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## MENINGOCOCCIC MENINGITIS

## A CLINICAL STUDY OF ONE HUNDRED AND FORTY-FOUR EPIDEMIC CASES\*

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The present epidemic of meningitis in Indianapolis began in November, 1929. This report includes cases admitted to the Indianapolis City Hospital between Nov. 11, 1929, and April 1, 1930. One patient was received in November, 52 in December, 22 in January, 44 in February, and 25 in March. Less than ten other patients either died without treatment or were treated elsewhere. The epidemic is still in progress, cases being admitted at the rate of about fifteen a month. The disease at present appears to be less virulent than during the early months.

Practically 90 per cent of the early cases were employees or relatives of employees in two departments of a large industrial concern. Later, however, contacts were from several other sources, and eventually a considerable number could not be traced. Eighty-eight patients were white and fifty-six were Negroes. During the early weeks of the epidemic, almost all patients were received from homes which were unhygienic and insanitary, poorly ventilated and heated, and in which there was close contact between members of the family. As cases became more scattered and contacts more difficult to trace, a small number of patients came from better homes. Eleven families furnished from two to four cases each, comprising a total of thirty cases.

Not only have the exhaustive studies by Flexner<sup>1</sup> and his associates of a large series of cases over a period of several years contributed greatly to the knowledge and treatment of the disease, but their reports also include complete surveys of the literature. We shall therefore refer chiefly to these and other papers concerned with some phase of the disease we wish to emphasize.

## MANNER OF OBTAINING DATA

Histories of the patients were of necessity obtained from relatives in the home, as many patients were comatose when received. On admission to the hospital, a detailed physical examination was done and cultures of the blood were made before treatment. Spinal fluid pressures were measured on admission; daily routine spinal fluid examinations included cell counts, chemical tests for sugar and proteins, smears and cultures for organisms. Leukocyte counts of the blood were made on admission and at irregular intervals thereafter. Frequent urinalyses and repeated blood cultures were made, and, when possible, daily physical examinations. At intervals throughout the epidemic, organisms obtained from cultures of the blood and the cerebrospinal fluid were typed by means of agglutination and absorption tests. None of the patients were discharged from the hospital until at least two successive negative nasopharyngeal cultures, taken at four day intervals, were obtained.<sup>2</sup> Necropsies were obtained in sixteen of the ninety-two fatal cases.

\* From the Lilly Laboratories for Clinical Research, Indianapolis City Hospital.

1. Flexner, Simon: Results of the Serum Treatment in Thirteen Hundred Cases of Epidemic Meningitis, *J. Exper. Med.* 17: 551-576 (May) 1913.

2. Flexner, Simon: Mode of Infection, Means of Prevention, and Specific Treatment of Meningitis, *J. A. M. A.* 69: 721 (Sept. 1) 1917.

## EARLY CLINICAL OBSERVATIONS

The most striking information gained from the clinical histories was the nature of the onset of the disease. In the great majority of cases, the onset was sudden and violent. The clinical course was rapidly progressive and was characterized by extreme prostration, the degree of which was out of all proportion to the meningeal signs. Of the entire group, 56.9 per cent presented the textbook picture of the fulminating or hyperacute type.

Table 1 shows the more important early symptoms and physical signs, certain of which deserve further comment.

In 68 per cent of the cases the tongue showed a marked whitish furring over the dorsum, beefy red margins, and prominent bright red papillae, not unlike the strawberry tongue of scarlet fever. A large majority of patients had some degree of respiratory infection as evidenced by pharyngitis, nasal discharge, bronchitis or pneumonia. In the presence of intracranial pressure of from 35 to 52 mm. of mercury, cephalic cry and projectile vomiting were occasionally

