

## INTRAVENOUS TREATMENT OF MENINGOCOCCIC MENINGITIS WITH MENINGOCOCCUS ANTITOXIN

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It is necessary to scan the official statistics of a city or state in order to realize fully the high fatality rates that have usually prevailed for meningococcic meningitis. In Chicago, from 1916 to 1933, the fatality rate for this disease has exceeded 40 per cent in every year but one. This was in 1921, when the rate was 39.2 per cent. In 1925 and 1926 the fatality rates were 72 per cent and 65.9 per cent respectively. From 1916 to 1935 inclusive the total number of reported cases in Chicago was 4,028 and the average yearly fatality rate was 47.7 per cent. During the Detroit<sup>1</sup> epidemic of 1928 to 1931 there were 1,686 cases, with a fatality rate of 50.5 per cent. Tripoli<sup>2</sup> reported a rate of 65.15 per cent for patients treated in New Orleans in the years 1925-1934. In chart 2 is illustrated the expected and actual fatality rate per hundred cases for the years 1926-1935 in Chicago.

At the Cook County Hospital in Chicago, during a period of nineteen years prior to 1934, the fatality rate for meningococcic meningitis has varied from 35 to 90 per cent.<sup>3</sup> In those years all patients received serum intraspinally. At times, intracisternal, intraventricular, intravenous, intramuscular and intraperitoneal injections were resorted to, but only as auxiliary measures. Failures in treatment were frequently attributed to lack of agglutinins in the serum or to unusual virulence of the infecting organism. Although intraspinal therapy has been regarded as a necessity from the time the serum was introduced, response to this mode of treatment often has been most disappointing. The fatality rates mentioned are in accord with this feeling.

When evaluating fatality figures for meningococcic meningitis, certain factors should be given careful consideration. Age has quite as distinct a bearing on prognosis as the virulence of the infecting organism. This fact is disclosed in table 1.

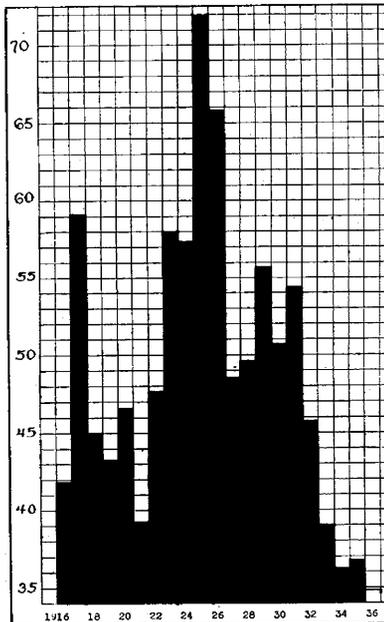


Chart 1.—Fatality rate per hundred cases of epidemic meningitis in Chicago from 1916 to 1935.

From the Municipal Contagious Disease Hospital, Board of Health, and the Cook County Hospital, Department of Contagious Diseases.

Read before the Section on Pediatrics at the Eighty-Seventh Annual Session of the American Medical Association, Kansas City, Mo., May 15, 1936.

1. Gordon, J. E.: Medical Report of the Herman Kiefer Hospital, Detroit, for the Five Years 1927-1931, section XXII.

2. Tripoli, C. J.: Bacterial Meningitis: A Comparative Study of Various Therapeutic Measures, J. A. M. A. **106**: 175 (Jan. 18) 1936.

3. Hoyne, A. L.: Meningococcic Meningitis: A New Form of Therapy, J. A. M. A. **104**: 980-983 (March 23) 1935.

All the patients represented in table 1 received Ferry's antitoxin<sup>4</sup> both intraspinally and intravenously. The fatality rate of 27.3 per cent for these 201 patients was regarded as very satisfactory. But it may be noted that for sixty-two patients who were 10 years of age or less the fatality rate was but 12.9 per cent. On the other hand, for eighty-three patients above the age of 20 the fatality rate was 45.7 per cent.

