5-1-1934

Serum treatment of scarlet fever

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THE SERUM TREATMENT
OF
SCARLET FEVER

By

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SENIOR THESIS

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April 13, 1934
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Scarlet Fever has probably caused more widespread interest through attempts at its prevention and serum treatment than any other infectious disease. However, in no other infectious disease has there been so much controversy among practitioners and at the same time such unanimity of opinion in the reports of experienced observers. Much of the work with serum therapy having been done before adequate methods were adopted for preparation, standardization and administration of the serum may account for some of the unfavorable results. Recent and careful investigators are much of the same opinion now in regard to the use of serum in the treatment of this disease. Among the general practitioners and some teachers of therapeutics there is still doubt as to practical use of the serum. Because of this existing controversy, I have chosen "The Serum Treatment of Scarlet Fever" as my subject. By a survey of the literature on this topic, I hope also to be the better enabled to decide on the merits of such treatment and to gain practical knowledge concerning its indications and administration.

In a study of any disease one of the most interesting phases is its history, and for that reason I have included a brief historical sketch of Scarlet Fever.
Scarlet Fever (44) is an acute infectious disease caused by Streptococcus scarlatinæ, and is characterized by sore throat, a diffuse scarlet rash and the frequent occurrence of a variety of complications and sequelae. The disease process consists essentially in a primary local infection from which a specific toxin is absorbed, and distributed by the blood stream. The specific toxemia is self-limited in duration. It gives rise to a series of symptoms, of which the rash is the most characteristic. The most important complications are of a septic nature, and are due to a spread from the primary lesion. The sequelae, of which acute nephrites is the most striking, occur during convalescence about the third or fourth week of the disease. The course and severity of the sequelae seem to be strikingly independent of the severity of the primary illness.

HISTORY

The works of Galen, Rhazes and other ancient writers contain various descriptions of a disease with throat symptoms and a diffuse red eruption suggesting scarlatinæ, but not until the sixteenth century was the disorder
differentiated from measles by Ingrassias, of Naples. The first accounts of what appears unmistakably to be scarlatina are those of Daniel Sennert, of Wittenberg, and his son-in-law, Michael Doerring, about 1625. They give us the typical description of scarlatina, the rash, desquamation, joint pains, anasarca and delirium. Sydenham in 1776, however, was the first to present a careful analysis of the disease with its medical characteristics and to give it the designation scarlatina or scarlet fever. He also differentiated it from measles, with which it was constantly being confused. The epidemic which gave Sydenham the opportunity for studying scarlet fever in large numbers was evidently a mild one, since he believed the disorder scarcely deserved to be considered a disease. But he was destined to change this belief fifteen years later when an epidemic of unusual malignancy, described by Morton broke out in England. Huxham (1740) appears to have been the first to call attention to the importance of angina in the symptom complex of scarlet fever (22) (51).

The disease was common in Europe during the eighteenth century and from the middle of the era spread over both hemispheres. According to Caiger, it first appeared in the North American Colonies in 1735, spreading over New England, reaching New York in 1746, thence extending to the coast states. By 1791 it made its appearance in the...
interior, reaching Canada and the Northern States during the early part of the nineteenth century. South America was not invaded until about 1830, and since then the disease has appeared often and at times in severe epidemic form, in nearly all of the countries of that part of the continent. During the middle of the nineteenth century scarlatina was reported from Polynesia, New Zealand, Tasmania, Australia and in distant Greenland and Iceland (51).

The recent history is more important from a standpoint of etiology.

In 1885 Crooke reported the presence of streptococci in the blood and organs in fatal cases of scarlet fever, and Loeffer obtained streptococci from the throat in scarlet fever, isolating the organism in pure culture. More striking were Kleins investigation of a milk born epidemic of scarlet fever in Dendon near London in 1885. He isolated streptococci in pure culture from a lesion in the udder of the cows, and also isolated similar streptococci in pure culture from the blood of scarlet fever patients during life and after death. He reproduced ulcerative lesions in cows with pure cultures of the human blood culture strains. He named the organism Micrococcus scarlatinae. In 1899 Class, and in 1900 Baginsky and Sommerfield described the regular presence of streptococci in the throat, early in scarlet fever. The former infected
swine with these organisms and observed a scarlatina form rash in these animals. Corroborating Klein, Haktoen in 1903, Jockman in 1905 and others found streptococci in the blood cultures during scarlet fever. In 1903 Schottmuller introduced the method of differentiating between hemolytic and non-hemolytic streptococci. From then on it was found that it was the hemolytic streptococci which was so frequently associated with scarlet fever. Moser in 1902 and Savcheska in 1905 immunized horses with streptococci obtained from scarlet fever patients in order to produce a therapeutic serum. The serums of both investigators were used with a certain amount of success but the favorable results could not be duplicated generally and the use of the serum was abandoned (44).

In 1905 Jockmann published a review of the work done along these lines and examined the claims made that the hemolytic streptococcus so frequently found in the throats of scarlet fever patients was the causative agent of the disease. He came to the conclusion that a good case had not been made out and that this streptococcus was not the causative agent but a secondary invader (36).

In 1907 Gabrichevski published the results of his work with a vaccine of killed cultures of streptococcus scarlatinae. He and his co-workers found that a large proportion of children inoculated with the vaccine developed a marked erythemia similar to localized scarlatinae
rash and that a smaller proportion developed a train of symptoms indistinguishable from scarlet fever. On subsequent inoculation in the same subject reactions were less marked or absent. Gabrichevski held that his findings clearly indicated that the scarlet fever streptococcus was a specific organism, that his results, taken with the fact that streptococci were usually not obtained in blood cultures early in scarlet fever, proved that the disease was a specific toxemia, and that streptococcus scarlatinae was the causative agent. Although his method of vaccination was used for a time in Russia with apparent success, his work was not carried further, but was over-looked or slighted, until quite recently. Work on the subject then lapsed and no important advance appears to have been made for some ten years.

In 1917 Schultz and Charlton, experimenting with serum from convalescent cases of scarlatina, found that this serum, when injected into the skin of acute cases of the disease, while the rash was well marked, caused complete blanching of the rash in a small area at the seat of injection. They also found that the serum from some healthy individuals produced this result, whereas the serum from cases in the early stage of scarlatina did not possess this power. This was a great step in advance, but was not so recognized at that time. In 1923 Mair repeating these experiments of Schultz and Charlton
explained this reaction thus: "Scarlet fever is apparently a general toxaemia and the rash only a manifestation of the toxin uniting with the tissue cells causing a capillary dilatation with swollen papillae. The serum injected neutralizes the toxin in the tissue and causes the disappearance of the rash. The negative reaction of the sera of acute cases of scarlet fever is simply due to the fact that antitoxin has not yet developed (44).

In 1919 Dochez, Avery and Lancefield devised a new method for the differentiation of bimotic types of hemolytic streptococci. This led to a further study of the hemolytic streptococcus so constantly found in the throats of scarlatinae patients. Reports by Dochez and Bliss (19), Tunnicliff (46), and Stevens and Dochez led to the conclusion that this hemolytic streptococcus was a specific type.

