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TREATMENT OF CEREBROSPINAL FEVER WITH SULPHAPYRIDINE

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Cerebrospinal fever appears to have been unknown in Shanghai until 1918; at any rate, there are no records of the disease in the vital statistics of the Public Health Department, Shanghai Municipal Council, although it is reported as occurring sporadically in the Yangtze Valley.

In 1918 an epidemic of cerebrospinal meningitis was experienced in Hong Kong which lasted from January to June. Over 1,000 cases were reported, of which only four were in Europeans. There were 760 deaths. A minor epidemic had also occurred in Manila in 1915. In view of these epidemics in adjacent ports a keen look-out was kept for epidemics in Shanghai, and thirteen cases were diagnosed in 1918. A memorandum on the aetiology, clinical features, diagnosis, and treatment of cerebrospinal fever was then issued by the Public Health Department for the guidance of medical practitioners, and the disease was made notifiable. In 1919 there were twenty-three cases with twelve deaths, of which three occurred in children. Then in 1920 a greatly increased prevalence of cerebrospinal meningitis occurred, which reached epidemicity. It decreased, however, during subsequent years until 1929, when it again became epidemic. It will be noted that the fatality rate for cerebrospinal meningitis varied between 31 and 70 per cent., with a mean fatality rate of approximately 50 per cent., despite the use of anti-meningococcal serum in large doses intrathecally and intravenously.

Routine Treatment in Shanghai during the Past Decade

The routine treatment of cerebrospinal fever at the hospitals of the Shanghai Public Health Department during the past decade was as follows:

1. On admission bath and isolation in a quiet darkened room with temperature as near to 70° F. as climatic conditions allowed.

2. A purgative was administered, usually castor oil. Lumbar puncture and withdrawal of cerebrospinal fluid for confirmation of diagnosis were then performed.

3. Administration of serum intrathecally, in amount depending upon the quantity of cerebrospinal fluid withdrawn. (Cerebrospinal fluid was withdrawn until normal pressure was established, then polyvalent anti-meningococcal serum in quantity 10 c.cm. less than the amount of cerebrospinal fluid withdrawn was slowly injected. The usual amount was 10 to 40 c.cm.)

4. Lumbar puncture was repeated every twelve to twenty-four hours until root-pressure symptoms and headache disappeared, but also depending upon the pressure and flow of the cerebrospinal fluid. Cistern puncture was employed as and when necessary; anti-meningococcal serum was administered until meningococci disappeared from films and cultures—usually in four to seven days.

5. The patient was allowed up by gradual stages after temperature had been normal for ten days, provided all signs of the infection had disappeared, and, if considered to be fit, was discharged three weeks after temperature had returned to normal. The average stay in hospital under this routine was six to eight weeks—the shortest period four weeks; occasionally patients have had three months' hospitalization.

6. The diet was regulated according to the digestive powers of the patient.

7. Sleep was induced by sponging and hypnotics. Any other treatment was entirely symptomatic. Careful attention was given to the condition of the bladder in the early stages.

Results from this routine have been on the whole satisfactory, although the fatality rates were higher than in Western countries. This is due to the lower vitality of hospital-class Chinese from causes with which this report is not concerned, but it is also due to the unusually advanced state of the disease on admission. Statistics for foreign residents show variations similar to those of the Chinese population, but on the whole are better.

Treatment in the Recent Shanghai Epidemic

In 1938 Messrs. May and Baker introduced a new drug—2-sulphanilyl-aminopyridine (sulphapyridine). It

was decided to investigate its value in the treatment of cerebrospinal fever in Shanghai.

The latest epidemic of cerebrospinal fever began in December, 1938 (municipal "health year" 1939), and in January, 1939, the treatment of cases was divided into two groups as follows:

A. Serum Group.—Lumbar puncture on admission, repeated every twelve hours if no improvement, but only every twenty-four hours once definite clinical improvement was noticed. Punctures were discontinued when fever, rigidity, and other clinical signs had subsided. Serum was administered on each occasion of puncture. Specimens of blood—10 c.cm.—were also taken each time lumbar puncture was performed.

