pointed out by others (Whipple, Opie, Ravdin) the clinician still firmly believes that an almost exclusively carbohydrate diet is necessary in severe liver damage. It may be that a combination of carbohydrate with protein, such as giving plasma intravenously along with dextrose, would be more useful. The question of the mechanism of this failure of vitamin K to work is also quite important. Is it that the liver is required to do something to the vitamin K intake? Does it furnish some co-factor? Or is it possible that in addition to damaging the liver some other factors come in? I did not see anything about fibrinogen determinations, and the prothrombin times were done by the Quick method, which will be definitely affected by lowered fibrinogen. I imagine the authors determined the fibrinogen and said nothing about it. Another question which comes up is whether or not there is an increase in some anticoagulant in the blood. In the original manuscript they determined whether or not heparin was responsible for this bleeding by giving protamine intravenously to their animals. They found no change, so that heparin can be eliminated, but it is possible that there might be some other anticoagulant which could be responsible for the bleeding.

DR. JONATHAN RHOADS, Philadelphia: We have been able to induce hypoprothrombinemias in Philadelphia with carbon tetrachloride, but we have not had as refined a technic as Dr. Bollman has shown you. We have simply given the material by mouth and it works well. Some years ago, when the question of the source of fibrinogen was being studied at the Mayo Foundation, Dr. Mann made the statement that the fact that a hepatotoxic agent will produce a given change cannot be used as proof that the liver is involved in the change. We were so impressed with the logic of this view that Dr. Richard Warren and I performed total hepatectomy in a number of dogs. The prothrombin level declined progressively in these animals until they died. The fall in the prothrombin level was much more rapid than the concomitant fall in fibrinogen concentration. We have observed several patients with hypoprothrombinemia who have failed to respond to vitamin K. While such patients do not all have a bad prognosis, many of them do. Two of these patients died within thirty-six hours after the prothrombin started to rise, another a little later. Sections of the liver obtained at autopsy showed extensive fibrous changes and only scattered liver cells having a normal appearance. With regard to the effect of diet on liver injury produced by carbon tetrachloride in rats, the results obtained by Dr. Bollman were somewhat at variance with those obtained by Goldschmidt, Vars and Ravdin in 1939, who found that in protecting rats against the effects of one hour of chloroform anesthesia much the best results were obtained with a diet that was high in carbohydrate but also high in protein. I should like to ask Dr. Bollman whether any analyses were made on the meat supplement. In Dr. Ravdin's laboratory, difficulty was encountered in using a supplement of beef heart. The expected results were not forthcoming, and it was found on looking up the analysis of beef heart that it contained a substantial amount of fat and that it was necessary to use a pure protein such as casein for the protein supplement.

DR. JESSE L. BOLLMAN, Rochester, Minn.: Dr. Maddock called attention to some things I forgot. He asked about fibrinogen determination. We did determine fibrinogen in our rats. I did not say anything about these determinations because our results were extremely variable. However, in using the Quick method for prothrombin I found it to be accurate in that I can add normal blood, which contains a normal amount of fibrinogen, and also a normal amount of prothrombin to bloods of low prothrombin content. I have diluted this blood; then adding the amount of diluted blood I can determine to a matter of 1 or 2 per cent, I am sure, the actual prothrombin content by the Quick method. Dr. Rhoads brought the difference between my results and the results of Ravdin and his associates. I believe that Dr. Rhoads will agree that changes in the liver, histologic changes in the liver that I showed you, are not of outstanding difference in those different animals. It is pretty much a matter of opinion. Also, considering the fact that Dr. Ravdin's experiments were acute experiments following the administration of one dose of chloroform, and I used carbon tetrachloride repeatedly, I am not surprised that we can get from a histologic standpoint a variation of opinion. With reference to the utilization of protein, we used muscle for our protein. We also have another series in which I have used casein and another series gelatin, and there is no essential difference among the three.