TABLE 1.—Early Symptoms and Physical Signs

	Num-Per ber Cent		Num-Per ber Cent
Headache.....	77 53.5	Pupillary changes.....	42 29.1
Pain in neck.....	50 33.8	Strabismus.....	45 31.3
Pain in back.....	18 11.1	Nystagmus.....	11 7.0
Joint pains.....	12 8.0	Fixed pupils.....	49 34.0
Generalized pains.....	21 14.5	Strawberry tongue.....	58 40.0
Photophobia.....	28 19.4	Upper respiratory infection	79 54.8
Vomiting.....	18 12.7	Cervical adenitis.....	62 43.0
Chills.....	30 20.8	Brachial breathing.....	25 17.3
Delirium.....	55 38.2	Rales.....	30 20.8
Convulsions.....	19 13.2	Enlarged heart.....	30 20.8
Coma.....	70 48.5	Enlarged liver.....	10 6.9
Ophthalmoscopy.....	62 43.1	Petechiae.....	60 42.7
Retraction of head.....	71 49.3	Constipation.....	39 26.8
Neck rigidity.....	137 95.2	Abdominal distention.....	20 14.0
Unilateral Kernig.....	118 81.7	Urinary retention.....	38 26.0
Unilateral Kernig.....	8 5.5	Urinary incontinence.....	12 8.3
Bilateral Brudzinski.....	14 9.4	Harpea.....	29 20.0
Unilateral Brudzinski.....	16 11.1	Cephalic cry.....	5 3.4

seen, while coma, stupor or delirium were usually present, although these conditions existed at times when the pressure was not markedly elevated. Obtunded ocular, cutaneous and tendon reflexes, not included in table 1, were present in a large majority of cases.

Cutaneous hemorrhages were observed in ninety-nine patients,<sup>3</sup> or 68.7 per cent. There was considerable variation in the appearance of the lesions, and three subdivisions were made: In the first group, comprising twenty-three cases, there were only a few scattered petechiae which usually did not exceed 3 mm. in diameter and which were most often seen over the dorsum of the hands, the knees, the ankles and the feet. In the second group, forty-six cases, the hemorrhages were little, if any, larger but were more numerous, were scattered over the trunk, and were especially numerous about the neck and face. In the third group, including thirty cases, are listed those in which there were innumerable hemorrhages, varying in size from minute pin-point petechiae, 1 to 2 mm. in diameter, up to great purpuric blotches several inches in diameter, appearing over the entire cutaneous surface of the body and always in the conjunctivae. The purpuric blotches were most commonly seen on the upper part of the trunk, the neck, the upper arms and the thighs.

3. Burrows, M. P.: A Clinical Study of Meningococcal Meningitis, *Am. J. M. Sc.* 179: 82 (Jan.) 1930.

4. Netter, A. and Salaviter, M.: Meningococcus in Purpuric Elements of Meningococcal Infection, *Brit. J. Child. Dis.* 24: 101 (April-June) 1917.

Cutaneous hemorrhages usually appeared on the first or second day of the disease. Recurrence of petechiae was noted in two cases.

#### CLINICAL COURSE AND COMPLICATIONS

The outstanding clinical features observed in the study of this series of cases, apart from the central nervous system involvement, were the extreme virulence of the organism, the very marked evidence of systemic infection<sup>6</sup> or intoxication, and the death of patients despite the rapid improvement in the spinal fluid. Systemic manifestations of the disease were numerous and severe; fever, anorexia and prostration were present frequently for hours or even days before meningeal signs or symptoms developed. The presence of cardiac involvement and pulmonary, upper respiratory and kidney complications (table 2) would seem to indicate either an overwhelming toxic process or a severe generalized septicemia. The high incidence of petechial hemorrhages and the large number of positive blood cultures<sup>6</sup> would strongly indicate the latter.

The interval between the onset of the disease and admission to the hospital varied considerably. In the earliest cases that we saw, the patients were admitted two or three hours after the onset of illness; however, these instances were rare. A large number had been ill two or three days before admission, and a few patients were received after a week or more of illness. Fully 40 per cent of the patients were moribund when they were admitted to the hospital, partly because of the virulence of the disease and partly because of failure to recognize the disease.

