CHEMOTHERAPY IN CEREBROSPINAL MENINGITIS IN THE SUDAN

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Introduction

The remarkable results achieved in the Sudan by Bryant & Fairman (1939) and by Somers (1939) in "field" treatment of cerebrospinal meningitis with sulphanilamide and sulphapyridine (M. & B. 693) have now been paralleled in the more favourable circumstances of European practice.

These results were at the time the subject of Editorial comment in the *Lancet* (1939, **1**, 937), when it was suggested that meningococcal meningitis might be more amenable to treatment in the Sudanese than in the European; and that similar results need not follow elsewhere. The further comment was made that "circumstances in the Sudan seem ideal for a therapeutic study adequate in scale if rather rough in method". The possibility of racial—or even tribal—peculiarity was noted by Bryant & Fairman and by Somers, and also by Banks (1939). But before results obtained in the Sudan can be assessed in relation to those obtained in European practice it remains to be shown that there is in fact no racial or communal peculiarity in response to infection, or to the drug or drugs employed in treatment.

Meningococcal meningitis in the Sudan does not differ clinically from the disease as observed in more temperate climates. It shows a similar, but more sharply emphasized and consistent, seasonal incidence. There is no significant variation between the mortality of the Sudan outbreaks and that observed in other countries. In the Sudan it has been remarkably constant in epidemics of varying extent over a period of years.

Table 1. *Case mortality in the Sudan*, 1929–38

Year	1929	1930	1931	1932	1933	1934	1935	1936	1937	1938
Reported cases	464	865	348	532	166	4231	3249	13,440	446	234
Mortality %*	73·0	77·0	68·0	72·0	78·0	79·0	66·0	66·0	66·0	64·0

* To nearest whole figure.

For comparison the following returns (Letheby Tidy, 1937) are quoted:

Year	Place	Cases	Mortality %
1904–5	New York, U.S.A.	6755	51
1907	Glasgow	998	71
1914–18	World War	—	60

Walsh (1938) found the mortality in the U.S.A. from 1920 to 1936 inclusive to range between 67·7 and 38·1% and to average 51·2%.

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It appears, then, that neither race nor climate materially affects the course of the disease. In the Sudan epidemic of 1936 figures for five provinces showed no significant variation though the outbreaks were widely separated and of various intensities.

Table 2. *Mortality in five provinces of the Sudan in* 1936

Province	Cases	Deaths	Mortality %
Blue Nile	1433	916	63·9
Kassala	67	41	61·9
Khartoum	360	251	60·0
Kordofan	2293	1386	60·4
Northern	220	130	60·0

Locality, diet, tribe and habit (for the population of these provinces ranges from the urban to the nomadic) have no effect on mortality, which is notably constant whether the outbreak is large or small.

It may also be noted that in the past hospitalization had no effect on mortality:

Table 3. *Mortality in hospitalized and non-hospitalized cases*

Blue Nile 1936	Cases	Deaths	Mortality %
Hospital treated	168	107	63·6
Total notified	1433	916	63·9

No part of the Sudan is altogether free of the disease, but the areas of epidemic outbreak vary yearly, and every year form a major problem in maintenance of Public Health. No measure previously adopted can be said to have modified the disease. Communities affected in one year may escape in a subsequent year, although their neighbours may be subject; and it is difficult to determine whether morbidity is appreciably affected by measures of quarantine and isolation, though evacuation of villages to temporary shelters, if possible sufficiently numerous to allow one shelter for each person, is considered to have limited the spread in affected communities. Prophylactic treatments and diets have been no more successful. Riding & Corkhill (1932) found vaccination ineffective. Corkhill (1936) reported on the addition of vitamin A to diet with the object of establishing resistance through improved nutrition, but the results were inconclusive. The epidemic disease is abruptly halted by the first rain of the year, but the mortality is not less severe at the end than at the beginning of the epidemic. Attention has been drawn by Corkhill (1939) to climatic conditions in relation to outbreaks of cerebrospinal meningitis, but whatever the effect on morbidity, climate *per se* has no appreciable effect on mortality. This depressing picture has been abruptly changed by the introduction of the sulphonamides, and the demonstration of their efficacy under field conditions.

OBSERVATIONS IN THE OMDURMAN OUTBREAK OF 1939

Shortly after the publication of the results of Bryant and his co-workers, an outbreak of meningitis occurred in Omdurman (May-June 1939), and the opportunity was taken to repeat their work. Fifty cases were taken, serially and without selection. In each the diagnosis was bacteriologically confirmed, and all convalescent cases were observed over a longer period than is possible in the field.