EPIDEMIC CEREBROSPINAL MENINGITIS (MENINGOCOCCIC)

THE TREATMENT OF 113 PATIENTS WITH ANTIMENINGOCOCCUS SERUM, MENINGOCOCCUS ANTITOXIN AND SULFANILAMIDE

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One hundred and thirteen cases of epidemic cerebrospinal meningitis, representing for the greater part a small epidemic of the disease in Rhode Island, have been admitted to the Charles V. Chapin Hospital since February 1935. The epidemic gave us an opportunity to study the method of treatment of the "genus epidemicus" type of the disease and also to determine the relative therapeutic value of the antimeningococcus serum, the meningococcus antitoxin of Ferry and sulfanilamide.

ANTIMENINGOCOCCUS SERUM

A routine method of treatment, similar to the one which had been used successfully at the Herman Kiefer Hospital by Gordon [1] during the 1927 to 1931 epidemic in Detroit, was adopted at the beginning of the epidemic when severe and fulminating cases were encountered. This consisted of alternate lumbar and cisternal injections of antimeningococcus serum at intervals of twelve hours during the first thirty-six or forty-eight hours. After this period treatment was administered once daily, preferably by the lumbar route. The doses for intrathecal treatment were from 5 to 10 cc. less than the amount of spinal fluid removed.

TABLE 1.—*Comparison of Case Fatality Rates in Two Groups of Cases Treated with Antiserum and Antitoxin*

	No. of Cases	No. of Deaths	Fatality Rate of All Deaths	Within 48 Hours		Excluding Deaths Within 48 Hours
				Deaths	Rate	
Antiserum	43	18	41.8%	7	38.9%	30.6%
Antitoxin	33	14	42.4%	8	57.1%	24.0%
Totals	76	32	42.1%	15	46.9%	27.9%

Immediately after the initial intraspinal injection and after a satisfactory sensitivity test for horse serum, a large dose of the antiserum (from 30 to 60 cc. for infants and young children and 90 to 120 cc. for older children and adults), diluted two or three times by volume in physiologic solution of sodium chloride containing 5 or 10 per cent dextrose, was given intravenously. These doses given once or twice were ordinarily sufficient but, in very severe cases and those showing persistent septicemia, larger amounts of the antiserum were given several times, preferably during

1. Gordon, J. E.: Medical Report of the Herman Kiefer Hospital for the Five Years 1927-1931, Detroit, Department of Health, Division of Epidemiology.

the first twenty-four hours. Intrathecal treatment was continued until two consecutive negative spinal cultures were obtained.

The first eight of the 113 patients were treated entirely with antimeningococcus serum of several standard brands. Five of these died, a case fatality rate of 62.5 per cent.

ANTIMENINGOCOCCUS SERUM AND MENINGOCOCCUS ANTITOXIN

About this time (March 23, 1935) Hoyne [2] reported 296 cases of epidemic cerebrospinal meningitis from the contagious disease department of the Cook County Hospital, Chicago. Eighty-five of these were treated with the meningococcus antitoxin of Ferry [3] and the remainder, or 211 cases, with two well known standard brands of antimeningococcus serum. The fatality rate in the antitoxin-treated cases was 23.5 per cent compared with 45.9 per cent for antiserum-treated cases.

TABLE 2.—*Cases and Deaths by Ten Year Age Groups*

Age Group	Cases	Deaths	Fatality Rate
1 to 10	35	10	28.6%
11 to 20	16	10	62.5%
21 to 30	10	5	50.0%
31 to 40	9	3	33.3%
41 to 50	3	2	66.6%
51 to 60	1	0	0.0%
61 to 70	2	2	100.0%

Early in the same year Banks [4] in England also reported twenty-five cases treated with the Ferry antitoxin with seven deaths, a case fatality rate of 28 per cent.

Inspired by these favorable reports, we decided to use the new meningococcus antitoxin. The plan was to give meningococcus antitoxin or antimeningococcus serum to alternate patients admitted without regard to the severity of the disease or to the age or sex of the patient. The method of treatment and dosages were the same as those already outlined for antiserum. Seventy-six patients were treated in this way, forty-three with antiserum and thirty-three with antitoxin. The difference in the numbers of cases treated is explained by the fact that patients transferred from general hospitals, where antiserum had already been given, were continued on antiserum, usually of the same make as that previously used.

