ADDRESSES AND ORIGINAL ARTICLES

CHEMOTHERAPY OF MENINGOCOCCAL MENINGITIS *

A REVIEW OF 147 CONSECUTIVE CASES

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SINCE the publication of a preliminary article on the use of serum and sulphanilamide in acute meningococcal meningitis (Banks 1938) some 55 additional cases have been treated in this hospital by chemotherapy alone. The whole of the material in which chemotherapy has been employed with or without serum may now be usefully reviewed in an attempt to assess the value of sulphanilamide and M. & B. 693. These two drugs were employed without selection, at first in alternate series of cases admitted, and later, when the number in each series became about equal, as far as possible in alternate cases admitted. The M. & B. 693 series is the larger because treatment with this drug had in some cases been started before admission, thus preventing strict alternation. The extended experience of chemotherapy alone provides new data on which a truer estimate of the comparative and auxiliary value of serum in meningococcal meningitis may be formed.

Serum and Sulphanilamide Series

Combined serum and drug treatment was adopted during the period May, 1937, to March, 1938, and most of the cases were included in the preliminary article. This treatment was not further pursued, but 9 additional cases which had received varying amounts of serum in general hospitals during the day or two before admission have to be considered. Of these, 3 had quite small amounts of serum, and on admission the cerebrospinal fluid still contained meningococci in direct smears and culture. Accordingly, as chemotherapy alone was used from admission, they have been included in the appropriate drug group. The remaining 6 cases treated with serum before admission and with sulphanilamide thereafter showed no organisms in the cerebrospinal fluid on admission, although polymorph cell-counts were still high. In these the effect of serum cannot be disregarded, and they have accordingly been placed in the combined series. This series has been thoroughly reviewed and now consists of 65 cases with 8 deaths, a fatality-rate of 12·3 per cent. allowing for certain exclusions mentioned below (see table II).

DOSAGE AND ADMINISTRATION

The serum used was with few exceptions "meningococcus antitoxin," the route intravenous, or intraperitoneal in infants, and the dosage high, averaging about 150 c.cm. in one or two injections. The intrathecal route was not employed as a routine because of the disadvantages specified in the former article, and also because sulphanilamide given in high initial dosage appears rapidly in adequate concentration in the subarachnoid space. No less than 32 of the 65 cases, however, had at least one intrathecal injection of serum of various makes before admission.

Sulphanilamide was employed exclusively in this series, except for 1 case treated with M. & B. 693. A scheme of dosage according to age-groups was gradually evolved (Banks 1938). This provides for a high initial dosage during the first two to three days' treatment and a gradually diminishing dosage for five or six days thereafter, the drug treatment being completed in eight or nine days. Age-periods are more convenient as a basis of dosage than body-weight in an acute disease, and provided that allowance is made for the more extreme variations they are quite satisfactory in practice. With certain early exceptions, the dosage scheme adopted during the first two to three days, whether with or without serum was as in table I.

TABLE I—DOSAGE OF SULPHANILAMIDE DURING FIRST TWO TO THREE DAYS

Age-period in years ..	*0 —*	*2 —*	*5 —*	*10 —*	*15 +*
Daily amount in grammes	3	4½	6	7½	9

The daily dosage during the initial period of about three days thus ranged from 3 to 9 g. The minimum of 3 g. daily is well tolerated by infants of two months and upwards. Occasionally the maximum of 9 g. was raised to 10½ g. in the first day for tall heavy adults. The daily dosage was divided into six equal portions at four-hourly intervals day and night, the patient being aroused at night for this purpose. Latterly the practice was adopted of doubling the first two single doses, 1–3 g. being then given instead of ½–1½ g. The total amount of drug for an adult ranged from 45 to 55 g.

The oral route is the most convenient and any other is rarely required. With sulphanilamide vomiting is uncommon and is not persistent. If an occasional dose is vomited in whole or part another should be given as soon as the patient is settled. In 2 cases head-retraction was so extreme that swallowing was mechanically obstructed for from twelve to twenty-four hours. During this period parenteral administration of the drug and of fluids was required. Sulphanilamide was actually given as a 14 per cent. oily suspension intramuscularly. (A better parenteral method now available is deep intramuscular injection of the sodium solution of M. & B. 693, or intravenous injection of a 1 in 10 dilution of it.) In comatose cases the swallowing reflex is rarely abolished and the tablets crushed to a fine powder can usually be given suspended in water or milk by nasal or pharyngeal tube. Intrathecal administration of a 0·5 to 0·9 per cent. solution of sulphanilamide was tried in a few cases but no advantage over the oral route could be observed. The amount of the drug that can be given in this way is minute and its level in the cerebrospinal fluid quickly falls to that of the blood.

