

THE RESULTS OF THE SERUM TREATMENT IN
THIRTEEN HUNDRED CASES OF EPIDEMIC
MENINGITIS.*

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I.

The serum treatment of epidemic meningitis, developed during the prevalence of the pandemic beginning in 1904 and not yet wholly at an end, has now been subjected to a rigorous test extending over a period of six years and embracing many different countries. The results of this trial have thus far been published in part only. The present publication deals with the analysis of the histories of cases, about 1,300 in number, that were treated with the antimeningitis serum prepared and distributed by the Rockefeller Institute. The histories have been collected not only from many different parts of the United States and Canada but also from several European and Asiatic countries to which the serum was sent. The large number of the cases and the diversity of the circumstances under which the serum came to be administered give to the following presentation a significance greater perhaps than that afforded by a strictly local report.¹

BIOLOGICAL DISTINCTIONS AMONG MENINGOCOCCI.

The bacteriological cause of epidemic meningitis is admittedly *Diplococcus intracellularis*. Formerly no fundamental biological distinction was made between meningococci; now differences of

* Received for publication, March 1, 1913.

¹ The 1,300 cases include the 712 cases previously analyzed (*Jour. Am. Med. Assn.*, 1909, liii, 1443). The number of physicians and hospitals making the reports is too great to enable me to thank them individually. In a previous paper (*Jour. Exper. Med.*, 1908, x, 690) many acknowledgments were made, to which I desire now to add the name of Professor A. Netter, of Paris, for his invaluable services.

virulence for animals, degree of digestibility in leucocytes, and power of resistance to solution by immune serum are being recognized. The pathogenicity of the meningococcus for laboratory animals is not great, but by the intraperitoneal injection of young guinea pigs the virulence can be tested and different strains more or less pathogenic can be distinguished. Some strains maintain a given virulence for a year or more and others lose this quality very soon after being obtained from human sources. Rarely a strain that shows no virulence for guinea pigs takes on suddenly a heightened activity. There is no sharp agreement in pathogenicity between strains that are virulent for guinea pigs and those virulent for monkeys or man. Some strains, but not all, can be adapted by successive inoculation to guinea pigs and to monkeys.

Opsonic experiments have disclosed the fact that meningococci derived from different sources are digested by leucocytes with varying facility. The kind of leucocytes employed appears unimportant and even the sera, whether normal or immune, play no obvious distinguishing part; the variations depend upon the strain of meningococcus. All meningococci are readily phagocyted in the presence of serum and dissolved ultimately by leucocytes; but while many strains are quickly digested, a small number resist disintegration far more tenaciously. In estimating the content of opsonizing substances in different samples of antimeningococcic sera the strains digesting slowly should be chosen.

Whether in meningitis in man a similar variation among meningococci occurs naturally can only be inferred. Exudates, as obtained from different cases of epidemic meningitis, differ in number and distribution of the contained meningococci. At one time the number of meningococci is small and at others large, and sometimes the meningococci lie chiefly within cells, while at others they occur mainly free in the fluid.

Under the influence of the antimeningitis serum injected into the subdural space the diplococci come, as a rule, to lie more and more within the leucocytes. As recovery from meningitis progresses, even where no antiserum has been employed, a corresponding phenomenon is noted. Moreover, the meningococci phagocyted under the influence of the serum undergo an accelerated disintegra-

tion. In how far resistance to solution in leucocytes is due to the quality of fastness of the meningococcus to the action of the intra-leucocytic enzymes is not certainly known; nor is it known definitely that the less readily englobed meningococci consist also of strains that are more or less resistant to immune opsonins or bacteriotropins. But indications exist supporting the view that certain examples of epidemic meningitis in man which respond imperfectly to the therapeutic action of the serum are caused by strains of meningococci fast to the antiserum employed. These strains tend to remain persistently extracellular and to multiply freely in the presence of the antiserum, even under conditions of its high concentration in the subdural space. The cases of human infection with the supposedly resistant strains fail not only to respond to the therapeutic action of the antiserum but can be inferred also not to ameliorate spontaneously and thus tend to a fatal termination. Certain biological differences have been noted among meningococci from different sources. These relate to the readiness with which they can be cultivated, to survival in cultures, and fluctuation in power to ferment carbohydrates. The variations in opsonic and leucocytic reactions would seem to be of a more fundamental character, just as they are of greater significance in respect to the pathogenic power of the meningococcus and to better control of epidemic meningitis by the employment of the antimeningitis serum.

MORTALITY OF EPIDEMIC MENINGITIS.

The establishment of the bacterial cause and the perfection of lumbar puncture made it possible, as never before in a widely spread epidemic of meningitis, to ascertain accurately the degree of its fatality. Mortality estimates based on earlier epidemics are far less trustworthy since they obviously could not have rested on such certain evidence of specific disease. The pandemic of 1904-9 afforded, therefore, the first opportunity to determine the actual mortality of epidemic meningitis as it affects countries and peoples of various nationalities and widely different social customs. Accurate knowledge of the mortality becomes imperative once we undertake to determine the value of the serum treatment. Com-

prehensive and accurate figures are available from the United States and Canada, Great Britain and Ireland, Germany, France, Belgium, and Italy, and Asia and Africa. The facts to be given immediately relate exclusively to the disease as it prevailed either before the serum treatment was introduced, or where it had not yet been applied.

In the period from 1904 to 1909 epidemic meningitis prevailed over a wide territory in the United States and Canada, and after an intermission reappeared in the winters of 1911-12 and 1912-13 in the Southwestern States. The fatalities recorded at several places are as follows: Greater New York City, 73 per cent.; Boston, 69 per cent.; Hartford, 76 per cent.; several cities in Ohio, 70 to 90 per cent.; Porterville, California, 90 per cent. During 1911-12 more than 1,500 cases arose in Texas and Louisiana among which (exclusive of cases treated with serum) the mortality was 75 per cent. or more.

The epidemic in Great Britain was equally severe. The mortality reports include Leith, 74.7 per cent.; Edinburgh, 80 per cent.; Glasgow, 74.8 per cent., and Belfast, 70 per cent.

