factors of age, sex, race, etc. The greatest increase for this industrial group has occurred among the males, and at the younger age periods as Dr. Schereschewsky has found for the general population. One of the largest increases is noted from cancers of the peritoneum, intestines and rectum. Cancer of the skin showed a very slight decrease, if anything, while deaths from cancer of the breast showed only very slight increases. A fairly recent note in the Statistical Bulletin, Metropolitan Life Insurance Company, calls attention to the importance of the cancers that occurred among the younger people, and I think this group of cancers, as well as those of "other organs and parts not specified," might be studied a great deal more extensively than we have in the past. This can be accomplished by subdividing the cancers of the various organs and parts covered by this important residual group into separate units, for statistical study.

Dr. J. W. Schereschewsky, Boston: The question of the hereditary factor in cancer is, of course, one of great importance. Because of the lack of available data it is not possible at present for any one, so far as I know, to make a thorough-going study of this factor in the human race. The hereditary studies that have been found in the literature have not been sufficiently extensive to give mass value or to exclude the operation of the laws of chance. So far as laboratory observations are concerned, the influence of the hereditary factor appears to be pronounced. In conformity with the experience of Mr. Hoffman and others, the results of this study, which was entered on in an unbiased way, show that the increase in cancer mortality is an actuality. Since this increase is here we must look to factors in our complex civilization which have brought about this great increase in cancer mortality. This means that we must redouble our assiduity along epidemiologic lines with the hope that tomorrow or next year or in the next decade, the solution of the baffling etiology of cancer will be within our grasp. I cannot believe that this increase in cancer mortality is going to continue indefinitely. Like all biologic phenomena, these processes tend to reach a state of equilibrium sooner or later. After the forces that have raised the human race to a new and higher level of susceptibility have spent themselves, I expect to see no further great increase in the cancer death rate.

SCARLET FEVER

ETIOLOGY, PREVENTION BY IMMUNIZATION, AND ANTITOXIC TREATMENT *

WILLIAM H. PARK, M.D.
NEW YORK

The etiology of scarlet fever has been under active investigation for many years. Loeffler,1 in 1884, and later other bacteriologists noted that the hemolytic streptococci were very abundant in the throats of acutely ill scarlet fever patients. Clinicians also noted the fact that in certain cases of wound infection and puerperal fever a scarlet fever-like rash developed. These observations led to the opinion that there was a close relationship between certain strains of hemolytic streptococci and scarlet fever. The majority, however, held that the hemolytic streptococci were merely very important secondary invaders. Repeated attempts by numerous investigators to produce any disease similar to scarlet fever in animals by the inoculation of throat secretion or cultures of hemolytic streptococci obtained from the throats of scarlet fever patients failed. It was therefore necessary to turn to tests on man.

Moser2 reasoned that, if the streptococcus was the cause of scarlet fever, a curative serum might be produced, and in 1902 published a report of the good therapeutic results obtained by the use of an antiscarlet fever serum produced by the horse after frequently repeated injections had been made of living streptococci together with the broth in which they had developed, so as to get the antigenic value of the organisms as well as of any toxins that might have developed in the broth. The stains of streptococcus used were obtained from a number of toxic cases of scarlet fever.

A Russian investigator, Savchenko,3 went a step further; he showed, in 1905, that the serum contained both scarlet fever antitoxin and streptococccie bactericidal bodies. He also proved that the filtered broth in which the culture had grown contained a strong toxin. He said:

"Immunizing with the microbes only, it is possible to obtain a very active antimicrobial serum, but not at all antitoxin; vice versa, by immunizing with a toxin, we obtain an antitoxic serum and, therefore, not acting on the microbes.

In scarlet fever, in which we have severe local infections and at times even general infections, together with the toxemia, we must have in the serum antitoxins as well as germicidal antibodies. Filtrates of our own cultures of streptococci from scarlet fever grown in different combinations of broth and serum to be nonpathogenic in rabbits, even in large doses. To conclude from this that there is no position in the medium would be just as erroneous as to infer that there is no tetanus toxin after we had tried it on chickens, which are insusceptible to it.

It is obvious that cultures grown on 2 per cent. ascitic broth are preferable for toxin production to those grown on sugar broth, even if the organisms are less luxuriant.

The same filtrate, injected under the skin of rabbits in amounts of 5 and even 10 c.c., produced no symptoms except a slight swelling. The filtrate turned out to be just as harmless for other laboratory animals.

These experiments showed that it is possible to obtain a sufficiently strong toxin, but they unfortunately also showed that by means of our laboratory animals it is impossible to gage either the amount of toxin—which is so important for proper immunization—or the amount of antitoxic substances in the serum, which is not less important for curative purposes. For the time being we are compelled to work, so to speak, by "feeling" our way.