In nearly all cases the level of absorption of the drug into the cerebrospinal fluid was determined biochemically each day during the first four or five days. Some variations in the amount of sulphanilamide absorbed were observed in certain cases which were approximately equal as regards age, body-weight and dosage. Nevertheless there was abundant evidence to show (1) that even in difficult cases associated for example with coma, delirium or vomiting, adequate amounts of the drug were in fact administered by mouth or tube; and (2) that the dosage outlined above was adequate to cover individual variations in absorption, and to produce an efficient level of circulating drug in the blood and cerebrospinal fluid. The cerebrospinal fluid level in the case of sulphanilamide is usually only slightly less than that of the blood. Data were given in my former paper, and also by Allott (1938). The

* This paper formed the basis of a contribution to the annual meeting of the British Medical Association, 1939.

opinion therein expressed that a minimum level of 3–5 mg. per 100 c.cm. of cerebrospinal fluid should be attained within twenty-four hours and maintained for at least three days was confirmed by subsequent work. Some evidence to be given below suggests indeed that the higher figure of 5 mg. per 100 c.cm. is the preferable standard for sulphanilamide. This is usually attained in twelve hours in small children and in twenty-four hours in adults with the given scheme of dosage. In the earlier period of the investigation lower dosage was occasionally employed. Allott (1938) gives the cerebrospinal-fluid concentration values for 36 of these cases. Of these the concentration never reached 5 mg. per cent. in 12, and of the 12 no less than 3 died. Amongst the remaining 24 there was only 1 death.

FAILURE WITH LOW DOSAGE

Much interest has been aroused by the excellent results obtained with sulphanilamide and M. & B. 693 in minute dosage under field conditions in the Sudan (Somers 1939, Bryant and Fairman 1939). These authors, however, have wisely pointed out that "it does not follow that the results of treatment here would have their counterpart in Europe," and again, "from our experience we consider that the drug should be pushed in big doses from the very first." The following brief notes on 6 cases of "failure" suggest that dosage in amount or duration lower than that of the standard scheme is not to be relied upon when sulphanilamide is the drug employed:

CASE 1.—Male, aged 5 months. First case treated. Dose 1 g. daily for ten days, then 2 g., and later 4 g. daily. Cerebrospinal fluid never became free from organisms. Died 17th day.

CASE 2.—Female, aged 5 months. Dose 3 g. daily, but drug stopped after three and a half days. C.s.f. then sterile but fatal relapse occurred some days later. P.M.: meningeal exudate with meningococci over vertex and base. Serum 90 c.cm. also given on admission intraperitoneally.

CASE 3.—Male, aged 2 years. Dose 3 g. daily commenced 10th day of disease; drug not taken well; this was confirmed by the c.s.f. estimation, which amounted to only 2 mg. per 100 c.cm. in nineteen hours after treatment was begun, and 4 mg. in fifty-four hours. The fluid was not sterile till seventy-two hours after treatment began, and the organisms reappeared four days thereafter and persisted many weeks. The child entered a long chronic stage of the disease with hydrocephalus; ultimate slow recovery occurred after many months. Serum 120 c.cm. given intraperitoneally a week after the drug was started.

CASE 4.—Female, aged 15 years. Dose 6 g. daily for only two days, then reduced to 3 g. daily (too low) for next three days; thereafter (on 6th day of treatment) raised to 6 g. daily. C.s.f. level too low—only 0·8 mg. after seventeen hours and maximum of 4·9 mg. only attained after seven days. The fluid was sterile after twenty-four hours, but meningococci reappeared on the 4th day of treatment and persisted for weeks, although the drug was then given in higher dosage. The organisms apparently became "drug fast" owing to low initial dosage. This case became chronic and was fatal from hydrocephalus after three and a half months. Serum to a total amount of 500 c.cm. was also given from admission intravenously and 20 c.cm. intrathecally.

CASE 5.—Female, aged 26 years. Standard dose 1·5 g. four-hourly given only for twelve hours, then reduced to 0·5 g. four-hourly—(too low) for four days. Organisms seen in direct smears but cultures sterile twelve and thirty-six hours after treatment commenced; thereafter they grew at first scantily, then profusely till death on 13th day of treatment. Organisms apparently became "drug fast" owing to low dosage after the first twelve hours. Serum was also given, 360 c.cm. intravenously, 20 c.cm. intrathecally and 20 c.cm. into the lateral ventricles.

CASE 6.—Male, aged 27 years. One of the earliest cases. Dose only 2 g. daily; serum 420 c.cm. intravenously; 20 c.cm. intrathecally and 20 c.cm. intracisternally. The acute stage cleared up but a relapse occurred three weeks later. The relapse cleared up rapidly on the scale dosage of sulphanilamide.

All 6 of these cases were failures, absolute or relative, and a common feature was low dosage. Dosage was either initially lower than the standard, or reduced or stopped too soon. Except in case 1, where the c.s.f. was never sterile, meningococci reappeared after a day or two of apparent sterility of the fluid and were then uninfluenced by higher dosage. Initial low dosage tends to make the organisms drug-fast.

AUXILIARY VALUE OF SERUM

In 4 of these 6 cases intensive intravenous dosage with serum did not apparently compensate for inadequate dosage of the drug. This was somewhat unexpected as these cases were not of exceptional severity or unfavourable ages. Cases 4 and 5 are particularly instructive. No adjuvant effect of even large doses of serum given intravenously could be demonstrated, when the dosage of the drug was inadequate.