In 1916 Dick and Dick (10) obtained negative results in a serological study of the organisms found in the throats in scarlet fever patients. In 1921 they (11) inoculated human volunteers with the various organisms derived from scarlet fever patients. Streptococcus scarlatinae was probably among these bacteria. Some of the volunteers contracted a sore throat but none developed scarlet fever. In October 1923 the same workers (12) published a second series of inoculation experiments in human volunteers with successful results. A culture of
hemolytic streptococcus, isolated from the infected finger of a scarlet fever patient was swabbed on the tonsils and pharynx of five individuals. After forty-eight hours one developed a mild but typical attack of scarlet fever; one had merely a sore throat and fever; three remained well. By intracutaneous tests in human volunteers Dick and Dick (13) soon demonstrated a highly potent toxin in bacteria-free culture filtrates of streptococcus scarlatinae, the toxin which Gabrichenski had found in his vaccine of killed cultures. They then developed a number of new important facts regarding this toxin which they showed to be scarlet fever toxin. In January 1924 they (14) described a skin test for susceptibility to scarlet fever, performed by intracutaneous injections of a standard amount of toxin. They (15) showed that an individual, picked by the test as susceptible, developed scarlet fever on experimental inoculation with streptococcus scarlatinae, while another control individual picked by the test as immune, remained well when similarly inoculated. They (16) neutralized the toxin in vivo and in vitro by convalescent human serum and also with the serum of actively immunized human volunteers. They (17) found that individuals, susceptible by their test, could be actively immunized with injections of toxin and these individuals then reacted negatively to the test and were immune to scarlet fever. In fact a series of 360 susceptible nurses and
internes actively immunized with the toxin, did not contract scarlet fever on subsequent prolonged exposure, ten per cent of a control series of 240 nurses and internes, not tested or immunized, developed scarlet fever on similar exposure. From this time on, the etiology of scarlet fever having been well established, most efforts were made to produce therapeutic serums for treatment and prevention.

**SERUM THERAPY**

All efforts to identify and isolate the specific cause of scarlet fever having failed, it had been impossible to produce an immune serum for therapeutic purposes in this disease similar to that employed in the treatment of tetanus, diphtheria, epidemic meningitis and pneumonia. However, it was naturally inferred that persons who had recently passed through an attack of scarlet fever would have specific antibodies in their blood, and should the antibodies be in sufficient concentration, that the serum of such blood might be of curative value when introduced into patients acutely sick with the disease.

Acting on this presumption, Weisbecker in 1897, treated five cases of scarlet fever with the blood serum of convalescents, but with little success. From 1897 to 1903 scarlet fever cases were treated by injection of
convalescent serum by Huber and Blumenthal, Von Leyden, Rumpel and Scholz. They did not reach any certain conclusion as to the value of the procedure. The serum was injected subcutaneously and in relatively small doses. Because of the absence of any decided advantage from this treatment and from the fear of transmitting syphilis and other infection the use of convalescent serum was abandoned for about ten years. By this time the Wassermann test made it possible to exclude syphilis from the donor of the serum, and experience in the administration of large quantities of serums had been acquired. Intravenous injection of serum had also been successfully employed in various cases. In 1912 Reiss and Jungmann treated twelve cases of severe scarlet fever by intravenous injections of 40 c.c. to 100 c.c. of convalescent serum with marked benefit in ten cases. They drew the blood from convalescents about the end of the third or beginning of the fourth week of the disease, tested each serum for syphilis and sterility and mixed the serums from several persons, since some persons seemed to yield larger amounts of antibodies than others. The next year Kock reported from the same clinic the treatment of twenty-two additional cases with one death. He emphasized the value of early administration. He noted a prompt fall in fever usually followed by a slight rise, and he was especially impressed by the rapid and marked improvement in the general condition of the
patient. In 1915 Reiss and Herts, and Kock reported still larger series of cases in which the results were most satisfactory (49).

In April 1915 Zingher (53) reported the treatment of scarlet fever with fresh blood from convalescents. In the fall of 1915 he reported the treatment of fifteen cases of very severe scarlet fever selected from 900 cases, with 4 deaths.

Zingher's method consisted in obtaining fresh human blood (convalescent or normal) from a parent or near relative, by means of a 30 c.c. record syringe and a needle inserted in the median cephalic vein at the bend of the elbow of the donor. The required amount is rapidly aspirated and immediately citrated by adding the blood to a 10 per cent sodium citrate solution in the proportion of 30 c.c. of blood to each c.c. of citrate solution, making a 0.33 per cent final dilution of the citrate. When the syringe is full, it is detached from the needle which is not removed, but is kept in place by an assistant who attaches to it a 5 c.c. record syringe containing a 1 per cent sodium citrate solution to keep the needle free from blood. In this way three or four syringefuls of blood can be obtained before it becomes necessary to wash out the large syringe with sodium citrate. The blood is collected in 100 c.c. bottles, each of which contains 2 c. c. of sodium citrate solution. To each bottle 60 c.c.
of blood are added. This is then shaken to distribute the sodium citrate. The required amount, 120-130 c.c. can be thus obtained in less than ten minutes.

The recipient is given intramuscular injections of the blood (at one sitting into the triceps, the lateral region of both thighs, the calves and both gluteal regions; the dosage being 15 c.c. for a young child and 30 c.c. for an older child or an adult, at each of the three sites of injection.

Two of the patients died from septic conditions, and the other two patients who died were moribund when they were received. Of the 11 patients who recovered, 5 were of the purely toxic type, the other 6 had additional septic complications. The 5 purely toxic cases showed a critical drop in temperature after which it remained normal or slightly above normal. In the 6 remaining cases the drop in temperature was less marked and was followed by a secondary rise which persisted for a number of days.

In 1918 Weaver (49) reported the treatment of 19 cases of severe scarlet fever selected from the cases that entered the Durand Hospital by use of the convalescent serum. His method was similar to that used by Zingher. The blood was drawn on the 20th to 28th day, using convalescent patients that were free from suspicion of tuberculosis and had negative Wassermann's. The serum from several patients were mixed, tested for sterility,
and stored, until used, in the refrigerator in portions for a single dose. The serum was injected intramuscularly in doses of 25-90 c.c., 60 c.c. being the usual dose. His results were favorable and coincide with those of Zingher.

Weaver (48) again in 1921 reports the treatment of 54 cases of scarlet fever, 38 of the toxic type and 6 septic complications, by use of intramuscular serum from convalescent patients. His results were very conclusive. Two of the patients died, one septic and one toxic, both bad risks.