The largest German figures relate to the Silesian epidemic. The lowest mortality reported is based on a group of 47 cases at Brieg and is 42.5 per cent., while in Breslau it was 62.3 per cent., and among the 3,085 cases collected by Flatten, 67 per cent.

The mortality in France was placed by Netter at 75 per cent.; in Belgium it is given at 77.7 per cent.; while the degree of fatality in Italy may be deduced from the figures for Milan which are 55.6 per cent.

The reports from Asia and Africa are few but they indicate severe infection. In Palestine the mortality was above 80 per cent.; in Greece (Athens) 58.6 per cent.; and in the Transvaal 74 per cent. Although accurate figures are not available, the epidemic prevailed in Java and in German East Africa.

The statement of von Ziemssen may be taken as a criterion of the views held in prebacteriological days of the severity of epidemics of meningitis. He states that the mortality fluctuates between 30 and 70 per cent., the average being about 40 per cent. There is, of course, something highly artificial in arriving at an average in

this manner, and the artificiality is brought out strikingly by the reliable figures of the recent pandemic.

There appears to have been little variation in the mortality according to the period at which the epidemic flourished, and as it affected the inhabitants of the mining districts of Northern Germany or the Transvaal, the industrial populations of Ireland or Scotland, the general population of France, the military garrisons of Belgium, the urban population of New York or Boston, the suburban population of remote districts in Ohio, California, Texas, and Louisiana, or the agricultural and artisan peoples of Greece and Palestine. Everywhere the upper limits of von Ziemssen's figures were reached or surpassed. Hence it appears that the virulence of the meningococcus was the chief factor in causing death, and differences among peoples, as represented by race and occupation, were far less conspicuous factors.

Meningococcus meningitis prevails also as a sporadic affection. The mortality of the sporadic disease is far more difficult to determine than that of the epidemic disease for the reason that vital statistics covering wide areas are difficult to obtain. Such data as are available tend to show that the sporadic disease, when bacteriologically diagnosed, is less fatal than the epidemic disease. Posterior basic meningitis, which is probably merely a variety of sporadic meningitis, has a less general distribution. This disease had claimed attention chiefly in England. The fatality of these affections may fall as low as 40 to 50 per cent.

MODE OF TERMINATION

Cases of meningitis are very varied both in respect to their intensity and evolution. In rare individual instances the disease sets in severely and yet terminates in recovery, sometimes in a few days, or the onset is mild although the infection later develops an alarming gravity; while again the disease progresses slowly or continuously through weary weeks or months to end usually, but not always, in death. The cases of ordinary severity pursue a middle course, while the fulminant ones arise and terminate within a few to forty-eight hours. There remains still another variety of the disease hitherto little remarked and the frequency of which is not

known; namely, the ambulant. The subjects are commonly little ill at any time, so that recovery is the rule. Nevertheless, in rare instances death may suddenly supervene, and somewhat more often the slight illness increases in severity until the ordinary type is evolved.

Neither the symptoms nor the mode of their evolution support a prediction as to the probable outcome of the disease. Several different types have been constructed out of the variety, complexity, and degree of severity of the symptoms, but a sharp discrimination between them is often wanting in practice. For this reason observation of individual cases affords little final information concerning the nature of epidemic meningitis, and the outcome of single cases is an uncertain guide to the value of a given therapeutic measure.

Death may be considered as taking place under three sets of circumstances: (*a*) rapidly, after sudden onset of illness, as in meningitis siderans, or so called fulminating meningitis; (*b*) through a gradual intensification of the symptoms and after a duration of from six to ten days; (*c*) slowly, in the course of which the acute stage has been survived and after the condition has become chronic.

Recovery, also, when it occurs is not by a single mode of termination, but by at least two modes. The transition to convalescence and recovery is generally by a process of gradual amelioration of the symptoms, or lysis. Sometimes, but more rarely, the transition takes place abruptly by a sudden or critical cessation of the symptoms that follow quickly upon the onset of the infection or after several days have elapsed.

Knowledge is lacking of the relative frequency with which the several types of meningitis occur in different epidemics. What would be particularly informing is accurate knowledge of the frequency of the extreme cases—the fulminant and the abortive, latent, rudimentary, or ambulant ones, so called. The throwing together of the abortive and ambulant cases is not strictly justified by their usually mild character, since the one sets in sharply and the other begins insidiously. While the former tends to terminate in recovery by crisis, the latter attracts attention by suddenly pass-

ing into the severe or even fulminant disease. That such mild cases of epidemic meningitis occur has now been conclusively shown by bacteriological examination of fluids removed by lumbar puncture. Exceptionally an epidemic has been composed mainly of them, as in Kehl. In many epidemics they have wholly escaped detection. Apparently their occurrence is infrequent, and excellent observers of large numbers of cases of epidemic meningitis have not encountered them.

The proportion of fulminant to ordinary cases can be inferred rather than asserted. At the beginning of a severe epidemic they appear to be more frequent than at the end. Certain epidemics have been noted for their absence. On the other hand, fulminant cases have appeared in associated groups, one case following another in rapid succession in barrack, school, or family. Some idea of frequency can be inferred from the duration of the illness preceding death. The chief danger in this inference arises from the uncertainty surrounding the period of onset of some of the cases. Among 1,481 fatal cases analyzed by Flatten, 29 died within six, 30 in from six to twelve, and 53 in from twelve to twenty-four hours of the appearance of symptoms. That is, 112, or 9 per cent., succumbed within the first twenty-four hours, while another 111 cases terminated fatally in the second twenty-four hours, giving 18 per cent. of the whole as having suffered from the fulminant disease.

DURATION OF THE DISEASE.

The duration may be considered according to the period elapsing before either death or recovery occurs. Among the 1,481 fatal cases just mentioned, 361, or 25 per cent., terminated in the first three days; 351, or 24 per cent., from the fourth to the seventh day; and almost 50 per cent. later than the seventh day of illness. Hence, it cannot be maintained that the survival of the first week of the infection affords great insurance of ultimate recovery. One half of the cases surviving the first week terminated between the fifth and eighth weeks, while 7 per cent. (107 cases) survived eight weeks or longer. Among Schneider's 80 fatal cases, 26, or 32.5 per cent., succumbed in the first three days; 18, or 22.5 per cent., in the next four days; and 36, or 45 per cent., later than the first week.