A synergistic action of serum and drug has been suggested by the laboratory experiments of Brown (1937) and Branham and Rosenthal (1937) with meningococci; Fleming (1938) with pneumococci; De and Basu (1938) with staphylococci and Loewenthal (1939) with hæmolytic streptococci. Fleming amongst others has shown that the drug is not of itself bactericidal but merely bacteriostatic and that the destruction of invading organisms must be completed by the immunity mechanism of the host. On the basis of this experimental work the combined action of serum and drug has often been advocated in the treatment of human infections. But not only the cases mentioned above but the whole of the data pre-

TABLE II—SERUM AND SULPHANILAMIDE *

Age-group	Cases	Bact. group				Deaths	Fatality-rate (per cent.)
		I	II	Inagg.	Not bact. verified		
0 –	10	2	5	1	—	1	10
1 –	10	3	3	—	—	2	20
5 –	22	7	1	—	1	1	4·5
20 –	17	6	3	—	5	2	11·7
40 –	3	2	1	—	—	1	33
50 –	1	1	—	—	—	—	—
60 +	2	—	—	—	—	1	50
—	65	21	13	1	6	8	12·3

* One of these cases was treated with M. & B. 693.

Excluded cases.—Recovering on admission 2; dying within five and twelve hours of admission 2; subarachnoid basal block, admitted in 5th week of disease 1; dying from intercurrent ascending pyelocystitis 1.

Deaths.—Cases 2, 4 and 5 above appeared to be associated with inadequate dosage of sulphanilamide. The other causes of death were: age 1 year, thrombosis of superior longitudinal sinus; age 2½, convulsions two days after admission; age 38, slow hydrocephalus; age 45, pneumonia; age 62, slow hydrocephalus.

Complications.—Deltoid paresis 1; relapse 2; temporary deafness 4; permanent absolute deafness 3; squint (ext. rectus paresis) 1; hemiplegia (temporary) 2.

sented in tables II, III and IV lend no support to this view in the case of meningococcal meningitis and/or septicæmia.

Combined serum in intensive intravenous dosage, and sulphanilamide in somewhat varying dosage (table II) does not turn out to be quite so favourable as adequate dosage of sulphanilamide alone or M. & B. 693 alone, or the two drugs in combination. In a series of 72 acute cases of all grades of clinical severity and representative of both bacteriological groups, chemotherapy alone has been found to be fully curative and serum as an auxiliary to be neither necessary nor even desirable, since serum administration is troublesome, expensive and not devoid of discomfort and risk. On the other hand chemotherapy is easy to administer and cheap, and its only practical danger, agranulocytosis, is remote if the period of administration is restricted to nine days. In the present series no sign of even leucocytopenia was discovered.

Chemotherapy Alone

In tables III, IV and V particulars are given of the treatment of 72 cases by chemotherapy. Of these 31 were treated with sulphanilamide without a death, 36 with M. & B. 693, 1 case being fatal, and 5 with a combination of the drugs without a death. For the purpose of assessing the effect of treatment, 4 cases, fatal, have been excluded, particulars being given under each table. The cases comprised in the tables, together with those excluded, represent the whole of the verified cases admitted to the hospital during the period May, 1937, to September, 1939. Of the sulphanilamide cases, 1 had septicæmia only when treated; there was a profuse rash, a positive blood-culture and normal c.s.f.; meningitis did not develop. In a similar case, a slight meningeal reaction developed (600 polymorphs per c.mm. and no organisms). In the chemotherapy series the gross fatality-rate was 5 cases out of 76 or 6·6 per cent., which is probably now a fair measure of the mortality of the disease as it is seen in London. For cases adequately treated with either or both of these drugs, however, the case-fatality rate in 72 cases was no more than 1·4 per cent.

TABLE III—SULPHANILAMIDE

Age-group	Cases	Bact. group			Deaths
		I	II	Not bact. verified	
0 –	2	—	1	—	—
1 –	10	4	2	—	—
5 –	9	3	3	1	—
20 –	8	5	1	—	—
40 –	1	—	1	—	—
50 +	1	1	—	—	—
—	31	13	8	1	—

Excluded cases.—(1) Case 1; first case treated; quite inadequate dosage. (2) Aged 44; second case treated; inadequate dosage; c.s.f. never free from organisms: sulphanilamide level in c.s.f. did not reach 5 mg. per 100 c.cm. until 6th day of treatment; severe intercurrent disease; pneumonia, cirrhosis of liver, &c., also present. Serum 120 c.cm. i.v. on 6th day of treatment had no effect on the course of the disease. (3) Aged 13; died two hours after admission, just after lumbar puncture, with symptoms of sudden failure of the respiratory centre.

Complications.—Case 3; hydrocephalus with slow recovery.

COMBINED CHEMOTHERAPY

The two drugs were used in combination, in 5 cases, all of which made a rapid recovery. Of these, 2 men and 1 woman, aged twenty-three and thirty-six and twenty-five respectively, all moderate to severe

TABLE IV—M. & B. 693 *

Age-group	Cases	Bact. group			Deaths
		I	II	Not bact. verified	
0 –	5	—	3	—	—
1 –	10	7	1	1	—
5 –	13	3	3	1	—
20 –	6	4	—	—	—
40 –	1	1	—	—	1
50 +	1	—	—	—	—
Total	36	15	7	2	1

* Of the 36 cases, 11 were treated with intramuscular injections of the sodium solution 25 or 33⅓ per cent. (table VI and fig. 2).

Excluded case.—Aged 2¼; 4th day of disease; died three hours after admission, after lumbar puncture; sudden failure of respiratory centre.

Death.—Aged 40; very severe 4th day case with deep coma and stertor from admission. Treated with sodium solution of drug; dosage rather low; level of drug in c.s.f. in thirty-six hours only 3·1 mg. per 100 c.cm. The c.s.f. forty hours after treatment commenced still contained meningococci in films but not in culture. Serum 120 c.cm. i.v. and 20 c.cm. i.t. given forty hours after chemotherapy commenced—probably too late to be taken into account. Died on 4th day of treatment.

