15%) for longer than 2 weeks (4 others had been ailing for some time and the exact date of onset of/

of the meningitic illness could not be fixed with any certainty), compared with 32.9%, 51.2% and 13.4% in the others (χ^2 = 1.206; with n = 2; P = 0.7 - 0.5) It was noteworthy, however, that of the 3 patients in the series with an illness of longer than 3 weeks, 2 were under 3 years of age. It is true that difficulties in early diagnosis are much greater in young children. Listlessness and irritability, which may be the earliest evidences of the disease, are often attributed to other causes. Infants do not complain of headaches, and the first manifestations of the disease may be vomiting, rigidity, squint, drowsiness or coma.

A factor which may well make a major contribution to the increased mortality in young children is that the disease seems to run a more rapid course in earlier age-groups. Rubie and Mohun (1949) attributed the poor prognosis in patients under 3 years to the rapidity with which they reach an advanced stage of the disease. Case 49 of this series, a girl of $2\frac{1}{2}$ years, was a striking example of this. Although she had a history of anorexia following measles 3 months previously, and a cough for one month her main symptoms - vomiting and irritability dated back only 3 or 4 days before admission to hospital. On admission she was only moderately ill and drowsy; there were no meningeal signs. Despite institution of streptomycin therapy on the day after admission, she died suddenly on the following day.

Choremis and his associates (1948) pointed out that tuberculous meningitis in very young children is often associated with active primary tuberculosis or with miliary tuberculosis and suggested that this may well contribute/

contribute to the diminished prospects of survival. They added that the antigenic resistance in infants is lower than in older children. In this series the proportion of young children with miliary mottling in the lung fields - 11 (57.9%) of the 19 cases under 3 years examined was significantly higher than in other age-groups - 17 (20.7%) of the other 82 ($\chi^2 = 10.63$ with $n = 1$; $P = 0.01 - 0.001$) and this may well have been the major cause of the higher mortality in infants, the meningitis in these cases being simply a local manifestation of a widespread haematogenous dissemination of tubercle bacilli. This was certainly the case in the child already referred to (case 49), post-mortem examination of whom revealed extensive miliary tuberculosis, but only very early meningeal inflammation.

Finally MacCarthy and Mann (1950) made the observation that a good initial response is dependent to a large extent on a free circulation in the cerebrospinal spaces and they suggested that the younger the patients the greater would be the danger of mechanical obstruction to the flow of C.S.F. That this could not have been a factor in this series is seen by the comparative infrequency of spinal block in these patients (see Table 94).

Whatever the factors mainly responsible it is evident that not only are young children most susceptible to tuberculous meningitis; they are also, by the time they reach hospital, most resistant to treatment. The obvious corollary is the value and importance of protection of all infants and young children exposed to tuberculosis.

DURATION AND SEVERITY OF ILLNESS.

The paramount importance of early diagnosis and institution of treatment has been repeatedly emphasized in the literature on tuberculous meningitis. Lorber/

Lorber (1954b) from his studies of 549 patients in five different centres concluded that the most important prognostic factor was the stage of illness on admission. The incidence of sequelae, as well as the actual survival rate, was related to the severity of the initial illness. In the series, 66.6% of early cases survived compared with less than 50% at an intermediate stage and 20% of advanced cases. Moreover, 9% of early cases, 22.6% of intermediate cases and 54.8% of late cases showed neurological sequelae. These findings led to the conclusion that patients with early disease had a five times better chance of complete or useful recovery than those with advanced disease.

Most writers have followed the M.R.C. (1948) in their classification of stages of disease, namely:-

"Early :- Patients with mainly non-specific symptoms with little or no clinical signs of meningitis, with no paresis, in good general condition, and fully conscious. Diagnosis established mainly on findings in C.S.F.

Advanced :- Patients obviously extremely ill, deeply comatose or stuporose, or with gross paresis.

Medium :- Patients in a condition between those of the first two groups."

The following are samples of some of the reported mortality rates in relation to these categories:

Authors	No.of Cases.	Mortality Rates. Early	Medium	Advanced
M.R.C. (1948)	92	46%	66%	86%
Mann (1948)	33	40%	80%	93.3%
Rubie and Mohun (1949)	54	44.4%	68.2%	92.2%
Department of Health for Scotland (1949)	81	33%	54%	88%
Calnan (1951)	114	33%	48%	89%
Lincoln and Wilking (1951)	39	14.3%	25%	60%
Robertson and Gairdner (1952)	146	33.3%	47.8%	85.7%
Illingworth and Lorber (1951)	82	26.3%	64.9%	65.4%

In the last-named series, only 3 of the 9 survivors who had advanced disease on admission were mentally normal (and only 1 completely normal, mentally and physically) whereas 12 of the 13 survivors who had early disease were mentally normal. The Department of Health for Scotland (Dunlop et al,1953) reported 60% recoveries in cases classified as early compared with an average of 39% in a series of 266 cases; the Ministry of Health (1953) in a summary of findings in 369 cases, found for early cases a survival rate of 48% compared with 10% for late cases; and Choremis and his fellow-workers (1951) reported that 44 patients out of 53 in good clinical condition survived compared with 28 out of 60 with advanced disease.

While there is general agreement on the high degree of correlation between the stage of illness and the recovery rate there is not a corresponding unanimity about the prognostic value of the duration of illness prior to institution of treatment. The M.R.C. (1948) found that, in general, patients with a short history suggesting meningitis were clinically at an earlier stage than others, but there were many exceptions; 8 patients with a suggestive history of more than a week's duration were still at an early stage on admission, while 7 patients with a similar history of less than 4 days' duration were at an advanced stage. The length of non-specific illness bore little relation to the condition on admission. Rubie and Mohun (1949) could find no constant relationship between the length of the period of illness before admission and the stage of disease on admission. Beveridge (1952) could not correlate the prognosis with the length of the history/

history; and Brainerd and Eagle (1950) also found that the duration of disease before the institution of treatment did not appear to affect the outcome; their patients who had improved with treatment had an average duration of illness of 13.5 days, compared with 12.6 days in patients who did not improve. Likewise Perry (1952) concluded that early institution of treatment had no effect on survival; 4 of 13 cases who were treated within 10 days of the onset of illness survived, compared with 3 of 13 cases with an illness of longer than 10 days. Of 43 patients reported by Bunn (1948) 11 had less than a week's illness - and 5 died, 4 within a fortnight, and 12 had an illness of longer than two weeks - and 6 survived; the duration of survival in patients who died did not appear to be affected by the promptness of therapy. Riley (1953) treated 60 cases and had only 4 survivors; 3 of these were in the second week of illness when treatment was commenced, and 1 in the third week; 9 with less than a week's illness died. On the other hand, Howard (1949) found that the average duration of illness before treatment in fatal cases was 22 days, compared with 13 days in survivors. Lorber (1951b), making a plea for early diagnosis, asserted that the mortality was considerably affected by delay in instituting treatment. In a series of 66 patients, the average delay from the first symptoms to the beginning of treatment was 14.2 days; the mortality rate in cases whose treatment was commenced after this was 88.2%; when treatment was begun earlier, the mortality rate was 47.8%.

Tables 7 to 9 present the inter-relationships of duration and severity of illness and the outcome in the 102 cases in this series. The classification suggested by the M.R.C. has been used in estimating the severity of the illness but with more emphasis on the general condition than on the state of consciousness (which is considered separately in Table 15). Thus some patients who were obviously severely ill - drowsy, confused, irrational, obstreporous, with or without pareses - were classified as "severe" although they were not stuporose or comatose; and some patients who had no meningeal signs or only mild meningism (this, also, being considered later at Table 13) were classified as "moderately" ill if their clinical condition justified it. With these slight exceptions the "mild", "moderate" and "severe" categories correspond/

correspond with the "early", "medium", and "advanced" groups respectively in the M.R.C. classification. When considering the duration of the illness it was sometimes difficult to differentiate between the vague indefinite illness preceding the meningitis and the symptoms that heralded the onset of meningitis itself. In 6 patients, indeed, separation was impossible and these have been classified as "indefinite". In all others the "duration of illness" referred to the period from the beginning of meningitic symptoms to the institution of treatment.

The trend, observed in the other series, of progressive increase in mortality rates with increasing severity of illness is very evident (and significant) in this series as is seen in Table 8. Mortality rates of 10%, 25.9% and 58.8% were recorded in mild, moderate and severely ill patients respectively. A similar relationship, however, could not be demonstrated between the duration of illness and the outcome (Table 7). It is noticeable that the mortality rate (28.6%) in patients whose illness was longer than a fortnight was even lower than that (32.6%) in patients who had been ill for less than a week; and, further, that 3 of 6 patients with illness shorter than three days died. These latter, as would be expected, were all children whose illness may well have been longer had they been accurately observed; they were aged 2, 4 and 7 years, and died 1 week, 2 weeks and 1 month respectively after the institution of treatment. Finally it is clear from Table 9 that there was no constant relationship between the length of history and the clinical stage of the disease. While there is a suggestive trend, this/

this is not at all significant. It can be seen, for instance, that 3 of 6 patients with less than 3 days' illness and 9 of 34 who had been ill for less than a week were already at an advanced stage of illness.

Does it follow, then, that early diagnosis is unnecessary and early institution of treatment of no value, as Perry (1952) seemed to suggest? Surely not! For various reasons, the estimation of the duration of the illness must necessarily be inaccurate. Many cases in this series - and, doubtless, in most series - came from large families living in poor home conditions where parental interest in the children is slight, and ignorance of signs of illness is marked; consequently it is very often difficult to obtain a satisfactory account of a patient's illness. In children, moreover, especially in infants and younger children the difficulties are increased by the inability of the child to register specificcomplaints such as headache. In many cases, as already indicated, the actual meningitic illness is preceded by a period of weeks or months of vague ill-health which merges, often imperceptibly, into the features of meningitis, so that it becomes well-nigh impossible to fix a date when one ends and the other begins. It is obvious, therefore, that figures given for the duration of illness in Tables 7 and 9 (and in other series) are not by any means accurate or reliable estimates and too much stress should not be placed upon them. Added to this is the fact, already noted, that the disease seems to progress more rapidly in some patients, particularly children, than others; so that without treatment while some patients might linger for 3 or 4 weeks or longer, others might deteriorate rapidly and die within a week of onset.

Despite/

Despite these figures, then, it is obviously true that, while for the assessment of prognosis, the clinical impression of the patient's condition is a much more accurate guide than the length of the history of illness, which at the best is unreliable, institution of treatment as early in the course of the illness as possible will enhance the patient's chances of survival, while delay will result in progression of the illness from a mild to a moderate or advanced stage with corresponding increase in the mortality rate. As Lincoln and Kirmse (1949) have pointed out, in many cases the danger of hydrocephalus and chronic meningitis developing can only be avoided by early recognition of symptoms and prompt institution of treatment. Further, since (a) organisms seem rapidly to become embedded in granulation tissue (with increasing immunity to circulating streptomycin); (b) the organisation of the exudate tends to prevent the circulation of the C.S.F; and (c) ischaemic changes resulting from endarteritis cause irreversible lesions in the central nervous system (see Smith et al, 1948) it is obviously important to commence treatment early before these changes develop.

MENTAL, NUTRITIONAL, MENINGEAL AND REFLEX STATE.

Of all the particular features of the initial illness in tuberculous meningitis, the one which has been most frequently emphasised as a prognostic guide is the state of consciousness.

In a very early paper, Debré and his co-workers (1947) stated, "Of all the unfavourable signs, there is only one which in our opinion has absolute value and that is coma, by which we mean complete abolition of consciousness, absolute insensitivity to the strongest stimuli. This is the only condition in which we consider hope to be lost." MacCarthy and Mann (1950) considered that the advancement of the meningitis is probably closely paralleled by the height/

height of the intracranial pressure and the resulting cerebral depression is more closely reflected in the child's mental state than in any other symptoms or signs. They were of the opinion that the commonly used subdivisions (early, medium and advanced) of the stage of the disease were too vague and suggested a classification dependent on the mental state. In their series of 40 patients (3 others being infants not assessable) 8 out of 18 in the first stage of normal mentality died, compared with 3 out of 5 in the second stage of delirium and confused mental activity and 15 out of 17 in the third and fourth stages of stupor and coma. Smith and Vollum (1950) also regarded the state of consciousness as the main factor in prognosis but emphasised that some patients who were wholly conscious died whereas some deeply stuporose recovered. In a series of 38 cases with 28 survivors, Lorber (1954a) found that 25 (92.6%) of 27 who were conscious on admission recovered - and neither of the deaths was due to tuberculous meningitis. Beveridge (1952) also concluded that the better the state of consciousness on admission the brighter the outlook. Very little reference, however, has been made to the prognostic value, if any, of other features of the initial illness such as the state of nutrition, severity of meningeal signs and the character of the reflexes.

In this series too, the state of consciousness was closely related - although perhaps to a lesser degree - to the ultimate outcome. Table 10 shows an obvious and significant trend indicating increasing mortality with increasingclouding of consciousness (from 14.8% of 27 patients who were mentally bright on admission to 64.7% of 17 stuporose and comatose patients). It is perhaps surprising, however, that 3 out of 6 patients who were comatose on admission survived, one (13) without any mental or physical upset, one (38) totally deaf but without other sequelae, and one (39) mentally deficient. On the other hand, of 27 patients who were perfectly clear mentally without even any trace of drowsiness, 4 died. It may be concluded, therefore, that the initial state of consciousness, while a good guide to prognosis, is only a rough one and not altogether reliable.

A clear positive correlation is seen to have existed in this series between/

between the nutritional state and the recovery rate (Table 11). All 5 emaciated patients died compared with only 5 of 26 who were well-nourished; 80.9% of well-nourished patients but only 46.2% of poorly nourished or emaciated patients survived. Table 12 shows that there was a significant relationship between the nutritional state and the stage of the illness: 7 of 10 patients at an early stage were well-nourished and none poorly nourished, whereas only 2 of 34 patients at an advanced stage were well-nourished and 25 were poorly nourished or emaciated; all 5 emaciated patients were at an advanced stage of illness. A reasonable hypothesis would be that patients with impaired nutrition and consequently, diminished resistance, are more likely to have rapidly progressive disease and therefore be discovered at a late stage. An obvious corollary is the importance of measures directed towards the replacement of nourishment by whatever route possible in order to increase the patient's ability to counteract infection. In a number of patients in this series, oral administration of food and fluids was impossible or inadequate on account of unconsciousness, recurrent vomiting or simple refusal to swallow; in these cases nasal feeding was used, or transfusions of blood, plasma or glucose-saline given.

That the presence of meningeal signs is by no means a constant finding in tuberculous meningitis was emphatically stated by Illingworth (1956) who found no meningism in 25% of 173 cases (in a series of 236 cases) in whom the presence or absence of meningism was noted. Meningism in his series was found much less often in younger children than in older ones and 71% of early

cases/

cases had no meningeal signs. In only 7 (6.9%) of the 102 cases in this series was there no evidence of meningism but in one-third of the patients the signs were slight (Table 13). The presence and degree of meningism did not appear to greatly influence the outlook; indeed it is noteworthy that a higher proportion of patients with moderate meningism survived than of those in whom signs were absent or slight. The high mortality (51.9%) in the 27 patients with marked meningism is just significant, but, since the difference is not gross, it is possible that other factors played a part in this e.g. the severity of the illness. One would expect that patients with longer history would have more marked meningeal signs, but, while Table 14 does show a suggestive trend, this is not statistically significant. It may be concluded that while marked meningism was associated with higher mortality, lesser degrees of meningism did not seem to affect the outcome.

The severity of the illness is reflected also in the state of the deep reflexes; diminution or loss of these reflexes occurs in infective conditions, in coma and in the final stages of raised intracranial pressure. In this series (Table 15) a significantly higher proportion of patients with average or exaggerated reflexes survived than of those with diminished or absent reflexes (75.8% compared with 51.4%). Taken with other signs the state of the deep reflexes could be useful as a prognostic guide; in itself, however, it is clearly not reliable - one of the two patients with totally absent jerks survived.

TEMPERATURE AND ERYTHROCITE SEDIMENTATION RATE (E.S.R.)

Fever is one of the well-recognised symptoms of tuberculous meningitis. Professor Choremis, at the U.N.I.C.E.F. conference of tuberculosis in childhood in/

in 1950, described fever, vomiting, headache and constipation as the principal early symptoms of tuberculous meningitis in young children. It is, however, by no means an invariable feature, and a marked pyrexia is uncommon. Illingworth (1956) found that 27% of 276 children with tuberculous meningitis had no pyrexia when first seen in hospital. 8 (7.9%) of the 102 patients in this series were apyrexial prior to the institution of treatment, and in only 9 (8.8%) was the initial temperature higher than 102°F. Over half of the patients had a moderate fever of between 100°F and 102°F. Bunn (1948) has pointed out that fever is no guide to the prognosis; he reported that several afebrile patients died within a month and patients with high temperatures sometimes recovered. These were the findings also in this series (Table 16), in which 55% of 40 patients with normal temperature or mild pyrexia (up to 100°F) survived, compared with 71% of 62 patients with moderate or marked pyrexia (over 100°F). 2 of 8 patients with normal temperature died and 8 of 9 patients with temperature over 102°F survived. This lack of correlation between temperature and outcome may be the result of the conflict of two factors: (1) acute and severe illness would be expected to be associated with higher temperature; (2) on the other hand the pyrexial state may be partly a reflection of the response of the patient to infection; a high temperature being an evidence of high resistance with adequate response to infection. Thus, the 8 survivors whose initial temperature exceeded 102°F may have been demonstrating a good response to the infection.

The E.S.R. is, rather surprisingly, not consistently raised in tuberculous/

tuberculous meningitis. This was noted by Choremis and his associates (1948) who concluded that it was of no help and rather inconstant and irregular. In the present series (Table 17) it was under 10 mm. in the first hour in one-third of the 78 patients in whom it was carried out at the time of admission to hospital; and in over 70% it was under 20 mm. in the first hour. Only 1 (Case 60) gave a reading of over 50 - 78 in the first hour; this was a young woman of 19 years with concomitant miliary tuberculosis, who died after 6 weeks, in which time the E.S.R. had fallen to 14 in the first hour despite clinical deterioration. It is evident that the initial E.S.R. had no bearing on the outcome - of 26 patients in whom the first hour reading was less than 10, 6 died while of 13 patients in whom the reading was over 30, 8 survived.

RADIOGRAPHIC ABNORMALITIES IN CHEST.

In a high proportion of cases of tuberculous meningitis, chest X-Rays reveal tuberculous lesions in the lungs or pleura. There are three types of abnormality that may be present; (a) Primary Complex - indicated by the presence of definite hilar adenitis with or without evidence of pulmonary collapse; (b) Miliary tuberculosis - presenting the typical "snowstorm" appearances indicative of haematogenous dissemination of the tubercle bacilli; (c) Adult phthisis which may be active or quiescent. In addition, a considerable number of patients with clear X-Rays do, in fact, have intra-pulmonary disease which is only revealed on careful post-mortem examination. A primary complex may be so small or so situated that it does not show itself in a straight X-Ray of the chest. It is well known, too, that/

that many cases of miliary tuberculosis, proved at autopsy, have a clear X-Ray during life. For example, Illingworth and Wright (1948) reported 9 cases (out of a series of 65 with miliary tuberculosis and tuberculous meningitis) who did not have radiological evidence of miliary tuberculosis during life but in whom post-mortem examination revealed miliary tubercles. Emery and Lorber (1950) showed that miliary tuberculosis was diagnosed radiologically in only 18 of 52 cases in whom miliary spread was found at necropsy. It is clear, therefore, that it is impossible to assess accurately the effects on the outcome of the presence of either primary or miliary tuberculosis since many of the survivors and also of non-survivors in whom necropsy is not performed have abnormalities which are not detected in X-Rays taken during life. On this account the prognostic significance of chest disease should be assessed only on the evidence of radiological examination during life and not on combined X-Rays and autopsy findings.

Conflicting views on the prognostic value of radiological appearances have been expressed in the literature. It is fairly unanimously agreed that patients with adult phthisis have, as would be expected, a reduced prospect of recovery, which is largely influenced by the extent and severity of the pulmonary lesions and their response to treatment, rather than by the meningitic disease. Persistent activity of the pulmonary disease adversely affects the prognosis of the meningitis, and, moreover, the presence of phthisis may itself be the cause of death in cases where meningitis has been cured. Smith, Stevens and Pile (1951) found a much higher mortality in patients in whom meningitis followed chronic phthisis - 5 of 6 such patients died, in a series in which the overall mortality was 52%. The significance of a primary complex or even of miliary tuberculosis is not, however, quite so clear. Many writers associate the finding of snowstorm mottling in the lung fields with a worsened prognosis. In the M.R.C. report (1948), for instance, 75% of patients with miliary tuberculosis or a primary complex died, compared with 57% of others. Robertson and Gairdner (1952) reported recovery in 49 of 99 patients with meningitis alone, but only in 20 of 57 in whom there was associated miliary tuberculosis. Similarly Beveridge (1952) had 13 recoveries among 29 patients with meningitis alone, but only 3 among 28 patients/

patients who also had miliary tuberculosis; and Finberg (1951) reported that 11 of 20 patients with meningitis alone survived, compared with only 2 of 15 patients with concomitant miliary tuberculosis. Debré (1952) reported an overall mortality of 46% in patients with tuberculous meningitis; in 108 cases in whom there was associated miliary tuberculosis, the mortality was 60%. On the other hand, Illingworth and Lorber (1951) could find no significant difference in the outcome between patients with and those without miliary mottling in chest radiographs. They pointed out that the prognosis appeared much worse in cases of combined miliary and meningeal tuberculosis if patients were included in whom the diagnosis of miliary tuberculosis was only made at autopsy. In 1953 a sub-committee of the Scientific Advisory Committee (Dunlop et al) correcting an earlier impression (1949) that the outlook was less favourable in cases where the chest X-Ray showed a snowstorm appearance, reported that in 266 cases there was no difference in mortality in groups with and without miliary tuberculosis - 53%, compared with 52%. Perry also (1952) could find no significant difference - 2 of 13 patients with miliary tuberculosis survived compared with 4 of 13 without it. Lorber (1954a) had similar results in treating 38 children - 8 of the 10 with miliary tuberculosis survived.