Viewed from the side of recovery the period of duration of the disease has fluctuated with the type. The abortive cases are said to terminate in recovery in from one and one half to five days (von Ziemssen, Strümpell). Strümpell states that the critical period falls between the fifth and tenth days, when either death results or convalescence begins. Schneider's analysis of 52 cases shows 3 recoveries from the fifth to the ninth day, 26 from the eleventh to the fortieth day, and 45 from the forty-first to the one hundred and tenth day. Rieger discharged 25 patients from the hospital on the average of the fortieth day. Heubner states that the average duration of the disease terminating in lysis is three to four to six weeks; von Ziemssen gives for favorable cases two to three weeks, and for less favorable ones three to four weeks. Holt states that in the New York epidemic of 1904-5, among 350 cases which recovered, the duration in 3 per cent. was one week or less, and in 50 per cent. five weeks or longer.

Thus we may conclude that in the recent past the tendency of epidemic meningitis has been to terminate in death, and of the fatalities about one half arose in the first week of the illness. On the other hand, among the recoveries a small percentage took place in the first week, and almost all after several weeks or months of illness.

INCIDENCE AND MORTALITY ACCORDING TO AGE.

Young persons are more subject than older ones to epidemic meningitis. This conclusion, arrived at by Hirsch and others, is supported by recent more accurate studies. Certain epidemics affect children almost entirely, and nurslings rather than older children (Hirsch, Heubner). Among the 2,916 cases in Silesia in 1904-5 analyzed by Flatten, 247 arose in the first, 239 in the second, 293 in the third, 334 in the fourth, and 271 in the fifth year. Hence about one half (1,384) of the cases occurred in the first five year period, one third (844) in the second, one eighth (338) in the third corresponding period, and the remainder (350) later than the fifteenth year of life. Göppert noted among 629 cases 102, or 17 per cent., in nurslings. Since in children below three years of age the symptoms of meningitis are often masked, it follows that the

bacteriological diagnosis accounts for the greater number of infants shown to be attacked during the pandemic.

The mortality is affected by the age of the attacked. Hirsch states that the disease is most fatal in children and in adults after the fortieth year. During the epidemic in New York the mortality among infants of two years and under approximated 100 per cent. Flatten's figures based on the Silesian epidemic show approximately the same result. The number of cases analyzed was 2,976. They may be divided as follows: under one year, 255 with 89 per cent. of deaths; under two years, 243 with 83 per cent. of deaths; between two and five years, 866 with 72 per cent. of deaths; between five and ten years, 920 with 62 per cent. of deaths; between ten and fifteen years, 346 with 56 per cent. of deaths; between fifteen and twenty years, 187 with 63 per cent. of deaths; between twenty and thirty years, 76 with 59 per cent. of deaths; and between thirty and seventy years, 83 with 83 per cent. of deaths.

Hence, in the past, epidemic meningitis has been most fatal to infants and adults after the third or fourth decennium, while the intermediate age periods have been somewhat more favorable to spontaneous recovery. The favorable period begins to be apparent about the fifth year and endures until the twentieth or thirtieth year, when it diminishes with increasing rapidity as age advances.

COMPLICATIONS AND SEQUELS.

We shall consider briefly the chief complications and sequels only. The common secondary infections of the respiratory tract, etc., will be neglected. In some instances the meningococcus causes a complicating pneumonia, endocarditis, or serositis exclusive of the joints; in very rare instances it has produced general infection or septicemia.

Of greater importance are the involvements of the central nervous system, peripheral nerves, and sense organs in the infective process. True motor paralyzes occur infrequently and permanent ones are rare. Of the nerves of the head the facial and hypoglossal are oftenest affected. The frequency has varied with different epidemics and the complication has been noted in abortive as well as severe cases and tends to arise at the end of the first week. Hemi-

paresis, a rare condition, affecting an arm and less often a leg, comes on usually later than the second week. These paralyzes, regarding which figures are scant, are attributed to focal lesions in the brain and spinal cord extending inward from the meninges.

The ear complications are numerous. Both the middle and internal ear may be affected. Inflammation of the middle ear is frequent and increases with the duration of the illness. Thus 35 per cent. of the inflammations arise in the first, 70 per cent. in the second, and 59 per cent. in the fourth to the sixth week (Göppert). Recovery tends to be complete. Inflammation of the internal ear is far more serious. The frequency varies in different epidemics. Percentages range from 33 (Mannkopff and Heller), 16 (Göppert), and 12 (Bauer). Probably 12 per cent. approximates the average among large numbers of cases (Göppert). The involvement usually occurs early in the attack and arises even in the abortive disease. Both ears tend to be affected and hearing is often already lost when the patients enter the hospital. Among sixty-four cases Moos observed affections of one side in three. When the accident occurs in infancy deaf-mutism results. Following epidemics of meningitis the number of deaf-mutes in institutions has greatly increased.

The eyes may suffer slightly or severely, and injury may be temporary or permanent. Muscular affections are common (12 per cent.), ptosis is rare, and pupillary irregularities are frequent (24 per cent.); all tend to be temporary, except ptosis. Iritis and iridochoroiditis, retinitis, and periretinal hemorrhages all arise but often disappear without causing permanent injury. Keratitis, with or without ulceration of the cornea, occurs, followed either by recovery or loss of the eye. A condition of basilar amaurosis, from which slow recovery has taken place, has also been described (Göppert). The most serious complication is metastatic ophthalmia, due to the meningococcus, affecting one eye or both, and leading to destruction of the ball. Eye complications have been a variable factor in different epidemics. Göppert reports 14 instances of metastatic ophthalmia (affecting both eyes in 4, and one eye in 10 patients) among 136 cases (10 per cent.). Uhthoff states that among 110 Silesian cases lesions of the optic nerve occurred in 17, metastatic

ophthalmia in 4, and keratitis in 3. Morax noted iridocyclitis in from 3 to 6 per cent. of cases during the Parisian epidemic.