P.M.: meningeal exudate with dilatation of ventricles.

Complications.—(1) Absolute deafness, in a boy of 13 years, treated with low dosage of drug (4 g. daily) before admission for 2½ days: c.s.f. sterile on admission, but level of drug in c.s.f. only 1·2 mg. per 100 c.cm. seventy-two hours after treatment commenced; maximum 4·2 mg. per 100 c.cm. reached after seven days.

(2) Partial deafness and L. vestibular nerve paresis in a man of 25 years: Dosage rather low: (6 g. daily), c.s.f. level 3·7 mg. per 100 c.cm. in forty-four hours, 4·3 mg. in sixty-eight hours.

(3) Convulsions of Jacksonian type some days after treatment commenced in 2 cases aged 9 months and 9 years respectively; complete recovery.

(4) Bulbar paresis (transitory) for a few days in a girl aged 10 years. Complete recovery.

TABLE V—COMPARATIVE CLINICAL AND BACTERIOLOGICAL DATA

Cases	Serum and sulph.	Sulph.	M. & B. 693	Sulph. and M. & B. 693
	65	31	36	5
Clinical classification:				
Mild	11	5	4	—
Moderate	35	17	16	2
Severe	15	8	15	3
Very severe	4	1	1	—
Eruptive	17	10	9	—
Duration of symptoms *before treatment*:				
1–3 days	17	10	12	3
4–6 days	34	15	17	2
7 days +	14	6	7	—
C.s.f. free from organisms:				
12–24 hours, smears	46	24	31	5
— culture	48	26	35	5
24–48 hours, smears	56	30	35	5
— culture	57	30	35	5
48–72 hours, smears	62	30	35	5
— culture	62	30	35	5

cases, were treated with M. & B. 693 in scale dosage for about forty-eight hours, and thereafter with sulphanilamide in similar dosage which was gradually reduced.

The c.s.f. was in each case sterile within twenty-four hours, but the drug was changed in the men on account of nausea and vomiting, and in the woman because of vomiting, depression, "weariness" and insomnia. These symptoms disappeared promptly after the change of drug to sulphanilamide, the patients felt better, the c.s.f. remained sterile, and the cell-count rapidly dropped. There was, of course, an increase of cyanosis and also mild mental confusion at times, but as the dose of sulphanilamide was rapidly diminished these side effects cleared up in a few days.

The fourth case, an infant aged nine months, a severe case with convulsions and a group II infection, had the reverse combination—viz., sulphanilamide for forty-four hours in scale dosage followed by M. & B. 693. The c.s.f. in this case was also sterile within twenty-four hours, and the drug was changed because rapid respirations suggested a possibility of latent pneumonia, although chest signs were negative.

TABLE VI—SULPHANILAMIDE LEVEL IN C.S.F. (mg. per 100 c.cm.)

Titre	12–20 hours	20–44 hours
Average	5·8 *	10·7 †
Highest	19·0	34·0
Lowest	1·8	3·6

* 22 cases. † 19 cases.

The c.s.f. remained sterile and the cell-count rapidly dropped. Pneumonia did not develop, but on the fifth day of treatment convulsive twitchings of the right side of face and arm persisted for some twelve hours. Thereafter the infant rapidly recovered. The fifth case was a girl aged 10 years who vomited frequently after sulphanilamide. Intramuscular injection of the sodium salt of M. & B. 693 was substituted with excellent results.

COURSE OF THE DISEASE

Chemotherapy in adequate dosage not only saves the patient but markedly affects the course of the disease. The temperature generally returns to normal and acute symptoms and most of the rigidity clear up in two to six days. There is often a marked amelioration within twenty-four hours, especially in those delirious or semicomatose on admission. Nursing of these cases, formerly so difficult, is generally quite easy after the first twelve hours. Some form of restraint may be necessary during this period. A bed with cot sides is useful. Fluids are restricted to 3 pints daily for adults since too much fluid reduces the concentration of the drug in the tissues. Lumbar puncture rarely requires a general anæsthetic, especially after the first day. The c.s.f. is usually sterile within twelve to twenty-four, or at most forty-eight hours, but in a small proportion (10–20 per cent.) meningococci which will not grow in culture may be seen in direct smears of the centrifuged deposit during this period (table V). The cell-count falls very rapidly after forty-eight hours, commonly dropping from about 10,000 cells per c.mm. to 500 cells per c.mm. or less on the third or fourth day of treatment. At the same time the proportion of mononuclears increases and is commonly 90 per cent. on the fifth or sixth day of treatment. In from ten to fourteen days the c.s.f. is usually quite normal, but occasionally shows a persistence of lymphocytes up to 30 per c.mm. for some weeks. No more than 3 or 4 lumbar punctures are required in the average case and then only as a guide to treatment. Provided that no intrathecal serum has been given, relief of pressure and drainage of fluid as a therapeutic measure is very rarely required after the first puncture. The *rapid* clearing of the c.s.f. indicates a rapid absorption of the meningeal exudate (a fact confirmed at several post-mortem examinations in the serum and sulphanilamide series) and a consequent freedom from relapses and complications due to pressure and adhesions of the exudate. The data in tables II, III, IV and V show that the various series were clinically and bacteriologically comparable and that bacteriological groups I and II infections were equally responsive to chemotherapy.