He presents charts showing the best drop in temperature curve in those cases that were given serum earliest. Fourth week serum was preferred by him. Seventh week serum was found to be still active. Mixed sero were best liked. Donors having mild attacks gave just as an efficient serum as those with severe attacks. Serums several months old were not as efficient as fresher serum. Bernbaum (2) in reviewing the literature reports that M. J. Synnott, New York, successfully treated one case desperately ill, with citrated convalescent blood. Temperature fell by lysis. Hoyne reports its successful use in the contagious hospital of Cook County. C. Kling and G. Widfelt, Stockholm, report the epidemic of scarlet fever that passed over the city of Stockholm in 1916-1917, when 2,165 cases were reported, showed a very large percentage of severe and fatal cases. Treatment of the severe cases by the serum
method prepared from convalescents was undertaken and showed excellent results. Before the serum treatment was attempted, the fatal cases of the severe form were 50 per cent or more. Of 237 cases treated, 195 proved successful and the percentage of deaths declined to 19.5 per cent in December and 6.3 per cent for January, although the relative number of severe cases had increased. The serum prepared from the blood of convalescents was found to be of equal value as taken from light, medium or severe form. The blood was usually taken from the fifth or sixth week after the first appearance of the disease, but was found effective when taken the fourth or seventh week. Healthy donors were selected. No secondary ill results were noted from the use of the serum in any case.

W. Schultze, Germany, reports serum therapy was employed in 184 cases, the injection being either normal human serum, convalescent serum or mixtures of both. Favorable results were secured, larger doses giving the more definite improvement in the condition. The serum should be given within the first three days of the disease.

H. F. Prinzing, Berlin, 1918, states that in patients who had not received serum therapy, the disease was followed by lymphadenitis in 34.6 per cent, by otitis media in 10.8 per cent, and by glomerular nephritis in 18.9 per cent of the cases. These conditions appeared in patients who had received serum in per cent of 15.9 - 9.3 - 8.2.
W. Grissback, Berlin 1919, reports that in a study of 21 cases, human serum was injected in 19 cases from convalescents, in two from normal individuals; 10 to 20 c.c. were given each patient. He states "The treatment is very efficient in modifying the duration and severity of the disease. The reactions following injection of serum are dangerous."

B. Bernbaum (2) reported 39 cases by Dr. Levy at the meeting of the Detroit Pediatrics Society in the Hospital. This was the number of cases treated at the Herman Fiefer Hospital with convalescent serum for the year ending July 1, 1921. Thirty-two lived and seven died. Of the seven who died, two were practically moribund, one died within 21 hours and the other 18 hours after entrance; one after eight days of acute hemorrhagic nephritis, one after eight days of septic complications. Three died of toxemia. Two of these received but 10 c.c. of serum and one 20 c.c.

Of the 32 who lived, 20 were toxic cases and 12 had septic complications. The average dose was from 10 to 35 c.c. intramuscularly. The serum was administered from the third to the eighth day of the disease. Children responded as well as adults. Eighteen cases were treated so far the fiscal year, beginning July 1, 1921. These were the most severe of all cases of scarlet fever admitted since that date. Of the 13, 5 died. The blood was taken from healthy donors in the fourth or fifth week of disease.
Snow and Fairbairn (37) in 1923 reported the cure of a grave case of scarlatinal sepsis with complications, in a boy twenty-seven months old, by a blood transfusion from a six month's convalescent donor.

Dochez (20) of New York described, in January, 1924, an antitoxic serum which he had produced in the horse by adopting a most ingenious method. In order to protect the streptococcus from the phagocytic action of the leucocytes of the horse he injected liquefied agar subcutaneously into the horse's neck, and when the agar had cooled and solidified, living Streptococci scarlatinae were injected into the agar. Thus protected the organisms survived and produced toxin which was taken up by the blood stream. After a course of immunization of six months the horse was bled and the serum tested in the cases of scarlatina.

Employing this antitoxic serum, Blake, Trask, and Lynch (3) obtained very good results in the treatment of cases of scarlatina, a single intramuscular injection of the serum in early cases being followed by prompt disappearance of the rash and symptoms of toxemia and a very rapid convalescence without complications. They found also that the serum, injected intradermally in cases with early scarlatinal rash, caused complete blanching of the rash at the seat of injection (Schultz-Charlton reaction). They also demonstrated that the toxin circulating in the
Blood of acute cases of scarlatina is completely neutralized within a few hours after the injection of Dochez's serum. They showed this by bleeding the patient immediately before treatment and obtaining positive Dick skin reactions in susceptible individuals, and by again bleeding at frequent short intervals after injection of Dochez's serum. Even in some very toxic cases the Dick tests were negative as early as four hours after the administration of the serum.

In April, 1924, the Dicks (17) reported the production of an antitoxin in the horse by a different method. Their methods as described by them is as follows:

"The Strains of hemolytic streptococci that caused experimental scarlet fever in human beings yield toxin of practically the same strength in all different lots, so that it is not necessary to standardize accurately toxin prepared from these strains for immunizing horses.

"Flasks of plain broth, containing 1 per cent sterile, defibrinated sheep's blood, are inoculated with pure cultures of the hemolytic Streptococci. Our first horses were immunized with toxin obtained from plain broth cultures; but with a small amount of blood in the broth, the toxin is somewhat stronger. We have used broth prepared with Witte's peptone, 1 per cent, and Liebig's meat extract, 0.3 per cent. After six days incubation, the cultures are filtered through filter paper until clear, and
then passed through a Berkefeld filter. The sterility of the filtrate is determined by culture, and it is kept in the refrigerator. Care must be taken to discard any contaminated flasks before filtration. The sterile toxin is injected subcutaneously in gradually increasing doses, beginning with 20 c.c. and increasing to 1 liter. The horses are then continued on injections of about 1,000,000 skin test doses of the undiluted toxin every five days.

"The sterile toxin does not cause abscesses and the horses remain in good condition. After preliminary tests show that the horse is producing a good antitoxin, it is bled, and the serum or plasma is concentrated. The concentration is essential, not because the antitoxin content of the unconcentrated serum is not high enough, but to avoid unnecessarily frequent and severe serum reactions.

"An amount of scarlet fever toxin corresponding to 1,000 skin test doses is capable of causing general malaise, nausea, vomiting, a fever of 101 degrees F. and a generalized scarlatinal rash in susceptible adults. In other words 1,000 skin test doses of toxin, if injected without previous immunization, produces a clinical condition resembling a mild attack of scarlet fever. We have taken the amount of antitoxin required to neutralize this dose of toxin as a basis for the standardization of scarlet fever antitoxin. Any antitoxin used should be of such strength that 1 c.c. of the concentrated serum will
will neutralize 1,000 skin test doses of the toxin. It is possible to obtain serum considerably stronger than this minimum requirement of potency.

"Method of Standardizing Antitoxin:

"For standardizing, the concentrated antitoxin is diluted 1 to 10 in sterile physiologic sodium chloride solution. Two cubic centimeters of this diluted antitoxin is mixed with 2 c.c. of a toxin solution. The solution of toxin used is 10 times as strong as the standard skin test solution, so that each cubic centimeter represents 100 skin test doses.