The higher intellectual centers of memory, intelligence, and speech suffer also, but while slight degrees of affection from which recovery takes place are common, only rarely does permanent incapacitation result. Actual mental defects of permanent character arise, according to Göppert, in from 1 to 3 per cent. of the recovered. Looft reports that among 539 Norwegian idiots, 3.7 per cent. were caused by epidemic meningitis.

Finally, hydrocephalus arises very often, especially among the young. In Silesia its occurrence was noted in one eighth of all cases. Recovery may occur without mental defect even where the degree is considerable. Deafness and hydrocephalus are frequently associated, but not as cause and effect.

II.

We may now proceed to consider what changes have been effected in the course and consequences of epidemic meningitis by the employment of the antimeningitis serum. The serum began to be employed in 1906-7, first locally and later more generally. Thus it failed to be used in certain places because the epidemic wave had passed, and in other places its employment was begun at the middle period or height of the epidemic, according to circumstances. There occurred coincidentally, almost without exception, cases of equal severity in which the serum was not administered. These served as checks, or controls. The mortality in them did not vary essentially from the figures already given for different countries (page 556). The analysis to follow is based upon cases treated in America, Europe, Asia, and Australia with the serum which was prepared at the Rockefeller Institute by a uniform method and widely distributed, and they therefore present at least this common factor. The chief variable was the experience or lack of experience in those charged with the administration of the serum, which is sometimes reflected in the results achieved. But since this factor will always operate in some degree, the results probably approach the normal.

The high degree of variability of the clinical course of epidemic

meningitis has been pointed out; hence it will not be as profitable to study the influence on individual cases as to consider the effects on the mortality and some other objective features of the disease.

MORTALITY OF SERUM-TREATED CASES.

The number of cases to be subjected to analysis is 1,294. They have not been selected and a single exclusion has been practised. In order to deny no one the benefits of the treatment where available, a small number of hopeless and dying persons were injected. When they survived the injection merely a few hours—less than twenty-four at the maximum—they were not included. The fulminant cases have been included in the analysis and, as will appear, they now seem not to be without the sphere of influence of the serum. The general mortality is shown in table I.

TABLE I.
Mortality of Serum-Treated Cases.

| No. of cases. | Recovered. | Died. | Per cent. died. |
|---------------|------------|-------|-----------------|
| 1,294 | 894 | 400 | 30.9 |

That the period of injection in the course of the disease affects the fatality has been previously shown.² The larger number of cases has been analyzed from this point of view and in accordance with the arbitrary periods previously employed. The results are shown in table II.

TABLE II.
Mortality according to the Period of Injection of the Serum.

| Period of injection. | No. of cases. | Recovered. | Died. | Per cent. recovered. | Per cent. died. |
|------------------------------|---------------|------------|-------|----------------------|-----------------|
| 1st to 3d day | 199 | 163 | 36 | 81.9 | 18.1 |
| 4th to 7th day | 346 | 252 | 94 | 72.8 | 27.2 |
| Later than 7th day | 666 | 423 | 243 | 63.5 | 36.5 |
| Totals | 1,211 | 838 | 373 | 69.2 | 30.8 |

The pronounced influence of the serum is strikingly shown by these tabulations which serve to confirm the earlier figures.³

² Flexner, S., *Jour. Exper. Med.*, 1908, x, 699.

³ Flexner, S., *ibid.*, pp. 700-1.

In some instances the precise period of first injection of the serum was not stated in the histories, which explains the smaller number of cases analyzed in table II. This table not only establishes the fact that the earlier the serum injections are begun the better the results, but it emphasizes the too common delay in making the diagnosis of epidemic meningitis or of bringing the majority of cases under the specific treatment. Less than one sixth of the cases had the benefit of early injection, and one half received the first injection later than the first week of illness. Doubtless as the serum is made more generally available and as confidence in its value extends, these disadvantages will be more and more removed.

That the mortality is affected by the age of the patient is commonly admitted. The influence of the serum on patients of different ages is shown in table III.

TABLE III.
Mortality according to Age.

| Age. | No. of cases. | Recovered. | Died. | Per cent. recovered. | Per cent. died. |
|------------------------|---------------|------------|-------|----------------------|-----------------|
| Under 1 yr. | 129 | 65 | 64 | 50.4 | 49.6 |
| 1 to 2 yrs. | 87 | 60 | 27 | 69.0 | 31.0 |
| 2 to 5 yrs. | 194 | 139 | 55 | 71.6 | 28.4 |
| 5 to 10 yrs. | 218 | 185 | 33 | 84.9 | 15.1 |
| 10 to 20 yrs. | 360 | 254 | 106 | 70.6 | 29.4 |
| Over 20 yrs. | 288 | 180 | 108 | 62.5 | 37.5 |
| Age not given. | 18 | 11 | 7 | 61.1 | 38.9 |
| Totals. | 1,294 | 894 | 400 | 69.1 | 30.9 |

TABLE IV.
Mortality according to Age and Period of Injection.

| Age. | Injected 1st to 3d day. | | | | Injected 4th to 7th day. | | | | Injected later than 7th day. | | | |
|-----------------------|-------------------------|--------------|-------|-----------------|--------------------------|--------------|-------|-----------------|------------------------------|--------------|-------|-----------------|
| | No. of cases. | Re-cov-ered. | Died. | Per cent. died. | No. of cases. | Re-cov-ered. | Died. | Per cent. died. | No. of cases. | Re-cov-ered. | Died. | Per cent. died. |
| Under 2 yrs. | 13 | 12 | 1 | 7.7 | 37 | 28 | 9 | 24.3 | 159 | 81 | 78 | 49.1 |
| 2 to 5 yrs. | 30 | 24 | 6 | 20.0 | 66 | 49 | 17 | 25.8 | 93 | 63 | 30 | 37.3 |
| 5 to 10 yrs. | 55 | 49 | 6 | 10.9 | 69 | 61 | 8 | 11.6 | 77 | 61 | 16 | 20.8 |
| 10 to 20 yrs. | 67 | 58 | 9 | 13.4 | 106 | 73 | 33 | 31.1 | 171 | 115 | 56 | 32.7 |
| Over 20 yrs. | 34 | 20 | 14 | 41.2 | 65 | 39 | 26 | 40.0 | 164 | 101 | 63 | 38.4 |
| Totals. | 199 | 163 | 36 | 18.1 | 343 | 250 | 93 | 27.1 | 664 | 421 | 243 | 36.6 |

Table IV gives an analysis of the data of the preceding tabulation according to the period of the disease at which the serum injections were begun.