The illness was frequently ushered in with a chill followed by a sharp rise in temperature to 103 or 104 F. Subsequently the temperatures were very irregular,<sup>7</sup> the daily peak coming sometimes in the morning, at other times in the afternoon or during the night. Usually at some time during the twenty-four hour period there was a decline in temperature to normal or nearly normal. In many patients who recovered, the temperature repeatedly reached alarming levels (106 F. or higher) and terminal temperatures of from 107 to 110 were not at all uncommon in fatal cases. Many times the temperature remained high after the patient had improved markedly. Defervescence was always by gradual lysis. Subnormal temperature was occasionally noted on admission but was never persistent.

The heart was frequently enlarged before other evidences of cardiovascular involvement developed. At the onset, the pulse was usually accelerated in proportion to the temperature, but during the subacute and convalescent states of the disease the pulse was frequently accelerated out of all proportion to the temperature.

Early involvement of the lymphatics was seen in practically every case, the adenitis being generalized but most marked in the posterior cervical nodes. The enlarged glands were usually rather soft and not infrequently tender to palpation. Adenitis usually persisted for some time after recovery.

In the early days of the disease, irritability and hypersensitivity were present to a high degree. Children especially resented handling. Light stimulation

of the skin or moderate pressure over the long bones usually caused an outcry in either children or adults. Meningeal signs showed wide variation in children from those in adults. In the infant, neck rigidity was in general less marked, and frequently opisthotonos was not detected until the child was placed on his side. Kernig's and Brudzinski's signs were frequently absent in young children. In older children and adults, however, neck rigidity was striking. The children from 4 to 12 years of age showed the most extreme degree of opisthotonos; although present in adults, it was usually less marked. Kernig's and Brudzinski's (leg) signs were more frequently and more easily elicited in adults.

Almost complete loss of appetite and profound asthenia were present in most cases. In the acute stage, loss of weight was extremely rapid, and in all protracted cases the patients were greatly emaciated. Patients who were comatose, of course, took food and fluids only by forced feeding. In spite of these facts, intercurrent infections were seen in only three instances.

Relapses occurred but were uncommon; recrudescences, on the other hand, were quite common, occurring in perhaps more than half of the ordinary type of case, and frequently necessitating resumption of serum therapy when this had been discontinued. In refractory cases, it was common to see patients become mentally dull, develop carphologia, subsultus tendinum, muttering delirium, marked tremors, and pathologic reflexes. At necropsy, two of these patients were found to have definite areas of brain softening or actual abscess formation.

Thirty-six cases were complicated by nephritis and four of these by hemorrhagic nephritis; some, but not all of these, had retention of nitrogenous products. Those cases showing albuminuria alone were not included in this group. Recovery occurred in three of the four cases complicated by hemorrhagic nephritis.

A few of the cases complicated by pneumonia presented the physical signs of the lobar type, but in those coming to autopsy only the bronchial or confluent bronchial variety was seen. Pneumonia was frequently, but not invariably, a fatal complication.

Pericarditis, in this series of cases, was a highly fatal complication, recovery occurring in only one of nine unmistakable cases. Endocarditis, however, seen in eight cases, was accompanied by a considerably lower mortality rate.

Arthropathies occurred in eleven, or 7.6 per cent of the cases. Both arthritis and peri-arthritis were seen, the former most frequently involving the small joints of the hands and feet, and in one of five cases accompanied by suppuration; the latter, nonsuppurative occurred in six cases, most frequently involving the knees.

Deafness occurred in eleven patients and was bilateral in two of these. Deafness in no case has disappeared entirely, and in most instances has not improved. Spinal accessory paralysis, giving rise to wry-neck, was seen particularly in the later and milder cases. Paralysis of both lower extremities was seen in one patient and finally cleared up entirely. Hemiplegia was present in two patients who recovered, having disappeared in one case with but slight residuum, and persisted in the second case, a later one. Spastic paralysis of the upper pharyngeal muscles occurred in three cases, all of which were fatal. Other cranial nerve palsies were usually transitory.