The results are in close agreement with those of Banks (1939, 1940), though obtained under different conditions of practice. They are now submitted in support of a routine system of dosage in the use of sulphapyridine; and as a rather belated answer to the questions raised in Editorial comment in the *Lancet*.

In the case series under review there were nine deaths—a gross mortality of 18%. The clinical features of the disease, and the incidence by sex and age, presented no material divergence from the usual descriptions and records, and all degrees of severity occurred.

Early experience had suggested that a proper assessment of dosage would be facilitated by a clinical grouping of cases, and four grades of severity of infection were based on clinical findings on admission. Cases in the series were accordingly grouped as:

I. *Acute, fulminating, toxic.* Marked delirium. Incapable of swallowing. Kernig sign and head retraction—not necessarily marked. Having a history of 24 hr. illness or less. Sometimes with high temperature. Requiring restraint.

II. *Acute.* Kernig sign present. Head retraction marked, possibly with opisthotonus. Stuperose. "Meningeal cry." Fever variable.

III. *Sub-acute.* Kernig sign present. Neck rigidity. Sensible. Complaining of severe headache. Illness of 24–48 hr. duration.

IV. *Advanced toxic.* Low muttering delirium. Coma. Kernig sign absent. No neck retraction. Illness of some days' duration (though this was not always the case).

Before the introduction of the sulphonamides few cases in Group I, and none in Group IV, survived. It is in these groups that the most dramatic results have been achieved with sulphapyridine.

Notes on the fatal cases are given in Table 4.

Of the nine fatal cases, two were treated with soluseptasine; of the remaining seven, nos. 2, 6, and 9 represent failure with sulphapyridine. In no. 9 the relapse on the third day of treatment was unexpected, for meningeal symptoms were not prominent, and the concentration of the drug in the cerebrospinal fluid was satisfactory at the time of the relapse (8 mg./100 c.c.). She appeared to succumb to toxaemia. No. 6 presented a similar picture. In this case no estimation of the drug concentration was made, but the fluid was

Table 4. *Notes on the nine fatal cases*

No.	Clinical grade	Sex	Age	Days sick before treatment	Treatment	Result
1	II	M.	22	1	2 c.c. M. & B. 693 oil emulsion intramuscularly, 4-hourly	Collapsed and died in 3rd day of treatment
2	II	M.	10	3	2 c.c. M. & B. 693 oil emulsion intramuscularly, 4-hourly = 7·0 g. orally divided in 4-hourly dose	Died 2nd day of treatment. No response to treatment
3	II	M.	12	2	10 c.c. soluseptasine intramuscularly	Died 4 hr. after admission
4	I	M.	20	4	2 c.c. M. & B. 693 oil emulsion intramuscularly	Died 2 hr. after admission
5	I	F.	4	2	(*a*) 5 c.c. M. & B. 693, 1 in 80 suspension in saline, intrathecally, before admission (*b*) 1·5 g. M. & B. 693 by mouth (*c*) 2·0 c.c. M. & B. 693 oil emulsion intramuscularly (*d*) 0·75 g. by mouth	Died 36 hr. after admission
6	I	F.	3	5	4·5 g. M. & B. 693 given as saline suspension, over 32 hr., in 4-hourly divided dose	Improved, but died suddenly 4th day after admission
7	IV	F.	3	11	2·125 g. M. & B. 693, in divided dose 4-hourly	No response. Died 44 hr. after admission
8	IV	F.	4	2	10 c.c. soluseptasine (two doses of 5 c.c. with 4-hr. interval)	Died 2 hr. after 2nd dose
9	I	F.	8	3	0·75 g. in saline suspension intramuscularly. 4-hourly total of 11·75 g. given	Improved, Relapsed abruptly 3rd day of treatment.* Died 5th day of treatment

* This case showed a concentration of 8 mg./100 c.c. in cerebrospinal fluid at time of relapse.

sterile on culture,[1] and no organisms were seen in direct smears following the first course.

It now appears that an insufficient initial dose was given to case no. 1, which was one of the first cases seen in the outbreak, and that a similar error was made in no. 7, who was moribund on admission. No. 2 failed to show any response to treatment.