Of the 101 patients in this series who survived sufficiently long for X-Ray examination to be carried out, 11 had evidence of active or quiescent adult pulmonary tuberculosis. The remainder could be divided almost equally into three groups (Table 18) - (a) those with miliary tuberculosis as indicated by radiological "snowstorm" appearances during life, (b) those with a primary complex - hilar adenitis with or without evidence of pulmonary collapse, and (c) those with no radiological abnormality. In a few cases of miliary tuberculosis X-Ray showed also a primary complex, and in one case of adult phthisis there was evidence of fresh haematogenous dissemination miliary in type. These were all included in the "miliary" group. It is clear that in this series the presence of either miliary or adult pulmonary tuberculosis had an adverse effect on the prognosis. More than one half of 28 patients with the former and 5 out of 11 with the latter died, in contrast

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to less than a quarter of 62 patients without evidence of either - a significant difference. Three of the cases of miliary and meningeal tuberculosis developed meningitis while having streptomycin treatment for the miliary condition, and 2 of these survived. In all the other 25 patients the miliary mottling in the lung fields was a concomitant finding - 56% of these died. The high proportion of children in the "miliary" group has already been noted - 11 of the 28 patients were under 3 years - and this may well have contributed to the significantly high mortality rate of these patients. 12 patients in all had evidence of adult phthisis - including the one who had also miliary spread and is classified with the "miliary" group. In 2 of these 1c the pulmonary disease appeared quiescent or healed; 5 of the remaining 10 died (and 1 other since the tables were compiled). In only 2 was collapse therapy - in the form of pneumoperitoneum - considered to be indicated. It is noteworthy that all of 5 patients over 30 years of age had evidence of adult phthisis - these included the 2 patients in whom the disease was considered to be quiescent (1 of whom survived) and the patient who had superimposed miliary mottling. Doubtless the presence of pulmonary tuberculosis contributed to the high mortality in this group.

ABNORMALITIES OF THE FUNDUS OCULI.

The proportions of patients with choroidal tubercles vary widely in different reported series; so much so that one is tempted to suggest that the number of patients in whom tubercles were actually present may in many cases be quite different from the number in whom they were observed and that the differing proportions reported may well result from the varied skill and accuracy of observation. In an early paper, (1947) Debré and his associates quoted figures supplied by Monbrun and Lavat who observed choroidal tubercles in 18% of cases of meningitis alone, 75% of cases of miliary and meningeal tuberculosis and 50% of cases of miliary tuberculosis without meningitis. Monbrun/

Monbrun reporting at the U.N.I.C.E.F. Conference in February 1950 on 1000 cases gave the following figures for these groups in the same order - 17%, 87% and 51%. Illingworth and Wright (1948) found choroidal tubercles in 1 (5.6%) of 18 cases of meningitis alone; 18 (64.3%) of 28 cases of miliary tuberculosis with meningitis; and in 7 (50%) of 14 cases of miliary tuberculosis alone. Somner (1952) in a smaller series of 26 cases observed choroidal tubercles in 7 of the 10 patients with miliary tuberculosis but in none of the remaining 16 patients. Smaller proportions were observed by Rubie and Mohun (1949) - 5 (all with miliary) of 67 cases; the Department of Health for Scotland (1949) - 12 of 81 cases; Riley (1953) - 4 (all with miliary) of 60 cases; McGregor (1951 - quoting a figure by Still) - 2 of 150 cases; Lassen and Neukirch (1951) - 5 of 44 cases; and McSweeney (1950) - 3 (all with miliary) of 94 cases.

It is clear from these figures that choroidal tubercles occur much more frequently in cases of tuberculous meningitis with associated miliary tuberculosis, than in uncomplicated tuberculous meningitis. Indeed, McSweeney (1950) and Illingworth (1950) went so far as to say that they are not seen in the latter. That they do occur in cases of tuberculous meningitis without clinically recognisable miliary tuberculosis is evident from the figures already quoted, but these cases may well be examples of the anomaly already noted, namely, the absence of X-Ray changes in cases with proven miliary disease.

Of the 12 cases with choroidal tubercles, reported by the Department of Health for Scotland (1949) 11 died. The conclusion that the presence of choroidal tubercles adversely affected the prognosis was repeated in 1953 by the sub-committee of the Scientific Advisory Committee, although further evidence was not presented. Likewise Russell and MacArthur (1950) found a higher mortality in cases showing choroidal tubercles - 6 out of 8 cases with, and 12 of 25 without tubercles died. On the other hand, Choremis and his associates (1951) were of the opinion that the presence of choroidal tubercles was of no prognostic significance; and in Somner's series, already mentioned, 5 of the 7 patients with choroidal tubercles survived compared with 9 of the other 19 patients. It must always be remembered, in assessing the prognostic significance of choroidal tubercles that they occur in association with miliary tuberculosis, the presence of which appears to worsen the prognosis.

Of 92 patients in this series in whom ophthalmoscopic examination was carried out, 15 (16.3%) were found to have choroidal tubercles - 8 unilateral, and 7 bilateral (Table 19). I would hesitate to draw conclusions from these findings because, while examination of the fundus oculi was carried out personally and as carefully as possible at least at monthly intervals/

intervals, they were not confirmed by an ophthalmalogist and the number of observed cases is almost certainly less than the number of actual cases, especially in patients treated early in the series. This is probably particularly applicable to the patients who died shortly after admission to hospital, and in whom ophthalmoscopic examination was performed only once. Choroidal tubercles which had not been visualised at the first examination were sometimes detected at subsequent examinations. 8 of the 15 patients with choroidal tubercles were not known to have associated miliary tuberculosis during life; four of these survived so confirmation (or otherwise) of the absence of miliary disease was not possible. Autopsy was carried out in 2 of the 3 who died; in one (with a clear X-Ray) there was a small primary focus in the lung and fine miliary mottling throughout the lungs; in the other there was no evidence of miliary tuberculosis in the lungs, but a few miliary tubercles were seen in the kidneys. It is seen from Table 19 that 5 (19.2%) of 26 non-survivors examined had choroidal tubercles, compared with 10 (15.2%) of 66 survivors. The difference is not significant. Nor does it appear that the presence of papilloedema was an adverse prognostic sign in this series, as might have been anticipated in view of its indication of increased intracranial pressure. More than two-fifths of survivors were found to have papilloedema - and less than one-fifth of the non-survivors ophthalmoscopically examined. The three patients who had marked papilloedema all survived.

CEREBROSPINAL FLUID (C.S.F.) FINDINGS.

The value of the cytological and biochemical changes in the C.S.F. as a guide to the diagnosis of tuberculous meningitis is not open to question. Rubie and Mohun (1949) did observe 3 cases in whom the earliest C.S.F. examination/

examination revealed no abnormalities as much as 5 and 11 days after the onset of symptoms, but these are without doubt exceptional, and a firm diagnosis can certainly not be made in the absence of at least a pleocytosis. A cell-count varying from 30 to 1,000 per c.mm. is a constant finding; very rarely, in fulminating cases, the count is said to exceed 1,000 per c.mm. Usually the cell type is predominantly lymphocytic, but polymorphs may predominate in the early stages and in rapidly progressive cases. Almost invariably there is an associated rise in the protein content, which, in some cases where spinal block has developed may be 2 or 3 g. per 100 ml. Bunn (1948), however, had 5 patients with a normal initial C.S.F. protein, 4 of whom died. Reduction in the C.S.F. chlorides was at one time considered to be an important pointer to diagnosis; since the commencement of streptomycin therapy, however, it has become increasingly evident that the sugar level is a much more valuable diagnostic guide. Rubie and Mohun (1949) found that the chlorides were often normal in confirmed cases; Cathie (1948) stated that they may never be less than 700 mg. per 100 ml.; Mann (1948), reporting 33 cases, found the chlorides to be normal in 13; and Smith and Daniel (1947) considered that the C.S.F. chloride level reflected the plasma chloride level and was therefore reduced in patients who had been vomiting - they added that "there is no such thing as a pathognomonic chloride level". Most observers concur with Lincoln and Kirmse (1949 and 1950a) in their view that a reduced sugar level is the most characteristic change and the most valuable single diagnostic finding, or with Somner (1952) that it is the most valuable single factor in the early diagnosis of tuberculous meningitis not complicated by miliary tuberculosis (cases with miliary tuberculosis being diagnosed earlier before the decline in the sugar content). The finding of low C.S.F. sugar differentiates tuberculous meningitis from benign lymphocytic meningitis, tuberculous serous meningitis, and indeed all other causes of C.S.F. pleocytosis with the exception of purulent meningitis and some cases of poliomyelitis (Illingworth, 1956). Harvey (1952) stated that "on no occasion when a clear fluid was found deficient in sugar was the diagnosis proved not to be tuberculous meningitis." Nevertheless, a low C.S.F. sugar is not an invariable finding in proven cases of tuberculous meningitis and many cases have been reported in whom the level never fell below 45 or 50 mg. per 100 ml. before treatment - for example, by Bunn (1948), Mann (1948), Lincoln and Kirmse (1950 a and b), Cohen (1952), Riley (1953) and Alexander (1954). Illingworth (1956) reported as many as 14% of 236 children in whom the initial level of C.S.F. sugar was 50 mg. per 100 ml. or over.

The value of C.S.F. changes as guide to prognosis as opposed to diagnosis, has not been so fully reported, but the few statements that have appeared in the literature indicate that they are of little prognostic significance (Brainerd and Eagle, (1950)). Rubie and Mohun (1949) could find no relation between the cell count or protein content of the C.S.F. and the stage of disease on admission, except that a grossly raised protein indicated/

indicated spread of disease down the theca. Bunn (1948) found that the sugar level was no guide to the ultimate outcome and also reported that 4 out of 5 patients with normal protein at the onset died. Somner (1952) on the other hand, was of the opinion that the sugar level at the time of diagnosis was in accordance with the severity of the illness.

Tables 20 to 31 have been compiled to ascertain, if possible, the significance of the initial C.S.F. findings in this series. An attempt has been made to discover not only whether the degree of abnormality of each constituent bore any relation to the ultimate outcome of the illness but also whether the level was affected by the stage of the illness at which C.S.F. was examined. The findings recorded are those of the last specimen of C.S.F. examined before the institution of treatment.

CELL CONTENT (TABLES 20 - 23).

The initial C.S.F. cell-count varied from 31 to 900 per c.mm. (the patients with the extreme readings survived.) Contrary to what might be expected it is interesting to note that there was a significant inverse relation between the cell content and the mortality, i.e. the mortality was higher in groups of patients with lower cell count. Thus the mortality rate of cases with a cell count of less than 200 per c.mm. was 51.2%, whereas that of cases with a cell-count of over 200 per c.mm. was only 23.7%. 31.8% of 66 survivors, and 61.1% of the 36 who died had an initial cell-count of less than 200 per c.mm. Further, while half of the 16 patients with an initial cell-count less than 100 per c.mm. died, none of the 4 with readings over 600 and only 2 of 9 with readings over 500 died.

The reason for this apparent anomaly may be that the C.S.F. cell-count

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is not so much an index of the extent to which the meningitis has advanced as of the degree of tissue response to the meningeal invasion. A low cell-count may thus be evidence of poor meningeal reaction and a high cell-count, far from being an unfavourable sign indicating advanced disease, may well be a good sign and evidence of a satisfactory meningeal response. This conclusion is in harmony with the results of Tables 21, 22 and 23 which show that the cell-count did not appear to be related to the duration or severity of the illness or the degree of meningism.

PROTEIN (TABLES 24 - 28).

The protein level in this series varied from 10 mg. per 100 ml. to 1520 mg. per 100 ml.; a reading below 100 mg. per 100 ml. was recorded in exactly half the patients, and in only 2 was it over 500 mg. per 100 ml. It might be expected that a raised protein level, being perhaps an indication of more advanced and extensive meningeal disease, would carry a poor prognosis. No relationship could, however, be demonstrated in this series, the proportions of survivors in all groups being very similar. The fact that there were only 2 patients with a level over 500 mg. per 100 ml. renders it impossible, however, to draw rigid conclusions.

In 11 patients, the protein level was 40 mg. per 100 ml. or less, and 4 of these died - in 2 weeks, 3 months, 4 months, and over 2 years (the latter, after 3 relapses). The first 3 of these had associated miliary tuberculosis, and the one who died after 4 months developed meningitis in the course of treatment of the miliary condition. All of the 7 survivors with normal

initial/

initial C.S.F. protein had "snowstorm" mottling in the lung fields and 2 of these developed meningitis while having streptomycin for miliary tuberculosis. Thus all of the 11 patients with normal C.S.F. protein had associated miliary tuberculosis. In 3 of these, however, in whom the meningitis was discovered on routine C.S.F. examination, a low protein was to be expected in view of the comparatively early discovery of the meningeal invasion.

The higher protein levels tended, as might be anticipated, to be associated with longer illness prior to institution of treatment, more advanced disease and more marked meningism, but the figures, presented in Tables 25 to 27, were not sufficient to show any significance in any of these trends. A significant direct correlation was demonstrable, however, between the initial cell-count and the protein level. (Table 28).

CHLORIDES (TABLE 29).

As the chloride level was not reckoned to be of either diagnostic or prognostic import, this estimation was omitted in 12 patients admitted to Belvidere Hospital before 1950 and in the early months of that year. The figures obtained in the remaining 90 patients varied from 580 to 740 mg. per 100 ml. While both the lowest and highest levels were obtained in survivors, and although 4 patients who ultimately died had normal values (over 700 mg. per 100 ml.) at the beginning of treatment, Table 29 does show a highly significant degree of correlation between the initial C.S.F. chloride content/

content and the recovery rate. Thus it is seen that 75% of the 56 patients whose initial chloride level was over 650 mg. per 100 ml. survived; while the corresponding proportion of 34 patients whose initial chloride level was under this figure was only 44.1%. Since the C.S.F. chloride level is influenced by the plasma chloride level, it is quite probable that the higher mortality in patients with low C.S.F. chloride was due to other factors, namely excessive vomiting with dehydration and plasma electrolyte depletion. Moreover, the level cannot be used as a very reliable guide; 4 patients with normal readings on admission died after 1 month, 1½ months, 3 months and 6 months respectively, and the patient with the lowest initial reading made a comparatively rapid recovery uninterrupted by exacerbations or relapses.

SUGAR (TABLES 30 AND 31).

If a C.S.F. sugar level of 45 mg. per 100 ml. be accepted as the minimum normal finding, 12 patients (11.8%) in this series had a normal C.S.F. sugar when treatment was commenced. Even if, as Somner (1952) suggested, the line is drawn at 50 mg. per 100 ml. the number is as high as 11 (10.8%). These findings confirm the statements already gleaned from the literature, that a normal sugar level does not of itself invalidate the diagnosis of tuberculous meningitis. In view of the emphasis that has been placed upon the importance of the C.S.F. sugar, I have reviewed these 12 patients in greater detail, with particular reference to the alterations that occurred in the sugar levels in the course of treatment.

4 of the 12 died after periods of 1 week, 2 weeks, 3 weeks and 3 months respectively. Case 10 had an initial sugar level of 60 mg. per 100 ml. but died within a week, before another specimen was examined. In case 65, who survived for 2 weeks, an initial value of 52.6 mg. per 100 ml. was followed by other/

other 4 normal readings, but finally, 4 days before death by a reading of 43.4 mg. per 100 ml. Case 84, who died after 3 weeks of treatment, had an initial C.S.F. sugar of 58.8 mg. per 100 ml; the level never fell below 52.6, varying between this and 76.9 despite steady downhill progression. Case 47 survived 3 months, during which period 12 C.S.F. sugar estimations were made. Initially the figure was 58.8 mg. per 100 ml; after 1 week it had fallen to 40 mg. per 100 ml. but by the next week it had risen to 66.6 mg. per 100 ml; on only 3 other occasions was the level below 50 mg. per 100 ml.

8 patients with normal initial C.S.F. sugar survived. In Case 5, with an initial level of 58 mg. per 100 ml., normal values were maintained for the first month, but after this the figure fell to 41, remained low for a month and then, apart from 2 or 3 occasions, was normal throughout the rest of the course. Case 6 had an initial level of 72 mg. per 100 ml; one week after the institution of treatment it had fallen to 36 mg. per 100 ml. but returned at the next estimation to normal where it remained, with 3 exceptions, for 6 months. In Case 9, the original figure was 50 and for 2 months the level fluctuated between 50 and 65; then, for no apparent reason, it fell to 23, but returned to normal for a further fortnight; for the next few months, the level was persistently low (between 30 and 40 mg. per 100 ml.) No abnormal finding was ever recorded in Case 70, in whom the initial reading was 66.6 mg. per 100 ml. Cases 83 and 85 were both found to have meningitis on routine examination of the C.S.F. in the course of treatment of miliary tuberculosis. The pre-treatments C.S.F. sugar levels were 62.5 and 76.9 mg. per 100 ml. respectively. In the former, only 2 abnormal findings were observed throughout 6 months during which estimations were carried out weekly - 43.4 and 41.6 mg. per 100 ml., both occurring 2 months after the institution of treatment. In the latter the only abnormal figure, 43.4 mg. per ml., was obtained 1 month after treatment was commenced. Case 88 showed a steady fall in the C.S.F. sugar level from 58.5 mg. per 100 ml. before treatment, to 45.4 after a week, 40 after a fortnight, and 38.4 after 3 weeks, thereafter the level returned to normal and remained so. In case 98 the initial C.S.F. sugar level was 45.4 mg. per 100 ml; one week later it had fallen to 40 mg. per 100 ml., this being the only abnormal reading throughout the course of treatment.

These findings emphasise the necessity of exercising caution in drawing conclusions from the level of the C.S.F. sugar, whether in the initial specimen or during the course of treatment. Not only is it fallible as a diagnostic aid; in this series, at any rate, the initial C.S.F. sugar content was totally unreliable as a prognostic guide. This is evident from the fact that 3 patients/

patients (of the 4 non-survivors) who had a normal finding on admission died within a month, and also that the patients who had the lowest recorded C.S.F. sugar on admission - 7 mg. per 100 ml. - survived. Moreover, Tables 30 and 31 do not show any relationship in this series between the initial C.S.F. sugar level and either the outcome or the severity of the initial illness. Further, it is clear that, while the development of recrudescence or relapse is often heralded by a drop in the sugar reading, such a finding is not always a serious omen; nor on the other hand, is a normal reading necessarily a favourable finding since it was obtained in this series in moribund patients.

SUMMARY.

It is not possible to forecast with certainty how any given patient with tuberculous meningitis will respond to treatment with streptomycin. Doubtless many factors play a part which cannot be ascertained when the patient is seen for the first time; for example, the sensitivity of the invading organisms to the anti-tuberculous drugs, and the innate or acquired resistance of the patient to tuberculosis. Nevertheless, in this series, certain factors seemed to be of prognostic value, among which were the following:-

(1) Age: A higher mortality occurred in children under 3 years, and (although the numbers were too small to be significant) in adults over 30 years.

(2) Stage of Disease: In general the more advanced the disease, the poorer was the prognosis. In assessing this factor, however, the clinical impression of the patient's condition was much more accurate than the/

the length of history, which was neither related to the severity of the illness nor to the ultimate outcome.

(3) State of Consciousness: Increasing clouding of consciousness was associated with increasing mortality.

(4) State of Nutrition: A significantly higher proportion of recoveries occurred in well-nourished than in poorly nourished or emaciated patients.

(5) Chest X-Ray: The presence of miliary tuberculosis or of adult phthisis seemed to adversely affect the prognosis.

(6) C.S.F. Cell Count: The mortality rate was significantly higher in patients with a low cell-count than with a high reading. The reason for this may have been that the cellular reaction in the C.S.F. reflected the meningeal response to invasion.

(7) C.S.F. Chlorides: Lower figures were associated with a higher mortality, but this may have been due to the depletion of plasma electrolyte, the level of which influences the C.S.F. level.

Among the factors which did not seem to influence the prognosis were: duration of illness, temperature, E.S.R., C.S.F. protein and sugar.

B. INFLUENCE OF THE TREATMENT REGIME.

A study of the literature on tuberculous meningitis reveals almost as many different courses of treatment as papers written, suggesting that there is no optimal course which should be prescribed in each case. Indeed, the occurrence of exacerbation, recrudescence, and relapse necessitates variations in treatment in a single unit where the same average course is used. In general, however, in the pre-isoniazid era, it was almost a universal practice to give streptomycin both intramuscularly and intrathecally, to continue the intramuscular therapy for a period not less than 6 months, and to treat relapses with further full courses of streptomycin. The daily intramuscular dosage for adults, which at first was very high - quantities of 4, 5 or 6 g. being reported - was later reduced to 2 g. and even this is now recognised to be in excess of requirements and probably a factor contributing to the incidence of toxic complications and sequelae.

The necessity for intrathecal streptomycin has, however, been disputed by a number of writers who not only regard it as having no special benefit but as leading to undesirable complications such as hydrocephalus. While streptomycin does not normally reach the cerebrospinal fluid in adequate concentrations, it is argued that, when the meninges are inflamed, sufficient does cross the blood-brain barrier to prevent multiplication of bacteria.