5. Haden, R. L.: Meningococcic Meningitis at Camp Lee, Arch. Int. Med. 24: 514-519 (Nov.) 1919.

6. Herrick, W. W.: Early Diagnosis and Intravenous Serum Treatment of Epidemic Cerebrospinal Meningitis, J. A. M. A. 72: 612-617 (Aug. 24) 1918.

7. Dolan, P. L., and Neal, J. H.: Summary of Four Years of Clinical and Bacteriologic Experience with Meningitis in New York City, Ann. J. Dis. Child. 9: 1-16 (Jan.) 1915.

Spinal subarachnoid block\* occurred in a number of cases. Ventricular block was recorded in six cases but probably occurred more frequently since not all patients who had one or more "dry cisternal taps" were so designated; the condition was seen at the autopsy table when it had not been recognized clinically. To date, no patient with ventricular obstruction in this series has recovered. Intraventricular hemorrhage, diagnosed at necropsy, and in all cases attended by terminal extreme hyperpyrexia (107 to 110 F.), was also seen.

Table 2 shows the more important complications observed and the frequency and time of their occurrence.

TABLE 2.—Important Complications, Showing Frequency and Time of Occurrence

Week of Disease	Cases									
	1st	2d	3d	4th	5th	After 5th	Number	Per Cent		
Hemiplegia.....	1	1	..	1	..	..	3	1.4		
Monoplegia.....	1	..	..	..	1	..	1	0.7		
Paraplegia.....	1	..	..	..	2	..	3	2.1		
Deafness.....	5	3	..	2	1	..	12	7.0		
Oculomotor palsy.....	23	0	..	2	1	1	27	22.2		
Glossopharyngeal palsy.....	2	..	..	..	1	..	3	2.1		
Hypoglossal palsy.....	2	..	1	1	..	..	4	3.4		
Abducens palsy.....	10	5	4	1	..	8	28	15.0		
Trochlear palsy.....	2	1	1	1	..	1	6	4.1		
Facial palsy.....	10	0	2	3	1	..	16	15.9		
Spinal accessory palsy.....	5	4	..	3	1	..	13	11.1		
Ventricular block.....	1	..	1	..	..	..	2	2.1		
Brain abscess.....	1	..	..	..	2	..	3	2.1		
Brain hemorrhage.....	2	1	..	..	..	..	3	2.1		
Rhinocephalitis.....	2	2	2	1	2	1	10	6.9		
Hydrocephalus.....	1	2	3	..	..	..	6	4.1		
Pericarditis.....	4	2	1	1	1	..	9	6.3		
Myocarditis.....	41	13	1	3	1	..	59	40.3		
Endocarditis.....	5	1	2	..	..	..	8	5.3		
Pneumonia.....	25	5	..	..	..	1	31	22.5		
Nephritis.....	31	5	3	3	..	..	42	29.5		
Hemorrhagic nephritis.....	2	2	..	..	..	..	4	2.7		
Arthritis.....	3	3	..	..	..	..	6	4.1		
Periarthritis.....	1	..	1	..	..	..	2	1.4		
Otitis media.....	8	2	1	..	..	1	12	8.2		
Conjunctivitis.....	1	..	..	..	..	..	1	0.7		
Pneophthalmitis.....	0	3	..	..	..	..	3	2.1		
Ascites.....	1	2	2	3	1	1	10	6.9		
Anaphylaxis.....	12	2	1	..	..	..	15	10.4		
Serum sickness.....	3	11	6	1	..	..	21	14.5		

Palpitation, dyspnea and other evidence of myocarditis have been observed for weeks following recovery; strength and weight in some cases were very slow in returning. The mental condition, while quite sluggish in a few patients, has frequently shown improvement. All recovered patients who had sphincteric incontinence have regained control of the sphincters.

Serum sickness was frequently seen, most often appearing in the second week after treatments were started. In six instances in which prolonged use of serum was requisite, serum sickness occurred twice, and a seventh patient had three attacks of this ailment. When not attended by urticaria, this condition may be differentiated from a recrudescence by neurologic examination of the patient and examination of the cerebrospinal fluid. In the presence of serum sickness, when clinical and bacteriologic examination indicated active infection, the serum treatment was continued without apparent ill effects.