At first too much reliance was placed on the drug in oil emulsion but its

[1] In all cases the following routine was adopted in the bacteriological examination of the cerebrospinal fluids. The fluids were transferred immediately to the laboratory, and on arrival were centrifuged at fairly high speed for 10–15 min. in conical tubes. The deposit was then cultured into blood-agar slopes, prepared by adding blood in the proportion of 5% to melted 2% nutrient agar (*p*H 7·6). Cultures were incubated at 37° C. for at least 72 hr. before reporting an absence of growth. Direct films were made from the deposit and examined in the usual manner. It was noted on several occasions that colonies of meningococci appeared after 48 hr. at the margin of the water of condensation and spread as the water of condensation evaporated.

use in emulsion was soon discontinued. Bryant also had found that emulsification with oil affected the absorption of the drug, and this has been confirmed experimentally by Long (1939), who holds that the use of oil suspension is most inadvisable. In one case in this series no diazotizable substance was present in the cerebrospinal fluid after 12 c.c. of emulsion had been given intramuscularly (2·4 g. M. & B. 693); in another the same quantity produced the relatively low concentration of 1·6 mg./100 c.c. cerebrospinal fluid. In each case 2 c.c. of oil emulsion were given in four-hourly dosage.

It had been intended to compare the benzyl sulphonamide derivatives (proseptasine, soluseptasine) with sulphapyridine, but as two deaths, nos. 3 and 8, occurred in the few cases treated it was considered inadvisable to continue their use. In one case, 40 c.c. of soluseptasine (four doses of 10 c.c. four-hourly) given intramuscularly produced no response, though there was an immediate favourable reaction to sulphapyridine, with ultimate recovery. In an unspecified series Cook (1939) reported good results with proseptasine. Whitby (1938) found proseptasine and soluseptasine ineffective in experimental meningococcal infections, and this has been confirmed in clinical trial in the present series.

In ten cases the soluble sodium salt of sulphapyridine was employed as an initial treatment. The response was good, but not more so than with the injection of the insoluble drug in saline suspension after the method of Bryant, i.e. the injection into the glutei of a tablet of 0·5 g. broken up in 5 c.c. normal saline. The supply of the soluble salt was too small to provide a comparable series, but it will be given full trial in a subsequent outbreak.

The diverse administrations of M. & B. 693 were ultimately simplified, and the drug employed either orally or intramuscularly, the standard 0·5 g. tablet being used. There is little to choose between oral and intramuscular administration in efficacy, provided the patient can swallow freely.

In view of the generally rapid absorption of sulphapyridine, whether given by the mouth or intramuscularly, and of its insolubility, it was considered that no useful purpose was served by continued intrathecal doses. Somers (1939) successfully used the intrathecal route, but in all but three of his reported cases this had been supplemented by intramuscular or intraperitoneal injection. The general opinion is against intrathecal injection; of the authors quoted Banks, Bryant & Fairman, and Whitby concluding that it is unnecessary. When solutions of sulphapyridine are introduced into the theca, the concentration in the cerebrospinal fluid rapidly falls to blood level. In a selected case, however, this method could be employed rapidly to supply a useful, if transient, concentration pending the gradual building up of a sufficient concentration in the blood by oral administration.

The rapid establishment of adequate concentration in this manner is held to explain the results obtained by Somers with so remarkable a dosage.

The intramuscular route employed with much success by Bryant is of particular use in initiating treatment of the comatose or violent patient. It

should not be employed where the patient can swallow, for such injections frequently cause a transient febrile reaction, and are very painful; nor is it safe to employ this method as a massive "one shot" treatment. The immediate results are good, though in the average no better and no more rapid than with oral administrations. Generally, the temperature subsides rapidly, reaching normal in the second day, with great improvement in the general condition.

In the acute case, provided that treatment was promptly undertaken, remarkable results could be obtained by a total dosage of 3·0 g. of sulphapyridine. The disease might even be aborted by the brief intensive treatment advocated by Bryant. But there are objections to the use of massive single doses, apart from the reaction and discomfort they cause. When dosage is discontinued after such brief treatments, there is a notably consistent tendency to an abrupt rise in temperature or even to frank relapse.

There is experimental evidence to suggest that relapse may be associated with the elimination time of the drug. Elimination may be affected by the amount of fluid taken, and in a hot dry climate is probably more rapid than in a temperate one. In all cases, therefore, observation and treatment should be continued for a minimal period of seven days, however favourable the initial response.

In six cases in this series repeated treatments were required. One case required three courses of treatment. There was nothing to suggest that the organism became "drug-fast" under these circumstances. Relapses responded as rapidly to treatment as first infections.