TABLE VII—M. & B. 693 CONCENTRATION IN C.S.F. (mg. per 100 c.cm.)

20 cases; tablets by mouth			11 cases; sodium solution intramuscularly		
Age	12–20 hours	20–44 hours	Age	12–20 hours	20–44 hours
5/12	7·0	7·0	6/12	3·1	2·7
5/12	6·6	12·5			
9/12	5·2	10·6	9/12	0·5	2·0
1 2/12	2·5	4·9			
1 4/12	4·2	10·1	1 3/12	2·4	1·4
2 6/12	—	2·8			
2 6/12	—	1·5	3 9/12	3·6	4·2
2 10/12	4·4	8·0			
3	—	5·0	5	4·4	2·8
3	—	8·7			
4	6·0	5·6	5 9/12	1·8	1·8
5 11/12	trace	1·3			
10 6/12	—	4·4	18	0·7	1·3
15	—	1·5			
17	2·0	5·0	26	traces	traces
18	3·6	5·1			
18	4·8	4·4	28	0·5	1·5
25	2·0	3·7			
25	2·5	5·9	40	1·2	3·1
29	2·8	3·8			
			51	traces	traces

TABLE VIII—M. & B. 693 LEVEL IN BLOOD AND C.S.F. (mg. per 100 c.cm.)

	Blood		C.S. fluid	
Titre	12–20 hours	20–44 hours	12–20 hours	20–44 hours
Average ..	4·4 (*a*)	7·9 (*b*)	3·6 (*c*)	5·4 (*d*)
Highest ..	9·2	12·1	6·6	12·5
Lowest ..	0·8	4·3	0·5	1·3
Sodium solution (M. & B. 693 soluble)				
Average ..	2·1 (*e*)	2·6 (*f*)	1·7 (*g*)	1·9 (*h*)
Highest ..	5·9	5·3	4·4	4·2
Lowest ..	traces	traces	traces	traces

Cases examined: (*a*) 19; (*b*) 7; (*c*) 11; (*d*) 15; (*e*) 5; (*f*) 6; (*g*) 11; (*h*) 11.

ABSORPTION OF SULPHANILAMIDE AND M. & B. 693

The average level of sulphanilamide in the c.s.f. in 22 cases of the sulphanilamide series in from twelve to twenty-four hours is shown in table VI to have been 5·8 mg. per 100 c.cm., and in from twenty to forty-four hours 10·7 mg. per 100 c.cm. There was considerable variation, infants and children having higher values, because they received larger doses than adults in proportion to body-weight. The highest values at the times stated were 19 and 34 mg. and the lowest 1·8 and 3·6 mg. respectively. The latter occurred in 2 cases on dosage lower than the scale, and in neither

case was the c.s.f. free from organisms within twenty hours. The values in the first forty-eight hours are the most important. High values at a later date may be comparatively ineffective on account of the development of drug fastness.

M. & B. 693 is rapidly absorbed from the stomach into the blood-stream and excreted somewhat more slowly than sulphanilamide. Elimination from the blood is completed in just over twenty-four hours, and from the urine in about fifty hours (Whitby 1938). Hobson and McQuaide (1938) found some striking individual variations in the capacity to absorb the drug from the stomach. They also found that the concentration of the drug in the c.s.f. in meningitis was approximately 56 per cent. of that found in the blood. This is considerably lower than the corresponding value for sulphanilamide. The values obtained by Dr. E. N. Allott in this series (tables VII and VIII) are in substantial agreement with these findings. In fifteen to twenty hours the *average* concentration in the blood in 9 cases was 4·4 mg. per 100 c.cm. and in the c.s.f. 3·6 mg. for 11 cases. In twenty to forty-four hours the average blood level in 7 cases was 7·9 mg. and the c.s.f. level 5·4 mg. for 15 cases. The highest and lowest values shown in the table indicate the very considerable variation in absorption that occurred. Tables VII and VIII also show the absorption levels in blood and c.s.f. for 11 cases treated experimentally with the sodium solution (M. & B. 693 soluble) by intramuscular injection. The values are all low compared with those above, because, owing to rapid absorption by this route, the dosage employed, weight for weight of drug, was less than half and sometimes only a third of the scale dosage for the drugs given by mouth.

In fig. 1 typical curves of absorption of M. & B. 693 into the blood and c.s.f. are shown for 2 cases aged four and seventeen years, on four-hourly or six-hourly dosage by mouth. These show the c.s.f. concentration to be little more than half of that of the blood. The c.s.f. levels are maintained above 3 to 5 mg. per 100 c.cm. for at least three days and then gradually reduced. In fig. 2 similar curves of absorption are shown for three typical cases aged five, eighteen and