"Two control solutions are made, one of equal parts of toxin and salt solution, the other of equal parts of the diluted toxin and salt solution. These three mixtures are incubated one hour. Skin tests are then made with 0.1 c.c. of each mixture in persons with positive to strongly positive skin reactions. Persons with slightly positive reactions are not acceptable for these tests.

"On observation, at the end of twenty-four hours, the test made with the antitoxin alone should be negative. If this is positive, the person is sensitive to horse serum, and is not useful for the standardization. The test with the toxin alone should be positive. The test with the toxin-antitoxin mixture will be negative if the antitoxin is sufficiently strong.

"At the end of forty-eight hours, another observation
is made. The weaker antitoxin, like convalescent serum, may hold the toxin in combination twenty-four hours, but release it after that so that the toxin-antitoxin test that was negative at the end of twenty-four hours may be found positive at the end of forty-eight hours.

"For further standardization, the same tests are repeated with higher dilution of the antitoxin.

"We decided to employ as a therapeutic dose an amount of antitoxin sufficient to neutralize twenty times the quantity of toxin known to produce the characteristic symptoms of scarlet fever in adults. For convenience we speak of this amount of antitoxin which neutralizes 20,000 skin test doses as a therapeutic dose. Each patient in the antitoxin series received one such dose, and in a few of the most severe cases, two therapeutic doses were given.

"In their conclusions they state that injected intramuscularly, the serum blanches the rash, lowers the temperature and improves the general condition of scarlet fever patients. If given early it shortens the course of the disease and incidence of complications, and sequelae is greatly diminished. One therapeutic dose, as described above, suffices in early cases of moderate severity."

With the production of the Dochez serum and that of Dick and Dick numerous investigations were made immediately concerning their merits.

In May 1925 Thenebee (40) reports favorable results
from the use of Dochez's antiscarlatinal serum by intravenous injections. In September, 1925, Thenebee (41) reports further observations on administration of Dochez's antitoxin in the treatment of forty-two patients. In this series of patients he used both concentrated and unconcentrated antitoxin, by intravenous and intramuscular injections. He states that the unconcentrated antitoxin is the safer procedure for intravenous administration, while the concentrated antitoxin is safer for intramuscular injection.

Blake, Lynch and Trask (3) and Blake and Trask (5) in October, 1925, reported the treatment of 57 cases of uncomplicated scarlet fever; 48 cases of scarlet fever with septic complications, and seven cases of post-scarlatinal sepsis, with Dochez's unconcentrated antitoxin by intramuscular injection. The 57 uncomplicated cases were all promptly cured within 12 to 36 hours irrespective of the severity of the disease at the time of treatment. All but 5 remained well: of these two subsequently developed a mild non-suppurative cervical adenitis late in convalescence, one an otitis media, one a transient fibrinous pleurisy and one an acute nephritis. Of the 48 complicated cases all but one were promptly and permanently cured of the specific toxemic phase of scarlet fever as shown by fall in temperature, rapid fading of the rash and prompt neutralization of toxin in the blood.

Blake (4) in July, 1924, reported concerning the use
of Dochez's serum as follows: "Intramuscular injection of the serum in therapeutic doses early in the disease is followed by rapid clinical cure as evidenced by critical fall of temperature and pulse to normal, rapid fading of the rash and prompt return to a state of well being. The specific toxic substance present in the blood of patients with scarlet fever is neutralized in vitro by Dochez's serum. It promptly disappears from the blood stream following serum treatment. The blood serum of scarlet fever patients acquires the capacity to blanch the rash in scarlet fever within a few hours after serum treatment. Graham (25) in using the Dochez serum had twenty-one patients develop serum disease out of thirty-one cases. Most of his patients were given serum after exposure to scarlet fever before symptoms had developed.

Parks (32) October, 1925, makes the following report concerning the use of antitoxin:

"Scarlet fever antitoxin was first administered by us in January, 1924. This was made possible through a supply of serum by Dr. Dochez. The first serum was only moderately potent, and in the doses given by the intramuscular method, the results though good were not striking. In January, 1925, it was decided to give it to alternate patients, and in severe cases to give it intravenously. The antitoxin most used was our own preparation obtained from two horses that had received increasing toxin
injections for nine months and more; but in about one fourth of the cases we used a new preparation of the serum sent us by Dochez. The results of the intravenous injection was so striking that the medical board decided in March, 1925, to give all patients having a rash and a temperature of 101 degrees F. or higher, antitoxin and to give it to alternate patients having a temperature lower than 101 degrees F. It was given intravenously in all severe cases.

The potency of the antitoxic serum was tested either by the Schulz-Charlton blanching test or by the more accurate Dick neutralization tests of the toxin. Its potency ranged from 50-150 units per cubic centimeter; that is, 1 c.c. of the serum neutralized between 5,000 and 15,000 Dick test skin doses of toxin.

Most of the serum was not refined. About fifty patients however, received the refined antitoxic globulin solution. The therapeutic results were alike, but rashes occurred in about 60 per cent after the injection of the unrefined serum and in only about 30 per cent after injection of the refined. The rashes and other symptoms of serum disease that did occur were more severe with the unrefined. No serious after-effects occurred in any case, but the serum sickness in some was very annoying. A sufficient dose should be given at the earliest possible moment. An amount should be given in the first dose to make and keep the fluids of the body antitoxic. If, however, the temperature rises after the drop, a second injection should be given.
The size of the dose is influenced by the weight of the individual and the severity of the case. Intravenous injections of sufficient size give the most striking results. The fluids of the body become quickly antitoxic, as shown by the Dick test. This when done even an hour or two afterwards, is always negative, if a sufficient dose has been given, and remains negative if done later in the disease.

The results from sufficiently large intramuscular injections are certain, but they develop more slowly. The Dick test is positive for from six to twelve hours after an intramuscular injection. It then becomes negative.

The results as noted at the bedside in the majority of patients are very striking. The higher the temperature and the more toxic the case, the more striking will be the results if the serum is given very early in the disease. After an intravenous injection in an early uncomplicated case, the patient, as a rule, finds within a few hours that the throat is less sore, the mind clears, vomiting ceases, the appetite returns, and the temperature and pulse begin to fall. Within from six to eight hours, a delirious and a very sick patient is often convalescent. With a larger dose given intramuscularly the same results follow, but more slowly. With insufficient dosage there is less rapid improvement, and the toxic symptoms may return.

In 1926 Lewis (31) reported favorable results for the
cure and reduction of complications in scarlet fever by the use intramuscularly of antitoxin. He thinks the intravenous injection is indicated only in critical conditions.

Stovall (39) in reviewing the advances in treatment of scarlet fever stated that the therapeutic value of antitoxin is established and constitutes the really well proved advance in its treatment. It is effective in the cure of the toxemia of scarlet fever and probably indirectly lowers the incidence of complications in those cases. He states it should be used early in all cases of scarlet fever, but it is only the occasional circumstance which calls for its use for prophylactic purposes.