#### LABORATORY OBSERVATIONS

White blood cell counts on admission fell between the extremes of 4,000 and 64,000, the majority of patients having a leukocytosis of from 15,000 to 25,000. Those cases with very low and those with very high counts were almost invariably fatal. Differential leukocyte counts showed a polymorphonuclear percentage of from 80 to 98. Those cases with a very high

percentage of polymorphonuclear cells were fatal. The red blood cell count was usually unaltered.

Spinal fluid pressures, while in general greatly elevated, showed wide variation. The mercury manometer was used, and pressures recorded ranged between zero and 52 mm. When the pressure was subnormal, the fluid was either too thick and turbid to flow from the needle or subarachnoid block was present. Spinal fluid cell counts made on admission varied from zero to 109,000.

It was found that a clear cerebrospinal fluid, without leukocytosis (by the usual methods of counting) does not rule out the diagnosis of meningococcic infection. In six cases in which the number of cells was not elevated, the clinical diagnosis was substantiated only by cultures of the blood or spinal fluid or both. All these showed a leukocytosis of the spinal fluid after serum had been administered intrathecally.

Very few of the spinal fluids obtained from first puncture reduced Benedict's solution, but when the active infection had subsided the tests became positive. In several instances, when the spinal fluid sugar was repeatedly negative over a period of several days, blood sugar determinations were normal.

We have used the Pandy test for spinal fluid proteins. All variations of positive reactions were seen. Persistently strong reaction was usually a bad prognostic sign. When the spinal fluid cell count reaches 400 or below, the sugar reaction is positive, and the Pandy test shows decreasing amounts of proteins; it is advisable to discontinue intrathecal administration of serum.

Direct smears and cultures\* were made from all cerebrospinal fluids when the patients were admitted. It was found that when no organisms were seen in stained smears of centrifugated cerebrospinal fluid the bacteria could rarely be grown. On the other hand, cultures were frequently negative in fluids from which meningococci had been obtained in direct smears. Only rarely, and then most often during a recrudescence, could the organisms be obtained in culture after serum had been administered intrathecally, and even when seen in direct smear the appearance of the organism was considerably altered. Spontaneous coagulation of cerebrospinal fluid (the syndrome of Froin) was seen in a few instances and was usually a bad prognostic sign. At some time in almost every case the cerebrospinal fluid became xanthochromic, but little importance could be attached to this occurrence.

Cultures of the blood were made on admission and at intervals thereafter, blood enriched agar plates and semisolid testicular agar (tubes) being the mediums used (pH 7.6). We have obtained positive cultures of the blood repeatedly from the same patients, in one instance as late as the nineteenth day, and in another as late as the thirty-fifth day of the disease.

Repeated examinations of blood and cerebrospinal fluid<sup>10</sup> from convalescent patients have failed to show the presence of agglutinins for the causative strain of organism. In one instance only were agglutinins found, and then in the blood of a patient who had been treated with antimeningococcic serum plus a vaccine to which had been added convalescent serum.

At intervals throughout the four months' period, cultures selected at random were typed by means of

\* Mitchell, A. G., and Reilly, J. J.: The Introduction of Antimeningococcic Serum by Sterile Puncture, *Am. J. M. Sc.* 264: 66 (July) 1922.

9. The bacteriologic and serologic studies were made by H. M. Powell, A.B., Sc.D., and F. G. Jones, of the biologic department of the Lilly Research Laboratories.