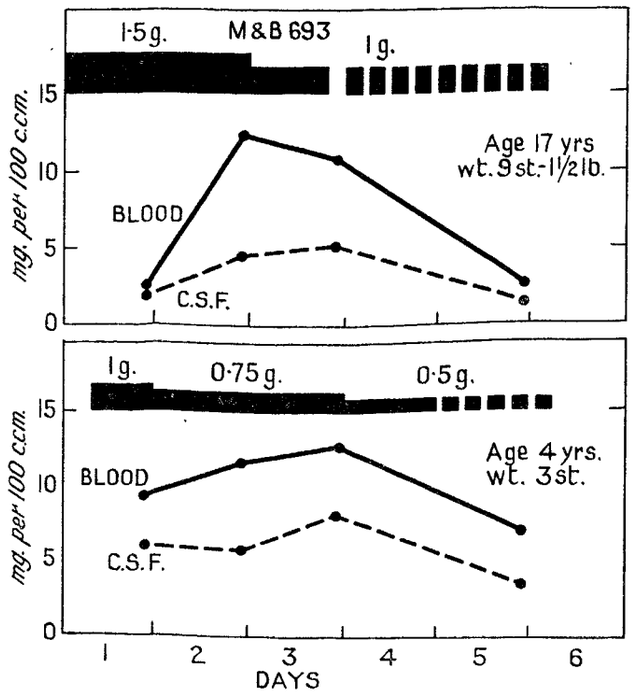

FIG. 1—Amounts of M. & B. 693 recovered from blood and cerebrospinal fluid in 2 cases receiving the drug by mouth.

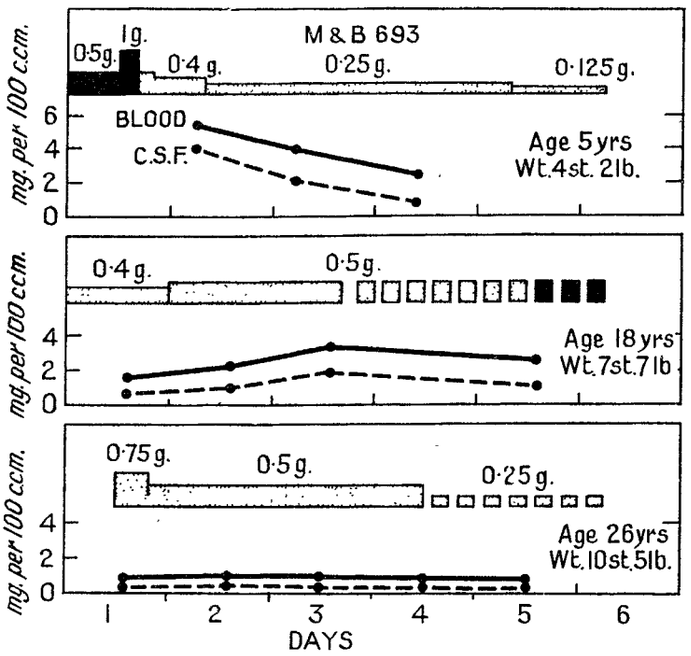

FIG. 2—Amounts of M. & B. 693 recovered from blood and cerebrospinal fluid in 3 cases during administration of M. & B. 693 (black rectangles) I. and M. & B. soluble (stippled).

twenty-six years, treated with four-hourly or six-hourly injections of the sodium solution. The blood and c.s.f. concentrations here, while considerably lower, show similar relative values. One of these curves shows blood and c.s.f. values constantly less than 1 mg. per 100 c.cm.—i.e., mere traces of the drug. In this case the c.s.f. was free from organisms within twenty-four hours and recovery was rapid. Only 1 case amongst the 11 receiving the sodium solution failed to make a rapid recovery—namely, the fatal case mentioned under table IV. The evidence obtained from the series receiving the sodium solution seems to indicate that low c.s.f. concentrations of M. & B. 693, such as 1–2 mg. per 100 c.cm. or even less are quite efficient in meningococcal meningitis. In this respect the drug differs from sulphanilamide where lower concentrations than 5 mg. per 100 c.cm. are distinctly unsafe. When M. & B. 693 was given by mouth in the present series, low dosage was not tested.

TOXIC EFFECTS OF THE DRUGS

The toxic effects met with were all of a minor nature. With sulphanilamide on the scale dosage, cyanosis constantly appeared within twenty-four hours and was generally quite deep in thirty-six hours, especially in adults. It remained as a rule until the dosage was substantially reduced. There is a widespread belief that cyanosis is always or usually due to meth- or sulph-hæmoglobinæmia. About half the cases dealt with in this article were examined for these pigments by Dr. E. N. Allott, usually some twenty-four hours after withdrawal of the blood, and only negligible amounts were ever found. Hobson and McQuaide (1938) were unable to detect either pigment in 6 cases of meningitis. Marshall and Walzyl (1937) found complete active hæmoglobin in 7 cyanotic patients, and considered that the colour was probably due to aniline black, a dark oxidation product. Similarly, Ottenberg and Fox (1938) considered it due to coloured derivatives of the drug staining the red corpuscles. Chesley (1938) found no methæmoglobin in 8 cyanotic patients, and considered with Marshall and other recent writers that this pigment is of no

importance except perhaps in an occasional patient. On the other hand, Bensley and Ross (1937) found about 20 per cent. methæmoglobin in 1 case. They continued the drug for sixteen days and the proportion of methæmoglobin did not increase nor was sulphæmoglobin formed. Paton and Eaton (1937) found methæmoglobin in 4 of 19 cases and considered it to be the true toxic result of the drug, and that sulphæmoglobin was only formed when sulphur compounds were available—e.g., from the bowel in large amounts.