RESULTS

Eighteen of the forty-three patients treated with antimeningococcus serum died, a case fatality rate of 41.8 per cent. Of the thirty-three meningococcus antitoxin-treated patients fourteen died, a case fatality rate of 42.4 per cent. If patients who died within forty-eight hours of admission are considered insufficiently treated, the rate is 30.6 per cent for the antiserum and 24.0 per cent for the antitoxin.

It is apparent from a comparison of the percentage mortality rates in table 1 that meningococcus antitoxin was no more beneficial than an effective brand of antimeningococcus serum in the treatment of epidemic cerebrospinal meningitis. However, judging from the percentage of deaths occurring within forty-eight hours, it appears that the cases treated with antitoxin were, on the whole, more severe than those treated with the antiserum.

A study of table 2, arranged in ten year groups and respective fatality rates, shows that antiserum and antitoxin were given to equally unfavorable subjects. The youngest patient in these two groups of cases was 3 months and the oldest 64 years old, averaging 14.2 years. The average age of the patients treated with antitoxin was 15.6 years and the average of those treated with antiserum was 13.2 years.

COMPARISON OF OUR RESULTS WITH THOSE OF HOYNE

Our case fatality rate of 41.8 per cent in cases treated with antiserum compares favorably with the 45.9 per cent cited by Hoyne,[2] but our rate of 42.4 per cent is nearly twice as high as the 23.5 per cent reported by him in his antitoxin-treated cases. The explanation for this difference in results is not obvious. An analysis of factors involved in the therapy of this series of cases fails to reveal any specific reason.

The meningococcus antitoxin used by us was obtained from the same firm [5] that supplied Hoyne with material for the treatment of his eighty-five cases.

Our method of intrathecal therapy differed from that of Hoyne. We gave alternate lumbar and cisternal injections of the antitoxin every twelve hours during the first thirty-six or forty-eight hours, then followed with one injection daily, by the lumbar route. Hoyne gave lumbar injections once daily, using the cisternal method only when there was a block in the lower route. The fact that our fatality rate among cases treated with antimeningococcus serum compares favorably with that reported by Hoyne seems to indicate that our method of intrathecal treatment was not a factor acting against a favorable rate in the antitoxin-treated cases.

The amount of antitoxin given by us seems to have been adequate. A study of table 3 shows that the average amount of antitoxin administered intrathecally and intravenously in our series of successfully treated cases exceeded that given by Hoyne.

That the answer to this question depends wholly on the therapeutic value of the antitoxin itself may be derived from experience in the use of antimeningococcus serum. It is generally known that standard brands of antimeningococcus serum may vary widely in their therapeutic value and that even an effective brand may fail to produce uniformly good results in a given epidemic.

TABLE 3.—*Amount of Meningococcus Antitoxin Received by Patients Who Recovered in Our and in Hoyne's Series of Cases*

	Total Average	Smallest Amount	Largest Amount	Average Amount Parenteral Administered	Average Amount Intrathecal Administered
Our series	283.0 cc.	145.0 cc.	620.0 cc.	132.0 cc.	151.0 cc.
Hoyne's series	161.7 cc.	75.0 cc.	360.0 cc.	58.5 cc.	115.1 cc.

This is likely to be true in epidemics occurring in different parts of the country. It is believed to be due to the difference in the strains of meningococci prevailing in a particular epidemic and the strains used in developing the antibacterial serum. Gordon [1] discarded standard brands of antimeningococcus serum and succeeded in lowering the mortality rate in the 1927 to 1931 epidemic in Detroit by the use, among other measures, of an antiserum developed through immunizing horses with the prevailing strains of the meningo-

2. Hoyne, A. L.: Meningococcic Meningitis: A New Form of Therapy, J. A. M. A. **104**: 980 (March 23) 1935.
3. Ferry, N. S.; Norton, J. F., and Steele, A. H.: Studies of the Properties of Bouillon Filtrate of the Meningococcus: Production of a Soluble Toxin, J. Immunol. **21**: 293 (Oct.) 1931.
4. Banks, H. S.: Note on Ferry's Meningococcus Antitoxin in the Treatment of Acute Cerebrospinal Fever, Lancet **1**: 856 (April 13) 1935.
5. Meningococcus Antitoxin, Parke, Davis & Co., Detroit, New and Nonofficial Remedies, J. A. M. A. **104**: 1007 (March 23) 1935.

coccus. Wright and his colleagues [6] stated that, when a patient with meningococcic meningitis fails to respond to treatment, one cannot justifiably conclude that the strain of organism encountered is resistant to serum therapy but only that the serum used is not specific for that organism.