Is it proper to refer to the disease called meningococcic meningitis as an acute infectious disease of the central nervous system? Is there not justification in regarding the meningitis as a complication of an acute systemic infection? Such an interpretation is not far different from that which is now commonly placed on

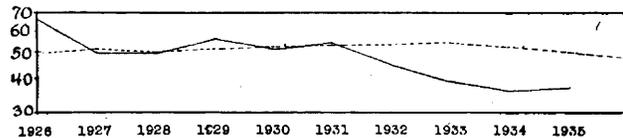


Chart 2.—Expected and actual fatality rate per hundred cases of epidemic meningitis in Chicago, based on ten year moving average (1926-1935). Solid line, actual fatality; broken line, expected fatality.

poliomyelitis—a disease in which “paralysis may occur, but not usually.” As an inclusive term for all classes of meningococcic infection, the word “meningococcia”<sup>5</sup> has been suggested. Meningococcic nasopharyngitis, meningococcemia without evidence of meningitis, meningococcemia with meningitis, and meningococcus carriers would all be embraced by the one name indicative of meningococcic infection. This classification assumes that when meningitis develops it is secondary to a blood stream infection. Herrick<sup>6</sup> expressed such an opinion nearly twenty years ago in regard to the mode of travel of the meningococcus in the body. It is largely on the same theory that my associates and I have abandoned intrathecal therapy and concentrated our attention on the toxicity of the disease.

Our present procedure of treating patients for meningococcic infections is as follows: Immediately on admission to the hospital a sample of blood is obtained for culture. If the patient has petechiae, the blood culture is nearly always positive. Should there be little or no rigidity of the neck, a lumbar puncture need not be done at this time. Preparations are then made for intravenous therapy. Later, if the blood culture is negative, at least one spinal puncture is performed for the purpose of confirming clinical diagnosis.

It should be stated at this point that antimeningococcus serum or meningococcus antitoxin has been given to alternate patients in order to compare therapeutic effects. This was done irrespective of the age, day of disease, or condition of the patient. Whether meningococcus antitoxin or antimeningococcus serum is to be injected, it is given diluted in 10 per cent dextrose in physiologic solution of sodium chloride of at least twice the volume of the therapeutic agent. From 5 to 15 minims (0.3 to 0.9 cc.) of epinephrine is added to the mixture. It is then administered by the gravity method at body temperature. The flow should approximate about 60 drops per minute. If difficulty is encountered in inserting the needle, venesection is always justifiable. Any suitable vein in an extremity

4. Ferry, N. S.: Meningococcus Antitoxin: I. Prophylactic and Therapeutic Tests on Guinea-Pigs, J. Immunol. **23**: 315 (Oct.) 1932.

5. Hoyne, A. L.: Meningococcia (Meningococcic Infection), Arch. Pediat. **52**: 418-421 (June) 1935.

6. Herrick, W. W.: Early Diagnosis and Intravenous Serum Treatment of Epidemic Cerebrospinal Meningitis, J. A. M. A. **71**: 612-616 (Aug. 24) 1918.

may be selected. Whether the arm or leg is chosen, the part should be immobilized on a splint. It is unnecessary to state that aseptic methods should be adhered to.

When meningococcus antitoxin is used the initial dose is usually from 50,000 to 100,000 units. The smaller dose may suffice for a child, the larger one for an adult. Thirty cubic centimeters of the unconcentrated antitoxin contains 10,000 units; therefore, by volume the quantity will be 150 cc. for 50,000 units, or 300 cc. for 100,000 units. If one of the standard antimeningococcus serums is selected, the dose is generally from 150 cc. for a child to 200 or 300 cc. for an adult. In either instance antitoxin or serum may be repeated at twenty-four hour intervals if it seems indicated. Frequently only one large dose of antitoxin or serum will be required. However, very recently we administered 100,000 units of antitoxin intravenously on four consecutive days. The patient was a woman who had been ill for six days prior to admission to the hospital. She entered in coma and continued in this state for three days after admission. She made a complete recovery without complications and was discharged after being in the hospital for twelve days.

Nearly all patients receiving intravenous therapy develop urticaria from five to seven days later. Seldom, however, are there any serious reactions. When the therapeutic agent is diluted as described, reactions are no more severe than when undiluted serum is injected intraspinally.