B. Sulphapyridine Group.—Lumbar puncture was performed on admission, and every twelve hours if no improvement, but every twenty-four hours after clinical improvement was noticed. Ten c.cm. of blood was taken on each occasion in addition to lumbar puncture. The dosage of sulphapyridine for adults was 4 tablets of 0.5 gramme on admission after lumbar puncture had been performed, repeated in four hours' time; then subsequently 2 tablets were given four-hourly for a further twenty-four hours, followed by 1 tablet thrice daily (total dosage about 40 tablets—that is, 20 grammes). When no improvement was noticed the dosage was maintained at 2 tablets every four hours. The dosage for children under 6 years and over 3 years was 1 tablet four-hourly; and for those under 3 years $1\frac{1}{2}$ to $3\frac{1}{4}$ tablet four-hourly. In severe cases double doses were given on admission. No other drug or treatment was administered to this group save ordinary stimulants. Diet and general nursing, however, followed the usual routine.

Precautions Observed.—Needles used in taking blood and cerebrospinal fluid were dry and were not dipped in alcohol. Specimen tubes were sterile and also absolutely dry. Waxed corks were used. The temperature of water in "containers" was 40° C. precisely. The tubes were labelled, stating (a) the time when the specimen was taken (hour and minute); (b) whether the case belonged to the serum group (A) or to the sulphapyridine group (B); (c) the number of the lumbar puncture and the total dose of sulphapyridine or serum given up to that time. Specimens were sent to the laboratory in containers immediately they were taken.

One hundred cases (fifty in each group) were treated according to the above plan. The fatality rate for Group A was 38 per cent. and for Group B 32 per cent. Though there was little if any difference in the statistics quoted, it was gratifying to find a fatality rate of only 32 per cent. in a group of cases in which no serum was used, bearing in mind both the fatality rate for cerebrospinal fever before the use of serum and also the high fatality rate in Shanghai in most epidemics previously experienced even when serum was used promptly and in large quantities. The amounts of serum used from 1927 to 1938 were as follows:

1927	3 litres	1933	9 litres
1928	12 "	1934	14 "
1929	29 "	1935	12 "
1930	50 "	1936	8 "
1931	20 "	1937	7 "
1932	13 "	1938	29 "

Clinically the cases in Group B followed a more favourable course. Headache disappeared rapidly, and most of the patients, even if unconscious on admission, could answer questions intelligently after twenty-four hours' treatment. Rigidity also disappeared more rapidly than in the serum group and fewer punctures of the theca were required.

It was then decided to combine these two bactericidal agents as a third group (Group C) and to institute one

further investigation—namely, the effect of sulphapyridine plus meningococcal antitoxin (P. D. and Co.)—that is, a bactericidal agent and an antitoxic agent (Group D). Alternate cases were placed in Groups C and D.

Group C.—Dosage with sulphapyridine was exactly the same as in Group B. Treatment with serum was administered on precisely the same lines as in Group A.

Group D.—Dosage with sulphapyridine was identical with that of Groups B and C. Meningococcal antitoxin was also given in full doses (20 c.cm.) intravenously on admission, and simultaneously a similar dose of antitoxin was injected intramuscularly. The intramuscular dose was repeated in twelve hours if the condition of the patient had not improved. Subsequent dosage was determined by improvement or otherwise in the clinical condition.

Treatment was unaltered in any other manner. Groups C and D, however, contained only thirty cases each owing to the subsidence of the epidemic.

The fatality rate for Group C was 26.6 per cent., while that of Group D was 20 per cent. These statistics were superlative for Shanghai, but as the groups were so small statistical deductions are open to criticism. Some further comments are necessary from the clinician, however, since he usually has a secret contempt for mere figures and sees each patient as an individual in whom success must be 100 per cent. or *nil*. The outstanding observation was the rapid disappearance of symptoms in cases treated with sulphapyridine: furthermore, relapse, which occurred in approximately one-half of the cases treated with serum, was a rarity with sulphapyridine therapy. Cases might not improve with the drug, but if improvement began it was almost always maintained. The following figures will give an impression of the comparative recovery rate for each group:

Group	Total Cases	Recovered Cases	Fit for Full Diet in 1 Week	Discharged in 4 Weeks
A	50	31 (62%)	50.0%	32.2%
B	50	34 (68%)	76.4%	67.6%
C	30	22 (73.3%)	95.6%	90.9%
D	30	24 (80%)	91.6%	83.3%

Note.—The last two columns apply to recovered cases.