As long as the broth cultures were shown to contain toxin, it appeared most proper to immunize horses with living cultures with the accompanying toxic broth, because in this way both antitoxic and antimicrobial substances should be obtained.

After reading the paper of Savchenko, no one can doubt that he produced by the filtrate a true antitoxic serum.

HUMAN IMMUNIZATION AGAINST SCARLET FEVER

AND VALUE OF THIS EVIDENCE IN FAVOR OF THE CAUSAL RELATIONSHIP OF STRAINS OF STREPTOCOCCI TO SCARLET FEVER

Gabritschewsky4 had finished an experimental study on a streptococcal infection of horses in which an appreciable rash developed, and believed he had proved that a vaccine of toxin and dead streptococci was able to develop a moderate degree of immunity. He then turned to the question of utilizing a streptococcus vaccine made from the toxin and the cells of streptococci obtained from scarlet fever. His vaccine was made of bouillon in which the streptococci had grown for four days plus the streptococci themselves. The toxic bouil-

Ion containing 3 per cent. by volume of the streptococci was heated to 60 C. to kill the streptococci, and then preserved with 0.5 per cent. phenol (carbolic acid). Three doses were given subcutaneously one week apart. For infants under 2 years the dose was 0.25 c.c.; for children between 2 and 10 years, 0.5 c.c., and for those over 10 years, 1 c.c. The results in children were most important. Langowi, using his vaccine, found that of 120 children inoculated, 13.3 per cent. developed a fine scarlet fever-like exanthem which was not followed by desquamation. A few developed a sore throat and strawberry tongue, and fewer still vomiting. He states that these symptoms are those which are characteristic of scarlet fever, and these results of the vaccination add an extremely important proof "for the specificity of a scarlet fever streptococcus and its toxin." There is no question that Gabritschewsky considered the bouillon to contain a true toxin, not only from his language, but also because he was in contact with Savchenko, and their articles appear together a little later in the same Russian journal. He found that the second and third injections, although they were twice and four times as large as the first, rarely produced a rash. This he considered as evidence of the rapid development of immunity.

Gabritschewsky, in 1907, gives further evidence in favor of vaccination. Of 248 children receiving injections of the vaccine, Nikitin noted the rash in 17.3 per cent. In six he noted a generalized rash, vomiting, a strawberry tongue and an angina. In seven cases, the lymph glands were slightly swollen; in ten cases, albumin appeared in the urine for a day. In one case there was an acute nephritis, which ended in recovery.

Twenty-six children who had previously had scarlet fever showed either no reaction or only a slight local swelling. A group of children tested during their fourth week of convalescence showed a greater percentage of reactions than those who had been convalescent for a long time. At Gabritschewsky's suggestion, Langowi vaccinated twenty children with a vaccine made in the same way as the scarlet fever vaccine from the streptococcus of erysipelas. None of these developed a rash. These cases are too few to prove that the result would have been the same if a larger number had been vaccinated, but they are suggestive of the specific character of the scarlet fever toxin.

Gabritschewsky closes his article with five conclusions, of which I quote the last two:

The fact that a scarlet streptococcus vaccine (toxin and culture) is able to produce a scarlatiniform rash and the other symptoms of scarlet fever is a decisive proof in favor of accepting a streptococcus as the specific cause of scarlet fever.

This decisive proof adds a scientific reason for the use of Moser's serum and my vaccine.

Gabritschewsky's death prevented him from following up the practical results of his vaccine. The following statement by Polotovekova is one of several encouraging reports:

A severe outbreak of scarlet fever took place in my district, with 600 cases of the disease. Not only the children, but also adults between 20 and 50 years of age were among the sick. The form of the disease was also severe, very often involving suppulsive affections of the mouth, nose and upper respiratory tract. Owing to the extreme poverty of the peasants of this district, where very often milk could not be obtained for the sick, the only hope was in the preventive immunization. In about 90 per cent. the results were such that in the sick, vaccination took place only one or two or no cases at all were observed; in villages in which no vaccination was carried on, the number of sick would reach from six to 175 cases. The author vaccinated her own three children.

Gabritschewsky considered that he had added to the proof already gathered sufficient evidence so that scarlet fever could be considered to be in the same class as diphtheria. The scarlet fever streptococcus produced its toxins in the throat. The absorbed toxins produced the rash, the fever and the other symptoms due to toxemia. The lowered resistance allowed the scarlet fever streptococci or other streptococci to invade distant parts and make the so-called complications. Additional evidence of the causal relationship was the development of a case of scarlet fever by the accidental inoculation in our laboratory of the throat of one of the assistants by a culture of several strains of streptococci including a scarlet fever strain. A typical case of scarlet fever developed, but attempts to reproduce the disease in animals with the culture failed.