In table 2 are shown the results secured in the treatment of sixty-six meningococcic patients without resort to intrathecal therapy. In these cases the clinical diagnosis was confirmed by blood culture or spinal fluid examination in all but four instances. The patients were treated during the years 1934, 1935 and 1936 and constitute all patients so treated in the contagious disease department of the Cook County Hospital during those years up to April 11, 1936. Since January 1 of this year, no meningococcic patient admitted to either the Cook County Hospital or the Municipal Contagious Disease Hospital has received any intraspinal therapy. At the Municipal Contagious Disease Hospital, thirty patients have been treated in this man-

patients was 14.2 per cent. This wide difference in apparent therapeutic efficiency between the antitoxin and serum groups is not usually so marked.

Additional figures illustrative of our results in the treatment of meningococcic meningitis without intraspinal therapy at the Cook County Hospital during the present year are as follows:

From Jan. 1 to April 11, 1936, fifty-two patients were admitted. Among these the fatality rate was 19.2 per cent. The average number of days of illness

TABLE 2.—Meningococcic Meningitis Treated Without Intraspinal Therapy at the Cook County Hospital Contagious Disease Department

Age	Sex		Total	Anti-toxin	Serum	Recov-ered	Died	Fata-ly, per Cent
	Male	Female						
Under 1.....	2	0	2	1	1	2	0	0
1-5.....	7	8	15	12	3	15	0	0
6-10.....	6	1	7	5	2	7	0	0
11-15.....	6	7	13	5	8	12	1*	7.6
16-20.....	4	2	6	3	3	6	0	0
21-30.....	12	2	14	3	11	12	2†	14.2
31-40.....	4	1	5	2	3	3	2†	40.0
41-50.....	0	3	3	0	3	2	1*	50.0
51-65.....	0	1	1	0	1	0	1*	100.0
Total.....	41	25	66	31	35	59	7	11.8

For forty-three patients 20 years of age and less, the fatality rate was 2.3 per cent.

For thirty-one antitoxin-treated patients, the fatality rate was 6.4 per cent.

For thirty-five serum-treated patients, the fatality rate was 14.2 per cent.

\* Serum treated patient.

† One patient was treated with antitoxin and one was treated with serum.

on admission for this group was 3.8. The average number of lumbar punctures for forty-two recovered patients was 2.1. The average dose of antitoxin per patient was 221,000 units, and the average dose of anti-meningococcus serum was 363 cc. The number of hospital days averaged 14.5 for the antitoxin group and 15.3 for serum-treated patients.

The number of meningococcic patients treated exclusively by the intravenous route at the hospitals named was ninety-six. The fatality rate for the combined groups was 15.9 per cent.

When serum or antitoxin is administered in adequate dosage intravenously there is usually a marked decline in temperature, which may reach normal within twelve hours. If satisfactory response to the initial dose of antitoxin or serum is not apparent within twenty-four hours, the dose is repeated. Frequently in severe cases a second dose of antitoxin or serum is administered twelve hours following the first. If there are evidences of intracranial pressure two or three days after the beginning of treatment, a second lumbar puncture may be made. When this is done a pronounced decline in the cell count of the spinal fluid is usually noted. Often, too, a smear and culture of the spinal fluid will show the absence of organisms. This seems surprising when one considers the long accepted opinion<sup>7</sup> in regard to the necessity for bringing the specific serum into direct contact with the meningococci. During the past year we have frequently observed that patients with high spinal fluid cell counts and positive cultures for meningococci at the time of first antitoxin or serum administration intravenously will have low cell counts and sterile spinal fluids two or three days later. In some

7. Zinsser, Hans: Resistance to Infectious Diseases, ed. 4, New York, Macmillan Company, 1931, p. 597.

TABLE 1.—Antitoxin Treated Cases According to Ten Year Age Groups

Age	Cases	Deaths	Fatality, per Cent	Age	Cases	Deaths	Fatality, per Cent
Under 1	4	0	0	41-50	17	12	70.5
1-10	58	8	13.7	51-60	2	2	100.0
11-20	56	10	17.8	61-70	1	1	100.0
21-30	43	10	23.2	71-80	1	1	100.0
31-40	18	11	61.1	Unknown	1	0	0.0
Totals	179	39	21.7	Totals	22	16	72.7
			Cases				Fatality, per Cent
Grand totals.....			201				27.3

ner between January 1 and April 11, 1936. For the latter group, the fatality rate was 20 per cent.