Perry (1952), for example, drew the conclusion from rather a small number of cases that intrathecal therapy did not influence the outcome - of 8 patients treated without intrathecal therapy, 3 survived, compared with 4 of 13 in whom intrathecal streptomycin was used. Lassen and Neukirch (1951) strongly supported the viewpoint that intrathecal therapy was unnecessary, maintaining/

maintaining that, in the presence of meningitis, the intrathecal concentrations of streptomycin following intramuscular injection were 16 - 32 times that required to prevent resistance developing. Levinson and his co-workers (1950) in a pathological description also stated that intrathecal streptomycin was unnecessary for healing and caused undesirable complications; they demonstrated that zones in which least healing had taken place were at the periphery of the exudate - which would be in freest contact with the cerebro-spinal fluid. Hoyne (1948) gave a variety of reasons why intrathecal therapy is contraindicated in all types of meningitis (including tuberculous); these included discomfort to the patient; risk of secondary infection, of injury to the intervertebral discs with consequent permanent disability and of haemorrhage or thrombosis of vessels; increased liability to adhesions and consequent block and to relapses; and the absence of any lowering of fatality rates. Certainly from all points of view - patient, doctor, and nurse alike - it would be most advantageous to be able to dispense with intrathecal streptomycin and the advent of isoniazid has, in the conviction of many physicians, made this possible. Prior to that, however, it was considered by most, particularly in this country, that intrathecal administration of streptomycin was a necessary evil, and indeed a corner-stone of treatment. The Medical Research Council, in one of the earliest reports in 1948, concluded that intrathecal therapy was indispensable, pending further research. Intramuscular treatment had been tried alone in 33 patients in view of the possible trauma of injections and the irritant effect of streptomycin on the meninges. 5 of these did not respond and were given intrathecal treatment. Of the other 28, 22 (78%) died, compared with 42 (58%) of 72 patients on combined therapy - a statistically significant difference. Not one of 9 children treated by intramuscular streptomycin alone survived. It was noted that patients having intramuscular treatment only showed a favourable initial response - uncomplicated by the irritation of intrathecal therapy; the general infection was controlled for several weeks, but it seemed that the meningeal infection was controlled only at borderline level, and the suggestion was made that the streptomycin concentration in the C.S.F. was only at a bacteriostatic, not a bactericidal level. Many other writers have confirmed these findings. Choremis and his associates (1948) for example, expressed their belief that "intrathecal therapy is indispensable in the treatment of tuberculous meningitis". Mann (1948) reported uniformly bad results with intramuscular therapy alone. At the Ministry of Health conference reported in the British Medical Journal in 1950 it was stated that only exceptionally did a patient suffering from tuberculous meningitis respond satisfactorily to intramuscular treatment alone, and even more rarely when the patient also had miliary tuberculosis. Taylor (1954) reporting a series of 60 patients from Oxford, considered intrathecal streptomycin to be a sine qua non of satisfactory therapy, and Lorber (1954b) stated a case for using intrathecal treatment even in isoniazid treated patients; the best results had not been achieved without intrathecal treatment.

The duration of treatment of tuberculous meningitis has not been the subject of much difference of opinion. Regardless of initial response, a course of 6 months is generally considered to be essential. In this series 6 patients/

patients received an initial course lasting only 3½ months. They were representative of many who had been given such a course, and who, with few exceptions, relapsed and required further treatment. The clinical condition is no indication for stopping treatment and cessation before 6 months must be regarded as premature.

Somner (1952) found that most patients who had only 2 - 4 months of continuous streptomycin relapsed and died, but reported better results with continuous 6 month courses. Relapse occurred in 5 of 10 of his patients in whom treatment was stopped before the end of 6 months and only one responded when it was resumed. Bunn (1950b) in a review of the literature on tuberculous meningitis concluded that the duration of the ideal course was not less than 120 days and probably 6 months. Cairns, Smith and Vollum (1950) summed up the position when they stated that there was "ample evidence that streptomycin can be stopped too soon, none that it can be continued too long".

There are, however, considerable variations in the length of courses and frequency of injections (particularly intrathecal) that have been used in the treatment of tuberculous meningitis. The M.R.C. report (1948) suggested that the best results were obtained with least intrathecal streptomycin, but Smith, Vollum and Cairns in the same year felt that long continued intrathecal treatment was indispensable. Choremis and his associates (1948) advocated rest periods, but MacCarthy and Mann (1950), comparing 3 treatment regimes, concluded that there was little to be said for interrupted treatment and suggested that the best treatment for most cases was a 3 months' course of combined intramuscular and intrathecal streptomycin followed by intramuscular treatment until C.S.F. was normal on 2 occasions. At the Ministry of Health Conference reported in the British Medical Journal in 1950 it was stated that appreciably poorer results were obtained if intrathecal streptomycin was given on less than 50% of intramuscular treatment days; and Jamieson (1952) used continuous daily intramuscular and intrathecal treatment for 6 months. On the other hand, Lorber (1954a), claiming the highest long-term survival figures published in this country, obtained them with shorter intramuscular courses and fewer intrathecal injections than in other series. The incidence of relapses, spinal blocks and hydrocephalus was less, the condition of the survivors was better and there were fewer sequelae and late deaths. 45 intrathecal injections were given in the first 2 months and more were given only if tubercle bacilli were found in the C.S.F. or if the cell count did not fall below 100 shortly after. Likewise, Cathie and MacFarlane (1950) presented figures showing as good survival rates with 24 intrathecal injections as with much longer courses.

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The use of adjuvants has also met with varying success in different centres. Sulphetrone, streptokinase and intrathecal tuberculin, have all had their advocates and also their opponents. Sulphetrone was used in only one patient (Case 33) in this series - a survivor - so it is not possible to draw any conclusions about its use. The place of streptokinase and tuberculin will be considered when the courses including them are described.

In this series the necessity for intrathecal therapy was accepted from the outset and all patients without exception were given combined intramuscular and intrathecal treatment. It is not possible therefore to assess here the influence of intrathecal injections on the ultimate outcome. Further, in all but the 6 patients already referred to, the minimum duration of treatment was 6 months. Over the period of 4 years during which the patients were treated, several major changes of policy were made in treatment in order to achieve the best results - for example, the introduction of dihydrostreptomycin, streptokinase, tuberculin - but in the end, the circle having been completed, the treatment regime was not much different from that originally adopted. The different regimes are summarised in Table 32. It should be noted, however, that the courses described here were those given to the average patient in each group. As is well recognized, there are wide divergencies in individual response to treatment necessitating alteration in the course of treatment in some cases - for example, when deterioration occurs while treatment is being tapered off. On the whole,

however/

however, changes were infrequent, and the majority of patients received almost exactly the treatment regime of the group to which they belonged. Table 33 presents the dosage of streptomycin and P.A.S. administered to children. The adult dose of 1 g. streptomycin given by intramuscular injection twice daily for 3 months is now known to be in excess of requirements but, at the time when these patients were treated, it was the dosage generally recommended. The amount given to children is correspondingly greater than that now known to be required. It should be observed that the intramuscular dose is the quantity given at each injection, which is not necessarily the daily dose - in the first 3 months in all patients this was given twice daily. In Table 34 are presented the numbers of patients who received each course as their initial treatment. A number of these later relapsed and required a further complete course of treatment. Such additional courses were often different from the initial course but this has not of course been taken into account in Table 34. Table 135 gives a more comprehensive summary of all the courses of treatment given. The apparent discrepancy in the total number of cases in Table 34 (101 instead of 102) arises from the fact that the treatment of one patient (Case 33) could not be classified with any of the other groups. In addition to receiving sulphetrone, this patient - whose treatment was commenced before my transfer to Belvidere Hospital - had more intrathecal streptomycin (and dihydrostreptomycin) than the others in a quite different regime.

With the exception of the 6 patients in Group 6, the same pattern of intramuscular therapy was followed in all patients. Full doses of streptomycin (1g. twice daily in adults) were given for the first 3 months, followed/

followed by half of this dose for one month, a quarter in the fifth month, the dosage being tapered off during the sixth and final month.

The first 26 patients - Group A - were treated at Ayrshire Central Hospital with intramuscular and intrathecal streptomycin (sulphate), and without P.A.S. or other adjuvants. Intrathecal treatment consisted of an initial fortnight's intensive course of daily injections (100 mg. in patients over 5 years and 50 mg. in children under 5 years, half dosage being given in the first week of treatment throughout the series); followed, after a rest period of one week, by a further less intensive course of injections every second day for 2 or 3 weeks. Thereafter if no exacerbations occurred, intrathecal medication was confined to one injection weekly given at the time of the routine weekly lumbar (or cisternal) puncture for C.S.F. examination. Early in the series the practice of giving streptomycin at each lumbar puncture was continued even after the 6 months' intramuscular streptomycin had been completed, but it soon became evident that intrathecal streptomycin without intramuscular streptomycin gave rise to symptoms such as headache, vomiting, dizziness, diplopia, and in one patient, convulsions - which did not occur while intramuscular streptomycin was being given. Consequently, throughout the series, intrathecal streptomycin was terminated at the end of 6 months.

Group B consisted of 6 patients whose initial course of $3\frac{1}{2}$ months proved to be inadequate and who subsequently relapsed and required subsequent 6 months courses. The mortality rate among patients treated with/

with this regime was high and relapses were very frequent. Some of the patients appeared to make good progress, were well clinically and showed satisfactory improvement in the levels of the C.S.F. constituents when treatment was stopped. Some, indeed, were allowed to return home but kept under observation. Nevertheless, the fact that relapse was the rule rather than the exception showed that there was a persistent smouldering infection, that $3\frac{1}{2}$ months was too short to achieve complete control, and that even the reduced intramuscular therapy of the last $2\frac{1}{2}$ months in the remainder of the series seemed sufficient to control the infection in most cases.

The treatment of patients in Group C showed four distinct differences from previous regimes; by a remarkable coincidence, and not by any design, all of these changes were introduced simultaneously. Indeed, it was only on retrospective investigation that it was discovered that the first of these, the replacement of streptomycin by dihydrostreptomycin, coincided with the others. This alteration was made because dihydrostreptomycin was available in purer form and was considered to be less toxic to the vestibular apparatus than streptomycin. Too late - for the patients in this and other series - it was found to be more toxic in its effect on the cochlear component of the eighth cranial nerve. The second feature of treatment in this group was the intensification of intrathecal therapy. Comparison of the regime that had been adopted in Group A with those reported to have been used in other centres showed that, while the results obtained in Group A compared favourably with those obtained elsewhere/

elsewhere, the intrathecal dosage was much smaller than that generally recommended. It was just at this time (early 1950) that MacCarthy and Mann published their results in the "Lancet" and showed the advantage of continuous intrathecal therapy without any intervals. Consequently it was decided to intensify the intrathecal course and abandon the rest period that had previously been considered desirable in view of the unpleasant side-effects resulting from the irritation caused by intrathecal streptomycin. Daily injections for a fortnight were followed by injections on alternate days for 8 weeks, as shown in Table 32. In practice, the latter period was divided into 2 equal parts; in the first 4 weeks intrathecal dihydrostreptomycin was given on four days in the week - Monday, Wednesday, Friday and Saturday - after which the Saturday injection was omitted for the next 4 weeks. A total of 42 intrathecal injections was thus given over a period of 10 weeks and a further 14 at weekly intervals until the end of the course. At the same time it was becoming evident that para-aminosalicylic acid (P.A.S.), while not possessing marked anti-tuberculous properties when given alone, did act synergistically with streptomycin, and in particular, delayed the emergence of strains of tubercle bacilli resistent to streptomycin. The third alteration in Group C, therefore, was the addition of oral P.A.S. in the doses shown in Table 33 - an addition that was continued throughout the remainder of the series.

The final and most distinctive feature of the treatment in Group C

was/

was the use of intrathecal streptokinase. It had for some time been recognised that one of the main obstacles to successful treatment of patients with tuberculous meningitis was the formation in the meninges of fibrinous exudate in which tubercle bacilli lurked, and were comparatively inaccessible to streptomycin. Further, this fibrinous exudate was responsible for the development of one of the main complications arising during therapy, namely, spinal block - a complication associated with a high mortality rate. Endeavours to overcome this obstacle led to the introduction of streptokinase, a product of some strains of streptococcus with the ability to activate a naturally occurring profibrinolysin to produce fibrinolysin.

Cathie (1949) was the first to describe its use and was "greatly encouraged" by the improvement in recovery rate following its introduction. Using a course in which the duration of intrathecal treatment was reduced to 6 weeks, he obtained 11 recoveries in 19 cases, compared with only 3 in 14 treated with streptomycin alone. In a subsequent paper (1950) Cathie and MacFarlane describing the treatment of 60 children with tuberculous meningitis, reported that only 5 of the first 20 were alive, compared with 23 of the succeeding 40 patients. Streptokinase was in their judgment the most important single factor in this improvement. They showed that its main effect was the reduction of raised intracranial pressure; they also pointed out the life-saving value of ventricular drainage whenever there were any indications of raised intracranial pressure. They emphasised the necessity of giving streptokinase from the beginning of treatment; it was of no value late in the disease since it had no effect on already formed fibrous tissue. On the other hand, Lorber (1951a) found that streptokinase was of no benefit and suggested that the improved results obtained by Cathie and MacFarlane could have been attributed to factors other than streptokinase - the use of intrathecal sulphetrone, frequent ventricular catheterisation, and particularly increased experience; he went so far as to "suggest that streptokinase probably played no part in the good results obtained in the second series." He undertook a controlled investigation to determine the value of intrathecal streptokinase, 12 patients being treated with and 12 without streptokinase. The two groups were otherwise strictly comparable. Streptokinase did not appear to have any value in reducing the number of blocks occurring during treatment - indeed, more blocks occurred in the streptokinase treated patients than in those receiving streptomycin alone. Further/

Further it seemed to cause toxic features such as headache, listlessness, drowsiness, vomiting and marked C.S.F. pleocytosis. Necropsy findings in 3 patients treated with streptomycin and streptokinase did not differ from those in patients treated with streptomycin alone, the exudate being no different in nature and extent. High (1951) gave intrathecal streptokinase and streptodornase on 3 occasions to each of 2 patients and reported increased irritability following its use; fever occurred on 4 of 6 occasions, and convulsions once; white and red blood cells in the C.S.F. were increased for 48 to 72 hours and the streptomycin level was increased for 24 to 72 hours. The ultimate response was unsatisfactory, but the patients had been comatose and decerebrate for a month before, and, in any case, no conclusions can be drawn from its use in 2 patients. Craddock and Haddock-Suarez (1952) reported one case who had made little or no response to intramuscular and intrathecal streptomycin, and who was given an injection of streptokinase and streptodornase intrathecally; 6 hours later, the temperature rose to 106°F; a second similar injection was followed by pyrexia of 108°F and 2 days later the patient died.

The introduction of intrathecal streptokinase into the regime of treatment at Belvidere Hospital was also associated with alarming reactions, which were at first quite puzzling and difficult to explain. Initially, the intrathecal administration of the enzyme (6 units or 1 ampoule given with the intrathecal streptomycin) on successive days to 7 different patients produced no upset whatever. After a period of 9 days, supplies of streptokinase were exhausted and no more was given till 3 days later when fresh supplies arrived. All the patients on this occasion developed severe reactions beginning, within 3 hours of lumbar puncture, with excruciating pain in the back and legs, violent headache necessitating potent analgesics for control, vomiting, pain and stiffness in the neck and, in most cases, pyrexia in the region of 100°F - 101°F, but in one case reaching 104°F. On the following day, general symptoms were less, with sickness predominating; temperature began to settle; there was no leucocytosis in the blood but the C.S.F./

C.S.F. was turbid, in some cases yellow and purulent, with marked pleocytosis (up to 9,000 per c.mm.) and raised protein content (usually 200 - 500 mg. per 100 ml. but in one case 3.2g. per 100 ml.) Succeeding days saw a gradual return to normal in the patients' condition and in the C.S.F. While streptokinase was immediately considered as the cause of these reactions, it was difficult to incriminate it in view of the fact that it had been given for several days without upset. An intensive but vain search was therefore made for a possible irritant factor - the particular batch and type of dihydrostreptomycin, the adequacy of sterilisation of syringes and needles etc., the presence of impurities such as pyrogens in the diluent, and even the possibility of contamination with powder used with the gloves worn during lumbar puncture. It was only when streptokinase was again injected after an interval of more than 2 days that the development of similar reactions - in rather milder form in those patients who had already suffered - led to the conviction that it was the responsible factor. It seemed that continuous administration, day after day, or even, in most cases, on alternate days, was not associated with upset but reactions occurred if there was a lapse of more than 2 days between injections. The explanation appeared to be that streptokinase, like all toxins and enzymes, was antigenic and stimulated the production of antibody. So long as it was injected daily, an excess of antigen probably persisted, but after an interval in the course of injections, antibody was present in the C.S.F. which reacted violently when antigen was next injected. Whatever the explanation/

explanation, it was clear that the meninges developed a hypersensitivity to streptokinase if more than 2 days elapsed between the injections of the enzyme. Whether such reactions are desirable in the treatment of tuberculous meningitis - by causing an inflammatory reaction and so allowing streptomycin to penetrate into the exudate - it is difficult to say. At the time, such a possibility was given little, if any, consideration. From a humanitarian standpoint, in view of the torture experienced by patients, who were, literally, writhing in agony, avoidance of reactions was of prime importance. It was partly for this reason that the rest period in intrathecal treatment was abandoned, the initial fortnight of daily injections being followed by a month of injections given on 4 days of the week. Streptokinase - 1 ampoule, or 6 units - was injected on each of these occasions during the first 6 weeks of treatment, and then discontinued. Its use on succeeding weeks would obviously have precipitated reactions on the Mondays after the lapse from Friday to Monday. In any case, Cathie and MacFarlane had suggested that 6 weeks' treatment was adequate.

Regime D. It soon became obvious that streptokinase was not achieving the end for which it had been introduced into the treatment regime. As will be seen later, it seemed to be able neither to prevent the development of spinal block nor to remove any obstructions that developed. Moreover, the overall results, while not unfavourable, were not convincingly satisfactory. Accordingly it was decided to abandon streptokinase without altering the rest of the treatment. Treatment in Group D, then, was exactly the same as that in Group C with streptokinase omitted.

Regime E./

Regime E. In August 1950, Smith and Vollum reported successes following the use of intrathecal tuberculin in what had been considered to be hopeless cases of tuberculous meningitis, manifesting decerebrate rigidity. In view of the continuing mortality rate of 50%, the uncertainty in prognosis except in cases with decerebrate rigidity (a sign that invariably indicated a fatal outcome), and the constant necropsy finding of a thick collar of exudate round the midbrain, in which organisms were protected from streptomycin in the blood and C.S.F., they postulated a factor other than the drug organism relationship and suggested that it was related to the host response. They noted the remarkable day to day fluctuations in the C.S.F. cell count and protein content in the first few weeks of treatment, beginning between the 4th and 14th day of treatment and gradually flattening out in successful cases. They found that these changes were specific for tuberculous meningitis treated with streptomycin and were not due to infection or streptomycin irritation. Their development when organisms were disappearing from the C.S.F. suggested that they might be caused by the liberation and accumulation of bacterial breakdown products, i.e. tuberculin, into the C.S.F. of sensitised patients. In order to confirm this hypothesis they injected tuberculin intrathecally into 2 patients in whom treatment with streptomycin had failed and all fluctuations in C.S.F. cells and protein had disappeared. Both developed marked clinical and C.S.F. reactions, but the commencement of tuberculin marked the turning points in the illnesses of these patients, both of whom thereafter made gradual improvement. Another child, in whom tuberculin (P.P.D.) was started on the 15th day of

treatment/

treatment on account of her rapid deterioration, survived for 25 weeks and autopsy showed no exudate in the cisterna ambiens or Sylvian fissure - a result quite different from those treated without P.P.D. It seemed clear to the writers, therefore, that tuberculin caused a resolution of the intense exudate, and they proceeded to use it in other cases with a bad prognosis. They felt that the acute inflammatory reaction was in itself beneficial in that it might result in a fibrinolytic process which would bring streptomycin into closer contact with the organisms. They suggested that, when using tuberculin, bilateral cranial burr-holes should be made as soon as the diagnosis was confirmed; the Mantoux should be done and the severity of the reaction noted - the more strongly positive the reaction, the greater the dilution of the P.P.D. solution used intrathecally; beginning with minute doses of P.P.D., these should be increased continuously till reactions were obtained; thereafter the dose should be repeated and gradually increased to avoid too severe reactions; and injections should be continued until convalescence when patients were free of signs and symptoms of active meningitis.

Reports on experience with P.P.D. from different centres have been rather conflicting. Atkins and Cummings (1952) described the treatment of one patient, a negro male aged 24, who was given 5 doses of intraventricular P.P.D., no improvement having occurred 7 weeks after the commencement of a second course of treatment for tuberculous meningitis. There was a marked reaction following each instillation of P.P.D. and dramatic clinical improvement occurred after the completion of therapy. P.P.D. was discontinued after a block in the posterior fossa had been relieved. The writers recognised that, while the results in this case were good, the type of therapy could be dangerous and should be used very cautiously. Lorber (1954a) used P.P.D. in 12 of 38 children with tuberculous meningitis; 9 of these were at an advanced stage on admission; and 3 who had been at an intermediate stage on admission had deteriorated progressively despite routine treatment. Burr-holes/

Burr-holes were made in all cases in whom the fontanelle was already closed. 6 patients survived, including the 3 who were in the intermediate stage on admission - the writer felt that these were probably helped by P.P.D.; 2 of the other 3 were decerebrate at the time of writing. The writer concluded that P.P.D. seemed to be of little benefit in most of the advanced cases, in 1 of whom death was probably accelerated by its use. In his opinion, the routine use of intrathecal tuberculin was unjustifiable. Choremis and his associates (1951) reserved P.P.D. for severe cases and applied it periodically, each period lasting not longer than 3 to 4 weeks. Beveridge (1952) found it disappointing, and Fletcher (1951) who used it in 6 patients, saw no evidence of benefit; his results suggested that, instead of causing any lysis of the exudate, tuberculin may have contributed to its formation - 2 cases developed fresh blocks during treatment and 1 other developed transient sub-tentorial block during the phase of acute hydrocephalus. He adduced clinical and laboratory evidence to show that any possible benefit of intrathecal tuberculin treatment in tuberculous meningitis was not apparently derived from specific lysis of fibrinous exudate.