10. Taylor, F. E.: The Antibody Content of the Cerebrospinal Fluid in Meningococcal Infections, *Lancet* 1: 418 (March 17) 1917.

agglutination and absorption tests. This work was done according to the classification and technic suggested by Gordon.<sup>11</sup> All cultures so treated were found to be type III, comparatively rare according to Blackfan.<sup>12</sup> It is true that we have not typed organisms from each patient, but, since the cultures were selected at random and throughout the entire four months, it is fair to presume that other cases were likewise caused by a type III organism.<sup>13</sup>

## TREATMENT

The treatment has remained essentially the same throughout the epidemic. The routine adopted included, on admission, a skin sensitization test, rhachicentesis and intrathecal serum, intramuscular serum and (especially during the second month of the epidemic) serum intravenously. Intravenous administration of an antiseptic solution was tried and found wanting despite the *in vitro* activity of the agent.

Commercial serums were used throughout, except a small lot from a state health board from which no conclusions relative to efficiency could be drawn. The agglutinating powers of all serums used were determined and found to be adequate.<sup>14</sup> Furthermore, neutralization tests on animals according to the method of Schwartzman<sup>15</sup> were used to determine the efficacy of the various serums.

As to the efficiency of the three brands of serum used, there appeared to be little difference. We favor, for intrathecal use, however, a concentrated serum for the reason that it is less bulky and the entire quantity may be given even to the small child. In view of the septicemic nature of the disease, as Herrick, Blackfan and others have pointed out, and as we have found, and in view of the high incidence of petechiae and positive blood cultures, it would seem that intravenous serum is indicated, and results bear out these opinions. However, we have unfortunately found that one of the commercial serums used intravenously is attended by extremely dangerous reactions and that alarming reactions were experienced, although less frequently, with the other serums used. These reactions took place despite negative skin or conjunctival sac sensitization tests in some instances. The idea is quite prevalent that, in the administration of serum intravenously, if 3 or 4 cc. can be given slowly with safety, the patient will not have an immediate anaphylactic reaction. We have found that this is not wholly true, as reactions of alarming proportions have occurred after administration of 30 cc. of serum. In some instances there appeared to be a daily decreasing tolerance to repeated intravenous serotherapy, necessitating abandonment.

Both lumbar and cisternal punctures were used as a routine. In numerous patients, spinal subarachnoid block necessitated cisternal puncture. Serum was used intracisternally also in refractory cases not responding well to intraspinal treatment. The usual gravity method for intrathecal administration of serum was employed with the least possible pressure,<sup>16</sup> the volume administered being at least 5 or 10 cc. less than the amount of fluid removed. Neal and Dubois and others

have described a condition of "shock" following intrathecal administration of serum, characterized by cessation of respiration while the heart continues to beat. This phenomenon was not infrequently seen in our cases and has resulted fatally in a few instances.<sup>17</sup> This condition has been ascribed to sudden elevation of intracranial pressure by the serum, but it is suggested that a sudden decrease may also be the cause.

Reinjection, intramuscularly, of spinal fluid, proposed by Lauzer,<sup>18</sup> was employed as an adjunct to serotherapy in a number of cases without well marked evidence of beneficial effect.

Following the idea advanced by Caronia<sup>19</sup> for the treatment of typhoid, a lysed vaccine, to which had been added convalescent serum, was administered subcutaneously to twenty-nine patients. Some of the group received this material on admission and throughout the period of active infection, and others only when serum therapy had failed and death was imminent. In every instance it was used only as an adjunct to serum therapy. The procedure was instituted at a time when cases were becoming less virulent, and the series of patients thus treated is so small that the results have not been convincing. Additional work along this line seems to be justified.

Flexner and others have reported the high incidence of positive nasopharyngeal cultures, and it was deemed advisable to attempt to combat this source of infection. The first antiseptic solution employed was discontinued when nasopharyngeal cultures were positive after several days of intranasal administration. The procedure finally adopted was: ephedrine sulphate, 3 per cent, in each nostril followed by sodium-ethylmercuri-thiosalicylate (Merthiolate) 1:4,000 twice daily. Following the institution of this therapy no nasopharyngeal cultures were positive. Further than the foregoing, the treatment was symptomatic.

## MORTALITY

Table 3 shows the distribution of cases by age and race with the mortality for each.