In table 2 it will be noted that the fatality rate for all cases was only 11.8 per cent. What is still more significant is the fact that for the forty-three patients who were 20 years old or less, the fatality rate was only 2.3 per cent. For the thirty-one antitoxin-treated patients, irrespective of age, the fatality rate was 6.4 per cent. The fatality rate for all serum-treated

instances only a single lumbar puncture has been made, and even though meningococci were found on smear and culture no subsequent puncture was done. Such patients have made excellent recoveries without complications. The period of their hospitalization has been brief. In many cases it has been extended beyond the requirements of the patient merely for the purpose of complying with quarantine regulations. In Illinois the minimum quarantine is fourteen days from the onset.

As further evidence that intrathecal administration of an antiserum is not necessary in the treatment of meningococcic meningitis, attention is directed to table 3. Here nine patients are represented. No puncture was made on any one of these patients. The ages varied from 8 months to 6 years. All had petechiae. In each instance the blood culture was positive for meningococci. There was very little rigidity of the neck in most of the members of this group. In some cases the temperature was between 105 and 106 F. when intravenous treatment was started. One child was in coma and cyanotic when admitted to the hospital; he stopped breathing in the receiving room and was given artificial

TABLE 3.—Meningococcic Meningitis: Intravenous Therapy Without Lumbar Puncture (1934-1936) at the Municipal Contagious Disease Hospital and the Cook County Hospital, Contagious Disease Department

Patient	Age	Sex	Pete- chiae	Blood Culture	Units of Anti- toxin	Serum, Cc.	Recov- ered	Died	Hos- pital Days
I. R.	5 yrs.	♂	++	+	80 M.	...	+	..	11
E. Mc.	4 yrs.	♀	++	+	.....	245	+	..	12
R. Mc.	4 yrs.	♀	++	+	110 M.	...	+	..	14
J. Mc.	8 mos.	♂	++	+	100 M.	...	+	..	13
L. L.	6 yrs.	♀	+	+	150 M.	...	+	..	13
W. W.	3 yrs.	♂	+++	+	120 M.	...	+	..	13
H. B.	1½ yrs.	♂	+++	+	.....	300	+	..	21
F. S.	4 yrs.	♀	++++	+	180 M.	...	..	+	3
A. M.	5 yrs.	♂	++	+	.....	270	+	..	11
Recovered Cases									
Average dose antitoxin.....								120,000 units	
Average number of hospital days.....								12.8	
Average dose serum.....								271 cc.	
Average hospital days.....								14.6	

respiration. During the administration of 100,000 units of meningococcus antitoxin intravenously, his color returned to normal. Twelve hours later his temperature was approximately normal and he was mentally alert. His recovery was complete five days after admission, except for a serum rash that developed on his seventh hospital day.

Most of the fatal cases at the Cook County Hospital among those treated by the intravenous method exclusively occurred among patients who were extremely bad risks. For example an alcoholic patient, aged 39, a woman, aged 64, a patient with aortitis, and one with multiple fibroids and other pathologic conditions of the abdomen.

On several occasions, patients with meningococcic meningitis who appeared to be suffering from an overwhelming toxemia responded slowly to intravenous treatment. Usually these were patients who had been ill for a number of days before hospitalization. They assumed the picture of an encephalitis as the spinal fluid approached normal. Several patients of this character eventually made complete recoveries and have remained well after discharge from the hospital. In a few instances death occurred after the spinal fluid had been found negative for organisms by culture. Autopsies in these cases showed no evidence of meningitis but did disclose the presence of encephalitis, which we

ascribed to the toxic action of the meningococcus. There was no pus in the ventricles, though in one case the ventricles appeared dilated; an internal hydrocephalus had probably developed. These changes seem to uphold still further the important part played by the toxic action of the meningococci.

When meningococcic meningitis patients are treated by the intraspinal route, opisthotonos is common. Increased irritation of the meninges is undoubtedly caused by the introduction of a foreign substance into the intrathecal sac. If this form of treatment is adopted early in the septicemic stage, meningitic signs almost invariably become more pronounced. As a matter of fact, it seems to me that meningitis may be induced when there was formerly no evidence of its presence. On more occasions than one, we have found that examination of spinal fluid withdrawn early in an attack of a meningococcic infection did not reveal the presence of meningococci, nor did a high cell count exist. In view of these facts, should we not devote more attention to the systemic infection and think less of the organisms? Too often the toxic action of the meningococci is ignored while intraspinal therapy is being carried out. Moreover, with intraspinal therapy, problems relating to blockage are sometimes encountered. Secondary infections are also a possibility which cannot be totally overlooked. The frequent subsection of the patient to discomfort, pain and perhaps permanent injury of the vertebral column as the result of numerous spinal taps is a further objection to frequent lumbar punctures.