The results for Group C were considerably better than for either Group A or Group B. Presumably two anti-bacterial agents were better than one. On a theoretical basis Group D should have given the most satisfactory results. Statistically this appears to have occurred,

TABLE I.—Clinical Days of Disease, Treatment, and Length of Stay of Recovered Cases

Duration of Disease Before Admission					Period of Treatment					Stay in Hospital				
Days					Days					Weeks				
Cases					Cases					Cases				
A	B	C	D		A	B	C	D		A	B	C	D	
1-3	22	20	13	17	1-3	3	2	1		3	1	6	1	1
4-7	7	9	6	6	4-7	18	23	19	21	4	9	17	19	19
8-14	1	4	2		8-10	8	7	1	1	5	15	9	1	3
15-30	1	1		1	11-14	2	1			6	4	1	1	1
Over 30					15-21	2				7				
?			1		22-28	1				8	2			

although clinically there was little if any observable difference in the reaction to treatment of cases in Group D from that of Groups B and C. Recovery in Group D cases appears to have been somewhat slower than in Group C cases. Table I gives the number of clinical days of disease and days of treatment of recovered cases, with their length of stay in hospital.

TABLE II.—Effect of Treatment for Various Age Groups

Age	Cases				Died				Fatality per cent.			
	A	B	C	D	A	B	C	D	A	B	C	D
Under 6 months	3	5	3	1	2	2	2	—	66.6	40	66.6	—
" 1 year ..	2	4	1	1	2	2	1	1	100	50	100	100
" 5 years ..	5	11	4	2	2	5	4	—	40	45.4	100	—
" 10 " ..	8	9	5	6	1	3	—	1	12.5	33.3	—	16.6
" 20 " ..	23	13	11	10	6	3	1	1	26	23	9	10
" 30 " ..	5	4	3	5	2	1	—	—	40	25	—	—
" 40 " ..	2	3	1	4	2	—	—	2	100	—	—	50
" 50 " ..	2	1	1	1	2	—	—	—	100	—	—	—
" 60 " ..	—	—	—	—	—	—	—	1	—	—	—	100
Total ..	50	50	30	30	19	16	8	6	38	32	26.6	20

Table II shows the effect of these forms of treatment for various age groups, but the numbers per group are too small for any accurate statistical deduction.

TABLE III.—Incidence of Rash and Septicaemia

	Rash			Septicaemia	
	Extensive	Scanty	Negative	Positive	Negative
A (Cases ..	2	12	36	3	15
Died ..	—	7	12	3	1
Fatality ..	—	58.3%	33.3%	100%	6.6%
B (Cases ..	2	7	41	13	37
Died ..	1	2	13	6	10
Fatality ..	50%	28.5%	31.7%	46.1%	31.2%
C (Cases ..	3	8	19	7	23
Died ..	2	—	6	3	5
Fatality ..	66.6%	—	31.5%	42.8%	21.7%
D (Cases ..	4	5	21	4	26
Died ..	—	—	6	1	5
Fatality ..	—	—	28.5%	25%	19.1%

One very important factor is considered to have a bearing on the severity of the case—namely, the occurrence of septicaemia (Table III). This may appear in mild cases or in the severe fulminant type, which has a high fatality rate. A characteristic petechial rash is found in both forms, but in the severe form ecchymoses and haemorrhages are also of common occurrence.

Bacteriological Note

All specimens of cerebrospinal fluid received were centrifuged; films were then made and stained by Gram's method. Cultures were put up on blood-trypsin agar plates from the centrifugized deposit. A positive report was issued on finding Gram-negative diplococci morphologically resembling meningococci either in direct films from the cerebrospinal fluid or by isolation on culture. Trypsin broth was used for blood culture, 5 to 10 c.cm. of blood being added to 50 c.cm. of broth in a 125 c.cm. Erlenmeyer flask. Cultures reported negative were either contaminated by extraneous organisms or remained sterile after ten days' incubation at 37° C. Three of the strains isolated were agglutinated by Mulford anti-meningococcal polyvalent serum to a titre of 1/320. Agglutination tests on the remainder were not done.