In 1918, Schultz and Charlton described the reaction known by their name. When 1 c.c. of a diluted convalescent serum is injected intracutaneously into the reddened skin of a scarlet fever patient, a blanching occurs in an area several centimeters in diameter. In December, 1923, Mair published further results and concluded that this reaction is due to the action of an antitoxin on the scarlet fever specific toxin. This brings us to the discoveries of the Dicks and of Dochez. In spite of the proof, which was largely unknown to most workers, the majority still believed that the hemolytic streptococcus found in scarlet fever was only an important complicating infection. In October, 1923, the Dicks inoculated five volunteers who had lived in the country, with a streptococcus culture from a case of scarlet fever. One developed a typical case of moderate scarlet fever. The throats of five others were inoculated with the filtrate of a broth culture. None of these developed the disease, but when the same persons were inoculated with the streptococcus, one developed it. This proved that the infection agent was not a filtrable virus attached to the streptococci. It was found by them that the streptococci isolated by them from scarlet fever differed from one another in the ability to ferment mannite. The first two cases had been caused by an organism that fermented mannite. The Dicks then tried out the effect in the human skin of the toxin discovered by Gabritschewsky and Savchenko. They found that weak solutions of the toxin may be employed in skin tests to determine susceptibility.

Table 1.—The Dick Test at Different Age Groups (Zingher)

<table>
<thead>
<tr>
<th>Age</th>
<th>Total Tested</th>
<th>Dick Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-6 months</td>
<td>29</td>
<td>44.8</td>
</tr>
<tr>
<td>6-12 months</td>
<td>65</td>
<td>56.9</td>
</tr>
<tr>
<td>2-3 years</td>
<td>233</td>
<td>71.6</td>
</tr>
<tr>
<td>3-4 years</td>
<td>204</td>
<td>64.5</td>
</tr>
<tr>
<td>4-5 years</td>
<td>541</td>
<td>60.3</td>
</tr>
<tr>
<td>5-10 years</td>
<td>1,065</td>
<td>58.8</td>
</tr>
<tr>
<td>10-15 years</td>
<td>2,065</td>
<td>25.8</td>
</tr>
<tr>
<td>15-20 years</td>
<td>981</td>
<td>16.8</td>
</tr>
<tr>
<td>20 years up</td>
<td>718</td>
<td>34.4</td>
</tr>
<tr>
<td>Total</td>
<td>7,700</td>
<td>29.8</td>
</tr>
</tbody>
</table>


The toxin is first carefully standardized and diluted so that 0.1 c.c. represents a skin test dose. The test consists of an intradermal injection of exactly 0.1 c.c. of the skin test dilution on the flexor surface of the forearm. The reaction is observed at the end of twenty-four hours. An area of reddening 2 cm. in diameter indicates marked susceptibility; 1 cm. in diameter, some degree of susceptibility to scarlet fever.

In a series of skin tests, reported in January, 1923, the Dicks found a positive or strongly positive reaction in 41.6 per cent. of the persons who gave no history of scarlet fever, and negative or only slightly positive reactions in all the convalescent fever patients tested. Zinger’s observations fully corroborate these findings and show that the results in age groups from the Dick test were very similar to the results from the Schick test.

This skin test was developed before they attempted to produce experimental scarlet fever with the type of streptococcus that does not ferment mannite. In selecting their volunteers for inoculation with this type of streptococcus, they chose one with a negative skin reaction, and one with a positive reaction. The two volunteers were inoculated with the same culture. The one with a negative skin test remained well, while the volunteer who had shown a positive test developed scarlet fever.

In the instances in which they had an opportunity to observe the skin reaction before and after an attack of scarlet fever, it was positive before the attack, and negative during convalescence. It is now known that there are about 10 per cent. of exceptions to that rule.

These authors also found that if persons with positive skin tests received convalescent scarlet fever serum intramuscularly, their skin tests became negative. With more definite doses than Gabritschewsky used they then attempted to immunize persons against scarlet fever and utilize later their skin test to determine the development of antitoxic immunity. They found that, by proper dosage, they were able to immunize persons with positive skin tests so that their skin tests became negative and they did not contract scarlet fever on exposure.

They report a series of 125 persons exposed to scarlet fever. In this series, sixty-three showed negative skin reactions, and were not immunized. Fifty-two had positive skin tests, and were immunized with toxin. None of these persons contracted scarlet fever. They emphasize the importance of carrying the immunization to the point of a negative skin test. By the employment of three graded doses of toxin, they have been able to eliminate severe reactions.

While the Dicks were adding to the proof as to the causal relationship of certain strains of streptococci to scarlet fever, Dochez11 was developing an antitoxic serum through a method developed by himself of injecting subcutaneously into animals masses of nutrient agar infected with scarlet fever streptococci. These injections, repeated from time to time in increasing amounts during from six to eight months, were found to develop a potent antitoxin. The serum of horses that had been subjected to such injections was found to give the Schultz-Charlton test, even when the serum had been diluted several thousand times. The serum was used in cases in New Haven and in New York, and the same results were regularly obtained as had been formerly obtained with unstandardized serum by Moser and Savchenko; but now the potency of the serum was established by the striking results with the Schultz-Charlton reaction. These were a demonstration to all that antitoxin was truly present.