Branham [7] expressed the opinion that various lots of antitoxin undoubtedly vary in efficacy, as do those of antibacterial serum, and this will result in conflicting reports of its value until such time as standardization becomes more satisfactory.

Therefore it seems logical to conclude that our less successful results were due in part or wholly to the difference in action of the meningococcus antitoxin itself.

SULFANILAMIDE

In the spring of 1937, among the many startling reports on the curative power of sulfanilamide, was one by Schwentker and his associates [8] on ten cases of meningococcic meningitis and one of meningococcemia. Recovery occurred in all but one of the cases of meningitis, indicating the effectiveness of the drug against human infection as well as experimental infection in mice reported earlier by Buttle [9] and confirmed by Rosenthal and his associates.[10]

Encouraged by these reports, we decided to include meningococcic meningitis on our list [11] of diseases for treatment with sulfanilamide. The routine method of treatment already described was in no way to be changed except that sulfanilamide would be substituted for antiserum and antitoxin and that intrathecal injections (lumbar) would be given once a day until two negative spinal fluid cultures were obtained.

DOSAGES

The doses of sulfanilamide are summarized in table 4.

The initial dose of sulfanilamide is calculated on the basis of 15 grains (1 Gm.) per 20 pounds (9 Kg.) of body weight up to 100 pounds (45 Kg.). Above this weight it is rarely necessary to exceed a total of 90 grains (6 Gm.). We believe it is important to obtain, as soon as possible, blood and spinal fluid concentration of from 10 to 15 mg. or more of the drug per hundred cubic centimeters and to keep the concentration at this level with adequate maintenance doses. It is better, it seems to us, to err on the side of too large rather than too small doses. We have had patients whose blood and spinal fluid reached a level of 25 mg. of the drug without causing any deleterious effects. Depending on the method of administration, the maintenance dose should be given either every four or eight hours, day and night, during the acute stage of the disease. This procedure is followed until the patient has shown unmistakable signs of improvement. The night doses are then omitted. The daily doses must be continued well into convalescence, usually for from seven to ten days, if relapses are to be avoided.

A check on the level of the drug in the blood should be made from four to eight hours after the large initial dose to determine whether satisfactory concentration has been reached. If found below the desired level, the next maintenance dose should be doubled, followed in four hours by the regular maintenance dose by mouth. Another determination of the blood level of the drug is advised at the end of twenty-four hours. This is to check on the adequacy of the maintenance doses.

Sulfanilamide is excreted principally through the kidneys. Consequently, to maintain a high and even concentration the fluid intake should be restricted to about 2,000 cc. in twenty-four hours in adults, and proportionate amounts in children.

Sulfanilamide is given in tablets or crushed in water or milk. An equivalent amount of sodium bicarbonate should be given with each dose of sulfanilamide in order to avoid acidosis. This condition is apt to develop in infants and young children. We have seen it in two of our small children. For parenteral administration, a solution containing 1 per cent of sulfanilamide in physiologic solution of sodium chloride or one-sixth molar sodium lactate is used. When the latter is utilized, sodium bicarbonate is unnecessary.

If the initial dose of the drug is administered by venoclysis, the first maintenance dose by mouth should be given immediately afterward rather than after four hours. This is advisable because of the rapid excretion of the drug by the kidneys as a result of diuresis, which usually follows venoclysis.

TABLE 4.—*Doses of Sulfanilamide in the Treatment of Epidemic Cerebrospinal Meningitis*

Tablets for Administration by Mouth			
During Acute Stage of the Disease	Initial Dose	Maintenance Dose	Intervals (Day and Night)
Adults (100 lbs. and over)	50-90 gr.	15-20 gr.	4 hrs.
Adults (50-90 lbs.)	30-50 gr.	10-15 gr.	4 hrs.
Children (25-50 lbs.)	20-30 gr.	5-10 gr.	4 hrs.
Babies	10-20 gr.	5 gr.	4 hrs.