Blood cultures were made in 126 of the 160 cases treated. The first thirty-three cases in Group A and a case in Group B were not tested and are not considered here; the remaining 126 cases had the following death rates:

	Cases	Died	Death Rate
Blood culture positive ..	26	12	46%
" " negative ..	100	21	21%
Total ..	126	33	26.2%

Groups in which sulphapyridine was employed, particularly Group D, gave the best results. Table IV shows

TABLE IV.—Effects of Treatment on Bacterial Activity

Group	Total Cases	Re-covered Pos. Mc. Cases	When Meningococci Disappeared after Treatment					
			Within 12 Hours	Within 24 Hours	Within 48 Hours	3-7 Days	Above 1 Week	Above 2 Weeks
A	50	27	11.1%	11.1%	14.8%	44.5%	14.8%	3.7%
B	50	22	41.0%	9.0%	18.2%	31.8%	—	—
C	30	20	55.0%	—	10.0%	35.0%	—	—
D	30	19	31.6%	21.0%	5.3%	42.1%	—	—

the effects of treatment on bacterial activity. Group C was supreme in bacteriostasis, as expected, while Group A lagged somewhat behind the others. Table V shows the

TABLE V.—Dosage of Sulphapyridine in Relation to the Bacteriostatic Effect of the Drug in vitro in the Recovered Group B Cases

Age	Average Dose in Tablets (0.5 gm.) Q. 4 h.	Pos. Mc. Cases	When Meningococci Disappeared				
			Within 12 Hours	Within 24 Hours	Within 48 Hours	2-4 Days	Above 1 Week
Under 6 months	1-1	1	—	—	—	1	—
" 1 year ..	1-1	1	—	—	—	1	—
" 5 years ..	1-1	3	—	—	1	2	—
" 10 " ..	2-1	1	—	1	—	—	—
" 20 " ..	2-1	3	1	—	—	—	—
" 30 " ..	2-1	1	1	—	—	—	—
" 40 " ..	3-1	1	1	—	—	—	—
" 50 " ..	4-2	3	2	1	—	—	—
" 60 " ..	4-2	2	2	—	—	—	—
" 70 " ..	4-2	1	1	—	—	—	—
" 80 " ..	4-2	3	—	—	1	2	—

Note.—Throughout the experiment the average adult dose was two tablets (that is, 1 gramme) every four hours until clinical improvement was noticed, then gradually reduced to a maximum of 40 tablets, or 20 grammes. The initial two doses were given in double dosage. Dosage in children was reduced according to age.

specific effect of sulphapyridine on meningococci in the cerebrospinal fluid. In the majority of cases it is seen that meningococci have disappeared from the cerebrospinal fluid within twelve hours, while in all cases they were absent within seven days.

Concentration of Sulphapyridine in Cerebrospinal Fluid

This was estimated by the following method: Five c.cm. of cerebrospinal fluid was diluted to 20 c.cm. with distilled water and 5 c.cm. of 20 per cent. trichloroacetic acid was added. The mixture was then vigorously shaken and filtered. An aliquot portion of the filtrate, generally 20 c.cm., was cooled in ice to 0° C.; 1 c.cm. of 1 per cent. sodium nitrite was added and was then followed by an excess of 1 per cent. thymol in 20 per cent. sodium hydroxide. The yellow-to-orange colour was compared with a cerebrospinal fluid (from a normal patient who had not received drug treatment) to which a known amount of sulphapyridine was added in the laboratory and which was then treated in a similar manner. Pure alpha-aminopyridine treated as above gives no indication that the colour is due to the sulphonamide portion of the molecule.

Six hundred and sixty-four samples of cerebrospinal fluid were tested for sulphapyridine content. Sulphapyridine varied from 0.3 to 23 mg. per 100 c.cm. of fluid. No correlation could be found between the dose of sulphapyridine administered and the quantity detected in the cerebrospinal fluid.

Conclusions

Sulphapyridine appears to be a drug of exceptional therapeutic value in the treatment of cerebrospinal fever.

The value of the drug is probably greatest when combined with serum or antitoxin therapy.

The number of cases treated was too small for dogmatic statistical deduction, but results indicate that subsequent

epidemics should be treated with sulphapyridine in combination with either serum or antitoxin for further trial.

Dosage with sulphapyridine may be increased with impunity in subsequent trials and with the likelihood of improving results still further.

Summary

One hundred and sixty cases of cerebrospinal fever were treated in four groups: serum (50 cases), sulphapyridine (50 cases), sulphapyridine plus serum (30 cases), sulphapyridine plus antitoxin (30 cases).

Satisfactory results were obtained, fatality rates for the groups being 38, 32, 26.6, and 20 per cent. respectively.

The recovery rate was accelerated in the groups where sulphapyridine was employed.

Blood cultures were performed in 126 cases only; positive cultures were obtained in 100 cases, twenty-one of which ended fatally.

Concentration of sulphapyridine in the cerebrospinal fluid was estimated, but the concentration appeared to have little if any relation to the dosage.