Hartman, Perley and Barnett (1938) reported that they were able to demonstrate the presence of methæmoglobin in every case of cyanosis, and by giving methylene-blue 0·01 g. per kg. of body-weight intravenously, or gr. 1–2 orally every four hours obtained reconversion of methæmoglobin to hæmoglobin. Wendel (1939), who was amongst the first to advocate the methylene-blue treatment, found in 100 cases of cyanosis methæmoglobin present in traces in 90 and present to the extent of 15 per cent. or more of the total hæmoglobin in 35 cases. It was not, however, proportional to the amount of sulphanilamide in the blood.

Such conflicting findings are difficult to reconcile. Campbell and Morgan (1939) have recently suggested a possible explanation. They state that in examining for methæmoglobin or sulphæmoglobin two precautions are necessary—(1) a dilution of not more than 1 in 5 of the blood must be used; and (2) the specimen should be examined as soon after withdrawal as possible. In cases where the amount of methæmoglobin is not large it may be entirely absent in twelve hours. They consider that with such technique it may be unnecessary to speculate on the possibility of any coloured derivative of aniline being the causal agent of the symptom, since methæmoglobin or sulphæmoglobin is so frequently detected.

In the present series of cases no aperients other than phenolphthalein and liquid paraffin were given, and these but rarely. Movement of the bowels was usually obtained when necessary by glycerin enemata or suppositories. No excessive dietary precautions to exclude sulphur were taken, two eggs daily and even onions being given at the height of the cyanosis. Except in such conditions as severe anæmia, or dyspnœa from concurrent respiratory disease, early cyanosis was not considered an indication for reducing dosage.

Other toxic effects of sulphanilamide were drowsiness, disorientation, mental confusion (probably distinct from that produced by the disease), occasionally hallucinations, and in 2 cases papular rashes. Nausea and vomiting were uncommon.

With M. & B. 693, cyanosis was much less marked, but nausea and vomiting were troublesome especially in adults. The older patients also complained of malaise and mental depression. Transient hæmaturia, lasting one or two days, was seen in 2 children, aged two and a half and five years; they showed no casts and no hæmatoporphyrinuria. Of these, 1 also had diminished urinary output, 10 oz. in twenty-four hours (cf. Southworth and Cooke 1939); the drug was stopped and the condition cleared at once. In one of these cases the drug was resumed without harm after being stopped for twenty-four hours. Vomiting was present in both these cases. In neither was the concentration in the c.s.f. high, the maximum being 2·5 and 1·8 mg. per 100 c.cm. In this connexion, Antopol and Robinson (1939) observed in laboratory animals the formation of uroliths, consisting of needle-like crystals of the acetyl derivative of M. & B. 693. Backhouse (1939) observed the characteristic crystals in the urine of Melanesian natives.

It may be said generally that patients on high dosage of sulphanilamide look ill, owing to cyanosis, and those on M. & B. 693 feel ill, owing to depression and nausea. In the blood no diminution of granulocytes was observed, although counts were frequently made. In the acute stage a polymorph leucocytosis was invariably found in these counts. A mild secondary anæmia, not necessarily due to the drug, was common.

Summary

First, 65 cases of acute meningococcal meningitis were treated with serum in intensive intravenous dosage and sulphanilamide in somewhat varying dosage. There were 8 deaths, a case-fatality rate of 12·3 per cent. for treated cases, 13 complications and 3 known sequelæ (deafness). These figures are exclusive of 6 cases in which treatment could not be applied, and of these 4 were fatal. The gross mortality from the disease during the currency of this series was, therefore, represented by 12 deaths in 71 cases or 16·9 per cent.

Next, 72 cases, comparable to a high degree, were treated by chemotherapy alone in high dosage, 31 with sulphanilamide, 36 with M. & B. 693, and 5 with a combination of both drugs. There was 1 death, giving a case-fatality rate of 1·4 per cent. for treated cases, 6 complications and 2 known sequelæ (deafness). 4 cases, untreated or inadequately treated, and all fatal, were excluded from this series. The gross mortality from the disease during the currency of this series amounted, therefore, to 5 deaths in 76 cases, or 6·6 per cent.

Initial dosage of sulphanilamide sufficient to maintain a c.s.f. concentration of 5 mg. per cent. for three days and a lesser concentration for a further period of five or six days is the minimum reliable standard. Low initial dosage is distinctly unsafe.

Intensive intravenous serum therapy does not compensate for low dosage of sulphanilamide. No evidence in favour of auxiliary treatment with serum was obtained.

Similar high dosage is recommended for M. & B. 693, although there is evidence that lower dosage of this drug will often be successful.

Persons of all ages were amenable to chemotherapy. Infancy is not now an age of unfavourable prognosis, but further experience is required for prognosis in the age group over forty.

Groups I and II meningococci are equally susceptible to chemotherapy.

The oral route can be used throughout in most cases. For vomiting or difficulty in swallowing, an occasional intramuscular injection of M. & B. 693 soluble (sodium solution) is convenient.

In certain cases a combination of M. & B. 693 and sulphanilamide is serviceable.

The sulphanilamide (Streptocide) was kindly supplied by Messrs. Evans, Sons, Lescher and Webb, through the Therapeutic Trials Committee of the Medical Research Council, and the M. & B. 693 tablets and sodium solution by Messrs. May and Baker. The pathological work was done at the Southern Group Laboratory, and the biochemical work at the Group Laboratory, Lewisham Hospital, L.C.C.

I have to thank the medical superintendents of the L.C.C. general hospitals for transferring their cases so promptly. Without their active coöperation it would have been impossible to accumulate the material.