During Convalescence	Maintenance Dose	Intervals
	10-15 gr.	Four times daily
	5-10 gr.	Four times daily
	5 gr.	Four times daily

One per Cent Solution of Powdered Sulfanilamide in Physiologic Solution of Sodium Chloride or in One-Sixth Molar Sodium Lactate for Parenteral Administration During Acute Stage of the Disease

	Initial Dose	Maintenance Dose	Intervals
Adults (100 lbs. and over)	700 cc.	500 cc.	8 hrs.
Adults (50-90 lbs.)	300-500 cc.	200-300 cc.	8 hrs.
Children (25-50 lbs.)	100-300 cc.	100-200 cc.	8 hrs.
Babies	100 cc.	100 cc.	8 hrs.

Intrathecal Administration

5 to 10 cc. less than amount of cerebrospinal fluid removed

METHODS OF SULFANILAMIDE THERAPY

The treatment of epidemic cerebrospinal meningitis has been based principally on the premise that the antimeningococcus serum, in order to be effective, must come in direct contact with the organisms in the meninges. This necessitated the introduction of the serum directly into the subarachnoid space by way of the lumbar region, cisterna magna or the lateral ventricles.

Since the World War the administration of antibacterial serum intravenously in addition to the intrathecal injection has been generally used on the theory that meningococcemia precedes the meningitis. It has been the belief, however, that little or no antiserum reaches the meninges when given intravenously or subcutaneously.

In 1935 Hoyne [2] predicted that eventually it would be shown to be entirely unnecessary to administer any

6. Wright, I. S.; DeSanctis, A. G., and Shepler, Adele: The Determination of the Value of Serum in the Treatment for Meningococcus Meningitis, Am. J. Dis. Child. **38**: 730 (Oct.) 1929.

7. Branham, Sara E.: Serum, Antitoxin and Drugs (Sulfanilamide) in Treatment of Meningococcus Meningitis, M. Ann. District of Columbia **7**: 1-5 (Jan.) 1938.

8. Schwentker, F. F.; Gelman, Sidney, and Long, P. H.: The Treatment of Meningococcic Meningitis with Sulfanalamide: Preliminary Report, J. A. M. A. **108**: 1407-1408 (April 24) 1937.

9. Buttle, G. A. H.; Gray, W. H., and Stephenson, Dora: Protection of Mice Against Streptococcal and Other Infections by P-Aminobenzenesulfonamide and Related Substances, Lancet **1**: 1286-1290 (June 6) 1936.

10. Rosenthal, S. M.; Bauer, Hugo, and Branham, Sara E.: Studies in Chemotherapy: Comparative Studies of Sulfonamide Compounds in Experimental Pneumococcus, Streptococcus and Meningococcus Infections, Pub. Health Rep. **52**: 662 (May 21) 1937.

11. Stevens, R. E.: Sulfanilamide in the Treatment of Other Bacterial Infections, Rhode Island M. J. **21**: 145-148 (Oct.) 1938.

serum intrathecally if sufficient antitoxin was injected intravenously. A year later he [12] reported ninety-six cases treated exclusively by intravenous injections of antitoxin with a fatality rate of 15.9 per cent.

The advent of sulfanilamide has placed this method of treatment of epidemic cerebrospinal meningitis on a more rational basis. Banks [13] and Willien [14] had reported the cure of meningococcic meningitis with sulfanilamide given by mouth or subcutaneously without intrathecal administration. Marshall and his associates [15] reported that they had found sulfanilamide in all body fluids, including the spinal fluid, when the drug was given by hypodermoclysis as well as by mouth. Allott [16] found that the concentration of the drug in the spinal fluid was very nearly that in the blood. We arrived at the same conclusion after a large number of tests.