No toxic reactions were experienced in any of the cases treated with sulphapyridine.

We wish to thank Messrs. May and Baker for their courtesy in supplying sulphapyridine (M & B 693) free of charge for this test upon request. We also wish to thank the staff of the hospitals and laboratories, especially Dr. K. W. J. Lieu, for their co-operation. We are indebted to Mr. L. H. Barton for the estimations and also to Mr. Fanthorpe.

GASTRIC DISORDERS IN THE SERVICES

BY

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Study of many medically unfit soldiers sent for treatment to civil hospitals since the outbreak of war indicates a very high incidence of disorders of the stomach and duodenum as causes of disablement among our troops; this applies both to troops evacuated from abroad and to those falling sick while on service in this country. Similar experience is being encountered by the medical boards, and it is true to say that gastric and duodenal disorders are the commonest medical causes for which soldiers are discharged from the Army as unfit for service.

Examination of 260 medical cases sent from France to sector hospitals in this country shows that no fewer than sixty-five (25 per cent.) were attributed to disorders of the stomach and duodenum, not including reflex dyspepsia secondary to appendicitis and cholecystitis. This group of disorders, which includes gastric and duodenal ulcers (approximately 50 per cent.), chronic gastritis, and functional dyspepsias, outclasses in incidence any other group.

Statistics from the War of 1914-18

The incidence of disorders of the stomach and duodenum admitted to hospital is given in tabular form in the *Official Medical History of the Great War* under "Statistics." Here is recorded the number of patients admitted to hospital under disease groups in (a) the B.E.F., 1914; (b) the B.E.F., 1915; and (c) British troops

stationed in the United Kingdom. The heading "Indigestion, Inflammation, and Ulceration of Stomach and Other Diseases of the Stomach" occupies the eleventh, twelfth, and ninth places respectively in order of incidence, being preceded by (1) rheumatic fever, (2) disorders of locomotion; diseases of (3) the respiratory system, (4) intestines, (5) nervous system, (6) and skin; (7) venereal diseases, and (8) influenza.

It will be seen that gastric and duodenal disease at the highest rate occupies only a relatively minor place in case incidence so far as can be ascertained from the figures in the official table, whereas our figures show that this group has outclassed all other disabilities. This discrepancy can be ascribed to the following factors:

1. *The Greater Frequency of Gastric Disorders, particularly of Gastric and Duodenal Ulcer, in Recent Years.*—This has been a general experience, but the stoppage of the London Central Omnibus Service in 1937 provides further evidence (Hill, 1937). This was due to the feeling among the workers that their health was suffering as a consequence of working conditions up to that time. The Court of Inquiry subsequently held that the complaint was the high incidence of gastric disorders, which had been growing higher as the years passed and was attributable to a variety of causes bound up with working conditions. The Medical Research Council justified the workers' complaints and suggested remedies to reorganize the service (*Health of the London Central Busman*, 1939). The statistics showed a preponderance of gastric disorders in the service over the rest of the population and a higher incidence in drivers and conductors of buses than in tram-drivers or bus-maintenance workers. Many of these bus-drivers were sent over-seas for transport duties early in the war, and some figure among those returned sick to England with recurrent symptoms.

2. *Insufficiently Thorough Medical Examination before being Called Up in the Early Stages of the War.*—It is apparent that many of these men had suffered from gastric or duodenal ulcer for several years, while some had been investigated on various occasions in hospitals in the past. These facts were not elicited in the medical examinations at the outbreak of the war; these sufferers were accordingly admitted to the Army as fit men. In some cases the men carefully concealed their past histories in their endeavour to enlist.

Conditions in Civil Life preceding the War

Between January and September, 1939, all new outpatients seen by me at St. Mary's Hospital were classified. Study of male cases in the age groups (21 to 47) corresponding to those of the sixty-five patients mentioned above reveals that twenty-two out of sixty-eight (32.4 per cent.) were sufferers from disorders of the stomach and duodenum. These numbers are too few to be of much value. At the same time it must be realized that many of these patients were sent up by their doctors primarily for the purpose of being radiologically examined. Accordingly this percentage incidence is many times higher than the incidence in the general sick population and does not counter an assertion that the incidence of gastric disorders in the group of soldiers most of whom fell sick soon after arrival in France was excessively high, since less than a few months previously these men had been pronounced fit to be sent to the front line.

The present study is of a convoy of cases from France in the earlier stages of the war admitted to a sector