At the beginning of October 1950, when supplies of P.P.D. were obtained at Belvidere Hospital, it was decided to give the benefit of this treatment to 2 patients (Cases 31 and 45) who had been doing badly on routine measures. The former had relapsed twice and a third course of streptomycin was having little apparent effect; he was steadily deteriorating, had severe headaches and troublesome vomiting and was incontinent. The latter had just completed one course of streptomycin to which he had never shown a satisfactory response; mental deterioration was so marked that he was by that time almost vegetating; the C.S.F. cell count was under 20 per c.mm. but the sugar level was 20 mg. per 100 ml. suggesting a poor meningeal cellular response in the presence of persistent infection. Both of these patients were given a course of streptomycin with intrathecal tuberculin (Course E), but the results were disappointing. Neither showed any clinical or C.S.F. reaction for fully a month, by which time undiluted standard solutions of P.P.D. were being used in both patients. After more than/

than a month both developed reactions of mild severity, with C.S.F. pleocytosis more marked in Case 31. When P.P.D. was discontinued at the end of 4 months, Case 45 had deteriorated further and he died 2 months later. Case 31 began to improve after the first month, and at the end of treatment he was slightly better. After treatment was discontinued he seemed to make good progress and was eventually able to go home. Unfortunately he relapsed within a fortnight and died 2 months later. This case may be regarded as a partial success for P.P.D.

Intrathecal tuberculin was used as a routine in 9 patients admitted from October to December, 1951, and in 1 other patient who relapsed during this period. The regime was similar in all cases and was modelled on the scheme outlined by Smith and Vollum, with the exception that burr-holes were not made in the skull, the lumbar or cisternal intrathecal route being used in every patient. The standard solution of P.P.D. containing 7.5mg. per ml. was diluted 10 fold, 100 fold and 1000 fold, and regardless of the Mantoux reaction which was performed in each patient, the first intrathecal dose in each case was 0.5ml. of the 1000 fold solution. This was repeated on the following day, then doubled if no reaction occurred. Each dose was similarly given on 2 successive days and then doubled if no reaction took place, - the dose after 4 ml. being 0.5 ml. of the lower dilution. If a reaction occurred - vomiting, headache, C.S.F. pleocytosis - a rest of a day to several days was given, depending on the severity of the reaction; on resuming treatment the same dose was usually repeated.

Sometimes/

Sometimes rest periods of 1 to 5 days were given in the absence of specific reactions if it was evident that the patient was generally reacting badly to the P.P.D. injections. Intramuscular dihydrostreptomycin and oral P.A.S. were used exactly as in other courses and intrathecal dihydrostreptomycin was given with each injection of tuberculin, and also on days when tuberculin was withheld, a course similar to that in Group C being adopted.

Within 4 months of introducing P.P.D. it was evident that no dramatically good results were being obtained. Indeed, on the contrary, it seemed that patients who were expected to do well were deteriorating. The frequency of occurrence of spinal block was becoming alarming, and, on the whole, the progress made was most unsatisfactory and in marked contrast to that of patients in pre-tuberculin days. This, together with the disturbing reactions, completely transformed the atmosphere in the meningitis ward from one of brightness, cheerfulness and hope, to one of gloom, disappointment and despair. The final straw was a very genuine threat of resignation by an excellent ward sister whose efficiency, brightness and insight were such that her loss at this stage would almost have spelt disaster. It was therefore decided to abandon Course E and revert to Course D. By this time, 3 patients (including the 2 described above) had been treated with tuberculin for 4 months, 1 for 3 months and 5 for 1 month; 2 others had died at the end of a month and 1 after a fortnight. 2 of the 5 who had been treated for a month were in a moribund condition and died, one in a few days and the other a fortnight later. None of the survivors was

in/

in very good shape and all were most grateful to be relieved of the torture of intrathecal tuberculin. Probably as relieved as any was the ward sister, who, happily, withdrew her resignation.

Regime F. The years 1950 and 1951 saw an alarming increase in the incidence of deafness in survivors and in non-survivors who lived sufficiently long to develop it. Careful review of the patients developing deafness led to the discovery that it occurred mainly in patients in the treatment groups C, D and E, and only in 2 patients in groups A and B. The common factors in Groups C, D and E were (a) the use of dihydrostreptomycin (b) more intensive intrathecal therapy, and (c) the introduction of P.A.S. The latter factor was discounted as it had been widely used in the treatment of all forms of tuberculosis without apparently causing deafness. The suggestion that dihydrostreptomycin - probably particularly by intrathecal administration - was responsible for the high incidence of deafness was greeted with absolute incredulity by representatives of manufacturing firms. After all, it was the purest form of streptomycin yet manufactured; moreover its use in large doses and in prolonged courses in other forms of tuberculosis had not been reported to cause deafness, and patients treated with it were remarkably free of vestibular upset. Accordingly it was decided, before incriminating it, to exclude the possibility that the intensification of intrathecal streptomycin therapy was the cause. For this reason, regime F was introduced, which differed from D only in the reduction of intrathecal injections - 28 injections in 6 weeks instead of 42 in 10 weeks. In practice, after an initial fortnight of daily injections, intrathecal/

intrathecal dihydrostreptomycin was given on Monday, Wednesday, Friday and Saturday for a fortnight, on Monday, Wednesday and Friday for a further fortnight, and, thereafter, weekly until the end of the 6 months' course.

Regime G. It was not long before it became evident that deafness was still occurring just as frequently as with the three earlier courses and therefore, that dihydrostreptomycin must be the responsible factor. On this account the latter was abandoned and replaced by the calcium chloride complex of streptomycin, the course (G) otherwise remaining unaltered.

CONCLUSIONS.

For several reasons, it is not possible to evaluate accurately the effectiveness of each particular regime in this series. It is obvious from Table 34 that the numbers in each group are too small to permit of comparisons being made and rigid conclusions drawn. Moreover, as already pointed out, the table presents only the ultimate outcome in patients treated initially by each regime; some patients, classified as "dead" responded to the initial course of treatment, but later relapsed and received another - often a different course; others "alive" also relapsed and required another course - often different - to complete their "cure". It is obviously neither justifiable to incriminate the initial course completely in the former cases, nor to give it the total credit in the latter. Table 34 would suggest, for example, that treatment B is a very adequate and effective regime, being associated with a high recovery rate; but, in point of fact, all the 6 patients in this group required at least 1 further course before recovery was complete, and it was quite evident

that/

that the course was inadequate. The factor has been incorporated in Table 135 and will be considered in the section dealing with relapse. Finally, since this was not a planned or controlled investigation to assess the relative values of particular courses of treatment, the patients in the series being treated with the course that was considered to be the best at the time of diagnosis, it is clearly impossible to draw any deductions unless it can be shown that the samples in each group were similar in all important respects. That this was not so is seen from Tables 35 to 39 which have been compiled in an attempt to evaluate the influence in each group of several factors which have already been shown to have some bearing on the outcome.

The only factor which seemed to show major differences from group to group was age (Table 35). It is noteworthy that of the 24 patients under 5 years of age (1 other was unclassified) 22 were among the 66 patients in Groups A, D and F and all of the 5 adults over 30 also belonged to these categories. The proportions of young children in Groups A, D and F - 38.5%, 30.8%, 28.6% respectively - were significantly higher than in the remaining groups - 5.7% of 35 patients. As would be expected, the highest proportion of young children was in Group A where there was no selection of cases. Three of these died within a week of commencing treatment; and obviously the outcome in these cases could not have been affected, whatever regime was adopted (it is significant that only 1 other in the series died within a week). Two others in this group died within the/

the first month, and it is unlikely that alternative treatment (without isoniazid) could have influenced the results in these. Thus it is clear that this single factor must very largely account for the comparatively high mortality in Group A - 50%, compared with 30.3% in the remainder of the series.

The slight differences observed in Tables 36 to 39 are incorporated in the following brief review of each group:-

Group A. Only 50% survived of 26 patients in this group whose treatment showed remarkably little difference from that of the final group in whom the recovery rate was 100%. Inexperience in the treatment of tuberculous meningitis may have been a factor in the high mortality in this group, and the lack of P.A.S. may have contributed slightly, but it seems most likely that, from the start, the scales tended to be weighted against a high survival rate in these patients compared with the rest of the series. Thus, in addition to the fact that 11 of the 26 patients in the group were under 5 years or over 30 years, a comparatively higher proportion were at an advanced stage of illness and in poor nutritional state. It would therefore not be justifiable to draw any conclusions from the higher mortality associated with this early treatment.

Group B. Sufficient has already been said to indicate that this $3\frac{1}{2}$ months course of treatment was unquestionably inadequate.

Group C. As many as 7 of the 10 patients treated initially with streptokinase survived (and, indeed, only 3 deaths occurred on the 14 occasions/

occasions in which streptokinase was included in a treatment course - Table 135). Only 1 however was under 5 years - a child of 2 years (Case 39) who survived but was mentally deficient; none were over 30 years; only 2 had radiological evidence of miliary tuberculosis (compared with an average of 27.7% for the series) and none had adult phthisis. On the other hand, 3 of the 6 comatose patients were in this group, and also a higher proportion of severely ill and poorly nourished patients than in other categories. From the small numbers of patients, it is obviously wrong to be dogmatic on the place streptokinase should or should not have in the treatment of tuberculous meningitis. Its value in relation to the problem of spinal block - the main reason for its introduction - will be discussed later.

Group D. The 26 patients in this group included 8 children under 3, 3 of the 5 adults (all of whom died) and 7 of the 10 patients with adult pulmonary tuberculosis, but none of the 6 patients who were comatose on admission. In view of these high proportions of "poor-risk" patients, the recovery of 16 of the 26 patients seems fairly reasonable and does not suggest that the use of dihydrostreptomycin raised the mortality rate.

Group E. The high mortality rate in this group - 5 out of 9 who received P.P.D. as initial treatment, and 6 out of a total of 12 (Table 135) was largely responsible for the small number of patients treated with intrathecal tuberculin. It is true that one third of the 9 patients were either stuporose or comatose at the time of diagnosis, compared with an average of one/

one sixth for the series as a whole; but, on the other hand, apart from 1 child aged 6 months who died, all the patients were from age groups favourable for recovery and in other respects were comparable with the rest of the series. It would therefore appear, although the numbers are too small to justify firm conclusions, that the type of treatment was itself largely responsible for the poorer survival figures. It must be admitted, however, that the treatment was not given exactly as described by Smith and Vollum, in that cranial burr-holes were not made in any of the cases, and this may have had a bearing on the results.

Group F. Apart from the higher proportion of children in this group already noted, the initial features were on the whole slightly favourable compared with the rest of the series. A recovery rate of 71.4% in 14 patients does not suggest that reduction of intrathecal streptomycin was a retrograde move - longer courses do not appear to have any special value.

Group G. It is most gratifying, indeed, to have a succession of 10 patients with tuberculous meningitis who respond satisfactorily without any mortality. That this can perfectly well occur by chance in a condition with over 60% survival rate is obvious; particularly when, as in this series, there are no children under 5, adults over 30, comatose patients or cases of phthisis, and when other factors tend to be slightly favourable. These facts must modify any conclusions one might wish to draw from such results.

SUMMARY.

Seven different regimes of treatment were used in 101 patients in this series, the other patient being unclassified and receiving sulphetrone.

Intramuscular/

Intramuscular and intrathecal streptomycin or dihydrostreptomycin was given to all, and in all but 6, treatment was continued for a minimum of 6 months. 3½ months' treatment proved to be quite inadequate and was associated with a high relapse rate and a high mortality rate. Even in the presence of satisfactory clinical and C.S.F. findings, intramuscular treatment should not be discontinued before the end of 6 months. The necessity for intrathecal treatment was assumed. The courses used varied somewhat from group to group but even the most intensive were shorter than those described in most of the reported series. On the whole, it did not appear that prolonged or interrupted intrathecal therapy had any special advantages over a shorter continuous course with injections daily or on alternate days. The final regime, in which 28 intrathecal injections were given in the first 6 weeks and only weekly injections thereafter, seemed perfectly adequate and as satisfactory as any. The use of dihydrostreptomycin was not associated with any rise in mortality, but its continued use in view of the incidence of deafness seemed unwarranted. It could not be demonstrated that the addition of P.A.S. had any marked effect on the recovery rate, but, even although bacterial resistance is not a very great problem in tuberculous meningitis, it does sometimes arise and the effect of P.A.S. in delaying the emergence of resistant strains may have contributed to the improved results later in the series. Streptokinase and tuberculin were used in the initial course in 10 and 9 patients respectively and altogether in 14 and 12 courses respectively. From these small numbers, it is impossible to assess the value of these adjuvants but in this series neither seemed to have special value and P.P.D. seemed to be harmful.

C. TYPE OF RESPONSE TO TREATMENT AND ITS EFFECT ON THE OUTCOME.

Perusal of the literature on the treatment of tuberculous meningitis with streptomycin and personal experience of such treatment leave a marked impression of the different types of response that may be obtained. Between the two extremes of cases who are completely uninfluenced by treatment and those who, from the very outset, respond to it and make a complete and uninterrupted recovery, there is a very wide range and variety of courses that any given case may follow.

The types of response have been classified in different ways. Thus, the Medical Research Council (1948) divided 23 survivors into 3 groups:

(1) 12 who made uninterrupted improvement,

(2) 8 who made continuous improvement after an initial period in which they were stationary or deteriorating, and

(3) 3 who improved after relapse.

Of 60 fatal cases in this series, (1) 20 made no response to treatment, deteriorated rapidly and died within the period expected for untreated cases, (2) 19 made slow progressive deterioration with no period of improvement - death seemed to be merely delayed, sometimes for a long period, (3) 9, after a short initial period of improvement, deteriorated progressively and died, and (4) 12 relapsed after a long period of improvement.

MacCarthy and Mann (1950) classified their series of 43 patients into 3 broad groups:

(1) 13 made an immediate response - 3 subsequently died,

(2) 10 had a delayed response - 5 died later, and

(3) 20 made no response; 15 of these were stuporose on admission.

Robertson and Gairdner (1952) described 3 main patterns of response: (1) rapidly successful - clinical improvement within 7 days; sitting up and mentally alert by 14-21 days; (2) decerebrate rigidity in 47 patients, none of whom recovered; and (3) a fluctuating course, the clinical and

C.S.F. state fluctuating for several months, and improvement rarely occurring within 4 months; this latter group showed a high proportion of mental disturbances.

Spangberg and Granath (1952) divided their patients into other 3 groups: (1) those completely uninfluenced by treatment, (2) those who recovered and (3) those who improved but later relapsed.

In considering the response to treatment, two main questions arise:

(1) What factors determine the type of response to treatment? Can the mode of recovery in surviving patients, for instance, be related to the clinical or C.S.F. features at the commencement of treatment, or is it affected at all by the type of treatment adopted? This would appear to be of more than academic interest since, other things being equal, a treatment regime resulting more frequently in a speedy recovery will be preferred to one that tends to cause delayed or interrupted recovery.

(2) Has the initial response to treatment any bearing on the ultimate course of the disease? In other words, in any given patient, can one make a firm prognosis within a few weeks of the institution of treatment, on the basis of the progress being made? As a corollary to this investigation, I have taken individual features and endeavoured to discover whether the early disappearance of symptoms or restoration of C.S.F. elements to normal is related to the initial features or is affected by the treatment regime; and, finally, whether any indication of the ultimate outcome or the incidence of relapse can be obtained from such a study.

GENERAL PROGRESS.

I have considered the survivors and non-survivors separately and divided the types of response in each in the different categories shown

in/

in Tables 40 and 48. Taking, first of all, the 66 patients who recovered, it is seen from Table 40 that more than one-third (24) of these showed an immediate and sustained response to treatment (I). Within a few weeks, they were clinically improved, temperature settled or settling and meningeal signs subsiding, and this progress was maintained until recovery was complete. Mann (1948) considered that such a course was exceptional occurring, as it did, in only 5 (15.2%) of a total of 33 cases. In this series, just under one quarter (23.5%) of all patients made steady, rapid progress towards complete recovery. A second group of 14 patients in all (1 not included in Table 40, because her treatment did not correspond with any of the regimes described) took rather longer to recover (II); a sharp line of demarcation between these and Group I was for obvious reasons impossible to draw. 12 patients (III) did not appear at first to respond to treatment, and only began to improve after an initial phase of deterioration. Lincoln and her associates (1948) described this as the usual mode of recovery; even cases treated at an early stage, they found, deteriorated to the meningitic phase and might remain in that state for several weeks to several months; the comatose stage might develop during treatment and yet be followed by complete recovery. Finally, in 16 patients, recovery was punctuated by periods of deterioration or relapses. (IV).

From the patient's point of view, Progress I is obviously the most desirable, and, since the main object of this investigation is to differentiate between this group of patients who progressed rapidly and steadily, and those making slow or interrupted improvement, in assessing

significance/

significance, I have in general amalgamated Groups II, III and IV.

Tables 41 to 47 suggest that the type of recovery in survivors was influenced by several factors apart from the treatment given: (1) A significantly higher proportion of patients aged 5-14 years made a steady rapid recovery than in other age-groups - 48.6% compared with 22.6%. (2) The milder the initial illness, the speedier was the recovery made. Patients with a shorter history also tended to recover more quickly, but the differences were not significant. (3) The character and speed of recovery was apparently directly related to the degree of mental clarity on admission. (4) Patients with no meningism or only mild meningism had a much better chance of uninterrupted speedy recovery than others. (5) The nearer the initial C.S.F. protein and chloride levels to normality, the greater the tendency to uncomplicated recovery. (6) No relationship could be demonstrated between the type of recovery and the X-Ray appearances or the cell-count or sugar-content of the C.S.F.

In view of the small number of patients in each treatment group, it is clearly impossible to draw conclusions based on the progress made by survivors in individual groups; any deductions must be made on the basis of combinations of such groups. The 5 patients in Group B all relapsed due to the inadequacy of the initial course and so none were in progress group I; they should, therefore, be omitted from any assessment. The high proportions of cases in columns F and G (Table 40) who made steady, rapid recovery are noticeable/

noticeable, and it is interesting that these two regimes together with A were those with the shortest intrathecal therapy. A significantly higher proportion of survivors who were treated with a shorter intrathecal course, made a rapid and uninterrupted recovery - 51.5% of 33 cases, compared with 25.9% of 27 others. However, this may be accounted for, at least in part, by the inclusion, in the groups having prolonged intrathecal treatment, of streptokinase and tuberculin treated patients, only 2 out of 11 of whom made a rapid recovery. The proportion in the remaining group (D) was 31.25% of 15 patients, and the difference between this and the 51.5% of 33 cases in groups A, F and G is not now significant. The figures do suggest, however, that intrathecal therapy - particularly streptokinase and tuberculin - tends to delay or interrupt the clinical progress made; a finding which emphasises the benefit of restricting intrathecal medication to a minimum. Finally, once again, no significant differences can be seen between the effects of streptomycin and dihydrostreptomycin in relation to the progress towards recovery.

Of the 36 patients who died (Table 48) more than half went steadily downhill and died within a few days or weeks of admission, showing little or no response to streptomycin. In some of these, the drug appeared merely to prolong the act of dying and had no evident influence on the disease process. These were undoubtedly the most fortunate of the non-survivors because they did not have the prolonged suffering associated with long and repeated/

repeated courses of injections, and their relatives were spared the long suspense of anticipating the final outcome. Just under one-third of the 36 patients showed some initial improvement and appeared for a time to be responding to treatment; some of these had successfully completed a course of treatment and had even reached the stage of going home, only to relapse later, thus blasting the hopes of relatives and friends. Perhaps the worst type of case, from all points of view, belonged to the third category - fortunately, in this series, a small proportion - one-sixth of the fatal cases and less than one-twelfth of the series. These showed alternating improvement and deterioration, lingering on for months, perhaps even a year or more; hopes and fears mingling all the while in the minds of physicians, nurses and especially relatives.

The second question to be considered is what guidance can be provided by the initial response to treatment in the assessment of prognosis. Choremis and his associates (1948) concluded that, if the clinical picture was normal after 4 or 5 weeks, the prognosis was good; this impression had been confirmed when they wrote in 1951 that, provided the clinical improvement was steady, the prognosis was, as a rule, satisfactory. MacCarthy and Mann (1950) found that the proportion of full recoveries in any series depended much more on the number of initially responsive cases included than on the particular rhythm of treatment adopted.

Reference has already been made to the weekly entries, made in stencilled sheets, of each patient's general condition, symptoms and C.S.F. findings. These have been used in constructing the succeeding tables from

49 to 90. The general progress indicated by these charts has been summarised in Table 49 which shows the number of patients who were well, improving, stationary or deteriorating at the end of each month as compared with their condition one month before. For obvious reasons, while the number of survivors remains constant at 66, the number "dead" diminishes from month to month from 21 at the end of the first month (15 having died within a month) to 6 at the end of 6 months. It is evident from this table that the majority of survivors were already improving by the end of the first month, 50 by this time being either well or improved. Some, however, had deteriorated, and, at the end of each month up to the 6th, with the exception of the 2nd, 1 or more patient had shown some deterioration over the preceding month. This in itself, therefore, is not necessarily an ill omen. The most remarkable feature, however, in view of the literature just quoted, is the proportion of non-survivors who were apparently improving clinically at the end of each month. Thus, at the end of the first month, of 60 patients who were well or improving, 10 ultimately died - and these constituted nearly half of the fatal cases who were still alive at that time. The findings at the end of other months were similar. Indeed, at the end of the 4th month, of 11 non-survivors still alive, 5 were improving and 1 was actually clinically recovered and symptom-free; by the next month, he had deteriorated. Thus, it does not appear that one can be dogmatic in making a prognosis from a consideration of a patient's general response to treatment.

INDIVIDUAL FEATURES.

This conclusion being reached, namely that the general progress made early/

early in the course of treatment is no certain guide to the future, the question arises - are there any individual features, e.g. early settling of temperature or disappearance of meningeal signs or restitution of C.S.F. normality, which, when they occur, are favourable portents? Tables 50 to 89 have been constructed with a view to ascertaining this. In the columns of non-survivors, only those (21) who lived longer than a month, are included. In estimating the return of any feature to normal, a transitory return was discounted if it was followed within a short period of a week or two by reappearance of abnormality; the time taken for each feature to settle refers to the time till normality was re-established for a period of several weeks or months or permanently.