These facts, together with the relatively simple technic [17] for determining the concentration of the drug in the spinal fluid and blood, make the intravenous, subcutaneous or oral therapy of meningococcic meningitis entirely feasible. Lumbar puncture is done only for the purpose of diagnosis and drainage. Consequently we changed our original method of sulfanilamide therapy. At first we reduced gradually the number of intrathecal injections and finally omitted all but one injection following the first diagnostic lumbar puncture.

istration or by Levine tube, if necessary, every four hours (day and night) during the acute stage of the disease. In mild cases the administration of sulfanilamide in adequate doses by mouth is sufficient.

RESULTS OF SULFANILAMIDE THERAPY

Since the spring of 1937, twenty-nine cases of epidemic cerebrospinal meningitis have been treated entirely with sulfanilamide. This plan of treatment with sulfanilamide has been continued in spite of the fact that experimental [18] and clinical reports [19] have indicated that the combined use of the drug and antibacterial serum or antitoxin is more effective against meningococcic infection than sulfanilamide alone. Our justification for the continuance of this plan is the fact that our results have been very satisfactory. Also there are clinical reports [20] showing good results in the use of sulfanilamide alone in the treatment of meningococcic meningitis.

Five of the twenty-nine patients died, a fatality rate of 17.2 per cent. Four of these were in the group of nineteen patients who received daily intrathecal injections as well as parenteral and oral administrations of the drug, and all these deaths occurred within twelve hours of admission to the hospital. The other death was in the group of eight patients who received but one intrathecal treatment in addition to the parenteral and oral therapy and took place fifty-one hours after admission. Two patients who were treated entirely by oral administration of the drug recovered.

TABLE 5.—*Influence of Age on Results of Antiserum, Antitoxin and Sulfanilamide Therapy*

	Cases			Deaths			Fatality Rates			
	Antiserum	Antitoxin	Sulfanilamide	Antiserum	Antitoxin	Sulfanilamide	Antiserum	Antitoxin	Sulfanilamide	All Cases
Under 1 year	4	2	3	0	2	0	0.0%	100.0%	0.0%	22.2%
1 to 5 years	13	10	5	5	2	1	38.4%	20.0%	20.0%	28.6%
6 to 10 years	6	5	4	4	0	2	66.6%	0.0%	50.0%	40.0%
11 to 20 years	12	6	6	7	4	1	58.3%	66.6%	16.6%	50.0%
21 to 30 years	7	4	7	3	3	0	42.9%	75.0%	0.0%	33.3%
31 to 40 years	5	4	2	2	1	1	40.0%	25.0%	50.0%	36.4%
41 to 50 years	2	1	1	1	1	0	50.0%	100.0%	0.0%	50.0%
51 to 60 years	1	0	1	0	0	0	0.0%		0.0%	0.0%
61 to 70 years	1	1	0	1	1	0	100.0%	100.0%		100.0%
Totals	51	33	29	23	14	5	45.1%	42.4%	17.2%	37.1%

Because of the seriousness of epidemic cerebrospinal meningitis, we consider it imperative that measures to combat this disease be instituted with as little delay as possible. It follows that any method which could quickly bring the concentration of the drug to the optimum level in the blood and spinal fluid should be used. To do this we inject a 1 per cent solution of the drug into the spinal canal at the initial lumbar puncture and immediately follow this with a large dose intravenously or by hypodermoclysis. This helps to raise the blood and spinal fluid level rapidly. It also helps guarantee an adequate concentration against the possibility of poor absorption in the gastrointestinal tract, vomiting or other mishaps which may occur in the management of severely sick and uncooperative patients. When this is accomplished the optimum concentration of the drug is maintained by oral admin-

Excluding the four deaths within twelve hours, the corrected case fatality rate was 4.0 per cent. This result was impressive. It should be explained that these twenty-nine patients were admitted toward the end of the epidemic when the severity of the disease was decreasing, whereas those treated with antiserum and antitoxin were seen at the peak of the epidemic in 1935 and 1936.

Except for two small children who developed acidosis, there was no serious reaction to sulfanilamide. In no case was the drug discontinued because of its toxic action.