TABLE 3.—Distribution of Cases by Age and Race, with Mortality for Each

Age in Years	0 to 1	1 to 5	5 to 10	10 to 20	20 to 30	30 to 40	40 to 50	50 to 60	60 to 70	70 to 80	80 to 90	90 to 100	Over 100	Total	Per Cent
Number of cases....	5	31	20	25	18	8	3	3	3	1	1	1	1	144	....
White.....	3	19	10	10	10	4	1	1	1	1	1	1	1	88	....
Died.....	3	12	6	8	12	11	3	1	1	1	1	1	1	57	64.7
Recovered.....	..	7	10	8	3	2	1	..	..	..	..	..	..	31	35.3
Negro.....	1	12	10	9	10	6	4	2	2	2	2	2	2	50	....
Died.....	1	5	7	4	6	3	3	2	2	2	2	2	2	35	62.5
Recovered.....	1	7	3	5	2	2	1	..	..	..	..	..	..	21	37.5
Per cent of mortality by age.....	60	54.8	50	48	50	77.7	75	100	100	100	100	100	100		

Three patients died before treatment could be administered. Thirty-five others died within twenty-four hours after admission to the hospital and received only one serum treatment. Of the ninety-two fatal cases, only twenty-five were in the hospital more than seventy-two hours. In the remaining sixty-seven cases (those who died in seventy-two hours or less after admission) the sudden onset, rapidly progressive clinical course and early fatal outcome would obviously require the designation of fulminating or hyperacute. Indeed, the number of fatal cases by no

11. Gordon, M. H.: Identification of the Meningococcus, *J. Hyg.* 17:290-315 (July) 1918.

12. Blackfan, K. D.: The Treatment of Meningococcal Meningitis, *Medicine* 1:139-212 (March) 1922.

13. Kennedy, A. M., and Worster-Drought, C. C.: The Relation of the Type of Cocci to the Type of Disease in Meningococcal Meningitis, *Brit. M. J.* 1:261-262 (Feb. 24) 1917.

14. Ames, H. L.: Notes on the Standardization and Administration of Antimeningococcal Serum, *J. A. M. A.* 68:1137-1140 (Oct. 6) 1917.

15. Schwartzman, Gregory: Therapeutic Antimeningococcal Serums, *J. A. M. A.* 68:1965-1969 (Dec. 21) 1929.

16. Koplik, Henry: The Serum Treatment and the Prognosis Under Various Forms of Therapy in Cerebrospinal Fever, *M. Rec.* 74:557-560 (Oct. 3) 1908.

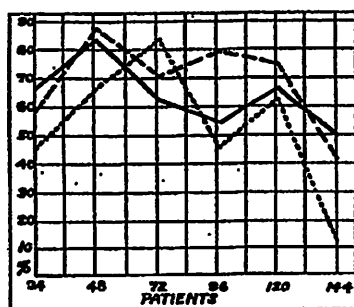
17. Flexner, Simon: Accidents Following the Subdural Injection of the Antimeningococcal Serum, *J. A. M. A.* 60:1937-1940 (June 21) 1913.

18. Lauzer, K. S. (Rock Springs, Wyo.): Personal communication to the authors.

19. Caronia, Joseph: The Nature and Use of Lysed Typhoid Vaccines, *Am. J. Dis. Child.* 30:1-3 (Jan.) 1930.

means includes the entire number of patients critically ill on admission; many others were stuporous, delirious or comatose, suffering from hyperpyrexia, from numerous severe complications, as pneumonia, pericarditis and nephritis, or were otherwise violently ill and recovered. These statements are made not only in order to emphasize the severity of the illness but also to distinguish between the clinical picture of true epidemic meningococcic infections and the milder, far less alarming sporadic cases.

Since the treatment has not varied appreciably during this epidemic, a review of the mortality statistics should give accurate information on the trend of the epidemic regardless of therapeutic agents in use. There was in the beginning a sharp rise in mortality rate to a peak and then a gradual decline which corresponded fairly well to the evidences of septicemia and severity of the cases. This would naturally be confusing if the treatment at the time of the peak<sup>20</sup> had been abruptly changed, that is, from one brand of serum to another.<sup>21</sup> We therefore believe that clinically the comparative evaluation of various brands of serum or other therapeutic agents can be accurately determined only by alternate clinical controls throughout an entire epidemic.