In the treatment of 500 cases of scarlet fever, Cushing (9), using both the Dick serum and the Dochez serum intramuscularly, states that the disease is cut short and relief from all its early manifestations was obtained. From his observations he thinks it lessens the number and severity of the complications and definitely lowers the mortality of the disease. He believes the serum should be used early in every case except one which is extremely mild.

Levy (30) in July 1926 treated 37 cases with scarlet fever antitoxin using both concentrated and unconcentrated serum. In severe and toxic cases they used intravenous injections and in the moderate cases intramuscular injections. Their results show the serum to be of value as a therapeutic
measure. They state that serum should be given early before complications have occurred. In moderate cases give intramuscularly and in severe or toxic, intravenously. Also the serum sickness is often more annoying than the scarlet fever in mild cases. Before administering any foreign serum they give adrenalin chloride 1-1000 solution subcutaneously. They also warm the antitoxin to body heat and transfer to a glass luer syringe before injection.

P. A. Bly (6) in 1926 reported concerning the treatment of 34 scarlet fever patients by the use of the Dochez serum and convalescent whole blood. He states that the serum appeared to bring about a more rapid improvement in the symptoms of the toxemia, and particularly an earlier disappearance of the exanthem.

Platou and Collins in November, 1926, reported observations over 100 cases of scarlet fever which were treated with antitoxin. These are compared with a control group of 100 cases simultaneously observed which received no serum. Two of the concentrated commercial preparations were used. One made according to Dick's method, the other according to that of Dochez. Each patient receiving the antitoxin was given a single "therapeutic" dose (10-14 c.c.) as prepared by the manufacturer. All of the antitoxin was given intramuscularly in dosages sufficient to neutralize from 200 to 500 thousand skin test doses of toxin. Intravenous administration was not done because of the fear of serious reactions. Rapid blanching of positive Dick
tests was noted after the antitoxin was given.

Serum reactions: Although there were no immediate anaphylactic reactions noted, the urticaria and serum sickness, which developed in 25 of the 100 antitoxin cases must be considered seriously. Eleven of these were of the intense, recurrent type which persisted for three to five days and caused the most extreme discomfort to the patient. In eight of them, there was a history of toxin-antitoxin administration four to fifteen months before, and some of the most severe reactors were in a group of nurses who previously had been immunized against diphtheria.

Toomey (42) in December, 1926, reported the treatment of 345 cases, 300 by intramuscular and 45 by intravenous injections, using a variety of the commercial preparations. Fifty cases were used as controls and did not receive the serum treatment.

"The reactions resulting from the intramuscular injections were comparable with other sera. Some antitoxins cause more serum sickness than others. With intramuscular injections, the serum reactions ranged from 10 to 70 per cent: dependent upon the antitoxin used. Chills occurred even with intramuscular injections, and had the usual sharp rise in temperature. This resulting serum sickness was rebellious in nature, was hard to take care of, and in some instances was even accompanied by edema of the epiglottis and trachea, and by persistent vomiting. In two
instances (both nurses) the serum sickness was associated with marked arthritis, dyspnea, cyanosis, and edema of epiglottis. Frequently, the pain associated with serum sickness arthritis, overshadows the whole clinical picture, so that the complication causes the patient to forget the disease for which he has been originally treated.

"With intravenous medication, we have been unfortunate. About 54 cases were injected, but the reactions were so severe that we discontinued this method of treatment, having 3 fatal cases occurring 5 hours to 36 hours after injection."

Gordon (24) using a concentrated antitoxin, prepared by the Dick method, treating over 300 cases mentions no difficulty with serious reactions and says that scarlet fever antitoxic serum exerts a favorable and well marked effect in reducing the severity of the febrile stage of the disease, on the course and duration of the fever, on the extent and duration of the skin lesions, and on the period of isolation. He states there are fewer complications in patients receiving the serum, also a favorable effect on complications evidenced by a lessened severity and duration, as well as incidence.

In January, 1928, Eley reported 465 consecutive and unselected cases occurring at the Willard Parker Hospital in which 250 of the patients did not receive antitoxin. He concluded that scarlet fever antitoxin is of definite value,
but that the mild and moderately sick patients do not receive enough benefit to warrant its use. He also stated that the serum rash is often most distressing and causes more suffering than a moderate attack of the disease.

Toomey (43) in November, 1923, reported that the mortality rate of scarlet fever had not been lowered by the use of antitoxin. He refers to the fact that the mortality had dropped to its low rate before the introduction of antitoxin and that there had been no appreciable decline either in hospital mortality rate or general rate in the years since antitoxin had been used.

Place (33) in February, 1928, and Pritchett and Fletcher (35) in August, 1929, studying the effect of antitoxin stated that it had a definite favorable effect on toxic cases of scarlet fever but its effect on the complications were doubtful. Pritchett and Fletcher also stated that the serum reactions are more severe than mild scarlet fever.

Welford (50) studied the effects of antitoxin on 492 cases of scarlet fever entering the Municipal Contagious Disease Hospital at Chicago from January to June 1928. He stated that scarlet fever antitoxin seemed to exert a beneficial effect in lessening the toxemia of scarlet fever in 60 per cent of the cases—classified as toxic or severe.

During the period October, 1926-1927, Craig (9) treated 500 cases of simple scarlet fever, 10 cases of septic scarlet
and 2 cases of the toxic type of the disease. The practice followed was to administer serum, on the day of admission to hospital, to every definite case of scarlet fever of the simple type within the first three days of disease.

Sera from two different companies were used, and they in turn standardized by use of the Schultz-Charlton blanching test or the Dick test. A dose of 10 c.c. of the concentrated serum was given to each case intramuscularly.

Serum reactions:—Out of the total of 500 cases receiving serum 41 per cent showed reactions at periods varying from 4-16 days after the injection. In no case did the symptoms give rise to alarm. In 25 per cent of these cases there was only a rash, which lasted from a few hours to three days in the most severe cases. The remaining 16 per cent showed definite signs of serum disease: slight pyrexia, adenitis, fleeting joint pains, and an urticarial eruption.

They further state that the administration of antitoxic serum within the first three days of disease produces a favorable effect on counteracting the specific toxemia. The full therapeutic dose should be given at the earliest possible moment to obtain the best results. When given within the first three days of disease it lessens the incidence and reduces the severity of subsequent complications and total period of hospitalization.

Burton and Salmain (7) September, 1929 used antitoxin
in the treatment of scarlet fever patients by intramuscular injections and obtained favorable results. They state that the intravenous serum was not used because it was considered unjustifiable to expose young children to a possible fatal therapeutic risk in a disease which at the present time is usually non-fatal. They state that Toomey and Dochez had three deaths with anaphylactic symptoms out of 40 patients injected intravenously.

Hill (26) in October, 1929, stated the beneficial effects that may be expected by using serum in scarlet fever patients are a prompt subsidence of temperature, a quicker disappearance of the rash, a lessening toxicity, and perhaps the occurrence of a few less complications. He also stated that its chief value is in the treatment of severe cases.