The age factor affects the outcome of the serum treatment just as it affects spontaneous recovery, only its influence is even more marked in the former. The most favorable cases for the specific treatment fall between the five and ten year period and the least favorable ones fall in the period above twenty years. The favorable period doubtless extends to and even beyond the twentieth year although the analysis given fails to make an exact discrimination for these ages. To subdivide farther the periods risks increasing the statistical error inherent in small numbers; but the reports of certain hospitals covering cases arising during the third decennium indicate no great decrease in response to the serum. What is particularly impressive is the change wrought in the fatality among infants, and while the astonishing result for the first injection period can scarcely be maintained through the vicissitudes of large numbers of cases, yet the outlook is highly promising. The exact coincidence of the favorable ages for spontaneous recovery and for recovery under the serum treatment indicates that the serum provides artificially the means that the body itself employs when it can fabricate them to suppress the infection, and that two factors, one provided by the body and the other by the serum, coöperate in the end result. The change wrought in the manner of termination of the disease enforces the same conclusion.

MANNER OF TERMINATION AND DURATION.

The usual mode of spontaneous termination of epidemic meningitis is by gradual subsidence of the symptoms, or lysis, and the exceptional mode is by abrupt cessation, or crisis. While precise figures showing the number of cases subsiding by crisis in ordinary epidemics are not available, yet it can be said that it has never been observed to be large and that sometimes this class of cases has been wholly absent. The histories of 830 cases embraced in our tabulation permitted of a judgment as to the manner of termination, and it was ascertained that in 30 per cent. the cessation was abrupt, or by

crisis. In our previous tabulation of 400 cases⁴ the percentage was placed at 25, which apparently was too low.

A consideration of the manner of recovery according to the age groups brings out some facts of suggestive interest. The data are given in table V, from which it will be seen that among cases of all ages termination by crisis and by lysis occurs about equally when the injection of the serum was begun in the first three days of illness, while when the injection was begun later the number of cases terminating by lysis rose steadily. One other point is indicated by the tabulation; namely, that the proportion of cases that resolve by crisis is highest in the age periods more favorable, and lowest in those less favorable to recovery, whether spontaneously or through specific treatment.

TABLE V.
Recovery by Lysis or Crisis according to Age Periods.

| | 1st to 3d day. | 4th to 7th day. | Later than 7th day. | Total. |
|----------------|----------------|-----------------|---------------------|--------|
| Under 1 yr. | | | | |
| By lysis..... | 3 | 6 | 36 | 45 |
| By crisis..... | 2 | 6 | 8 | 16 |
| 1 to 2 yrs. | | | | |
| By lysis..... | 4 | 10 | 26 | 40 |
| By crisis..... | 3 | 6 | 8 | 17 |
| 2 to 5 yrs. | | | | |
| By lysis..... | 10 | 31 | 53 | 94 |
| By crisis..... | 14 | 18 | 10 | 42 |
| 5 to 10 yrs. | | | | |
| By lysis..... | 26 | 43 | 43 | 112 |
| By crisis..... | 23 | 18 | 19 | 60 |
| 10 to 20 yrs. | | | | |
| By lysis..... | 28 | 46 | 92 | 166 |
| By crisis..... | 30 | 27 | 23 | 80 |
| Over 20 yrs. | | | | |
| By lysis..... | 11 | 22 | 85 | 118 |
| By crisis..... | 9 | 17 | 14 | 40 |

With the manner of termination is obviously bound up the period of duration of the active symptoms of the disease. Epidemic meningitis pursuing its usual or typical course passes through a series of reinfections of the cerebrospinal meninges, whence its intermittent or remittent character. To determine, therefore, just

⁴ Flexner, S., and Jobling, J. W., *Jour. Exper. Med.*, *loc. cit.*, p. 690.

what constitutes a relapse of the infection is sometimes difficult or even impossible. The most trustworthy guide, next to long and complete intermission of symptoms, is afforded by bacteriological examination of the cerebrospinal liquid, since the meningococci tend not to disappear wholly during the intermissions, while they do so disappear between true relapses. Having in mind these criteria we have separated from the 1,294 cases 56 that showed relapses after greater or less intervals of time. Prompt resumption of the serum injections often but not invariably sufficed to control and suppress the reinfections. Of the 56 cases 40 recovered and 16 died. Among them the mortality was 28.6 per cent., indicating that the relapses respond somewhat less well to the serum than the primary infections.

RESPONSE OF RESISTANT OR FAST STRAINS.

In some instances the meningococci having been at first readily controlled by the injections appear to develop resistance or fastness to the serum. This has been noted in certain cases of relapse going on to a fatal termination. Hence under special circumstances the meningococci seem to acquire a serum-fastness that thwarts its specific action. A variety of serum-fast meningococci exists in a small number, at least, of cases of epidemic meningitis before the serum has been applied. This original fast strain seems not to be of common occurrence and its biological properties have not been minutely studied. It is not known whether serum fastness and indisposition to opsonization and leucocytic digestion go hand in hand or not. Nor is it known whether merely one or many fast strains distinct from one another exist in nature. Information on these points is highly desirable, as is the utilization of fast strains of the meningococcus in the preparation of the antimeningitis serum. Should a true polyvalent serum of high titre carrying immune bodies for the fast strains be developed it is probable that the mortality percentages would come to be depressed still further.

COMPLICATIONS AND SEQUELS.