The important factors in effective treatment are the time between onset and dosage and a sufficient initial dose. It cannot be too strongly emphasized that it is not the clinical severity of the disease, but the interval between onset and treatment which affects the end result. After a certain stage in the progress of the disease intensive chemotherapy is futile, for where a profound toxaemia has developed no concentration of sulphapyridine, large or small, is at all likely to affect the ultimate course. It is this toxaemic factor which, increasing with delay in treatment, affects the issue irrespective of dosage. Proom (1937) found experimentally that the efficacy of sulphanilamide diminished markedly with increase of the time interval between infection with meningococci and commencement of treatment. That this is equally the case with sulphapyridine has ample clinical confirmation in the results of Bryant & Fairman and in the present series. It is essential that an adequate initial dose be prescribed, and that the subsequent treatment should allow of a sufficient concentration being maintained. No good purpose is served by a long-drawn-out treatment, and a good result cannot be expected when treatment is applied to a late case, already gravely toxic. Celerity, quantity and brevity are the keys to management.

The concentrations of sulphapyridine reached in the cerebrospinal fluid were found to vary greatly between individuals, even with constant uniform

dosage, as shown by estimations of diazotizable substance carried out in twenty-two cases by Marshall's (1937) method. There appeared to be considerable individual variation in degree and rate of absorption, and the concentration showed no constant relation to the course of the disease or response to treatment. Concentrations of 2 mg./100 c.c. cerebrospinal fluid appeared to produce effective bacteriostasis, and it was found that even before the drug had reached an appreciable concentration in cerebrospinal fluids in which organisms were seen on direct smear, these failed to grow in culture. The concentration of 2 mg./100 c.c. could be reached within 24 hr. on a total dosage of 2 g. M. & B. 693 given intramuscularly as saline suspension, in divided dosage at four-hour intervals. On the other hand, one case died after achieving a concentration of 8 mg./100 c.c., an instance of toxaemia against which sulphapyridine is powerless.

It seems that a concentration of 2 mg./100 c.c. represents the minimal effective value for sulphapyridine. On trial administration, using 2 g. dosage, Hobson & MacQuaide (1938) obtained concentrations of 2 mg./100 c.c. They found that concentrations of 3 mg. sulphapyridine per 100 c.c. cerebrospinal fluid produced effective bacteriostasis, and that concentration of the drug proceeded more slowly in the course of actual treatment than in trial administration, but that a higher relative concentration was ultimately reached in the presence of inflammation of the choroid and meninges. The Council of Pharmacy of the American Medical Association (1939) is of opinion that concentrations of 4 mg./100 c.c. in blood which would approximate to 2 mg./100 c.c. cerebrospinal fluid, seem necessary for a prompt therapeutic response. Unfortunately a precise relation between dosage given and concentration achieved cannot be relied on. The mild case may require more prolonged treatment than the acute.

The feature of variable absorption and concentration makes it difficult to establish routine dosage, but on the basis of published results and in relation to the clinical groups described the following systems were evolved, and employed with very satisfactory results in the great majority of cases.

Group I. Initial intramuscular injection of 2·5 g. in saline, followed by 1·0 g. given four-hourly. Total injections not exceeding four. Lumbar puncture to precede first dose, and to be repeated after 2nd and 4th dose. Subsequent oral dosage 0·5 g. four-hourly. The total quantity of sulphapyridine in single course not exceeding 20 g.

Group II. An initial intramuscular injection of 1·0 g. may be required if patient cannot swallow. 1·0 g. is given at commencement and repeated in 2 hr., thereafter being given four-hourly. On the average, the total amount given does not exceed 15·0 g. Lumbar puncture as for group I.

Group III. As for group II, but without preliminary intramuscular injection. Lumbar puncture before treatment. This may or may not require to be repeated.

Group IV. Injection intramuscularly of 1·0–1·5 g. Repeated lumbar

puncture, with intravenous injection of hypotonic saline. Abundant fluids. Sulphapyridine 1·0 g. four-hourly, orally or by intramuscular injection.

It may be noted that repeated lumbar puncture of itself has no effect on the progress of the disease, but Bryant & Fairman (1939) have noted that it effectively accelerates the action of sulphapyridine. It was employed in the majority of cases in this series and was found to enhance the action of the drug and to relieve headache.

For children the above doses do not require to be modified to any significant extent. Hobson & MacQuaide (1938) gave 5·0 g. per day for 10 days to a child weighing only 16½ lb., without producing toxic symptoms. Banks (1938), on the data of Marshall *et al.* (1937), assessed the oral dosage as 1·0 g. per stone body weight, and computed that infants tolerate and require about 3 times, and children 1½ times, this standard. He now favours a high initial dose over 2½ days, with gradual reduction later, the course not exceeding 7–9 days (Banks, 1939). The dosage is rather higher than was found necessary in Sudan practice, but the system and results agree.