In November, 1929, Dick and Dick (18) report from their experience with scarlet fever antitoxin that it may be employed therapeutically with advantages in all cases of scarlet fever as soon as the appearance of the rash suggests diagnosis. The longer the patient goes without antitoxin, the less benefits from it when it is given. It should not be withheld until it becomes apparent that the attack is a severe one, but should be given in time to prevent the development of a severe attack.

They state that reports as to the effect of scarlet fever antitoxin in reducing the complications are sometimes
conflicting, due to delay in administering the serum in some cases, or to the use of poor preparations of antitoxin.

Gelkey (23) October, 1930, stated that unfortunately the neutralization of its toxin does not prevent the hemolytic streptococcus from further invasion. Septic processes are unmodified by the use of antitoxin, does not decrease the complications or lower the mortality because death is usually due to streptococcus invasion to other parts.

Tsuda (45) in April 1931 gave antitoxin prepared by the Hygienic Research Institute, South Manchuria Railway Company-1 c.c. of this preparation is said to neutralize 1000 skin test doses of toxin. He gave uniformly 40 c.c. for an injection and stated that other writers are not definite about the dosage they have used.

He further states: "Investigators hold different opinions in regard to whether the injection influences complications. Von Bormann stated that an injection at an early period prevents possible complications but an injection given five days after onset makes the patients more liable to complications. Benson said that an injection renders complications less likely; however, an injection on the first day of the disease does not always insure a patient's not being affected by complications. According to Schottmuller injections reduced cases of lymphadenitis by half. Deicher said that injections render complications less intense, but it is not certain whether or not the
injection prevents complications. According to Toyoda's recent work the injection of an antitoxin seems to have little if any effect in preventing complications and to have no effect on complications already developed in the patient. Buschmann also considered that an injection has no preventive effect against complications."

Banks (1) in a summary of the results in 2,430 reported cases of early uncomplicated scarlet fever in which specific streptococcus antitoxin was used shows that: (a) Temperature recession is usually more prompt in the serum treated cases than in control cases. (b) The duration of the eruption is shorter in the treated than in the untreated cases. (c) Early symptom improvement is more common in the serum-treated cases. (d) Desquamation is milder and more localized in those who receive serum than in those who do not. (e) Antitoxin exerts a favorable influence on the incidence of major complications. (f) Intravenous administration of serum probably gives the most striking therapeutic results. (g) Serum reactions are a menacing factor in about ten per cent of cases and can be the cause of death unless the most rigid precautions are employed.

Stevenson, Veldee, and Mitchell (33) in the treatment of 196 patients observed the therapeutic effects of scarlet antitoxin. 84 patients constituted the control, 74 the antitoxin A group and 38 comprised the antitoxin B group. Antitoxin A was purchased in the open market. It
was a concentrated serum prepared with 4 strains of hemolytic streptococcus, originally isolated from scarlet fever patients. The therapeutic package was labeled to contain 6,000 units of antitoxin in a volume of 15 c.c. However, because of an allowance for deterioration, each therapeutic dose given contained approximately 20 c.c. and possessed an antitoxin value of about 7,200 units.

Antitoxin B was not for sale in the open market. It was an unconcentrated serum prepared from a single strain of hemolytic streptococcus which had previously been isolated from a case of scarlet fever. Test made at the National Institute of Health determined that this antitoxin, although unconcentrated, contained in the therapeutic dose of 8 c.c. approximately 6,400 units of antitoxin.

The duration of the period of eruption in the combined antitoxin-treated groups was 4.4 days, as against 6.9 days in the control group.

Apparently, the antitoxin had no influence on the duration of the interval before desquamation began, nor did it have a pronounced influence on the desquamation period. There was a definite tendency for the desquamation to be localized and mild in character in the serum-treated cases but to be generalized and marked in the control patients.

An analysis of the temperature records failed to reveal any definite febrile reduction following an administration of antitoxin.
Excluding serum sickness, there were 75 per cent fewer major complications (cervical adenitis, otitis media, mastoiditis, nephritis and toxic arthritis) in the serum-treated than in the control group.

66.3 per cent of the serum-treated patients developed serum sickness of varying degrees of severity.

A previous injection of serum seemed to be the most important predisposing cause of serum sickness. 37.2 per cent of those patients who had received a previous injection of horse serum in any form and 85.3 per cent of those who had previously received serum only in the form of diphtheria toxin-antitoxin developed serum sickness.

In the group of patients who had received no previous injection of serum the total percentage of serum sickness was 40.8. In this group the incidence of serum sickness seemed to be directly influenced by the volume of serum injected, since 66.7 per cent of the patients receiving 20 c.c. of serum (antitoxin A) and 16.0 per cent of those receiving 3 c.c. of serum (antitoxin B) developed complications.

Banks (1) reported 1204 cases treated by intravenous antitoxin over a period of 4 years. These cases include those mentioned in his previous report (1929).

The table contrasts between the cases treated in 1927, when no serum was used, and those of the present series.
### TABLE I.

<table>
<thead>
<tr>
<th>Year 1927</th>
<th>Years 1928-32</th>
</tr>
</thead>
<tbody>
<tr>
<td>(No serum)</td>
<td>(Intravenous serum)</td>
</tr>
<tr>
<td>Complications of 285 Cases of Scarlet Fever</td>
<td>Complications of 1204 Cases of Scarlet Fever</td>
</tr>
<tr>
<td>Otitis media</td>
<td>6.7%</td>
</tr>
<tr>
<td>Mastoiditis</td>
<td>1.0</td>
</tr>
<tr>
<td>Nephritis</td>
<td>3.7</td>
</tr>
<tr>
<td>Arthritis</td>
<td>1.7</td>
</tr>
<tr>
<td>Total complications</td>
<td>33.0</td>
</tr>
<tr>
<td>Mortality</td>
<td>1.05</td>
</tr>
<tr>
<td>Average stay in hospital</td>
<td>46 days</td>
</tr>
</tbody>
</table>

I Rapid Arrest of Acute State.

"This comprised in the average case (a) fall of temperature by crisis in 6 to 12 hours, (b) disappearance of toxaemic symptoms with general feeling of well-being in 6 to 12 hours, (c) subsidence of faucial oedema in about 12 hours, (d) fading of rash in 12 to 24 hours.

"When these effects are obtained in any given case, certain substantial advantages follow. The rapid arrest of the fever restores comfort and brings about almost immediate return of appetite and normal sleep. Ordinary diet is tolerated after 24 hours. There is little, if any, loss of normal nutrition, and convalescence is correspondingly rapid. The patient may then be safely allowed up after 4 or 5 days.

"The rapidity with which faucial oedema subsides is even more important. It appears, indeed, to be the key effect, and to be particularly associated with antitoxin administered intravenously. As edema subsides, the pain
associated with swallowing is relieved, Eustachian drainage is quickly re-established, allowing middle ear inflammation to resolve, and the flow of septic material to the cervical glands is checked.