The number of cases here analyzed should serve to indicate the frequency with which the usual complications and sequels may be met with under the serum mode of treatment. Our earlier tabula-

tion suggested that the recoveries would, as a rule, be complete and the one severe sequel that would still remain, although in diminished degree, is deafness. It is impossible to know whether the histories returned noted all the sequels, but it is probable that the severer ones, which we are considering, were uniformly recorded. I have tabulated the reported instances of impaired hearing and vision and arthritis in relation to the day of the disease on which the first injection of serum was made. The circumstance that sometimes the defect already existed when the injection was made can be disregarded, since, as this fact cannot always be established and as a specific form of treatment may be presumed to be capable, at times, of suppressing the secondary localizations of the meningococci, no exclusion should be practiced.

TABLE VI.

Impaired Hearing and Vision and Arthritis in Serum-Treated Cases.

| Day of disease of first serum injection. | 1st day. | 2d day. | 3d day. | 4th day. | 5th day. | 6th day. | 7th day. | 2d week. | 3d-8th week. | Totals. |
|--|----------|---------|---------|----------|----------|----------|----------|----------|--------------|---------|
| No. of cases in which deafness occurred | 1 | 15 | 6 | 5 | 3 | 3 | 1 | 7 | 4 | 45 |
| No. of cases in which impaired vision occurred | 1 | | | 2 | 2 | | | 3 | 4 | 12 |
| No. of cases in which arthritis occurred | | 5 | 3 | 1 | | | | 2 | | 11 |

The instances of arthritis all recovered, as is the rule; and the recovery could be hastened by injecting the serum directly into the inflamed joint. Deafness was complete in 39 and partial in 6 of the 45 instances. Blindness occurred 3 times, some degree of impairment of vision 6 times, iridocyclitis, choroiditis, and metastatic ophthalmia (affecting one eye) once each. Impaired mentality occurred 3 times; in one instance the state is described as imbecile. Muscular paralyses were recorded in 11 histories as follows: strabismus in 5, paralysis of the lower extremity in 3, of the face in 2, and of the shoulder in 1. Deafness and impaired vision were combined in 2 cases, imbecility and impaired vision and arthritis and choroiditis occurred in 1 case each.

The severe and permanent sequels are those resulting from affections of the internal ear and the essential structures of vision. The former arose in about 3.5 per cent. of the serum-treated cases.

This constitutes a marked reduction of the percentages that have been observed among the spontaneously recovered; whether they can be still further diminished by a more prompt and vigorous employment of the serum cannot be predicted.

DISCUSSION.

The foregoing analyses demand merely a brief discussion since they carry their own forceful argument. They show indubitably that the mortality of epidemic meningitis can be greatly reduced by the application of the specific serum treatment and the extent of the reduction is determined by two main factors: the period of the disease at which the subdural injections of the serum are begun and the ages of the persons affected. In view of the fact that the average mortality during the pandemic was approximately 70 per cent., the gross reduction was somewhat less than two thirds. On the other hand, the statistics presented indicate that general early diagnosis and prompt institution of the serum treatment are capable of still further depressing the mortality.

Although at first regarded as doubtful it now appears that fulminant cases of epidemic meningitis are not wholly without the sphere of beneficial influence of the serum. This conclusion rests, first, upon specific statements of recovery of such cases under the influence of the serum, and, next, upon the definite change wrought by it in the mortality of the disease during the first three days of prevalence which is the period during which the fulminant cases terminate in death. Flatten's figures (page 559) and the figures given in table II afford a basis for comparison covering this point.

Undoubtedly it is the ordinary type of epidemic meningitis that responds best to the specific treatment. This fact is shown not only by the general reduction in mortality, but also by the common alteration of the manner of its termination from lysis to crisis. It is just this transformation and the general shortening of the whole course of the disease and the consequent suppression of the chronic form of the infection that bring conviction of the value of the serum not only by reason of statistical presentations but even more cogently to the hospital physicians who have large experience with the usual course and tendencies of the malady.

Other objective criteria of the action of the serum exist. One of the most conclusive is the effect exerted upon the meningococci through which multiplication is arrested and phagocytosis and intra-leucocytic digestion accelerated. This impressive evidence of the action of the serum has been recorded many times by different physicians in the histories upon which this paper is based

The complications and sequels are reduced in number. Indeed, the number of permanently injured among the serum-treated has become very small. Of all the severe sequels deafness has remained least influenced. Unhappily, injury to the internal ear takes place very early and sometimes before the diagnosis of meningitis has been made. In view of the great reduction in other severe effects we are permitted to hope that even this one may be diminished by a more uniformly early application of the serum. The arthropathies have not only been reduced in frequency but they have been shown to be amenable to direct injections of the serum. Undoubtedly the tendency to hydrocephalus in the young has been diminished, and the intraventricular injection of the serum has operated in several instances to abolish infection and inflammation of the cerebral ventricles and to reestablish communication between the ventricles and the subdural space of the spinal cord. Recovery, therefore, has been rendered complete.

III.

ADDENDUM.

In the preceding presentment the value of the serum treatment is based wholly upon the experience gained by the Rockefeller Institute during the several years it was engaged in preparing and distributing the antimeningitis serum. Three reports on the subject have been issued at different times; this report is the final one, since the Institute no longer prepares the serum and is collecting no more histories of cases treated with it. During the period of several years in which the serum was on trial, reports from other countries have also been published. The most important possibly are those of Levy and Netter. They support the value of the serum treatment, as do the many briefer ones published. Within the past

two years two widely remote epidemics of meningitis came under the serum treatment, of which the results are now available for study. One occurred in Greece, the other in the Southwest of the United States. Of the former a set of figures from Athens has been published. The serum employed was chiefly that prepared at the Rockefeller Institute and the cases were treated at the Anunciacion Hospital by Dr. Chrestomanós. The tabulation which follows gives the main important facts which are in complete accord with the corresponding data of our previous tabulation (table II).