(a) CLINICAL.

FEVER. (Tables 50 - 53).

The slow decline of fever has been repeatedly emphasised in the literature on tuberculous meningitis; for example, by Lincoln and her associates (1948, 1950a) who noted its persistence, in some cases, for several months, and Brainerd and Eagle (1950) who found that it usually persisted for over a month. Rubie and Mohun (1949) pointed out that, during streptomycin treatment, a varying degree of fever, loss of weight, anorexia, vomiting and skin rashes was to be expected, and Anderson, Kerr and Landsman (1953) describing treatment with isoniazid, expressed the view that the intrathecal streptomycin might have been responsible for the prolonged fever in streptomycin-treated cases. In 100 cases of miliary and meningeal tuberculosis reported by Bunn (1948), alleviation of fever occurred in both survivors and non-survivors, and he considered it to be of no prognostic significance. Any unexplained rise in temperature, however, (Debré et al, 1947; MacCarthy and Mann, 1950) should arouse attention as possibly heralding recrudescence or relapse.

The prolonged persistence of fever in this series is evident from the figures presented in Table 50. Only 8 of the 66 survivors were apyrexial by the end of the first month (including those who had been afebrile on admission,/

admission, some of whom developed fever in the course of treatment.) At the end of 3 months, 23 patients who ultimately survived, were still running temperatures. Of the 12 patients whose temperature had settled within a month, 4 died and 2 of the survivors relapsed. It is clear, therefore, that early subsidence of fever did not ensure against death or relapse, nor was its prolonged continuance necessarily a grave omen. The speed of settling of temperature in survivors was not related, to a significant degree, to the initial temperature or the severity of illness, although the trend in Table 51 does suggest that, the higher the initial temperature, the longer did it take to settle. The small numbers in each treatment regime again make it impossible to draw conclusions regarding the effect of treatment on the speed of settling of temperature, but there was no difference in this respect between the group receiving streptomycin and those treated with dihydrostreptomycin.

ANOREXIA. (Tables 54 - 56).

It is noticeable that appetite was restored comparatively speedily - within 2 weeks in over a fifth of survivors; within a month in over a third, and by the end of 2 months in considerably more than a half. This is particularly satisfactory in view of the association, already noted, between malnutrition and mortality. Provided appropriate measures are taken to tide patients over the periods of coma or vomiting with their consequent reduction in oral intake of food and fluid, the rapid recovery of appetite in patients doing well should maintain nutrition.

The return of appetite to normal in any given time could not be used as/

as an index of the ultimate outcome or course. Thus, of 30 patients who had regained appetite within a month, 6 died (2 after a relapse) and 4 of the survivors relapsed. As would be expected, appetite returned more slowly in patients in an advanced stage on admission than in those less seriously ill - only 2 of 14 of the former compared with 7 of 9 who were mildly ill had regained appetite within a month. It is noteworthy, though the numbers are obviously too small to warrant conclusions, that none of the 7 survivors treated with intrathecal streptokinase had recovered full appetite within a month. Table 56 suggests that the use of dihydrostreptomycin was associated with delay in the return of appetite in many patients, but the differences are not quite significant and may have been partly due to the inclusion in the dihydrostreptomycin group of patients having streptokinase and tuberculin.

HEADACHE. (Tables 57 - 59).

76 of the 102 patients in this series complained of headache as one of the manifestations of the initial illness. In 30 of these, the headache appeared to be severe, in 31 it was classified as "moderate" and in 15 others as "mild". Most of the remaining 26 patients were children who were too young to make specific complaints. Disappearance of headache was one of the first indications that the drug was having some influence on the course of the disease - over 50% of the survivors were free of it within a fortnight. Once again, however, this finding was of no prognostic value for 5 of these patients later relapsed, and 2 patients who had no headache after a fortnight ultimately died. More patients with mild illness were free of headache at an early stage than those with more advanced disease. Treatment regime did not/

not seem to have any effect on its early or late disappearance.

VOMITING. (Tables 60 - 62).

Vomiting was a feature of the initial illness in 80 patients in this series, and, like headache, was usually one of the first symptoms to disappear, one half of the survivors being free of it within a month. 5 patients who were not being sick at the end of a fortnight died and 2 others relapsed, so early disappearance was not necessarily a good sign, apart from enabling nourishment to be retained by the oral route. The severity of the initial illness again appeared to be a factor in determining the stage at which patients would be free of this symptom. Treatment did not seem to have any effect.

CONSTIPATION. (Tables 63 - 65).

This symptom seemed to be more intractable than the others - at the end of 3 months, 24 of the 66 survivors were still constipated to a greater or less degree. Like the other symptoms, its early disappearance was of no prognostic value; nor was it apparently influenced in any way by the treatment given. The association with the severity of the initial illness was less marked, and a slight trend was not in this case significant.

MENINGISM. (Tables 66 - 69).

Early subsidence of meningeal signs was also unreliable as a prognostic guide; less perhaps than the other features - in two thirds of fatal cases who lived longer than a month, meningism was never absent - a higher proportion than for any other single clinical feature. The stage at which patients were free of meningism was not only influenced by the severity of the initial illness (the more severe the illness, the longer to subside), but also by

the/

the degree of meningism already present; more marked meningism persisted longer. Patients treated with dihydrostreptomycin appeared to take longer to lose their meningism, though not significantly so. However, this was in all probability due to the inclusion in the dihydrostreptomycin group of the patients who had longer intrathecal courses and those who had intrathecal tuberculin and streptokinase. Table 69 shows a significant difference between the proportion of patients given prolonged intrathecal therapy who had persistent meningism after 2 months and that of those given shorter intrathecal treatment - 20 of 27 in the former case, and 13 of 33 in the latter. Even omitting from the former group the patients who also had tuberculin or streptokinase, the difference is still significant. Intrathecal therapy thus appeared to prolong the persistence of meningeal signs.

(b) CEREBRO SPINAL FLUID.

Clinical recovery from tuberculous meningitis is usually in advance of the restoration of C.S.F. normality. Choremis and his associates (1948) divided the course of cases responding favourably into 2 phases (1) the period of clinical improvement, lasting 4 - 5 weeks, (2) the phase of laboratory restitution continuing for 2 or 3 months. The fluctuations in the cell and protein content of the C.S.F. in the first weeks of treatment have been fully described by Smith and Vollum (1950). They pointed out that the levels of both constituents rose during this early period, but ultimately, in successful cases, as fluctuations ceased, the levels began to decline, protein lagging behind cells in this respect. These early changes they attributed to the effects of the liberation and accumulation of bacterial breakdown products in the C.S.F. It has frequently been noted (e.g. M.R.C. 1948; Rubie and Mohun 1949; Brainerd and Eagle 1950; Friedman et al, 1953) that a C.S.F. pleocytosis must be expected so long as intrathecal therapy is being maintained; the cell-count gradually returning to normal after the termination of intrathecal injections. At the U.N.I.C.E.F. Conference reported in 1950, however, Honor Smith stated that the return of cells and protein to normal was possible during intrathecal treatment. Ruziczka (1952), and Cohen (1952) found that the sugar, cells and protein returned to normal in that order. MacCarthy and Mann (1950) reported that the sugar might be normal for 6 months or more while cells and protein/

protein continued to fluctuate between normal and abnormal levels. Levinson (1949) found that in several patients the sugar had returned to normal within the first month, whereas the cells usually took 3 to 3½ months and the protein 4 to 5 months. Lincoln and Kirmse (1950b) and Brainerd and Eagle (1950) reported similar findings.

As would be anticipated, the prognostic value of C.S.F. changes occurring during treatment has received considerable attention. In an early report, however, the M.R.C. (1948) found that there were fewer factors of value in prognosis than would be expected. The sugar level has, in general, been accepted as a fairly reliable guide. Sommer (1952) was of the opinion that it portrayed accurately the progress made and the morbid state - the level seemed to fall with progressive disease and rise as the disease underwent resolution, and did not fluctuate so widely as the levels of other constituents. A persistently low sugar was an unfavourable sign; if it was less than 50 mg. per 100 ml., despite all other signs, he considered there was danger of recrudescence. A falling sugar after the institution of energetic treatment suggested a bad prognosis. Although the chloride level followed the same course as the sugar, he found it less significant and less reliable, while the cell and protein levels were not comparable in value. In general, these findings correspond with those of most other writers, e.g. M.R.C. (1948), Shamaskin et al (1949), Rubie and Mohun (1949), Cathie and MacFarlane (1950). Some writers, however, e.g. Debré et al (1947) emphasised the cell-count. McSweeney (1950), for example, felt that clinical improvement or deterioration was more closely related to the cell-count than any other factor; an increase in the cells often heralding relapse. MacCarthy and Mann (1950) were suspicious of a cell-count fluctuating between 10 and 20 per c.mm. Rubie and Mohun (1949) felt also that a rising protein was a bad omen suggesting extension of the disease down the theca. The M.R.C. (1948) placed more emphasis on a slowly rising protein as significant of impending relapse than on a sudden steep rise suggesting spinal block. Taking the C.S.F. as a whole, Choremis and his associates (1948, 1951) found that stabilisation of the fluid was a good prognostic sign; while it was at all abnormal, exacerbation was probable or even certain. Calnan and his co-workers (1951), however, questioned the significance of slight abnormalities in the C.S.F. occurring up to 2 years after treatment.

In the patients in this series also, the sugar was the first C.S.F. constituent to return to normal in most cases, being followed by the chlorides, protein and cells, usually in that order; I have already shown, when examining the cases who had normal initial C.S.F. sugar, that the sugar level in several of these patients was unreliable as a prognostic guide;

normal/

normal levels were obtained in some who died immediately or shortly after, and low readings occurred for no apparent reason in patients who were progressing favourably and continued to do well. Review of the other patients showed that these findings were by no means isolated but were repeated frequently throughout the series. It is true that, in some cases, sudden deterioration was heralded by a fall in the C.S.F. sugar, but only occasionally was this a lone sign; usually it was accompanied by other C.S.F. changes, particularly rising cell and protein content. There were occasions, however, when the C.S.F. sugar was the most accurate reflection of the patient's clinical condition; for example, in patients doing badly, the cell-count sometimes remained low while the sugar level was markedly reduced. As a general rule, a falling sugar level or rising cell or protein content - usually in combination - indicated imminent deterioration. Slight fleeting abnormalities, however, although rousing suspicion, were usually of no real significance.

In Tables 70 - 90, an attempt has been made to assess the significance of the time taken by any or all of the C.S.F. constituent to return to normal. The figures, taken as normal, were: Cells, 0-10 per c.mm: Protein : 0-40 mg. per 100 ml; Sugar : over 45 mg. per 100 ml.; Chlorides : over 700 mg. per 100 ml. The upper limit of normal for the cell-count is higher than has been often recommended, but it was found that, to fix it at a lower level, e.g. 5 per c.mm. would exclude many patients who had made a complete recovery and who remained well.

Considering/

Considering, first of all, the return of individual C.S.F. constituents to normal, the findings of Tables 70 - 83 may be summed up as follows:

(1) At the end of 3 months, the cell-count had been restored to normal in 6 patients (4 survivors), the protein content in 16 patients (all survivors), the sugar level in 33 patients (30 survivors) and the chlorides in 30 patients (all survivors). By the end of 9 months, in most patients, all the elements had returned to normal. At the end of a year, a higher number of patients (7) still had raised protein than any other abnormality.

(2) Death did not occur in any patient whose C.S.F. protein had fallen below 40 mg. per 100 ml. Return of the other constituents to normal, however, occurred, even within 3 months, in both survivors and non-survivors. Early restitution was not necessarily a favourable prognostic sign.

(3) Relapse occurred in patients in whom the C.S.F. elements had been restored to normal even at an early stage.

(4) The initial protein level had a direct bearing on the time it took to return to normal. This finding was also noted by MacCarthy and Mann (1950). The other constituents were not similarly influenced.

(5) No direct relationship could be proved between the severity of the initial illness and the rate at which any given constituent returned to normal.

(6) Significantly higher proportions of patients treated with dihydrostreptomycin showed delayed restitution of each C.S.F. element, but this may have been due to the inclusion among these patients of those who were given streptokinase and tuberculin; delay was specially evident in these groups.

Since/

Since the C.S.F. protein did not return to normal in any patient who subsequently died, it is clear that Tables 84 to 90 relating to the restoration of complete normality must apply only to survivors. Table 84 demonstrates that over 40% of the survivors had a normal C.S.F. at the end of 6 months and, 3 months later, the proportion was over 80%. 7 of the 11 survivors who relapsed did so after the C.S.F. had completely returned to normal, and, in 4 of these, normality had been reached by the end of 6 months. However, the fact that all the patients survived who relapsed after the C.S.F. was completely normal, suggests that, in these circumstances, a favourable outcome may be expected should relapse occur. Stabilisation of the C.S.F. was thus, in this series, (as with Choremis and his co-workers, 1951) a good prognostic sign.

The more severe the initial illness, the longer did the C.S.F. appear to take to return to normal - but the apparent trend was not statistically significant. The speed of restitution did not appear to be affected by the initial mental or nutritional state. Surprisingly enough, only 6 of the 23 patients with a clear X-Ray had a normal C.S.F. at the end of 6 months, compared with 9 of 13 patients with "snowstorm" appearances - a statistically significant difference. In interpreting this apparent anomaly, it must be remembered that these figures relate only to survivors. A higher proportion of patients with miliary tuberculosis died and 2 of those who recovered were already under treatment for miliary tuberculosis when meningitis developed, and were therefore "early" cases with slight C.S.F. changes.

SUMMARY.

Over one third of the survivors - just less than one-quarter of all

the/

the patients in this series - made a steady, rapid recovery without delays or interruptions. Such a course was observed in a significantly high proportion of patients aged 5 - 14; mildly ill, mentally bright; with mild meningism, or with low initial C.S.F. protein or high initial C.S.F. chlorides. Courses of treatment with more intrathecal injections were associated with delayed or interrupted recovery in a comparatively high proportion of cases. A good initial response was not necessarily a favourable sign - 10 of the 21 fatal cases still alive at the end of the first month were well or improving at that state. Early disappearance or long persistence of any of the main symptoms could neither be used as an index of the ultimate outcome - nor of the probability of relapse. A falling C.S.F. sugar level or a rising cell-count or protein content was usually ominous, especially when all were combined, but a normal sugar level was found on several occasions in dying patients, and transient abnormalities of any single constituent were usually of no significance. Death did not occur in any patient whose C.S.F. protein became normal, but 7 such patients subsequently relapsed. Return to normal of any of the other C.S.F. constituents, even at an early stage, was no guarantee against either a fatal outcome or the occurrence of relapse.

D. THE INCIDENCE AND INFLUENCE OF SPINAL BLOCK.

INTRODUCTION.

In the course of treatment of tuberculous meningitis, several complications can arise whose development alters the prognosis for the worse in cases doing well and confirms an unfavourable outlook in those already showing a poor response to treatment. The seriousness of decerebrate rigidity is well-known. Smith and Vollum (1950) found it to be the only finding in the clinical picture or the C.S.F. which had not been seen in both successfully and unsuccessfully treated cases prior to the use of P.P.D. Previously, it had been the only indication for stopping treatment and was uniformly fatal in 3 to 21 days. 47 patients in a series of 146 patients reported by Robertson and Gairdner (1952) developed it and none recovered. In this series, it was observed as a terminal event in only a few patients who were already considered to be beyond hope of recovery, and its development merely confirmed a hopeless prognosis.

Convulsions occurring in the course of treatment have also been considered to be of bad omen. Illingworth and Lorber (1951), for example, reported that 17 of 23 children (in a series of 86) who developed them had died, and 3 others were mentally defective. Epileptiform convulsions were a feature of the initial illness in only 1 patient in this series - a survivor, but occurred during the treatment of 7 others. 4 of these recovered - one without sequelae; one became deaf; one was incontinent of urine for 2 or 3 weeks after the convulsions, but thereafter made a complete recovery apart from/

from a severe degree of hamstring spasm which required orthopaedic measures but which cleared completely; and the other had occasional convulsions after recovery, requiring phenobarbitone for control. In addition, one other patient had periodic convulsions after recovery, unassociated with any return of meningitis.

Perhaps the most frequent complication which appears to adversely affect the prognosis is spinal block.

Lorber (1951a), in a paper evaluating streptokinase as an adjuvant in the treatment of tuberculous meningitis, cited the development of obstruction in the circulation of C.S.F. as the most important cause of failure in the treatment of tuberculous meningitis, from a pathological point of view. In another paper (1950) describing the use of penicillin as a trace substance in studies of the cerebrospinal circulation, he indicated several possible causes of this obstruction - tuberculous granulation tissue, fibrinous exudate, reaction to a "bloody tap", irritant effect of streptomycin and herniation of the brain into the foramen magnum or tentorium. Doubtless in most cases the initial cause of obstruction is gelatinous exudate, or clotted blood following the puncture of the spinal theca; later, in the absence of resolution, organisation takes place and the persistent block is due to the development of fibrous adhesions. It has been reported (Choremis et al, 1951; Somner, 1952) that in some cases an incipient spinal block may be precipitated by C.S.F. pleocytosis caused by streptomycin, and a few days' rest from treatment may lead to its resolution. The block may occur around the brain-stem in the cisterna ambiens, in the cisterns at the base of the brain, or round the cord in the spinal subarachnoid space (Lorber, 1951a).

The development of spinal block is usually recognised by (1) fall in C.S.F. pressure at the lumbar region, (2) poor response of C.S.F. pressure to compression of the jugular veins (Quenckenstedt's sign), (3) development of xanthochromia, (4) rise in C.S.F. protein, usually to over 1,000 mg. per 100 ml. (see Smith et al, 1948). Lorber (1950), however, found that these signs could occur in the absence of true block and were unreliable if the block occurred above the cisterna magna, when the rate of flow and the protein content might be normal. It was for this reason that he introduced and described the method of injecting penicillin into the lumbar theca and assaying/

assaying the penicillin content of the cisternal or ventricular fluid 5 or 10 minutes later. In general, however, the signs given above are taken as evidence of the presence of spinal block, and further investigations were not carried out in this series.

The frequency with which obstruction to the flow of C.S.F. develops in tuberculous meningitis varies considerably from series to series. The M.R.C. (1948) reported its occurrence in 20 (21.7%) of 90 patients; Smith, Vollum and Cairns (1948) in 4 (25%) of 16 patients; Brainerd and Eagle (1950) in 2 (7.4%) of 27 patients; Russell and MacArthur (1950) in 8 (24.2%) of 33 children; Cairns, Smith and Vollum (1950) in one-third of 93 patients (either partial or complete); Illingworth and Lorber (1951) in 20 (24.4%) of 82 children; Lincoln and Wilking (1951) in 4 (10.3%) of 39 children; Ravreby and his associates (1952) in 6 (15%) of 40 patients; Somner (1952) in 11 (42.3%) of 26 patients; and Riley in 8 (13.3%) of 60 patients. Wasz-Hockert (1951) found 20 "high blocks" and 17 "low blocks" in 60 patients - a proportion as high as 61.7%. McSweeney (1950), on the other hand, in treating 94 patients, found no instances of spinal block.

Repeated efforts have been made to devise some means of preventing the development of spinal block and of clearing it when developed. Streptokinase was introduced primarily for this purpose, and Cathie and MacFarlane (1950) reported considerable success as a result of using this adjuvant, claiming that, while it did not dissolve established blocks, it did prevent their development. Lorber (1951a) however, disputed this finding. In 2 comparable series, each of 12 cases, 5 patients in the group receiving streptokinase developed block (a proportion much higher than he had previously observed), compared with only 1 in the group in which streptokinase was not used. In a subsequent paper (1954a), Lorber advocated less prolonged intrathecal therapy and found that, with a reduced course, only 2 of 38 children (5.3%) developed block, compared with 24.4% previously. The use of intrathecal heparin in prophylaxis of spinal block was reported by the Department of Health for Scotland in 1949, but there was no evidence of benefit and this treatment was abandoned in view of the difficulty of obtaining a suitable mixture with streptomycin.

In a proportion of cases, spinal block resolves spontaneously. This occurred, for example, in 4 of the 20 cases reported by the M.R.C. in 1948 - 2 of these subsequently died, and 2 were making satisfactory progress; in a further case, resolution appeared to be taking place. In the early days, cessation of intrathecal therapy was recommended when block developed, as it was thought to aggravate the obstruction. Some form of intrathecal streptomycin, however, was necessary to maintain C.S.F. levels, and so administration by other routes - cisternal or ventricular - was attempted with apparent success. Thus, Illingworth and Lorber (1951) reported that, while death occurred in all their first five cases of spinal block, in whom intrathecal/

intrathecal therapy was abandoned, 8 of the last 15 cases, treated by cisternal injections, survived. Somner (1952) found that the only drawback to cisternal punctures was the occurrence of haemorrhage, causing severe headache, backache and pains round the trunk. Cairns and Taylor (1949) strongly advocated the use of ventricular streptomycin through cranial burr-holes, and pointed out that it was useless and dangerous to inject streptomycin by the lumbar route after spinal obstruction had developed. In 6 cases reported by Debre and his associates (1947), operations were performed to relieve the obstruction and were successful in 2; spinal block was found to be caused by a tuberculoma in 1 case and leptomeningitis in the other 5. This type of treatment has not, however, been used in many centres and has obvious difficulties and disadvantages.

FREQUENCY AND PROGNOSTIC VALUE.

Obstruction to the cerebrospinal circulation occurred in 22 (21.6%) of the 102 patients in this series, and was recognised by the criteria enumerated above, together with the finding, in the 16 patients in whom cisternal punctures were done, of gross difference between fluid obtained at cisternal and lumbar punctures. In most cases, the first indication of developing block was a rising lumbar C.S.F. protein level. The seriousness of a protein over 500 mg. per 100 ml. occurring in the course of treatment is indicated in Table 91, which shows the maximum protein levels recorded during treatment. The proportion of recoveries was significantly less among patients whose C.S.F. rose over 500 mg. per 100 ml. at any stage - 45.8% compared with 70.5%.