12. Hoyne, A. L.: Intravenous Treatment of Meningococcic Meningitis with Meningococcus Antitoxin, J. A. M. A. **107**: 478 (Aug. 15) 1936.
13. Banks, H. S.: Serum and Sulfanilamide in Acute Meningococcal Meningitis: A Preliminary Survey Based on One Hundred and Thirteen Cases, Lancet **2**: 7-13 (July 2) 1938.
14. Willien, L. J.: Sulfanilamide Therapy in Meningococcic Meningitis, J. A. M. A. **110**: 630-632 (Feb. 26) 1938.
15. Marshall, E. K. J.; Emerson, Kendall, Jr., and Cutting, W. C.: Para-Aminobenzenesulfonamide: Absorption and Excretion; Method of Determination in Urine and Blood, J. A. M. A. **108**: 953-957 (March 20) 1937.
16. Allott, E. N.: Sulfanilamide Content of Cerebrospinal Fluid During Treatment, Lancet **2**: 13-14 (July 2) 1938.
17. Schmidt, E. G.: The Determination of Sulfanilamide in Tungstic Acid Blood Filtrates by Means of Sodium Beta-Naphthoquinone-4-Sulfonate, J. Biol. Chem. **122**: 757-762 (Feb.) 1938.
18. Branham, Sara E., and Rosenthal, S. M.: Studies in Chemotherapy: Sulfanilamide, Serum, and Combined Drug and Serum Therapy in Experimental Meningococcus and Pneumococcus Infections in Mice, Pub. Health Rep. **52**: 685-695 (May 28) 1937. Brown, T. M.: Protective Action of Sulfanilamide and Antimeningococcus Serum on Meningococcus Infection in Mice, Bull. Johns Hopkins Hosp. **61**: 272 (Oct.) 1937. Branham, Sara E.: The Effect of Sulfapyridine and Sulfanilamide With and Without Serum in Experimental Meningococcus Infection, Pub. Health Rep. **55**: 12-24 (Jan. 5) 1940.
19. Waghelstein, J. M.: Sulfanilamide in the Treatment of One Hundred and Six Patients with Meningococcic Infections, J. A. M. A. **111**: 2172 (Dec. 10) 1938. Clyde, W. A., and Neely, M. G.: Clinical Experience in the Treatment of Meningococcemia and Meningococcic Meningitis: Analysis of One Hundred and Eighteen Cases Treated with Four Different Methods of Treatment, South. M. J. **32**: 594-601 (June) 1939. Banks.[13]
20. Bryant, Joseph, and Fairman, H. D.: Chemotherapy of Cerebrospinal Fever in the Field, Lancet **1**: 923-926 (April 22) 1939. Buttle, Gray and Stephenson.[9] Willien.[14]

ANALYSIS OF ENTIRE SERIES

There were forty-two deaths in the entire series of 113 cases, a case fatality rate of 37.1 per cent. Exclusion of the twenty-two deaths occurring within forty-eight hours of admission brings the fatality rate down to 21.9 per cent.

The influence of age on the fatality rate in epidemic cerebrospinal meningitis has been generally considered to be most favorable in the group between 6 and 10 years old and very unfavorable under 1 and over 50 years. Analysis of results in table 5 shows the youngest age group to be the most favorable with two deaths in nine cases, a rate of 22.2 per cent. The next favorable group is the 1 to 5 year group, with eight deaths in twenty-eight cases, a rate of 28.5 per cent. The expected favorable age group of 6 to 10 years has a fatality rate of 40.0 per cent.

It is admitted that statistics based on a small number of cases are subject to error and therefore inconclusive. They are presented here primarily for the sake of completeness.

In all but four of the 113 cases, diagnosis of epidemic cerebrospinal meningitis was confirmed by recovery of the organism either from the spinal fluid or from the blood. The four cases in which meningococcus was not found were diagnosed from the clinical observations alone. These were so definite and typical that a diagnosis of meningococcic meningitis was considered justifiable.

COMPLICATIONS AND RELAPSES

There were two complications in the entire series of 113 cases. One was paralysis of the external rectus muscle of one eye, which developed during the acute stage of the disease. The patient was a woman who was treated with meningococcus antitoxin. The other was total deafness in a child 2 years of age who was treated with antimeningococcus serum.