Suppurative processes are seldom encountered when the patient is treated by the intravenous method exclusively. Panophthalmitis is one of the most serious complications of epidemic meningitis. This complication has not occurred in any patient receiving exclusively intravenous therapy. Endophthalmitis, iridocyclitis and optic atrophy have occurred, but neither eye nor ear complications have developed in any antitoxin-treated patient after this form of therapy has been instituted. The few eye and ear complications that developed in serum-treated patients we attributed to toxic rather than to suppurative influences.

Strabismus is not an uncommon complication early in the attack of meningococcic meningitis, although the condition usually improves during the course of treatment. Facial paralysis and even complete hemiplegia at the time of hospitalization have recently been noted among our patients. These cases happened to be antitoxin treated and recovered completely. Hydrocephalus is very common among infants when treated by intrathecal injections of serum. With exclusive intravenous therapy it is encountered much less often. The old theory that frequent lumbar punctures are necessary to prevent hydrocephalus seems doomed to the discard on the basis of our recent experiences. In fact, it seems to me that numerous punctures serve to induce a greater secretion of spinal fluid. Hypertonic solutions such as sucrose intravenously are often of value.

Thus far we have had no discharged patients who were treated exclusively by the intravenous method reenter the hospital because of recurrences. In the past, when patients were treated intraspinally, this was not an extremely rare happening.

#### COMMENT

1. The fatality rate for meningococcic meningitis at the Cook County Hospital during nineteen years prior to 1934 varied from 35 to 90.4 per cent. The average was 50.6 per cent.

2. Meningococcic meningitis is interpreted as a blood stream infection with accompanying toxemia. Meningitis is regarded as a complication.

3. The intrathecal method of therapy prolongs recovery of the patient.

4. Massive doses of the therapeutic agent intravenously are advised.

5. For sixty-six patients who received only intravenous treatment the fatality rate was 11.8 per cent. For forty-three of these patients who were 20 years of age and less the fatality rate was 2.3 per cent.

6. A total of ninety-six patients were treated exclusively by the intravenous route, with a fatality of 15.9 per cent.

7. Of nine meningococcic patients treated intravenously without any lumbar puncture, only one died.

8. Suppurative complications were not encountered with intravenous therapy. Fewer complications occurred with Ferry's meningococcus antitoxin than with antimeningococcus serum.

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#### ABSTRACT OF DISCUSSION

DR. ALBERT G. BOWER, Hollywood, Calif.: Dr. Hoyne reports forty-three cases under the age of 20 years treated entirely by massive intravenous doses of antitoxin. His fatality rate was only 2.3 per cent. It has long been noted that the younger age groups show the greatest response to therapy, with the lowest death rate, but a rate as low as this is almost unbelievable in the light of past experience. The reason for a lower death rate in younger children is difficult to explain in view of the work of Silverthorne and Fraser on the action of human blood on the meningococcus. They showed that the blood of most adults is bactericidal to a high degree, whereas children and infants possess little or no bactericidal property in their blood. Does this mean that those adults who acquire epidemic meningitis represent a particularly susceptible, nonreacting class with regard to therapy? The data regarding the shortening of the duration of the disease, the stay in the hospital and the lessening of complications are likewise most significant. It must be remembered, however, that when meningitis and its treatment are discussed, the disease as it is known in one's own particular geographic location is being discussed. Nearly all investigators have long held that the meningococcus and its products exercise a selective affinity for the cerebrospinal system, and that with the exception of the hematogenous type its appearance in the blood stream has been quite transient. If this is so, a humoral immunity must develop quite rapidly and be reflected in the circulating blood stream. Yet it does not get through the choroid plexus to reflect its antimeningococcic effect in the spinal fluid, for these patients do not get well until additional serum treatment is instituted. I am convinced that in at least some cases this must be true, for since January I have successfully treated four cases with the patient's own serum administered intrathecally, after the intraspinal administration of commercial antimeningococcus serum failed to effect a cure. All patients lived when their own blood serum was given by spinal puncture. Mehrtens' work, showing that in 20 per cent substances introduced into the blood stream do not get over into the spinal fluid, tends to afford strong support to this view. When antimeningococcus serum is to be used instead of antitoxin, the best clinical results will be obtained by selecting that serum which agglutinates most rapidly and in the highest titers the organism cultured from the individual patient.