All but 2 of the patients whose C.S.F. protein rose above 500 mg. per 100 ml. were considered to have spinal block and showed other evidences of its presence. The other 2 patients did not show these features and in them the rise in protein was transient, lasting only a day or two (in one case, after a streptokinase injection). Both survived, and it is probable that they had a partial, fleeting obstruction. Of the 22 patients who had

complete/

complete and lasting spinal block, 13 (58.7%) died, compared with only 23 (28.75%) of the remaining 80 patients who did not develop block (Table 92), i.e. the mortality rate in cases of spinal block was more than double that in the remainder of the series. To put this another way, nearly 3 times as high a proportion of non-survivors as of survivors developed spinal block. This difference assumes added significance when it is remembered that many patients who died did so early in the illness and it is conceivable that had they survived longer, some at least may have developed block.

TIME OF ONSET. (TABLE 93).

In 2 patients, the obstruction was already present at the time of diagnosis, and half of the cases of block had become evident by the end of the first month. The mortality rate was particularly high in these 11 patients, 8 of them dying. Incipient spinal block was probably present in 2 of these - the C.S.F. protein being 260 and 460 mg. per 100 ml. on admission, and the flow of C.S.F. rapidly becoming sluggish; both survived. It is noteworthy that there were no survivors among 7 patients who did not have complete or incipient spinal block on admission and who developed block within a month. 2 other patients (survivors) developed spinal block during the second month, 4 (who died) in the third month, and 1 (who died) in the fourth month. In the remaining 4 patients, spinal block occurred in the course of a relapse, and all survived.

In only 1 case - a child of over 1 year - did the obstruction recur after being relieved; in this patient there were 3 recurrences of the block before he ultimately died.

TREATMENT.

Intrathecal therapy was discontinued when block developed in 3 cases treated early in the series. Later, streptomycin was administered by the cisternal route as often as possible and, simultaneously, by the lumbar route in the belief that it was essential to combat the infection which had obviously extended down the spinal theca. The usual routine adopted was that the normal intrathecal dose was divided, one half or three-quarters being given by the cisternal route and the remainder in the lumbar region. (In no case were cranial burr-holes made and ventricular streptomycin given; no patient showed evidence of blockage above the level of the cisterna magna.) Treatment was otherwise continued exactly as if no block had occurred. On occasions, however, when the spinal block developed after the first few weeks of intrathecal therapy, a further intensive intrathecal course (cisternal and lumbar) was given, usually lasting 2 weeks. 15 patients in all received cisternal intrathecal therapy and 7 survived. Cisternal puncture was performed unsuccessfully in one other patient who died, and terminally in another.

DURATION.

The duration of spinal block varied, in survivors, from 6 weeks to 1½ years as follows: 6 weeks, 2½ months, 5 months, 6 months (2 cases), 9 months and 18 months in cases who had cisternal treatment, and 5 months in the other 2. Cisternal treatment did not itself affect the course of the block but its purpose wasto maintain adequate concentrations of streptomycin in the C.S.F. - not to influence the actual obstruction. In 11 of the 13 patients/

patients who died, spinal block persisted until death - that is, for periods of 1 day, 8 days, 2 weeks (3 cases), 17 days, 3 weeks, 1 month, 6 weeks, 3 months, 4½ months. In the other 2 patients, it subsided during life. In one, already referred to, it lasted for a month but recurred on 3 subsequent occasions, subsiding in 6 weeks and 1 month in the first 2 of these, the last occasion being terminally. The obstruction cleared after 5 months in the other patient, who, however, relapsed later and died without developing further blockage.

FACTORS INFLUENCING DEVELOPMENT OF BLOCK.

The worsened prognosis in patients developing spinal block may conceivably be due to one, or both, of 2 factors:

(a) the mechanical effects of the obstruction,

(b) the incidence of block in cases with more severe and extensive disease.

In other words, spinal block and higher mortality may be related as cause and effect, or as being both effects from a common cause. Tables 94 to 98 have been constructed to find out if the higher mortality is due to the fact that spinal block occurred more often in patients who, because of their age, severity of their initial illness, etc. would have been expected, in any case, to do badly. In assessing the significance of each factor, I have compared the proportion of patients in any given group with the corresponding proportion of those who did not develop spinal block - obtained by comparison with earlier tables. Since spinal block did not occur significantly more often in younger age groups, in severely ill or stuporose and comatose patients, or in patients with miliary or adult pulmonary tuberculosis, it would appear that the higher mortality in patients/

patients with spinal block was due to the mechanical effect of the obstruction. The tables reveal the following interesting findings:-

(1) Spinal block developed in a significantly higher proportion of patients aged 10-19, and only in 3 of 25 patients under 5 years who might have been expected to be more liable to it in view of their increased mortality rate and narrower spinal columns.

(2) Although the figures are not significant, a comparatively high proportion of stuporose and comatose patients developed spinal block - 41.2% compared with 11.4% in other groups.

(3) The significantly high incidence of spinal block in patients whose initial C.S.F. protein was between 200 and 500 mg. per 100 ml. is worthy of note. More than half of the patients in this group developed block. It is conceivable that, in some cases at any rate, a C.S.F. protein of over 200 mg. per 100 ml. is evidence of partial or incipient obstruction to the cerebrospinal circulation. It is interesting that Lorber (1950) suggested that a C.S.F. protein of over 300 mg. per ml. arising in the course of treatment, was an indication for carrying out further investigations to test the patency of the cerebrospinal canal.

EFFECT OF PRECEDING TREATMENT.

Lorber's findings (1951a, 1954a) that prolonged intrathecal therapy and the use of intrathecal streptokinase were associated with higher incidence of spinal block, have already been referred to. It is unlikely that the former factor played a part in this series, since the most intensive/

intensive intrathecal regime used was less intensive than Lorber's shorter course. A study of Table 99, however, reveals that both streptokinase and tuberculin, far from preventing block, almost certainly played a part in its development. In drawing any conclusions from this table, it is obviously necessary to exclude from assessment the 2 patients who had obstruction before treatment was commenced (whom I have bracketed in the table): one in Group D who died within 17 days during which C.S.F. protein steadily rose from 1,520 mg. per 100 ml. on admission to 3,600 mg. per 100 ml.; and one in Group F, who recovered but had persistent spinal block for 6 months (the C.S.F. protein reaching 5,600 mg. per 100 ml. after $3\frac{1}{2}$ months). Moreover, the 3 patients in Group B and 1 survivor in Group A developed spinal block during treatment of a relapse. In 1 of the former, streptokinase, and in another, tuberculin, were being used in the treatment of the relapse at the time of onset of block. These 2 must therefore be added to the patients in Groups C and E who received streptokinase and tuberculin respectively, making a total of 6 and 7 patients in these groups who developed spinal block. In view of these high figures, I have analysed these groups of patients more carefully.

Streptokinase. Two of the patients in this group had developed spinal block early in treatment before streptokinase was given, so that altogether 4 patients developed block while under streptokinase treatment and 2 of these died. Table 135 shows that 14 patients received streptokinase either as an initial treatment or for treatment of relapse; 3 of these already had spinal block when streptokinase was commenced; 4 (36.4%) of the remaining 11 developed/

developed block during streptokinase therapy. It may reasonably be concluded that streptokinase did not prevent spinal block and may well have contributed to its development.

One of the 4 patients who developed spinal block while having streptokinase did so at the end of 6 weeks of treatment at a time when streptokinase was routinely withdrawn from the course. He did not have any further streptokinase; he eventually recovered, the spinal block persisting for 5 months. In the other 3 patients, and also in 3 who had developed cerebrospinal obstruction prior to the use of streptokinase, streptokinase was administered from the onset of spinal block but did not appear to influence the block. The block persisted for $2\frac{1}{2}$ months, 5 months and 1 year in 3 who survived; and until death in 8 days, 3 weeks, and 5 weeks in the other 3. It seemed, therefore, that streptokinase was of no value either in the prophylaxis or treatment of spinal block.

P.P.D. It seems more than suggestive that 2 of every 3 patients treated initially with P.P.D. developed spinal block and that all the fatal cases in this group had this complication. Altogether 7 (58.3%) of the 12 patients - see Table 35 - who received P.P.D. in the course of treatment, developed spinal block, and it is probable that this was the main factor in the high mortality in these patients.

Excluding the 2 patients who already had spinal block on admission, 9 (11.7%) of 77 patients who neither had streptokinase nor tuberculin, developed block, compared with 4 (36.4%) of 11 who had streptokinase and 7 (58.3%) of 12 who had P.P.D. These differences are very highly significant/

significant (χ^2 = 16.19, n = 1, P = less than 0.001) and there seems no doubt therefore that tuberculin, and, to a lesser extent, streptokinase, at least contributed to the development of spinal block.

SUMMARY.

Spinal block occurred in 21.6% of patients in this series and was associated with a significantly higher mortality rate. The complication did not occur significantly more often in patients who were severely ill or in whom, for other reasons, a higher mortality was to be expected. The incidence was significantly greater in patients with initial C.S.F. protein over 200 mg. per 100 ml. and it is suggested that these may have had incipient block at the time of diagnosis. The use of P.P.D. and, to a lesser extent, streptokinase, was associated with a significant increase in the incidence of block, and neither was of any value in relieving it.

E. THE INCIDENCE AND INFLUENCE OF RELAPSE.

INTRODUCTION.

The possibility of relapse occurring even after apparently complete recovery must make the physician constantly guarded in making a prognosis in any given patient. One of the greatest disappointments in medicine must be to see a patient, who, after being critically ill with tuberculous meningitis, had recovered and was discharged home, returning to hospital with fresh evidence of meningitis, with the prospects of yet 6 months more of painful treatment and lingering doubt about the ultimate outcome. Yet, such must have been the repeated experience of most, if not all, physicians concerned in the treatment of this dreaded disease.

The possibility and the danger of reactivation of tuberculous foci in other sites - e.g. the lungs - are well-known, and it is, therefore not surprising that tuberculous meningitis should also be liable to flare up after apparently successful treatment. Various causes have been suggested, any or all of which may play a part in the occurrence of relapse. The development of streptomycin resistance must always be borne in mind in patients who, having at first responded to treatment, begin to deteriorate, but it is widely recognised that tubercle bacilli very seldom become resistant during the treatment of tuberculous meningitis. The M.R.C. (1948) reported the results of tests on 22 patients several weeks after the commencement of treatment; in 19, the organisms were as sensitive as at the beginning. The fact that a high proportion of cases of relapse respond well to a second, or even third, course of streptomycin, indicates that bacterial/

bacterial resistance must not be a major factor in the occurrence of relapse. In many cases, relapses are almost certainly due to the breakdown of persistent foci of infection inaccessible to streptomycin, as suggested by the M.R.C. (1948). In this report, the frequent autopsy finding of obstruction at the base of the brain and internal hydrocephalus led to the suggestions that relapse was often due to mechanical obstruction subsequent to organisation of tuberculous exudate, and that the number of late relapses would be considerably reduced if this were prevented. Levinson and his co-workers (1950) found that cases of relapse that came to autopsy usually had some unhealed caseous focus, e.g. a lymph-node, and they felt that relapse may frequently be caused by a second haematogenous dissemination of tubercle bacilli. Other cases, they considered, were due to rupture of encapsulated caseous foci in the meninges. The importance of vascular involvement and endarteritis with consequent cerebral softening was stressed in a leading article in the Lancet in 1949. The high relapse rate in patients with residual neurological signs and therefore, with areas of cerebral softening, was noted and the need for early treatment before vascular damage occurred was emphasised.

The frequency with which relapse is reported varies considerably in different series, but one of the reasons for this is the lack of uniformity in the nomenclature used. A strictly accurate terminology was suggested and used by MacCarthy and Mann (1950), who limited the term "relapse" to the occurrence of fresh symptoms and signs in patients perfectly well and with normal or nearly normal C.S.F., and used the term "recrudescence" when deterioration occurred soon after treatment in a patient otherwise well but with abnormal C.S.F. Relapse occurred in 4 and recrudescence in 8 of 43 cases, a total of 27.9%, Illingworth and Lorber (1951) using the same terminology, reported 3 "relapses" and 5 "recrudescences" in 82 children (a total of 9.8%). Cathie and MacFarlane (1950) had 1 "relapse" and 5 "recrudescences" in a series of 60 cases (10%), and Robertson and Gairdner (1952) 1 "relapse" and 11 "recrudescences" in a series of 146 (8.2%). On the other hand, the M.R.C. report/

report (1948) used the term "relapse" to include not only return of symptoms in any patient who had completed treatment, but also deterioration in patients who had been progressing favourably for at least a month but were still having treatment; in none of the 17 cases reported had the C.S.F. returned to normal. The majority of writers steer a course midway between these 2 extremes and apply the term "relapse" (as it is used in this thesis) to all cases who show a return of the meningitis illness after the completion of treatment, whether the C.S.F. has been previously normal or not. Indeed, the Ministry of Health (1953) reported no clearly proven case of relapse occurring (in a series of 371 patients) after the C.S.F. had been normal. Most writers, however, have found, with Calnan and his associates (1951) that relapse may occur after full recovery and return of C.S.F. to normal - they had 3 cases of relapse in a series of 54 patients (5.6%). In 1948, Choremis and his co-workers reported no relapses in 21 (of 50) cases of tuberculous meningitis who were cured and discharged, and observed over a period of a year, but in 1951, in a series of 132 cases, they found 20 (15.2%) relapses in 87 patients who had been discharged. Other figures, culled from the literature are as follows: Lincoln and Kirmse (1950a) 3 in 18 cases (16.7%), Flori (1950), only 1 relapse in 152 recoveries in a series of 265 cases; Brainerd and Eagle (1950) 3 in 27 cases (11.1%); McSweeney (1950), 6 in 94 cases (6.1%); Lassen and Neukirch (1951) 5 in 44 cases (11.4%); Ravreby et al (1952), 3 in 40 cases (7.5%); Perry (1952), 5 in 26 cases (19.2%); Russell and MacArthur (1953) 9 in 33 children (27.3%); Riley (1953) 17 in 60 cases (28.3%). The proportions in different reported series must, of course, vary with the proportions who survived the initial course of treatment and the length of the period of observation.

Little has been written about the type of patient, if any, who may be especially prone to relapse. Choremis and his associates (1951) found that the incidence of relapse was independent of age. Illingworth and Lorber (1951) noted that all but 1 of 8 relapses and recrudescences (out of 82 children) occurred in cases with miliary tuberculosis, but Calnan and his co-workers (1951) found no evidence to suggest that cases with miliary tuberculosis were more liable to relapse. Persistent C.S.F. abnormality is widely recognised as being the precursor of relapse in many cases. Thus, Robertson and Gairdner (1952) stated that "until C.S.F. normality has been achieved, the outlook remains uncertain and relapse is an ever-present danger". MacCarthy and Mann (1950) pointed out the seriousness of a low C.S.F. sugar at the end of a course of treatment and found it a precursor, if not a sign, of deterioration. On the other hand, Calnan and his associates (1951) found occasional slight abnormalities in the C.S.F. up to 2 years after cessation of all treatment, unaccompanied by other evidences of activity, and were unable to assess their significance. They could find no precipitating cause for relapse.

Relapses/

Relapses usually occur within a short period of discontinuing streptomycin treatment. Choremis and his associates (1951) mentioned the first 3 months as the most dangerous period, and the second 3 months as less dangerous. Later, the danger was minimal. In MacCarthy and Mann's series (1950), all the recrudescences occurred within the first 3 months after treatment (5 within a month); the relapses took place after intervals of 3, 4, 4½ and 15 months. The 17 relapses in Riley's series (1953) all occurred within a few weeks to a few months of stopping streptomycin. In the 5 cases described by Lassen and Neukirch (1951), relapses occurred 8 days to 3 months after the completion of treatment. Bunn (1950a), however, reported that fatal relapse can occur as much as 2 years after treatment is stopped, and Russell and MacArthur reported 1 case who relapsed after 3½ years of good health, and died 6 weeks later.

The features of a relapse resemble, to a greater or less degree, those of the initial illness. Its occurrence may be detected either by clinical changes or abnormalities in the C.S.F. The M.R.C. report (1948) described the following features indicating impending relapse: vomiting (the most frequent symptom), drowsiness, irritability, character changes, apathy, increasing C.S.F. lymphocyte count and falling sugar. In all 4 cases of relapse and 7 of 8 cases of recrudescence described by MacCarthy and Mann (1950), the diagnosis was first suggested by the clinical picture and subsequently confirmed by C.S.F. findings; the sugar level, however, remained normal in 3 of them. The main clinical features in both relapses and recrudescences were headache, vomiting, fever and loss of weight. Loss of bladder control occurred in 2 recrudescences and, in 1 patient who had 2 recrudescences, gross papilloedema was noted both times. Meningism was an inconstant feature in both groups. In the report of the Department of Health for Scotland on 81 cases in 1949, it was also concluded that the clinical appearance was the best guide to the diagnosis of relapse. In the 7 relapses reported by Levinson (1949) the diagnosis was also made on clinical grounds - irritability, vomiting and lethargy. Meningism was absent or mild, 4 were afebrile, and the C.S.F. sugar was normal. He concluded that relapse was due to encephalitis rather than meningitis. Choremis and his associates (1951) found papilloedema among the first clinical signs.

On the other hand, Lincoln and Kirmse (1949) found that C.S.F. changes occurred before clinical evidence of relapse in all 3 of their relapsing cases; and Lincoln and Wilking (1951) asserted that recrudescence or relapse could only be diagnosed early by frequent lumbar puncture. Spangberg and Granath (1952) reported that in their 2 cases, relapse was first manifested by sudden rise in the C.S.F. cell-count.

In/

In the early days of streptomycin, it was considered that the onset of relapse made the outlook very bleak indeed. The possibility of recovering twice from an infection, one attack of which carried a high mortality, seemed rather remote, especially in view of the probability of bacterial resistance to streptomycin developing. The fact that the latter does not occur nearly as frequently as was feared is no doubt largely responsible for a statement like this being possible: "The gloomy prognosis we gave at the time these setbacks were encountered have not been fulfilled." (MacCarthy and Mann, 1950). If diagnosis is made and treatment instituted early, the outlook in many cases appears to be favourable. Choremis and his associates (1951) reported that the clinical and laboratory evolution of relapse was "usually regular" and the prognosis better than for the original illness. The 3 cases of relapse reported by Calnan and his associates (1951) all recovered. On the other hand, 6 of the children who relapsed in Russell and MacArthur's series (1953) died, and 2 others were disabled. Two of the 3 cases of relapse reported by Ravreby and his associates (1952) had died and the other was in very poor condition, and, in Robertson and Gairdner's series (1952), 7 of the 11 patients who had recrudescences died and 1 with true relapse was alive and well.

FREQUENCY.

In this thesis, the term "relapse" is applied to all patients who had completed an initial course of treatment and required a further course because of recurrence of symptoms or deterioration of the C.S.F. Some had shown complete clinical and C.S.F. recovery; others had recovered clinically but still had abnormal C.S.F.; still others had persistent symptoms at the end of the first course, and subsequent deterioration rendered another course of treatment necessary; in one or two cases, the courses of treatment were almost continuous, it being evident within a few days or weeks that all was not well.

16 (15.7%) of the 102 patients in the series relapsed; 2 of these relapsed twice and 1 relapsed 3 times but ultimately recovered (Table 100). In all, therefore, 20 relapses occurred. The proportion of relapses is, of course, increased by the inclusion of the 6 patients who were initially treated/

treated with an inadequate course of streptomycin lasting 3½ months and were therefore, on account of this, predisposed to relapse. All of these subsequently received a complete course of treatment lasting 6 months, and 1 relapsed again. It is evident that, in making any assessment of the incidence of relapse, the other 5 should be omitted. Thus, of a total of 97 patients who received 6 months' treatment, 11 (11.3%) relapsed. In addition to the patients who relapsed after completion of treatment, 8 patients who developed fresh symptoms or intensification of symptoms already present, or showed sudden increase in C.S.F. abnormalities, or deteriorated in other ways during the course of treatment, were given fresh intrathecal therapy or more intensive intramuscular treatment. These I have classified as having developed "exacerbations". One of the 8 patients developed 3 such exacerbations before ultimately succumbing.

FACTORS INFLUENCING RELAPSE.

In endeavouring to assess what factors, if any, played a part in the development of relapse in some patients and not in others, it is necessary to exclude (a) patients who had an inadequate course of treatment at the beginning and who, therefore, regardless of all other factors, were almost certain to relapse, and (b) patients who died within 6 months and who therefore did not live long enough for relapse to occur. Tables 101-119 are based on the remaining 66 patients in this series who lived longer than 6 months and were given an initial 6 months' course of treatment. 10 of these patients relapsed, with 3 deaths, and 2 of the remaining 56 patients, who did not relapse, died (these were included in the group having "exacerbations"). Dogmatic assertions on the basis of such small numbers are obviously/

obviously unwarranted, especially since this is virtually a selected series and excludes, in particular, a high proportion of fatal cases.

(a) Findings on admission. (Tables 101 - 115). 3 factors appeared to be related significantly to the incidence of relapse in this series:-

(i) Duration of illness (Table 103). Of the 10 patients who relapsed, 8 were admitted in the first week of illness, compared with less than half of patients who did not relapse. This surprising finding can no doubt be explained, at least in part, by the difficulty in accurately estimating the length of the initial illness.

(ii) Initial C.S.F. Cell-Count (Table 112). 7 of the 10 patients who relapsed had an initial cell-count under 200 per c.mm. compared with only two-sevenths of the others. This finding is in keeping with the hypothesis previously suggested that a low C.S.F. cell-count is an index of poor tissue response. Such patients had a high mortality and a high relapse rate.

(iii) Initial C.S.F. Protein (Table 113). The incidence of relapse was significantly lower in patients with initial C.S.F. protein 100 - 200 mg. per 100 ml. There is no obvious explanation for this finding.