"Finally, the rapid fading of the rash prevents desquamation. Desquamation was entirely absent as a rule if the serum was given not later than the third day of the disease, and modified to a fine powdering, with or without small flakes on the hands and feet, if administration of the serum was delayed to the fourth or fifth day.

II Reduction of Complications.

"Complications were reduced to a remarkable extent even when due allowance is made for the milder type of scarlet fever prevalent in recent years. The few complications which did occur were of short duration and so mild as to leave no ascertainable permanent damage.

III Reduction of Period of Residence in Hospital.

"The typical case, showing a normal response to intravenous serum treatment, shows no evident loss of nutrition, no desquamation nor complications, and may be discharged from hospital after 8 to 10 days, or a few days longer, if it is considered desirable that the patient should remain in hospital over the period of the serum rash."
"The serum used was that put out by the Park, Davis and Company and Burrough, Wellcome and Company— injected intravenously in adequate dosage; i.e., a single dose of approximately 20 c.c. for an adult, 12-15 c.c. for a child over 10 years and 10 c.c. for a small child. The Park, Davis serum appeared to have the advantage in that no immediate serum shock occurred in its use. No anaphylactic reactions in protein—sensitive or serum sensitive persons were met with in this series. The thermal reactions, with or without rigor, which may occur about 4 hour after intravenous injection, is in a different category. It is common and does not appear dangerous. It occurred in both makes of serum, the incidence varying from 7 to 100 per cent, according to the batch. It was always treated prophylactically and rarely gave rise to anxiety. In one case, however, (the only fatal case in the series) it was associated with convulsive twitching, and death occurred 12 hours after the serum injection.

"Generally it is of the utmost importance to obtain a serum of proved potency and known to be free from troublesome reactions. Each new batch of scarlatinal antitoxin used for intravenous injection in scarlet fever should be tested out in hospital in adequate dosage on a few cases in which complete tests for serum sensitiveness have been made."
INDICATIONS

"According to the experience gained in this series of cases, the indications for intravenous injections of antitoxin in scarlet fever would, except for the rare contraindicated cases, appear to be, in order of importance:
1. Toxic scarlet fever. 2. Septic scarlet fever, even late in the disease, provided that faucial edema is still present. 3. The severe forms of scarlatina simplex; e. g., that commonly occur in adults. 4. Definite cases of scarlet fever with faucial inflammation, rash and pyrexia, especially those treated in a hospital ward along with other cases:

CONTRA-INDICATIONS

(a) All cases with a history of asthma, eczema, hay fever, frequent urticaria or other manifestations of allergy.

(b) All cases that have had a previous injection of serum, especially within the previous two years, except when serum is urgently indicated, in which case desensitization may be attempted.

(c) Cases where any test for serum sensitiveness is positive.

(d) Very mild cases with little or no faucial
inflammation and little or no rash."

**Technique:** "The conjunctival, intradermal and scarification skin test for sensitiveness to the batch of serum to be employed, may be done as a preliminary, one drop of undiluted serum being used for each test. These are simple tests which can be performed in a minute or two. They were employed during the latter part of this investigation but no serum-sensitive individual was encountered. The first few drops of intravenous serum should be given as slowly as possible, this technique constituting a fourth test for serum-sensitiveness; viz., the intravenous test. In any case of doubt as to serum sensitiveness, the intravenous test in 1 in 10 dilution should be employed. A useful procedure in hospital cases is the subcutaneous injection of 1 c.c. horse serum by the nurse, one hour before the intravenous injection!"

"With all new batches of serum, adrenalin should be injected subcutaneously just before giving the serum. This prophylactic adrenalin may be given in all cases as a routine, but it is, as a rule, unnecessary when adequate experience of a particular batch of serum has been obtained."

After this procedure the serum is injected undiluted into a vein by the syringe method—best using a short rigid needle with a short bevel, a sharp point, and about 3/10 m. m. bore. After the injection,
the foot of the bed is raised for an hour, the patient being wrapped in a warm blanket, and hot bottles put into the bed."

Joepehen (28) calls attention to the fact that opinions about the serotherapy of scarlet fever are still divided. Joepehen made observations on 220 cases. Of these, 100 were treated with intravenous injections of serum, 20 with normal horse serum, and the other 100 received no serotherapy. He reaches the conclusion that intravenous serotherapy with small doses may be recommended and that it has advantages over the intramuscular method. However, it influences only the initial toxicosis, the exanthem and the fever, and does not prevent complications or reduce their severity. For this reason Joepehen employs serotherapy only in the toxic and severe cases, and he emphasizes that the injection should be made as early as possible.

Kohn and Josey (29) are of somewhat the same opinion in regard to the serum therapy. In an analysis of 302 cases of scarlet fever in adults and older children, of whom 127 received antitoxin, the report shows a definite favorable effect on the toxic symptoms of the disease. They state the high incidence of disability due to serum disease must be weighed against this effect. The incidence of complications is not affected by serum administration although their severity may be lessened.
November, 1933, in a study of 2,303 cases of scarlet fever in which 882 were treated with antitoxin states that the most important factors in the management of the disease are the early diagnosis and the administration of an adequate amount of scarlet fever antitoxin. The antitoxin used was a commercial concentrated and refined serum, standardized by means of skin tests in susceptible persons. One therapeutic dose (sufficient antitoxin to neutralize 300,000 skin test doses of toxin) was given intramuscularly in most cases, although in some of the severe cases two, three, four or more therapeutic doses were given.

Of the effect of antitoxin on the clinical course of the disease Hunt states: "If enough antitoxin has been given, the typical punctate rash fades within twelve to twenty-four hours and may be absent with only a subcuticular flush persisting. If the rash has been present for three or four days, the effect of the antitoxin on the rash is not so striking but it has a tendency to run a course somewhat similar to the rash in cases in which antitoxin has not been administered. Corroborative evidence that the skin lesions are milder is shown by the fact that the degree of desquamation is markedly less in patients receiving antitoxin, being usually slight and lasting sometimes for only a few days. With the disappearance of the rash there is a marked improvement in the general condition.
of the patient, especially noticeable in toxic cases. Another effect of the antitoxin is the unmasking of such complications as are already present. The removal of the toxic element of the disease makes the recognition and proper treatment of early complications more certain.

In regard to complications he stated (1) A large number of serious complications occurred in the mild cases in which antitoxin was not administered. (2) A large number of severe cases were free from complications in the series in which antitoxin was administered, in contrast to the large number of severe cases that showed complications in the series in which antitoxin was not administered. (3) A small number of complications occurred when the antitoxin was given during the first two or three days of the disease.

CASE HISTORIES

Illustrative Cases of Septic and Semi-septic Types (1).

Case I. Septic type fifth day.