Sulphapyridine and sulphanilamide are comparable in ultimate result, but the former is the more efficient. In the fifty cases under consideration only two developed permanent complications—in both, nerve deafness. One child developed a transient albuminuria. No case of haematuria occurred. No rashes were noted. Herpes labialis was common, but cannot be attributed to the drug. There was one case of transient arthritis. It appears that with sulphapyridine complications are generally less frequent than with sulphonamide, and that the period of convalescence is shorter. A comparison of four series is made below, though, admittedly, all the series are not strictly comparable and do not lend themselves to straightforward tabulation.

Schwentker *et al.* (1937) treated ten cases of cerebrospinal meningitis with one death, giving an average total dose of 1·6 g. intrathecally (146 c.c. of 0·8% solution) and 6·5 g. subcutaneously. The number of days under treatment averaged 6·5 and patients were detained on average 22 days. Two cases of transient arthritis occurred.

Crawford & Fleming (1938) record ten cases with one death. Their maximum total dosage was 71·0 g. (given over 26 days) and their minimum 21·0 g. over 7 days. On average, treatment occupied 12·5 days and the average dose was 29·2 g. They note that in a series of thirty cases treated with serum there were twenty-six deaths.

Banks (1938) reports sixteen cases treated with sulphanilamide with one death, thirty-eight cases treated with serum only with a mortality of 16%, and fifty-nine cases treated with serum and sulphanilamide, with a mortality of 11·8%.

Jewesbury (1938) treated six cases with serum supported by sulphanilamide, augmented in one case by sulphonamide and in two by soluseptasine. Treatment occupied on average 18 days, and patients were detained on average 50 days. Five showed a serum rash, one had arthritis, and two cyanosis, one developed diarrhoea and vomiting. Repeated daily lumbar punctures were carried out on these cases over period of 7–14 days. There were no deaths.

For comparison, results obtained with sulphapyridine are given in Table 5.

Serum was not employed in the Omdurman outbreak. Previously its use had been limited and disappointing, and in this outbreak expense and past experience precluded its use, and reliance was placed in chemotherapy alone.

Table 5. *The results of treatment with sulphapyridine*

Series	Cases	Mortality %	Av. total dose Min.	Av. total dose Max.	Av. days treatment	Av. days detained
Hobson & MacQuaide	6	Nil	25·0	90·0*	16·8	—
Bryant & Fairman	169	5	0·5	3·25	5·0	—
Somers	143	10	1·2	3·0	2·0	—
Buchanan	50	12†	3·0	20·0	4·0	10

* Total given to one case of relapse.

† Excludes two cases on soluseptasine only, and one case dying 2 hr. after admission.

Banks (1940) considers serum unnecessary, even as an adjuvant; but some consider that experimental evidence suggests that sulphanilamide is more potent in combination with serum than alone, and advise the combination in fulminant or comatose cases (*Lancet*, 1940, **1**, 467).

The system of dosage described gave rapid and satisfactory response under hospital and field conditions alike. Eight cases (not included in the series) were so treated by Sudanese medical orderlies. Though remote from qualified medical control, there were no deaths.

It remains to be seen whether it will be possible to employ sulphapyridine prophylactically, in the control of outbreaks. The circumstances and floating population of towns render it difficult to assess the effect of any prophylactic measure, but it may prove possible to gain useful data from the observation of isolated communities, and to compare new findings against past experience. It is unfortunately probable that the months of April, May and June will show the usual recurrent outbreaks in the Sudan and that ample material will be available for the further study of chemotherapy in cerebrospinal meningitis. Fortunately it is at least equally certain that the mortality and invalidism of previous years can be avoided.

SUMMARY

1. Meningococcal cerebrospinal meningitis in the Sudan does not materially differ in its progress and end result from the disease as found in Europe.

2. There is no racial peculiarity in response to infection or to chemotherapy.

3. There is no sex or age peculiarity in incidence. Both sexes and all ages respond to chemotherapy.

4. Sulphapyridine is superior to sulphanilamide in the shortening of invalidism and in the prevention of complications.

5. Oral administration of sulphapyridine is in the majority of cases as effective as intramuscular.

6. Dosage is related to the clinical stage of the disease, and to its duration before treatment. An initial *dose* of 2·5 g. sulphapyridine for adults, and 1·0–1·5 g. for children is prescribed for the serious case, with subsequent gradation of treatment to provide a maintenance dose.

7. Treatment, if it is going to give a good result, will produce a response

within 24 hr. It need not be prolonged beyond 7 days. The third, fourth and seventh days of treatment are critical.

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