Variation in incidence of petechiae, positive blood cultures, and mortality by groups of twenty-four cases in chronological order of admission: Solid line, mortality (63.8 per cent); broken line, petechiae (68.7 per cent); line of short dashes, positive blood cultures (63.8 per cent).

The apparent parallelism between the incidence of petechiae, the percentage of positive blood cultures and the mortality rate is quite striking. Twenty-five patients either died before cultures of the blood were made, or the only cultures made were contaminated. Of the remaining 119 cases, 63.8 per cent showed positive blood cultures, as shown in the accompanying chart.

In a few of the charts no mention was made of petechiae, but the statistics are quoted for the entire group. The data on mortality includes all cases, fulminating and otherwise.

When the fulminating or hyperacute cases are excluded (patients who were in the hospital less than seventy-two hours and received not to exceed three days' treatment) the mortality statistics are quite different. Sixty-seven deaths occurred within seventy-two hours of admission. Of the remaining seventy-seven patients, twenty-five died, the mortality being 32.4 per cent.

#### SUMMARY

A series of 144 cases of epidemic meningococcic meningitis (type III) has been studied, with the following observations:

1. In the fulminating type of cases, intrathecal administration of serum appears to be inadequate, regardless of rapid improvement in the condition of the spinal fluid.

2. Evidences of systemic infection would seem to be an indication for the intravenous administration of serum.

3. Dangerous anaphylatic reactions may follow the first or subsequent daily intravenous injections of anti-meningococcic serum.

4. Of 119 patients from whom blood cultures were made, seventy-six (63.8 per cent) were positive for meningococci.

5. There was an approximate parallelism between the incidence of petechiae, the percentage of positive blood cultures, and the mortality rate throughout the epidemic.

6. A serum the agglutination titer of which is adequate (Amoss) is not to be condemned on the basis of fatalities at the peak of an epidemic or to be overrated on the basis of results obtained when the virulence of the epidemic is on the wane.

## AGRANULOCYTOSIS

### REPORT OF A CASE\*

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The red marrow of the bones makes erythrocytes, granular leukocytes and platelets. In agranulocytosis, the factory that makes the granulocytes has shut down. The life of this cell in the normal conditions of health is three days or more,<sup>1</sup> and from three to five days by other evidences. Therefore should the red marrow stop manufacturing them for three, four or five days, they would after that time totally disappear from the blood stream. This is apparently what happens. In our patient there is evidence that it did happen. The factory divisions of the marrow that make the erythrocytes and the platelets seem to continue to work at approximately their normal output. There is little if any evidence that the granulocytes are formed normally in the marrow and destroyed in the blood stream. On the contrary, there is much evidence that the myelocytic function of the marrow stops and that the primary pathologic condition is in the bone marrow.

The cause of this pathologic condition is unknown. This whole question is theoretical. The evidence that the primary seat of the condition is in the marrow is threefold:

1. At necropsy, normoblasts and megakaryocytes are present but myelocytes and granulocytes are absent or nearly absent. The marrow is often liquid and varies from red to straw color. In other cases, particularly with the maintenance of the gross fatty structure, myelocytes may be completely absent or nearly so, but the erythrocytes, the lymphocytes and the monocytes are present. The latter two cells may be apparently actually increased. The aplasia of the marrow involves the granulocytes. If death occurs after regeneration of the granular cells has begun, the marrow may show evidence of acute hematopoiesis with cells normal in number and character and even myeloid hyperplasia. Buck's<sup>2</sup> case illustrates this point. Areas of patchy necrosis may occur in the marrow. Patients who recover from the

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Read before the Section on Practice of Medicine at the Eighty-First Annual Session of the American Medical Association, Detroit, June 26, 1930.

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