W.R., male, age 3½ years; admitted 10-28-30; notified as "Diphtheria". The child was drowsy and extremely ill: temperature 102.2 degrees F.; pulse 116; resp. 28; slight albuminuria. Inspection of the throat showed intense oedema of fauces and soft palate with extensive sloughing ulceration of tonsils, pillars and uvula, and copious muco-purulent naso-pharyngeal discharge. The cervical
glands were greatly enlarged, particularly on the right side, and there was some periglandular oedema. The tongue was of the "red strawberry" type. A scarlet fever rash was present, faintly marked on the trunk but more definite on the limbs, where it was of the "blotchy" character so often associated with sepsis. The case appeared to be a typical scarlatinal anginosa. Treatment on admission: 7 c.c. scarlatinal antitoxin intravenously, and 12,000 units diphtheria antitoxin intramuscularly, together with routine irrigation of fauces. Next morning the throat swab proved to be negative for diphtheria bacilli: faucial oedema was greatly reduced, but as the child was still very ill an additional 17 c.c. of scarlatinal antitoxin was given intravenously. The same evening the general condition showed marked improvement, faucial oedema had almost disappeared, although there was deep and extensive ulceration; temp. 97.4 degrees F., pulse 108. Next morning 10-30-30 faucial oedema was nil (36 hours) and nasal discharge had cleared up. Temperature remained normal from 24 hours after the first dose of serum, except for a rise to 100 degrees F. on the fourth day after admission. Urine was albumin-free 48 hours after admission. The faucial ulceration was practically healed in 6 days. A serum rash was present from the sixth to the eleventh day after admission. The child was allowed up on the fifteenth day and was discharged well after 25 days in hospital.
Case II. Septic type sixth day.

H. G., male, age 5 years; admitted 3-15-29; gravely ill: restless; delirious; semi-comatose. Faucial oedema was extreme, the fauces meeting in the middle line; copious purulent faucial and naso-pharyngeal exudate; profuse purulent nasal discharge; cervical glands enlarged to form a "bull neck"; tongue dry and cracked and with enlarged papillae; rash faded; dry rough skin; temp. 101 degrees F., pulse uncountable; cyanosis marked at times with imperceptible pulse. Treatment: 20 c.c. scarlatinal antitoxin intravenously; stimulants (camphor and ether) oxygen, and salines subcutaneously. Next day, the child was still gravely ill and not fully conscious; rash petechial in character; crepitations at bases of lungs; oedema of throat slightly reduced, allowing breathing to be easier; profuse purulent discharge from nose and throat; large piece of necrosed tissue douched out from throat; bowel washed out with good results. On March 17, 36 hours after admission, temperature was normal, pulse 106; condition was greatly improved; child could answer questions; glandular swelling greatly reduced; colour and pulse quite good. 24 hours later he was quite comfortable; faucial and periglandular oedema had disappeared, although ulceration was still extensive; a large discrete gland could be felt on left side of neck and a few smaller glands on right side. Temperature rose again on third evening after admission and remained elevated
while a gland abscess slowly formed on left side; this
was incised on March 22nd and a similar gland abscess on
right side was incised on March 25th. The child was dis-
charged well after 41 days in hospital. N. B. In these
two severely septic cases, otitis media did not develop.

Case III. Septic type seventh day.

C. B., male, age 4 years: admitted 8-21-30: child ill
with marked pallor and restlessness; intense oedema of
tonsils, palate and uvula with pultaceous exudate covering
both tonsils, profuse purulent nasal discharge, and marked
adenitis; "red strawberry" tongue; faded remnants of rash;
temp. 100.2 degrees F., pulse 136. Treatment on admission:
20 c.c. scarlatinal antitoxin intravenously, irrigation of
fauces, etc. Next morning general condition excellent;
playing with toys; faucial oedema practically disappeared;
deep and extensive ulcerated area involving whole of tonsil,
pillars, and uvula and covered with pus; adenitis reduced;
throat swab negative for diphtheria bacilli. Temperature
remained normal throughout this a day, then rose again,
and gradually fell to normal during next 6 days, while the
ulcerated surfaces healed; the general condition remained
good throughout this period. This case desquamated typi-
cally and was discharged well after 38 days in hospital.

(46)
Case IV. Septic type twenty-second day.

C. L., male age 2 years; admitted 2-2-32, about the seventeenth day of scarlet fever, which had followed burns of the forearm and abdomen on 1-13-32. On admission, there was intense injection and oedema of fauces, palate and pharynx, the tonsil meeting, and the whole area being ulcerated and covered with pus; profuse purulent nasal discharge and marked cervical adenitis; respirations rapid and noisy; dyspnoea and dysphagia from obstruction in throat; the child was desquamating typical, with flakes of skin on the hands. Temp. 101 degrees F., pulse 140. Serum was not given on admission owing to the late stage of the disease. On 2-7-32, the child was obviously going downhill: dyspnoea was continuous, and feeding was almost impossible; oedema, ulceration and discharge was, if anything, worse. The prognosis was grave, and it was decided to try the effect of intravenous antitoxin, 20 c.c. of which was given on this day. Six hours later, improvement was observed: the child sat up and talked for the first time. In 36 hours after the injection of serum, the faucial oedema had almost all disappeared; there was no dyspnoea and swallowing was easier; the throat was much cleaner and the extensively ulcerated area could be easily seen for the first time; the child was continually sitting up asking for food. Temperature remained normal for the next 24 hours, then rose again owing to otitis media. Left ear discharged on
February 13th. Serum rash was troublesome on February 16th and right ear discharged on February 27th. The faucial ulceration was healed on February 14th, 7 days after administration of serum. The child was discharged well on March 23rd, after 50 days in hospital.

Case V. Semi-septic type sixth day.

K. C., female, age 19 years; admitted 10-6-30, in sixth day of the disease; fauces oedematous and extensively ulcerated; profuse post-nasal purulent discharge; marked adenitis; "red strawberry" tongue; remnants of faded scarlatinal eruption present. The girl was uncomfortable, had not slept for several nights, and had considerable pain on swallowing. Temp. 101.2 F., pulse 110. Treatment 20 c.c. scarlatinal antitoxin intravenously. Next morning she felt "ever so much better": faucial oedema was markedly reduced; there was no pain on swallowing, although the faucial ulceration was still extensive; adenitis much reduced. Temperature became normal on October 11th and on October 13th the fauces were quite healed and she was allowed up. She desquamated freely. She was discharged well on October 21st, after 15 days in hospital.
CONCLUSIONS

1. Scarlet fever antitoxin exerts a favorable influence on the clinical course of the disease. This is evidenced by a lessened severity of the febrile stage of the disease, on the course and duration of the fever, and on the extent and duration of the skin lesions.

2. Antitoxin exerts a favorable influence on the incidence of major complications.

3. Most of the complications that occur in patients who have received antitoxin, appear to be in those who have received it relatively late in the disease.

4. Serious complications often develop from mild cases of scarlet fever treated without antitoxin.

5. Intravenous administration of the serum probably gives the most striking therapeutic results. If a good preparation of serum is used, intravenous medication is apparently just as safe as the intramuscular.

6. Serum reactions are a menacing factor in many of the cases, depending in part upon the serum used and in part upon the sensitivity of the patients. Every patient should be tested for sensitivity before the serum is given.
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