References at foot of opposite page

THE ELECTROSURGICAL OPERATION IN GALL-BLADDER DISEASES

RESULTS OF 13 YEARS' EXPERIENCE

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THE excellent healing obtained through the accurate covering of the liver bed with peritoneum after a subserous cholecystectomy without any drainage led me to seek similar results in more advanced cases also, where, owing to partial necrosis, advanced inflammation, or scars, an exact subserous cholecystectomy (with a knife or with scissors) was no longer possible. The idea was to destroy the inflamed mucosa and the whole of the inner layers down to the serosa from the *inside*, thus keeping the serous layer available for covering the liver bed with peritoneum.

I started my experiments in 1922. At first I used a thermocautery to destroy the inner coats of the gall-bladder. If the wall was thicker than usual, it was sometimes necessary to remove the superficial crust with a sharp spoon and to cauterise again until the inner layers were entirely destroyed. A technical improvement was made in 1926, when, instead of cautery, we began to use electrocoagulation, which is more quickly and more easily performed.

By varying the strength of the current, the form of the different secondary coagulation electrodes, and the pressure exercised on the tissue, the depth of the desired destruction can easily be regulated. The depth of the electrocoagulation effected is roughly in inverse proportion to the size of the electrode. The method enables one to necrotise, when required, only a thin layer over the serosa, but if necessary one can achieve deep coagulation down into the liver bed for necrosis and abscesses. Electrocoagulation destroys the inflamed and badly infected tissues, and the result is aseptic necrosis with a perfect tendency to heal.

TECHNIQUE

The technical procedure employed by me as a routine in more than 1000 cases is as follows:—

The abdomen is opened by a costal incision, and a self-retaining retractor is inserted in the edges of the wound. Stomach and colon are held aside with saline swabs. The excellent exposure obtained through the costal incision (Pribram 1930) enables the liver to be left in place. Traction and displacement of the liver, with consequent traction on the diaphragm, are sometimes responsible for a postoperative hypostasis or a massive collapse of the lungs, pneumonia, and other complications.

Attention must first be paid to the inflamed gall-bladder, which, especially when enlarged, hinders careful examination of the common duct. The whole field round the bladder having been protected with saline swabs, the liquid contents of the bladder are aspirated through a two-way syringe (fig. 1). The bladder is washed out several times, first with saline and then with a mild antiseptic solution (Rivanol 1 in 1000). The serosa over the cystic duct is incised and the latter laid bare and cut between two silk ligatures, after one has satisfied oneself about the condition of the hepatic duct and the absence of anatomical anomalies. The cystic artery is ligatured, when this can be done easily and quickly, but this is not essential. It is useful and generally easy to separate serosa flaps from the neck of the bladder with large scissors to cover the cystic stump.

Next, the bladder is opened (fig. 2), the stones are removed, and if possible the proximal cystic stump is excised, together with a small part of the mucosa of the bladder. This procedure facilitates electrocoagulation. The bladder now lies like an open book. The inside is electrocoagulated (fig. 3) down to the serosa. As mentioned, one sometimes removes the coagulated layer with a sharp spoon. In all cases, however, only the serous layers are preserved. If the gall-bladder wall is very thick, the inner coats can be removed with a cutting wire loop, as in electrocurettage, and then coagulated further, if necessary, with the normal button electrode. The serosa flaps are folded and sewn together in exactly the same way as in a subserous cholecystectomy (fig. 4).

After the liver bed has been accurately covered with peritoneum, the abdomen can be closed without drainage. The tendency to heal is perfect.

The following case seems to be of interest both from a clinical and technical point of view, because almost the whole technique of gall-stone surgery was exercised in this one case, and the tendency to heal after mucoclasis can be demonstrated. The patient was operated on in 1929, before the ether method (*Lancet*, 1939, **1**, 1311) had been introduced.

A woman, aged 41; operation under rectal anæsthesia. The gall-bladder was exposed through a costal incision and was found to be full of stones. The cystic duct was as thick as a finger and likewise filled with stones. Its aspirated liquid contents consisted of turbid mucus and pus. Subserous cholecystectomy was impossible. The bladder was opened and all stones were removed. The mucosa was coagulated down to the serosa, as was also an abscess in the liver bed. The cystic duct was incised down to the common duct, and the stones in it were removed. Palpation showed that the right and left hepatic ducts were full of stones. After a difficult removal of these stones through an incision in the hepatic duct, there was an ample flow of dark turbid bile.

On probing the common duct downwards towards the duodenum, the ampulla of Vater was found to be entirely closed, being tightly packed with stones which could not be driven either upwards or into the duodenum. A transduodenal choledochotomy was therefore performed—i.e., the duodenum was opened through an oblique incision and the papilla pushed forwards, probed, and incised on the right side. All the stones in the papilla were then removed and the common duct and papilla rendered accessible to a probe of small calibre. The papilla, however, appeared to be scarred and shrunken, and so narrow that it seemed inadvisable to use it as the only passage for the outflow of bile; so the duodenum was partly closed, the opening in the hepatic duct sutured, and a choledochoduodenostomy performed with the incision already made in the cystic duct.

All sutures were carefully covered, partly with the flaps of the duodenal ligament and partly with the flaps remaining from mucoclasis, the whole being accurately covered with peritoneum. The abdominal

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