TABLE VII.
Serum-Treated Cases of the Grecian Epidemic, 1911-12.

| Period of injection. | No. of cases. | Recovered. | Died. | Per cent. died. |
|------------------------------|---------------|------------|-------|-----------------|
| 1st to 3d day | 100 | 87 | 13 | 13.0 |
| 4th to 7th day | 54 | 40 | 14 | 25.9 |
| Later than 7th day | 32 | 17 | 15 | 47.0 |
| Totals | 186 | 144 | 42 | 22.6 |

During the past two winters (1911-12, 1912-13) Texas, Louisiana, and still other southern and western states have suffered in some degree from an extension or reappearance of epidemic meningitis. The serum was employed in many of the cases, and the reports from Texas⁵ and Louisiana are available for 1911-12. They are specially valuable since they indicate what can be accomplished by the employment of the serum not only inside hospitals but outside and, as often happens, under the disadvantages of poor surroundings and, doubtless, by physicians without previous experience in the performance of lumbar puncture.

The total cases reported from the cities (exclusive of Dallas) and counties in Texas numbered 1,956. Of them 562 received no serum and the mortality was 77 per cent. 1,394 were given one or more injections of the serum and the mortality was 37 per cent. Since the conditions for the care of patients tend to be better in the cities than in country districts, any treatment is likely to be carried out more effectively in them. The figures for three cities that suffered heavily in the epidemic follow.

⁵ Sophian, A., *Experimental Cerebrospinal Meningitis*, St. Louis, 1913.

Galveston: 83 cases treated with the serum; mortality 24 per cent.
 Houston: 169 cases treated with the serum; mortality 27 per cent.
 Dallas⁶: 444 cases treated with the serum; mortality 27 per cent.
 Dallas⁷: 180 cases treated with the serum; mortality 25 per cent.

The preceding figures are uncorrected and include all cases receiving the serum without reference to the quantity given or the period of the disease when first treated. Not a few cases came under treatment when already moribund. Among the group of cases observed by Dr. Sophian 19 were in a dying condition when first given the serum and survived the injection less than twenty-four hours. Excluding these almost hopeless examples lowers the mortality among the 161 remaining cases to 15.5 per cent.

TABLE VIII.
Shreveport Epidemic, 1912.

| | Serum-treated. | | | | Non-serum-treated. | | | |
|-------------------------------------|---------------------|------------|-------|-----------------|---------------------|------------|-------|-----------------|
| | Total No. of cases. | Recovered. | Died. | Per cent. died. | Total No. of cases. | Recovered. | Died. | Per cent. died. |
| | 176 | 123 | 53 | 30.1 | 74 | 11 | 63 | 85.0 |
| <i>Mortality according to Race.</i> | | | | | | | | |
| | Serum-treated. | | | | Non-serum-treated. | | | |
| | Total. | Recovered. | Died. | Per cent. died. | Total. | Recovered. | Died. | Per cent. died. |
| White | 67 | 47 | 20 | 29.8 | 27 | 7 | 20 | 74.0 |
| Colored | 109 | 76 | 33 | 30.3 | 47 | 4 | 43 | 91.5 |

The data given in the official report of the Louisiana State Board of Health relating to the Shreveport epidemic may be studied from various points of view. The total cases numbered 250. The results of my analysis of the cases are presented in the tabulation. The chief facts may be stated as follows: the mortality among the non-serum-treated cases was 85 per cent., and among the serum-treated 30 per cent.; white and colored patients responded equally to the serum, but without serum the colored patients succumbed in

⁶ Reported by Dr. Nash.

⁷ Reported by Dr. Sophian.

greater proportion than the white. Doubtless this difference arose from the generally poorer surroundings and care of the colored race rather than from any inherent lack of resistance to the infection. As a rule, the number of injections and the amount of serum administered have been given in the report. Where the administration was obviously futile the case has been reclassified.

CONCLUSION.

The data brought together in this report have been gathered from a wide territory and for a period extending over several years. The antimeningitis serum was first employed in 1906 and the latest figures relating to its use included in this report were furnished in 1912. There is no longer doubt that the serum has come to be applied under conditions fairly representing all known manifestations of epidemic meningitis. Hence the test of the serum treatment may be regarded as having been a rigorous one. The initial difficulties surrounding the administration by direct subdural injection have been largely overcome and doubtless will be still further mastered. Already the serum is being successfully applied in private as well as in hospital practice. This gain will probably be reflected in a still further diminution of the mortality since early injection plays such a large part in determining the results achieved.

The 1,300 cases studied in this report are a part only of a far greater number of cases actually treated with the serum supplied by the Rockefeller Institute. It was not found possible to secure histories of all the cases treated; but there is no reason to suppose that the results of the analysis would have been essentially different if reports of a still larger number of cases had been returned. The decision arrived at is not based upon statistical computations alone, but upon objective data as well that are not readily misinterpreted.

The conclusion that follows was first stated in 1909 as the result of an analysis of 400 serum-treated cases. It is supported by the study of the larger series of cases just presented.

“In view of the various considerations presented, the conclusion may be drawn that the antimeningitis serum, when used by the subdural method of injection, in suitable doses and at proper intervals, is capable of reducing the period of illness; of preventing, in large

measure, the chronic lesions and types of the infection; of bringing about complete restoration of health, in all but a very small number of the recovered, thus lessening the serious, deforming, and permanent consequences of meningitis; and of greatly diminishing the fatalities due to the disease."

BIBLIOGRAPHY.