DR. GERALD F. KEMPF, Indianapolis: Dr. Hoyne is to be commended for his courage in introducing the use of intravenous therapy alone. However, most of us would agree that in those cases which do not exhibit marked evidence of toxemia and bacteremia one probably should adhere, at least in some measure, to intraspinal therapy. His results, both with the antitoxin and with the antiserum, appear to speak for them-

selves. However, since the question of antiserum against antitoxin has been raised, I should like to say that last year my associates and I treated seven cases of meningococcic meningitis with antitoxin intraspinally and intravenously and lost the seven cases. At the same time we treated ten cases with antiserum and lost four. Conclusions cannot be drawn from such a small group, because I have seen as many as seven patients with meningococcic meningitis come into the hospital on the same day and all die within forty-eight hours. I should like to ask Dr. Hoyne whether, in his comparison, the 120,000 units of antitoxin in one group as against 271 cc. of unconcentrated antiserum in the other group is not actually 360 cc. of horse serum; in other words, the antitoxin treated group was getting 25 per cent more serum than the antiserum treated group. This may account for the small differences in mortality and morbidity.

DR. GILBERT J. LEVY, Memphis, Tenn.: It has occurred to me that in two diseases strikingly different methods of treatment have recently been employed: (1) In tetanus the recent teaching is that treatment by the intravenous and intramuscular routes is to be preferred to the time-honored treatment, that of spinal puncture and spinal therapeutics, (2) now the pendulum has swung in the case of meningococcic meningitis. It was formerly taught by Dr. Flexner that serum therapy by the spinal route was the ideal method and his results were strikingly good. Later, during the World War, Dr. Herrick urged large intravenous doses of the serum. This, too, combined with intraspinal therapy, proved effective. However, Dr. Hoyne's results are the best to the present time. Dr. Hoyne advocates the treatment by vein alone. My associates and I have attempted the use of the antitoxin during the past three years. In a series of over 200 cases our mortality was about 35 per cent. I must admit, however, that our intravenous medication has not been in the amounts advocated by Dr. Hoyne. This we intend to do. The death rate in our community has been parallel with that in Chicago. Our mortality average for a period of sixteen years has been about 50 per cent. However, during the past two and one-half years, with the use of the new antitoxin given both intraspinally and intravenously, the mortality has been reduced to 35 per cent. I should like to ask Dr. Hoyne whether it would be possible in the interest of economy to concentrate the antitoxin so as to make a smaller but a more highly concentrated dose.

DR. ARCHIBALD L. HOYNE, Chicago: There are great variations in the fatality rates of meningococcic meningitis in different sections of the country, and also in different years. We are comparing our present rates at the County Hospital with the years gone by, and while it is true that the fatality rate may rise again, the point is that at present it has never been so low, and therefore we think the treatment has a great deal to do with it. We have considered convalescent serum but have not administered it in the manner suggested by Dr. Bower. The idea of adding complement may be of great assistance, and perhaps in the future it will improve matters still more. The question of the permeability of the meninges is one that is often discussed. Exactly what happens may not be known but it is a fact that introduction of the serum in large quantities into the blood stream results in organisms disappearing from the spinal fluid. It is possible that, in the future, intraspinal therapy may be resumed. Our present results make it appear doubtful. In answer to Dr. Levy's question I think that if the serum should be concentrated it would be of great help. With Ferry's antitoxin we have not been concerned so much with the types of organisms as with the toxemia. Little attention has been paid to the power of the various standard serums to agglutinate. A few years ago, in Chicago, I followed cases in which serum was used and found that in many instances the best results were obtained with serums that did not agglutinate very well. It would be a great help to have the antitoxin concentrated. At present 100,000 units of antitoxin means 300 cc. of serum. In other words, in 30 cc. of unconcentrated antitoxin there is only 10,000 units. A small amount of the concentrated antitoxin was made up in which 10 cc. contained 20,000 units. We have lost far fewer eyes and had very much less deafness with the use of the Ferry preparation than we have had with any of the standard serums.