One relapse was encountered in a youth aged 20 years who had been treated with antiserum. He had recovered from the meningitis in five days. Twelve days later he developed meningococcemia. He recovered after a long period of treatment with antiserum, antitoxin, autogenous vaccine and finally sulfanilamide.

SUMMARY

One hundred and thirteen cases of epidemic cerebrospinal meningitis, representing for the greater part a small epidemic, were treated with antimeningococcus serum, meningococcus antitoxin and sulfanilamide. The case fatality rate for the entire series was 37.1 per cent.

A special study comprising seventy-six cases was undertaken to determine the relative therapeutic values of antimeningococcus serum and the meningococcus antitoxin of Ferry. Forty-three cases were treated with antimeningococcus serum and thirty-three with meningococcus antitoxin with a fatality rate of 41.8 per cent and 42.4 per cent respectively. The result in the latter group was not as favorable as that reported by Hoyne. The reason for this is not obvious but appears to be attributable to the inadequate action of the antitoxin itself.

In a group of twenty-nine cases treated with sulfanilamide alone the fatality rate was 17.2 per cent. In the treatment of these cases intrathecal administrations of the drug were reduced to one in each of eight cases and none in two.

Complications were confined to one each of the antiserum and antitoxin-treated cases and none in the sulfanilamide. There was only one relapse and this was in an antiserum-treated case.

These data and our personal experience in the care of patients with epidemic cerebrospinal meningitis during the last five years have led us to draw the following conclusions:

1. The therapy of epidemic cerebrospinal meningitis with antimeningococcus serum and meningococcus antitoxin is, at best, inadequate. The number of deaths is high, irrespective of the amount of serum used and the methods of treatment employed.
2. The meningococcus antitoxin of Ferry has not been impressive clinically. The results obtained with this form of treatment have not been better than those with standard brands of antimeningococcus serum.
3. Sulfanilamide has been shown to be highly efficacious even when used alone. The clinical results are impressive and in some instances dramatic.
4. Sulfanilamide offers the best means by which the treatment of epidemic cerebrospinal meningitis can be simplified. The drug enters the subarachnoid space readily when given intravenously, subcutaneously or orally. This makes intrathecal administrations of the drug more of an expedient than a necessity.

THE DESIVAC PROCESS FOR DRYING FROM THE FROZEN STATE

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During the past few years, evidence has been accumulating which supports the value of human blood plasma or serum as substitutes for whole blood transfusion.[1] In the case of traumatic shock without hemorrhage where there is hemoconcentration, plasma may even be preferable to whole blood.[2] Even when there is no hemoconcentration, the advantage of a blood substitute not requiring matching of type and one readily available immediately in the emergency is clear. The reduction in hemoglobin which patients can endure without danger is extreme; it is reduction in circulating blood volume which must be corrected promptly. In cases of nephrosis and of increased cerebrospinal fluid pressure as resulting from concussion, the advantage of concentrated plasma or serum is added to the other advantages by virtue of an increased osmotic effect to withdraw fluids into the circulatory system. In dry form resulting from desiccation from the frozen state the plasma proteins may be maintained in highly stabilized form, without refrigeration except for long time reserve-storage, and are instantly available for use by dissolving in water to the original or to a more concentrated volume. Although these proteins may be stored either as plasma or as serum, it appears that the former may be preferable by virtue of minimizing the danger of reactions.[3]

War-time emergency increases the importance of ready availability of large reserves of this agent in the

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The length of this article does not permit an extensive review of the literature, but from the key references cited a full bibliography may be obtained.

1. Strumia, Max M.; Wagner, Joseph A., and Monaghan, J. Frederick: The Use of Citrated Plasma in the Treatment of Secondary Shock, J. A. M. A. **114**: 1337 (April 6) 1940.
2. Moon, Virgil H.: Circulatory Failure of Capillary Origin, J. A. M. A. **114**: 1312 (April 6) 1940.
3. Strumia, Max M.; Wagner, Joseph A., and Monaghan, J. Frederick: The Intravenous Use of Serum and Plasma, Fresh and Preserved, Ann. Surg. **3**: 623 (April) 1940.