Other interesting but not significant findings were:

(iv) Age (Table 101) Half of the 10 patients who relapsed were aged 5 to 9.

(v) Severity of illness (Table 102) A trend is evident suggesting increasing relapse-rate with increasing severity.

(vi)/

(vi) Nutrition (Table 104). Half of the 10 relapses occurred in patients who were poorly nourished.

(vii) Mental State (Table 107). None of the 10 relapsing patients were mentally bright on admission.

(viii) Choroidal Tubercles (Table 108). A relatively higher proportion of patients with choroidal tubercles relapsed.

(ix) Chest X-Ray (Table 109) Half of the 10 relapses were in patients with either miliary tuberculosis or adult phthisis. In the group of 66 patients, one quarter of the patients with miliary mottling and one-half of those with adult tuberculosis, relapsed. This is not unexpected, since both of these types of patients have extra-meningeal foci from which a second haematogenous dissemination could occur (as suggested by Levinson et al, 1950).

(b) Initial Response (Tables 116 - 119). No relationship can be proved between the speed at which the clinical picture and the C.S.F. constituents were restored to normal, and the incidence of relapse. It did not appear to be possible in this series to judge the probability of relapse from the response to initial treatment.

(c) Initial Treatment Regime (Table 135). Apart from treatment B which was inadequate, the treatment regime did not appear to have any bearing on the incidence of relapse. The 10 patients who relapsed after a 6 months' treatment, were fairly evenly distributed amongst the other 6 treatment groups, but, of course, the numbers are quite insufficient to enable conclusions to be drawn.

TIME OF ONSET.

All the relapses occurred within 1 year of the completion of the previous course of treatment. 10 of the 16 patients relapsed within 3 months of terminating the initial course, and 2 of the further relapses took place within the same period after the end of the previous course. In 2 patients, the initial course of treatment had just been completed when the clinical condition deteriorated and it became obvious that a further complete course of treatment was necessary; the interval in another patient was less than 2 weeks. It was difficult to decide whether to classify these, and one or two others as "exacerbations" or "relapses", but, since they had completed the primary course and had improved, they were included among the "relapses". Two patients relapsed 8 months and one 1 year after the end of the previous course. Since relapses took place both in survivors and non-survivors up to 8 months after the initial course, it does not appear that the length of time elapsing before the development of a relapse is necessarily any indication of the ultimate outcome.

Eleven of the 16 patients had been completely symptom-free following completion of the first course and prior to the onset of relapse (Table 121). Complete symptomatic recovery had also occurred before 3 further relapses. Thus, 14 of the 20 relapses occurred in patients who were asymptomatic and clinically well - confirming what has already been emphasised, namely that disappearance of symptoms, even at an early date, is no guarantee against the possibility of relapse. The other 6 relapses took place in patients who had improved but had one or more residual symptoms (as did other patients who did not relapse), suggesting that complete healing had not occurred/

occurred - 3 of these were in patients who had an initial 3½ months' course of treatment. One of the 2 survivors who relapsed twice had been completely asymptomatic before each relapse occurred; and the patient who had 3 relapses before death had also made a complete clinical recovery before the second and third relapses.

It is noteworthy (Table 122) that 7 of the 16 patients who relapsed had a completely normal C.S.F. prior to the onset of relapse, and that all of these survived. One patient relapsed a second time after having twice been restored to complete clinical and C.S.F. normality. In most of these patients, while the upper limit of 10 per c.mm. was accepted as normal, the cell-count had in fact fallen below 5 per c.mm. In 5 survivors, none of the C.S.F. elements had returned to normal before the onset of relapse; 4 of these, following treatment, had a completely normal C.S.F., but the other relapsed again and required a third course of treatment before normality was restored. As has already been seen, the C.S.F. did not return to normal in any of the fatal cases in this series. In one of the 4 patients who relapsed before death, none of the C.S.F. constituents became normal after the first course, but the sugar-level was normal after the first relapse and both sugar and chlorides after the second. In the other 3, the cell-count became normal in 1, the sugar in 2, and the chlorides in 3. A normal protein level was never restored in patients who ultimately died.

FEATURES OF THE RELAPSE ILLNESS.

Patients who recover from tuberculous meningitis (or, in the case of children/

children, their relatives - if sufficiently interested!) are usually quick to recognise the symptoms of meningitis should they recur. On discharge from hospital, all patients (and relatives and practitioners) were warned of the possibility of relapse, and encouraged to return as soon as any suggestive symptoms presented themselves. Consequently, it is not surprising to discover from Tables 123 - 133 that in general, the relapse illness was shorter than the original one and its features less marked. All the 20 relapses were taken into consideration in constructing these tables. The duration of the illness indicating the development of relapse was significantly less than that of the initial illness (Table 123). Thus, in nearly one-half of all the relapses, treatment was commenced within 3 days of the onset of symptoms (compared with just over 1 in 20 in the case of the initial illness) and only 1 patient had symptoms for longer than a week (compared with over one-half, in the case of the initial illness).

Symptomatic upset was the first indication of relapse in most cases. Only 2, indeed, were symptom-free when treatment was commenced, clinical deterioration being preceded by C.S.F. deterioration in these. In other 2 patients, the relapse illness was little more than an exacerbation of the original illness occurring after discontinuation of treatment, the patients not having fully recovered. The prominent symptom (Table 124) in this series, as in reported series already referred to, was vomiting, which occurred in 14 of the 20 relapses (seven-ninths of those with clinical upset). Drowsiness, anorexia, and, to a lesser extent, headache, were the other main features. In a boy of 14, the onset of relapse was heralded by hysterical/

hysterical attacks occurring at nights, the patient (still in hospital) sitting up in bed staring strangely, not recognising any of the staff and calling for "daddy". After a few minutes he was able to answer questions, but subsequently was incontinent of urine and faeces. Incontinence of urine was the presenting feature in another patient, a man of 35, who had been well for 8 months apart from some mental instability. Irritability was a prominent feature in 2 patients.

Comparing the relapse illness with the original illness - Tables 125 to 133 - the main differences were: the relapse illness was less severe, meningeal signs less marked, and temperature lower than initially. None of the patients was comatose when treatment of the relapse was commenced, but the proportions of "bright", "drowsy" and "stuporose" patients closely paralleled those for the original illness. The C.S.F. cell-count tended to be lower - not significantly so - but a significantly higher proportion of high protein levels were obtained in the relapse illness.

TREATMENT OF RELAPSE.

The development of symptoms or signs pointing to the occurrence of relapse was the signal in all cases for the immediate resumption of intensive treatment. Battle was once again joined with the invading organisms which had now on more than one occasion brought their victims to the verge of death. Thus began another uphill struggle - in three patients for the third time, and in one, the fourth - which was to entail just as long a period of suffering, in the form of intramuscular and intrathecal injections, as had the first; indeed in some cases - those in Group B - this period was almost/

almost twice as long as the first. In all cases, a complete 6 months' course of intramuscular treatment, with appropriate intrathecal therapy, was administered. The planned attack on the invader was neither mitigated nor intensified because this was the second (or third, or fourth) time the battle was waged. Not in every case, however, was the same course embarked upon as at the beginning. In some cases, new weapons, in the form of streptokinase or tuberculin, were introduced into the attack; in others the same weapons - streptomycin and P.A.S. - were relied upon but the plan of campaign was altered. The treatment course now adopted was the one "in vogue", in routine use, at the time when the relapse occurred, and in most cases, this differed from the course initially given. Table 134 indicates the treatment given to the 16 patients who relapsed, and Table 135 is a comprehensive table incorporating the figures in Table 34 - the initial treatment given to all cases - and those in Table 134, which includes only those who relapsed. The mortality rates in Column V differ somewhat from those given in Table 34. In the latter, the mortality rate applied to patients who were given each course as their initial treatment (some of whom may have recovered, but later relapsed and died while having another course); in this table, only the deaths occurring while the treatment in question was in progress are recorded. Any deductions already made about the value of each treatment regime are unaffected by the slight differences between Tables 34 and 135. The mortality rate per course varied from 50% in Treatment E (using dihydrostreptomycin and P.P.D.) to 0% in Treatment G (using streptomycin with reduced intrathecal therapy). The relapse-rate per course (column VI) is seen to vary little from one treatment to another, with/

with the exception, of course, of Treatment B which had 100% relapse rate.

PROGNOSIS.

When confronted with a patient, who, having survived one attack of tuberculous meningitis at the cost of 6 months of arduous treatment, is once again the victim of attack by the same enemy, one might well ask if it is worthwhile waging war again against the invader and subjecting the patient once more to the rigours of 6 months of frequent injections. To what purpose? Fortunately, inasmuch as this series can give it, the answer is a favourable one; for the results correspond with those of MacCarthy and Mann who found them at least as good as for the treatment of the initial illness - and that despite the damage that may have already been done to the brain and spinal cord and their covering membranes; in spite, too, of the possible development of bacterial resistance in a few cases. Table 100 shows that 75% of 16 patients who relapsed survived, compared with 62.8% of 86 who did not relapse. Of 11 patients who relapsed after 6 months' treatment, 7 survived (63.6%). Thus there is still a very reasonable prospect of recovery even after relapse has occurred - just as reasonable as there is at the outset of treatment.

PROGRESS MADE IN RESPONSE TO TREATMENT.

Since patients usually come under treatment at an earlier stage when they relapse than when they are first diagnosed, it is to be expected that the response to treatment would be correspondingly speedier and uninterrupted. That this is not so is seen from Table 136 which shows that only 2 of the 16 relapses/

relapses successfully treated "went according to plan" i.e. without delays or interruptions. This proportion is significantly low when compared with the proportion responding satisfactorily to the initial treatment. No doubt factors already mentioned were partly responsible for this - namely, damage previously done, and developing resistance of organisms which had acquired fresh defences against the drug attack; it was not without a harder struggle that the invaders surrendered what might be their final opportunity to destroy their victim. Despite this, it is seen from Tables 137 - 142 that the temperature settled more quickly and headache tended to disappear sooner in the relapses than initially. Appetite, however, seemed to return more slowly, and other features showed no marked differences. Laboratory restitution, as described by Choremis and his associates (1951), was "regular".

SUMMARY.

Relapses - recurrence of symptoms, or deterioration, after treatment was completed - occurred in 16 of the 102 patients in this series; two of these had 2 relapses and one had 3, making a total of 20 relapses in 16 patients. Since only 4 of these died, the prognosis was not materially different from that for the initial illness. Strangely enough, patients admitted in the first week of the original illness and those with initial C.S.F. cell-count less than 200 per c.mm. seemed more prone to relapse than others. Relapses were almost invariable when an initial course of $3\frac{1}{2}$ months was given, but the incidence was uniform in patients treated initially with different 6 -month courses. Twelve of the 20 relapses occurred/

occurred within 3 months of completing the previous course of treatment, and no patient relapsed more than 1 year after the completion of treatment. Eleven of the patients who relapsed had been completely fit clinically, and 7 had a completely normal C.S.F. before relapse occurred. The others had all improved but had one or more residual symptoms and some degree of C.S.F. abnormality. No patient with a completely normal C.S.F. died. Relapses were usually detected on clinical grounds in the first place, vomiting being the most frequent symptom. C.S.F. changes occurred later, but in 2 cases, C.S.F. abnormalities occurred before symptoms developed. The relapse illness was of shorter duration and less severe, with features, in general, less marked than the initial illness. Treatment was by intensive intramuscular and intrathecal streptomycin, the regime being identical with that for patients admitted for the first time with tuberculous meningitis. Although the ultimate outcome was favourable in most cases, response to treatment tended to be delayed and interrupted.

F. THE INCIDENCE OF SEQUELAE, ESPECIALLY DEAFNESS.

INTRODUCTION.

No study of tuberculous meningitis would be complete which did not take into consideration the residual mental and physical disorders from which, unfortunately, a proportion of survivors suffer. In examining prognostic factors, one must be concerned with not only the quantity but also the quality of results, and so must endeavour to assess what factors, if any, are particularly associated with the incidence of sequelae and, on the other hand, what prospects any given patient may have of complete recovery without after-effects.

It would have been surprising if a disease such as tuberculous meningitis, affecting, as it does, the central nervous system, and causing prolonged incapacity, did not leave in its wake, in many cases, severe physical and especially mental handicap. That such defects should occur in a comparatively small proportion of patients is a cause for satisfaction. Nevertheless, many survivors do have a heavy price to pay, in the incapacity with which they are subsequently burdened, for the recovery they make. The first case reported to have been given intrathecal streptomycin by Cooke, Dunphy and Blake (1946) was a child who ultimately became mentally retarded and probably deaf. Since then, an increasing number of sequelae have been reported. The mental disorders that may follow vary from mild irritability - which may be the result of a combination of factors apart from the disease process, e.g. prolonged stay in hospital away from parental care and home influence - to grave mental deficiency. Various

neurological/

neurological sequelae may occur - e.g. palsies of different kinds up to complete hemiplegia; convulsions; visual upsets up to total blindness; and, of course, deafness. Physical disabilities as varied as stiffness and contractures of legs, obesity, and bone and joint complications, have also been reported.

In a comprehensive review of 549 cases (247 survivors) from 5 different hospitals in England, observed for a minimum of $2\frac{1}{2}$ years, Lorber (1954c) reported that 157 (64% of survivors) had no after-effects at all, and that the incidence of sequelae was related to the severity of the original illness. 75% of early cases who survived had no sequelae, compared with 60% of intermediate cases and 40% of advanced cases. A proportion of survivors, varying from 5% in patients with early disease to 20% in those with advanced disease, developed "moderate neurological sequelae" - hemiparesis, visual defects short of blindness, occasional fits, moderate degrees of mental and behaviour disorders. "Severe neurological disorders" - grave mental defect, often with blindness, deafness, and hemiplegia; severe behaviour disorders; complete hemiplegia; cauda equina syndrome - occurred in 10.5% of all survivors (4% of early cases, 8.7% of intermediate cases and 35.5% of advanced cases). 35 patients were vegetating and were considered failures. He concluded that delayed diagnosis not only prejudiced the chances of survival but also made the chances of complete recovery remote. Patients with early disease had a 5 times better chance of complete or useful recovery than those with advanced disease.

In other reported series, there is a marked variation in the frequency with which sequelae developed. In a Ministry of Health report (1953) on 102 survivors of 371 cases, 1 patient was blind, 1 had spastic paralysis of legs, 1 suffered from intermittent epileptiform attacks and a fourth from attacks of amnesia, dizziness and black-out. Choremis and his associates (1951) reporting a series of 132 cases, found that 4 developed hemiplegia either at the onset or early in the course of the disease; the patients recovered but the hemiplegia persisted although improving. A large proportion of children developed obesity of regular distribution, associated with a low B.M.R. and sometimes accompanied by increased C.S.F. protein. Illingworth and Lorber (1951) classified the 34 survivors of their series of 82 cases into 3 grades: (1) 22 who were mentally and physically normal, (2) 4 who were mentally normal but had some physical defect, and (3) 8 who were mentally retarded, with or without some physical defect. They pointed out that, when considering the patient's condition after treatment, account must be taken of the previous intelligence and behaviour, and also of the effect of a long illness, of missing school and maternal love, and of the attitude of parents when the child returns home. In a subsequent paper, Lorber (1954a) reported that 75%/

75% of survivors (in a series of 38, 28 of whom survived) were free from any defect, compared with 61% previously. 18% had some physical disability and 7% grave mental sequelae. Ruziczka (1952) noted that in his series of 114 children (61 surviving), changes of behaviour occurred in children already difficult to handle before the onset of disease - lengthened reaction time, difficulty in establishing contact, apathy, need for sleep - all tended to disappear. Hypertrichosis occurred on the face, back and extremities in several children but disappeared after a few months. 3 children developed spasticity with extensor and adductor spasms, which improved before discharge and disappeared later. The majority showed no severe psychological or neurological symptoms, nor any decrease in intelligence. Visual disturbances up to blindness occurred in 10 children, 5 of whom died. In Calnan's series (1951) of 114 cases (53 survivors), retarded development occurred in 6 children under 3, hemiplegia in 2, hemiplegia and homonymous hemianopia in 2, blindness in 1 and mental defects in 2. Of 14 survivors, out of43 children treated by MacCarthy and Mann (1950), 2 were mentally retarded (1 an idiot). On the other hand, 16 of 30 survivors treated by Ravreby and his associates (1952) were disabled; mental retardation occurred in 11 (thought to be due to reparative processes; in 3 there was associated hydrocephalus); motor disturbances in one or more extremities in 4; blindness in 4 (3 bilateral), and speech disorders in 2. Only 9 of 12 survivors reported by Russell and MacArthur (1953) were well (and 1 of these was mentally backward and 1 of low intelligence); the other 3 were mentally defective, one with hemiplegia and frequent epileptic fits; one with hemiplegia, epileptic fits, sexual precocity and intracranial calcification; and one blind with epileptic fits.

In view of the relatively high incidence of serious sequelae reported from other centres, the results in this series gave grounds for satisfaction. Only 1 of the 66 survivors was mentally defective (Case 39). He was an orphan child of 2 years admitted from a "reception centre", and his previous mental state was not accurately known; it seemed to be suspect to say the least. The child was admitted seriously ill, and comatose with a left-sided hemiplegia, which, however, receded during treatment. One other child of 6 (Case 44) was mentally backward and unstable, being very easily provoked to violent anger; the parents, however, when questioned, did not admit/

admit to having noticed much change in their son, so it is probable he was mentally backward before his illness. Two other patients (Cases 46, 56) were irritable and quick-tempered after the illness, but the prolonged spell in hospital may well have been sufficient to account for this in patients who may have previously been emotionally somewhat unstable. One of these (56) who relapsed twice was irritable after the first and second courses of treatment, but returned to normal after the third. In one patient (Case 89), hemiplegia was present from the beginning and persisted but improved; he was also in an advanced stage and was stuporose when treatment was instituted. Apart from the hemiplegia, he made a complete recovery and, following orthopaedic treatment given in another hospital, was able to walk reasonably well and had relatively little functional disability. Three other patients had orthopaedic treatment in the same unit, after the course of streptomycin therapy was completed. One of these (Case 30) developed tuberculous infection of a knee-joint - the only case in this series of subsequent extrameningeal haematogenous dissemination. The other 2 (Cases 43, 93) had developed marked contracture of the legs, resulting from long-persisting muscle spasm. Five others had marked hamstring spasm and leg stiffness but did not develop contractures, and in response to further physiotherapy (a routine measure in all cases), the spasm gradually relaxed leaving no permanent disability. Two patients (Cases 9, 35) both aged 17 on admission, were perfectly normal mentally and physically, apart from intermittent epileptic convulsions. The former gave a history of convulsions

at/

at the age of 7; he was seriously ill on admission, drowsy, but not in stupor or coma. The latter, who had no previous history of convulsions, was moderately ill, mentally bright, but with unilateral external rectus palsy; convulsions became sufficiently frequent in this case to consult a neurologist, who, however, found no underlying neurological abnormalities and prescribed pheno-barbitone; after this, the fits did not recur. One other patient (Case 67), while not developing convulsions, did have occasional dizziness and noticed an inability to concentrate when he was given responsible duties; he was helped by reassurance. Apart from deafness, the only other sequelae were obesity in 3 patients; foot-drop in 1 (Case 29) - responding to physiotherapy; and marked ataxia in 1 (Case 62). It is quite clear that with such small figures, it would be impossible to draw deductions about factors which may have played a part in the development of any of these sequelae.

During the years 1950 and 1951, the satisfaction of saving the lives of a high proportion of patients who, but a few years previously, would certainly have succumbed to tuberculous meningitis, began to be tempered with apprehension and misgiving because an alarming number of patients who survived - as well as many of those who died - did so at the expense of their hearing. In all too few of these, the impairment of deafness was slight; in most, it amounted to total or subtotal deafness, unrelieved by hearing aids and so constituting a most serious handicap. Tuition in lip-reading enabled many to enter to some extent into conversation but this was a very poor and inadequate substitute for normal hearing. It quickly became evident that the

main/

main weapon being used to combat the disease was itself responsible for the deafness; in other words, the auditory damage was not due to the disease process but was a toxic manifestation of the drug used - dihydrostreptomycin; a preparation that had been introduced because it was believed to have less neurotoxicity.

Even before the days of dihydrostreptomycin, however, deafness was a recognised complication of tuberculous meningitis whether untreated or treated with streptomycin. One of the earliest patients to be treated - by Vignec (referred to by Lincoln et al, 1948) - became deaf while under treatment, and died after several months. As far back as 1947, Debré and his associates had 15 cases of deafness in a series of 118 and were of the opinion that the number might really be higher were deafness not difficult or impossible to detect in unconscious patients. In the same year, McDermott, in a review of the toxic effects of streptomycin, reported 7 out of 100 cases (not all with meningitis) who developed 50% to 100% deafness; 5 of these had prolonged intramuscular and intrathecal streptomycin for tuberculous meningitis and the other 2 had renal insufficiency. He suggested that the main actiological factor was overdosage (in those early days, intramuscular doses of up to 5 g. were not uncommon, and intrathecal doses of 0.2 - 0.4 g. were occasionally given), and that the drug caused a liquefaction necrosis in the cochlear nucleus. Deafness was sometimes preceded by low-pitched tinnitus. Considerable recovery took place in some cases. Farrington and his associates (1947) also considered overdosage to be the cause of deafness in 2 of 16 cases of tuberculous meningitis treated by them with 3 g. of streptomycin intramuscularly and 0.1 g. intrathecally daily for 120 days, and in 3 of 15 patients treated subsequently, 2 of whom had tuberculous meningitis and 1 impaired renal function. Seven of 100 cases of miliary and/or meningeal tuberculosis (40 of whom survived) reported by Bunn (1948), had significant hearing loss, and 4 others had a lesser degree of impairment. Three who became completely deaf during treatment, failed to regain hearing; some degree of restoration occurred in the remaining 8, 6 being no longer deaf for conversational range of tones. By audiometric examination, hearing loss could be detected within the first month of therapy but it was not clinically evident till after 60 days. In the writer's opinion, the deafness was probably due to the meningitis, as the hearing loss in both ears was unequal and as impairment occurred in 28% of cases of meningitis but only in 1.2% of other types of tuberculous disease treated with streptomycin in similar doses. Smith and his associates (1948) did audiometric tests on survivors who were old enough for the tests and found that all showed moderate high-tone deafness by the conclusion of treatment; one other patient developed a severe global deafness in the 4th month of treatment. Cairns and Taylor (1949) also found high-tone deafness/

deafness in all of their 48 cases, occurring as early as the 11th day, and 6 had more serious deafness.