- Billings, J. S., Jr., Cerebrospinal Meningitis in New York City during 1904 and 1905, *Jour. Am. Med. Assn.*, 1906, xlvii, 1670.
- Bouché, G., Un nouveau cas de méningite cérébrospinale à méningocoque de Weichselbaum; sérothérapie; guérison, *Jour. de méd. de Bruxelles*, 1912, xvii, 61.
- Currie, J. R., and MacGregor, A. S. M., The Serum Treatment of Cerebro-Spinal Fever in the City of Glasgow Hospital, Belvidere, between May, 1906, and May, 1908, *Lancet*, 1908, ii, 1073.
- Discussion on Cerebro-Spinal Meningitis in the Seventy-Sixth Annual Meeting of the British Medical Association, *Lancet*, 1908, ii, 1339.
- Dunn, C. H., Animal Experimentation in Relation to Epidemic Cerebrospinal Meningitis, *American Medical Association Defense of Research Pamphlets*, 1911, No. 21.
- Feltsos, T. J., Cerebrospinal Meningitis in Greece, *Public Health Reports*, 1911, xxvi, 1006.
- Fischer, L., Klinische Beobachtungen über Meningitis cerebrospinalis und die Resultate der Behandlung mit Flexner-Serum in New York, *Arch. f. Kinderheilk.*, 1910, lii, 289; Cerebrospinal Meningitis in an Infant, Two Months Old, *New York Med. Jour.*, 1910, xci, 625.
- Flatten, H., Die übertragbare Genickstarre im Regierungsbezirk Oppeln im Jahre 1905 und ihre Bekämpfung, *Klin. Jahrb.*, 1906, xv, 211.
- Flexner, S., Experimental Cerebrospinal Meningitis and its Serum Treatment, *Jour. Am. Med. Assn.*, 1906, xlvii, 560; Experimentelle Cerebrospinalmeningitis und ihre Serumbehandlung, *Centralbl. f. Bakteriol., 1te Abt., Orig.*, 1907, xliii, 99; Contributions to the Biology of *Diplococcus intracellularis*, *Jour. Exper. Med.*, 1907, ix, 105; Concerning a Serum-Therapy for Experimental Infection with *Diplococcus intracellularis*, *ibid.*, p. 168; The Present Status of the Serum Therapy of Epidemic Cerebrospinal Meningitis, *Jour. Am. Med. Assn.*, 1909, liii, 1443; Meningokokken-Serum, in Wolff-Eisner, A., *Handbuch der Serumtherapie und experimentellen Therapie*, München, 1910, 142; The Local Specific Treatment of Infections, with Especial Reference to Epidemic Meningitis, *Edinburgh Med. Jour.*, 1912, viii, 389.
- Flexner, S., and Jobling, J. W., The Serum Treatment of Cerebrospinal Meningitis, *Jour. Exper. Med.*, 1908, x, 141; An Analysis of Four Hundred Cases of Epidemic Meningitis Treated with the Antimeningitis Serum, *ibid.*, 690; Kurzer Bericht über 400 Fälle von Meningitis, behandelt mit intraspinaler Einspritzung von einem Antiserum, *Zentralbl. f. inn. Med.*, 1908, xxix, 893.

- Göppert, F., Zur Kenntnis der Meningitis cerebrospinalis epidemica mit besonderer Berücksichtigung des Kindesalters, *Klin. Jahrb.*, 1906, xv, 523; Über Genickstarre, *Ergebn. d. inn. Med. u. Heilk.*, 1909, iv, 165.
- Heubner, O., Cerebrospinalmeningitis, in Eulenburg, A., Real-Encyclopädie der gesamten Heilkunde, Wien and Leipzig, 1894, iv, 425; Beobachtungen und Versuche über den Meningokokkus intracellularis (Weichselbaum-Jaeger), *Jahrb. f. Kinderheilk.*, 1896, xliii, 1; Zur Aetiologie und Diagnose der epidemischen Cerebrospinalmeningitis, *Deutsch. med. Wchnschr.*, 1896, xxii, 423; Noch einmal der Meningokokkus intracellularis, *Jahrb. f. Kinderheilk.*, 1902, lvi, 359.
- Hirsch, A., Handbuch der historisch-geographischen Pathologie, 2d edition, Stuttgart, 1886, iii, 379.
- Holt, L. E., The Treatment of Cerebrospinal Meningitis by the Serum of Flexner and Jobling, *Brit. Med. Jour.*, 1908, ii, 1336.
- Jobling, J. W., Standardization of the Antimeningitis Serum, *Jour. Exper. Med.*, 1909, xi, 614.
- Ker, C. B., The Treatment of Cerebro-Spinal Meningitis with Flexner's Serum, *Edinburgh Med. Jour.*, 1908, i, 306.
- Koplik, H., The Serum Treatment and the Prognosis, under Various Forms of Therapy, of Cerebrospinal Fever, *Med. Rec.*, 1908, lxxiv, 557.
- Levy, E., Erfahrungen mit Kolle-Wassermann'schem Meningokokkenheilserum bei 23 Genickstarrekranken, *Klin. Jahrb.*, 1908, xviii, 317; Serumbehandlung der epidemischen Genickstarre, Jena, 1911; Die Behandlung der epidemischen Genickstarre durch Seruminjectionen in die Seitenventrikel. Bericht über einen geheilten Fall, *Arch. f. Kinderheilk.*, 1912, lix, 72. *Louisiana State Board of Health Quarterly Bulletin*, 1912, iii, No. 2.
- Netter, A., Traitement de la méningite cérébro-spinale, Association française de pédiatrie, Congrès de 1910, Paris, 1911.
- Netter, A., and Debré, R., La méningite cérébro-spinale, Paris, 1911.
- Rieger, Die übertragbare Genickstarre im Kreise Brieg im Jahre 1905 und ihre Bekämpfung, *Klin. Jahrb.*, 1906, xv, 321.
- Robb, A. G., Some Observations on the Recent Outbreak of Cerebro-Spinal Fever in Belfast, *Brit. Med. Jour.*, 1907, ii, 1129; The Treatment of Epidemic Cerebro-Spinal Fever by Intraspinal Injections of Flexner and Jobling's Antimeningitis Serum, *idem.*, 1908, i, 382.
- Schepelmann, E., Genickstarre und Heilserum, *Wien. klin. Wchnschr.*, 1911, xxiv, 118.
- Schneider, Die übertragbare Genickstarre im Regierungsbezirk Breslau im Jahre 1905 und ihre Bekämpfung, *Klin. Jahrb.*, 1906, xv, 299.
- Sophian, A., A New Method for Controlling the Administration of Serum in Epidemic Meningitis, *Jour. Am. Med. Assn.*, 1912, lviii, 843; Epidemic Cerebrospinal Meningitis, St. Louis, 1913.
- Strümpell, A., Zur Pathologie und pathologischen Anatomie der epidemischen Cerebrospinalmeningitis, *Deutsch. Arch. f. klin. Med.*, 1882, xxx, 500.
- von Ziemssen, H., Meningitis cerebrospinalis epidemica, Handbuch der speciellen Pathologie und Therapie, Leipzig, 1878, pt. ii, 639.