It was not, however, until the introduction of dihydrostreptomycin that the frequency of deafness assumed a magnitude that gave cause for alarm. Paradoxically, dihydrostreptomycin was the result of a search for a remedy less toxic than streptomycin, and Edison and his associates (1948) wrote of it that "the neurotoxic action has been reduced without sacrificing the antimicrobial efficiency". Early reports of its use were favourable. Hobson and his co-workers (1948) concluded that, while it might cause damage to the auditory apparatus, it was not more toxic in this respect than streptomycin and in all probability less so (although 3 patients became deaf out of 12 who were treated with 3 to 5 g. of dihydrostreptomycin daily for up to 11 weeks). Hinshaw and his associates (1948) also found that it was much less toxic than streptomycin when given in comparable doses for similar periods. Further experience, however, failed to confirm these early reports. Allison et al (1949) found audiometric loss in 7 of 20 patients treated with 2 or 3 g. dihydrostreptomycin daily for 90 days, and Romansky et al (1949) reported deafness in 14 of 61 patients who had the same dosage. O'Connor et al (1951) using a daily dose of approximately 20 mg. streptomycin per kgm. body weight, found that streptomycin had little toxic effect on the auditory mechanism, no hearing loss developing in their cases. Using dihydrostreptomycin, which was much less toxic to the labyrinth than streptomycin, they found that 16 of 21 patients given a 6 months' course had significant auditory impairment, 2 being totally deaf. They expressed the view that the hearing-loss caused by dihydrostreptomycin was generally much more disturbing than the loss of labyrinthine function - which could be satisfactorily compensated - associated with the use of streptomycin. Mouriquand et al (1952) were also of the opinion that deafness in the course of treatment of tuberculous meningitis was due to the treatment and not the disease. While deafness from streptomycin was rare and only occurred following the use of large intrathecal doses, total bilateral deafness from dihydrostreptomycin was common, developing 4 to 14 months after the beginning of treatment. Biagi (1951) reported 4 cases of gross deafness among 8 recovered cases of tuberculous meningitis treated with dihydrostreptomycin, compared with none among 14 recoveries following streptomycin therapy. Grant (1951) found deafness in 10 of 15 survivors (out of 23 cases) treated with dihydrostreptomycin and no deafness in 2 survivors (out of 9 cases) treated with streptomycin. Cathie and Garrow (1951) were not only disappointed with the incidence of deafness but also with the poor survival rate in dihydrostreptomycin-treated cases: they had only 3 survivors (2 of whom were deaf) out of 14 treated with dihydrostreptomycin, compared with 22 survivors (with no deafness) out of 40 cases treated with streptomycin. Sher (1951) found 3 cases of deafness in 16 survivors treated with streptomycin but as many as 7 in 11 survivors treated with dihydrostreptomycin. Somner (1952) reported deafness in 7 of 8 survivors treated with dihydrostreptomycin, but only 1 of 6 survivors treated with streptomycin was slightly/

slightly deaf in one ear, and the deafness did not increase despite continued treatment. Of the 7 cases of deafness with dihydrostreptomycin, 3 had been treated entirely with this drug and were totally deaf; 4 were treated partly with the calcium chloride complex of streptomycin and 1 of these was totally deaf, while the other 3 showed varying degrees of deafness. Ruziczka (1952) encountered no deafness while using streptomycin, but 8 of 13 cases receiving dihydrostreptomycin became deaf after 5 to 6 months. I have previously reported (1952) on 77 patients in this series. Of 26 patients treated with streptomycin, only 1 had become slightly deaf, but 20 of 51 patients treated with dihydrostreptomycin developed hearing loss, these forming more than half of the patients who survived longer than 3 months, i.e. sufficiently long for deafness to occur.

With few exceptions - e.g. Riley (1953) who found deafness in 4 of 15 patients (26%) receiving dihydrostreptomycin and 9 of 45 (20%) treated with streptomycin - the evidence from reported series of cases points overwhelmingly to dihydrostreptomycin being the cause of the increased incidence of deafness in patients treated with it during the years 1949 to 1951. The subject was discussed in detail at the Royal Society of Medicine and reported in its Proceedings in 1952. Robson and Goulding stated that the degree of damage was related to the dosage level and suggested that 1 g. daily could be given without serious damage in the absence of impaired renal function. Ormerod, however, felt that, while 3 g. daily caused deafness in a number of patients and vertigo in most, 2 g. caused no deafness, but vertigo in two thirds; and 1 g. caused vertigo in one third. Dihydrostreptomycin very often caused perceptive deafness which might appear late in the course of treatment or after its completion and was irreversible (see also Somner, 1952). He too felt it to be a much more serious disability than the vestibular damage caused by streptomycin, which was ameliorated or disappeared as a result of compensatory adaptation. The lesion he considered to be probably not in the eighth nerve but in the end organs. Whetnal and Lucas found extensive tuberculous infiltration in the sheath of the eighth nerve and slight changes in the cochlea and suggested that the deafness was due to the meningitis and not the drug. Walker described the deafness in 30 patients in the series of 93 cases; in 17% it was subtotal. 65% of the patients treated with dihydrostreptomycin had severe deafness. The critical time for deafness to occur was the 5th or 6th month; in a few, it developed as early as the 3rd month or as late as the 15th month. He stressed the importance of detecting the hearing loss as early as possible with a view to commencing auditory training and lip-reading.

The importance of dosage of dihydrostreptomycin in the causation of deafness was stressed by Johnston (1951) who concluded that deafness could be avoided by administering only 1 g. of dihydrostreptomycin every 12 hours to adults, provided renal function was normal. He quoted Hinshaw (1951) as saying, "there is at present no convincing evidence that either streptomycin or dihydrostreptomycin is more toxic to the auditory function of the eighth nerve than is the other drug." This conclusion does not accord with other views/

views already referred to. Calnan (1951) did find, however, that deafness was more frequent since the prolongation of streptomycin treatment, especially intrathecally, and was of the opinion that the majority of deaf children would not have survived if the period of treatment had been appreciably shorter - no patient who became deaf had subsequently died. This was probably due, however, to death occurring before hearing loss became evident.

INCIDENCE.

Varying degrees of hearing loss (detected on clinical grounds and not by audiometric tests which were carried out in a few to confirm the clinical findings) occurred in 32 (31.4%) of the 102 patients in this series (Table 147). Four of these subsequently died and 28 survived. 42.4% of the survivors became deaf, most of them to a marked degree. When streptomycin therapy was commenced in this series, it was realised that complications such as deafness (and blindness) might be expected to develop as part of the disease process, but it was felt that, if these were not very frequent, the price paid for life and health in the majority of survivors would not be too high. The formidable proportion of cases who did become deaf, however, was disappointing in the extreme, the more so because of the high hopes that had been established as a result of the very favourable early experience of treatment of the disease. Of the first 26 patients, only 1 survivor had developed any hearing loss, and that of mild degree, and only after a second course of treatment given for relapse. Thereafter, streptomycin was replaced by dihydrostreptomycin, the intrathecal therapy was intensified and intrathecal adjuvants were introduced into the treatment regimes, these changes coinciding with a steep increase in the incidence of deafness in patients so treated. Hearing was impaired, however, in just as high a proportion of patients who were not given streptokinase or

P.P.D./

P.P.D. as of those who were, and deafness continued to occur when the intrathecal course was reduced in regime F (Table 148). The only satisfactory explanation seemed to be that dihydrostreptomycin was the main, if not the only, aetiological factor. Of 66 patients who received dihydrostreptomycin in the course of treatment (B - F), 65% survived, and 45% became deaf, in most cases markedly so, compared with 64% survivors in 36 patients treated with streptomycin, only 2 of whom developed mild hearing loss. All the patients in Group B, while initially treated with streptomycin, relapsed and were subsequently given dihydrostreptomycin. One of these, however, had 2 relapses, the first of these being treated with another $3\frac{1}{2}$ months' course of streptomycin, and the second with a 6 months' course of dihydrostreptomycin. On careful review of this patient's illness, it was found that deafness had in fact developed during the first relapse, i.e. before the use of dihydrostreptomycin. In Table 149, therefore, this patient is included among the 37 patients who did not receive dihydrostreptomycin and is one of the 3 whose deafness could not be attributed to its use. It is clear that in this series, contrary to the findings of Cathie and Garrow (1951), quoted above, the survival rate was not affected by the change to dihydrostreptomycin. There is no doubt, however, from the highly significant difference between the two groups, that the latter drug was responsible for the sharp rise in the incidence of deafness in patients treated with it. In Table 150, the incidence of deafness is presented in relation to the treatment regime actually being given or completed when hearing became impaired. While this more accurately apportions/

apportions the cases with deafness to their appropriate treatment groups, it does not substantially affect the proportions in each group except that most of the cases of deafness in patients treated initially with treatment B are now allocated to other groups. The figures in Group E are particularly affected: 6 of the cases of severe deafness were treated with P.P.D. when deafness occurred (50% of the 12 in this group) compared with only 12 in groups C, D and F (20% of 60 patients in these groups) - the difference is not, however, significant.

The adult dose of 2 g. dihydrostreptomycin per day was not exceeded in any patient in this series. This was regarded as a safe dose by Carr et al (1950), Johnston (1952) and Ormerod (1952), but other writers (e.g. Glorig, 1950; Robson and Goulding, 1952) recommended a maximum dose of 1g. daily. It was not considered justifiable to investigate the toxicity of this smaller intramuscular dosage in this series. Having continued to use dihydrostreptomycin, and reduced the intrathecal regime without apparent effect, one was rather loath to expose more patients to the risk of deafness and so decided to abandon dihydrostreptomycin and revert entirely to streptomycin. Don and Gregory (1952), however, did report a series of 26 cases (none with miliary or meningeal tuberculosis) treated with 1g. of dihydrostreptomycin per day, 4 of whom showed auditory impairment - 1 severe and 1 moderate. In the present series, even the most intensive intrathecal therapy was less intense than that used in most other centres; yet the incidence of deafness was not less, nor was it reduced when the shorter

intrathecal/

intrathecal course was used. It is seen from Table 150 that 52 prolonged courses were given (Groups C - E) and 19 cases of deafness occurred (36.5%) - including 14 (26.9%) cases of total or subtotal deafness; 20 shorter courses were used (Group D), and 10 patients became deaf (50%), 4 (20%) with serious deafness.

ONSET.

Impairment of hearing was not observed early in treatment, during the period of intensive therapy, when it might be expected to occur, but later, when intrathecal therapy, apart from weekly injections, had been completed, and usually when the intramuscular course was being tapered off. In 8 cases, indeed (Table 152), it was detected after all treatment was stopped. In only 1 patient (Table 151) was deafness observed within 3 months of instituting treatment, occurring late in the 3rd month. The average time of onset was during the 6th month of treatment. Eight cases occurred in the course of treatment of a relapse. Deafness was usually preceded by buzzing or ringing in the ears, lasting a week or so. At first mild, the hearing loss rapidly increased, reaching its maximum severity in a week or two. In no patient observed in this series was it reversible. It would seem that dihydrostreptomycin has a delayed neurotoxic effect; by the time deafness was detected, it was already too late to modify its course by reducing or discontinuing treatment; in most cases, indeed, this was routinely being done.

Since impairment of hearing was not detected before the end of the third month, it is clear that patients who died within 3 months had not lived sufficiently long to develop it. Had they survived, the incidence of deafness might/

might well have been higher. In this series, 15 of the 65 patients who were treated with dihydrostreptomycin died within 3 months, so only 50 lived sufficiently long for its neurotoxic effect to become evident (Table 153). 58% of these became deaf, nearly two-thirds being seriously handicapped. 59.5% of the 42 survivors were found to be deaf, three-fifths of these severely so.

FACTORS INFLUENCING THE INCIDENCE OF DEAFNESS.

Very little seems to have been written about the types of patients, if any, who may be particularly susceptible to the neurotoxic effect of dihydrostreptomycin and therefore predisposed to develop deafness. Only a proportion of patients given the same regime of treatment became deaf; why should they and not the others be affected? In my previous communication (1952) I was unable to relate the development of hearing loss to the stage of disease and degree of illness when treatment began, the X-Ray appearances, nor other factors that had been considered. Lorber also (1954c) could find no correlation between the stage of disease on admission and the incidence of deafness in the series of 549 cases, of whom 36 became deaf.

Tables 154 - 180 have been compiled in a further endeavour to discover, from this complete series, any pre-disposing factors concerned in the development of deafness. In making the assessments, I have taken into account only the 50 patients, already detailed, who were treated with dihydrostreptomycin and lived sufficiently long for deafness to be observed. The inclusion of patients who died within 3 months among the "not deaf" cases would obviously vitiate the conclusions since over half of these would probably

have/

have had hearing loss had they survived. 29 of these 50 patients were deaf (18 with moderate, subtotal or total impairment) and 21 were not deaf. Any significant difference between these 2 groups may have a bearing on the aetiology of deafness in dihydrostreptomycin-treated patients.

A. Features of the Initial Illness (Tables 154 - 168). The following significant findings seem worthy of note:

Age - (Table 154): While the incidence of deafness in other age-groups is fairly uniform, its absence in children under 5 years is of significance. It is, of course, possible that minor degrees of deafness were overlooked particularly in very young children, and, indeed, in at least one patient it was difficult to exclude hearing loss with certainty; nevertheless, no patient in this group was seriously handicapped.

Nutritional State (Table 158): The significantly high incidence of deafness in well nourished patients - 80% compared with 48.6% of others - and the trend suggesting a direct relationship between the state of nutrition and the development of deafness, are surprising and difficult to understand. Possibly the exclusion, from this study, of 15 patients who died early in the illness may have affected these figures, as these almost certainly included a high proportion of poorly nourished patients, who may have become deaf had they lived longer.

Meningeal Signs (Table 160): Absence of meningeal signs on admission was associated with diminished risk of deafness - 0 of 6 such patients becoming deaf; but in the other groups, there was a decreasing incidence of deafness with increasing meningism.

Temperature/

Temperature (Table 161) : A significantly higher proportion of patients with temperatures over 100°F became deaf, - two-thirds, compared with only two-fifths of those with lower temperatures. Moreover, five-sevenths of the former group developed serious hearing loss compared with three-eighths of the latter.

E.S.R. (Table 164) : Rather surprisingly, two-thirds of 30 patients with E.S.R. less than 20 became deaf compared with one-third of 12 patients with E.S.R. over 20. While this difference is not significant, the high incidence of deafness in patients with initial E.S.R. of 10 - 20 is. (12 of 15).

C.S.F. Cell-Count (Table 165) : Another surprising finding was the significantly lower frequency of deafness in patients with fewer than 200 cells per c.mm. in the initial C.S.F. - in view of the higher mortality rate among such patients.

The incidence of deafness did not appear to be related to the sex of the patient, the duration of severity of the initial illness, the initial mental state, the presence of choroidal tubercles, the X-Ray appearances or the levels of other C.S.F. constituents on admission.

B. Response to Treatment (Tables 169 - 180). The occurrence of deafness was not associated with any particular pattern of response to treatment; patients who made a steady rapid recovery being just as prone to develop it as those in whom recovery was delayed or interrupted. Symptomatic improvement occurred, on the whole, just as quickly in patients who became deaf as in those who didn't, although pyrexia, meningism and constipation/

constipation tended to persist longer in the former. The significant finding that none of 7 patients who, at the end of a fortnight, had no meningeal signs, became deaf is doubtless closely connected with the absence of deafness in 6 patients who had no initial meningism. Although normal C.S.F. protein and chloride levels were restored at an early stage in rather fewer patients who became deaf, there was no significant difference in the speed of restitution of C.S.F. constituents. A noteworthy feature, however, was the significantly high incidence of deafness in patients in whom higher C.S.F. protein levels were recorded during treatment and in those who developed spinal block. A high maximum C.S.F. protein seemed to be associated with increased risk of deafness.

SUMMARY.

32 of the 102 patients in this series became deaf, and 28 of these are still alive. In 17 the deafness was total or subtotal, in 2 it was moderate, and in 13, mild. The earliest date of onset was late in the 3rd month of treatment; the average time, in the 6th month. In 8 cases, treatment had already been completed when deafness was detected, and in other 8 it was observed during treatment of relapse. Dihydrostreptomycin was being or had been used in all but 3 of the cases, and there seems no doubt that it was the main aetiological factor. Of the patients who received dihydrostreptomycin, three-fifths of survivors developed detectable hearing loss as well as half of those who died but lived long enough for deafness to develop; in three-fifths of all these the auditory impairment was/

was moderate to total. There was no evidence that the dosage of the drug was an important factor; certainly, reduction in intrathecal therapy was not associated with diminished incidence of deafness. No patients under 5 years of age became deaf, nor did any who had no meningism on admission. The frequency with which deafness occurred was significantly higher in patients who were well nourished, or who had a higher initial temperature or an E.S.R. between 10 and 20 mm. in the first hour, or a C.S.F. cell-count over 200 per c.mm: but it did not appear to be affected by the duration or severity of the initial illness. Satisfactory response to treatment - with clinical and C.S.F. recovery - was observed in just as high a proportion of patients who became deaf as of those who did not. A high C.S.F. protein level in the course of treatment, however, was more often seen in patients who developed some degree of hearing loss.

SUMMARY AND CONCLUSIONS.

From a study of 102 cases of tuberculous meningitis admitted to Ayrshire Central Hospital, Irvine, and Belvidere Hospital, Glasgow, between June, 1948, and December, 1951, an endeavour has been made to analyse the factors that may have had a bearing on the ultimate outcome, expressed in terms of both quantity and quality of survivors. The patients were all treated with streptomycin, with or without adjuvants, in the pre-isoniazid era. Diagnosis was confirmed bacteriologically in 82% of the cases and was not in doubt in any of the others. 66 (64.7%) of the patients survived for a minimum of 5 years.

In order to determine the inter-relation of all the factors that have been taken into consideration and ascertain the individual effects of each on the ultimate outcome and on the incidence of complications and sequelae, it is clear that a much vaster experience would be required than can be gained by one person - for example, an investigation of the dimensions of the trials conducted by the Medical Research Council using many centres. In a comparatively small series such as this, in which the figures tabulated were obtained in the experience of one person, the results may admittedly be vitiated by the interplay of different factors. An attempt has, however, been made to assess the major factors, and the following are the main conclusions reached. The study was divided into six sections.

A. Factors prior to the institution of treatment. Prognosis was significantly better in patients (a) between the ages of 3 and 30 years,

(b)/

(b) with less advanced disease, (c) fully conscious, (d) well nourished, (e) without radiological evidence of miliary or adult pulmonary tuberculosis, (f) with high initial C.S.F. cell count and chloride content.

B. Treatment Regime: 7 different regimes of treatment were employed. All patients were given intramuscular and intrathecal streptomycin (or dihydrostreptomycin), and in all but 6 the duration of the initial course of treatment was not less than 6 months. Allowing for the limited numbers in each treatment group, it seemed justifiable to make the following deductions from the results; (a) less than 6 months' treatment was inadequate; (b) prolonged intrathecal therapy did not have any special advantage over shorter courses; (c) the use of dihydrostreptomycin was not associated with a significantly higher mortality rate compared with streptomycin; (d) neither streptokinase nor P.P.D. enhanced the results; the latter, indeed, seemed to be detrimental.

C. Type of response to treatment: A good initial response was not necessarily an indication of a favourable outcome. Nor could an accurate prognosis be made on the basis of early disappearance or long persistence of any or all of the main symptoms or signs. The C.S.F. sugar level was not found to have the same prognostic significance as other observers have attached to it. The C.S.F. protein level seemed of greater value in the assessment of prognosis than that of any other C.S.F. constituent; no patient died whose C.S.F. protein became normal - but 7 such patients relapsed.

D./

D. Incidence and influence of spinal block: A significantly higher mortality was noted in the 22 (21.6%) patients who developed obstruction to the flow of C.S.F. It seemed likely that patients with initial C.S.F. protein over 200 mg. per 100 ml. may have had incipient block as a significantly high proportion of such patients developed it. Neither streptokinase nor P.P.D. proved to be of any value in relieving the obstruction; indeed it appeared that both, especially the latter, may have been responsible for its development in some cases.

E. Incidence and influence of relapse: 20 relapses occurred in 16 patients who had completed a previous course of treatment; 1 of these patients succumbed after 3 relapses. The incidence of relapse did not appear to be related to the initial treatment regime provided this was of 6 months' duration, but a very high proportion of patients relapsed after an initial course lasting $3\frac{1}{2}$ months. All relapses occurred within 1 year, and most within 3 months, of the completion of the previous course of treatment. Most were detected by the recurrence of symptoms and signs and confirmed by C.S.F. findings. A full course of treatment was instituted as soon as relapse was diagnosed, and the prognosis proved to be as good as for the initial illness.

F. Incidence of Deafness: Deafness developed in 32 patients and was total or sub-total in 17 of these. In all but 3 of the patients who became deaf, dihydrostreptomycin was being or had been used and was undoubtedly the main aetiological factor - more than half of all patients so treated developed/

developed some impairment of hearing. The dosage or duration of the drug did not seem to be important but the differences in total dosages in different regimes was too slight to make comparisons possible. Deafness occurred significantly more often in patients who, at the beginning of treatment, were well-nourished, had a high temperature, an E.S.R. between 10 and 20 mm. in the first hour or a C.S.F. cell count over 200 per c.mm. or who, in the course of treatment, developed a high C.S.F. protein.

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