Shortly after Dochez announced his serum, the Dicks made a report on the production of antitoxin by the toxic filtrate standardized by their method. Whether the Dochez method or the various modifications of the toxin with or without killed or living streptococci will finally be adopted remains for further comparative tests to decide. This will depend largely on the value of an antimicrobial substance in the serum. The results with the Dochez serum or the Dick serum agree absolutely with the reports of the use of the Moser serum.

**ACTIVE IMMUNIZATION**

Earlier in this paper I gave the work of Gabritschewsky and his followers. In the light of the Dicks’ researches and the rashes that developed, it can be estimated that the Russian infants received about 1,000,

<table>
<thead>
<tr>
<th>Table 3.—Immunizing Results of Three Injections of 300, 500 and 1,000 Skin Test Doses of Scarlet Fever Toxin Given at Intervals of One Week</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Reaction to Dick Test</strong></td>
</tr>
<tr>
<td><strong>Reaction to Dick Test</strong></td>
</tr>
<tr>
<td><strong>10</strong></td>
</tr>
<tr>
<td><strong>12</strong></td>
</tr>
<tr>
<td><strong>18</strong></td>
</tr>
<tr>
<td><strong>22</strong></td>
</tr>
<tr>
<td><strong>27</strong></td>
</tr>
<tr>
<td><strong>Results with Injections of Double the Forgoing Amounts</strong></td>
</tr>
<tr>
<td><strong>Reaction to Dick Test</strong></td>
</tr>
<tr>
<td><strong>10</strong></td>
</tr>
<tr>
<td><strong>12</strong></td>
</tr>
<tr>
<td><strong>18</strong></td>
</tr>
<tr>
<td><strong>22</strong></td>
</tr>
<tr>
<td><strong>27</strong></td>
</tr>
</tbody>
</table>


it by formaldehyde. Yet, as the Dicks state, such chemical modification resulting in a decreased toxicity or toxoid is desirable, if it can be demonstrated that it accomplishes immunization with fewer doses or in a shorter time. The most suitable dose of toxin varies with conditions. If scarlet fever is prevalent, it is very desirable not to give sufficient toxin to make a rash in any of the very susceptible children, for there is no certain way of determining in such a case whether it is a case of light scarlet fever or of a toxin rash. Even if cultures are made, it is possible that streptococci which produce the scarlet fever toxin will be present, and yet the case will be due to a toxin rash. If, however, no scarlet fever is in the neighborhood, a slight scarlet rash is of no importance and larger doses can be given. The Dicks give an interesting summary of the relation of the total skin doses to the immunity results.

They advise skin doses for the first 500, for the second 1,500, and a considerably larger dose for the third.

Original investigations.—Tables 3, 4, 5, 6 and 7 show the results in our tests following the injection of from 600 to 10,500 skin doses. The tests in these tables, with the exception of the one by Zinger, were made by Schroder and read by her, Williams and myself.

Table 5.—Results of Five Immunizing Injections at the End of Three and One-Half Months Approximately 500, 1,000, 2,000, 3,000 and 4,000 Skin Test Doses

<table>
<thead>
<tr>
<th>Strongly positive cases</th>
<th>12 + or +</th>
<th>10 + or +</th>
<th>8 + or +</th>
<th>5 + or +</th>
<th>3 + or +</th>
<th>Moderate reactors</th>
<th>1 + or +</th>
<th>3 + or +</th>
<th>5 + or +</th>
<th>All positive reactors</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 or 2 cent. immune</td>
<td>1 +</td>
<td>1 +</td>
<td>1 +</td>
<td>1 +</td>
<td>1 +</td>
<td>1 +</td>
<td>1 +</td>
<td>1 +</td>
<td>1 +</td>
<td>1 +</td>
</tr>
<tr>
<td>5 or 6 cent. immune</td>
<td>2 +</td>
<td>2 +</td>
<td>2 +</td>
<td>2 +</td>
<td>2 +</td>
<td>2 +</td>
<td>2 +</td>
<td>2 +</td>
<td>2 +</td>
<td>2 +</td>
</tr>
<tr>
<td>10 cent. immune</td>
<td>3 +</td>
<td>3 +</td>
<td>3 +</td>
<td>3 +</td>
<td>3 +</td>
<td>3 +</td>
<td>3 +</td>
<td>3 +</td>
<td>3 +</td>
<td>3 +</td>
</tr>
<tr>
<td>15 cent. immune</td>
<td>4 +</td>
<td>4 +</td>
<td>4 +</td>
<td>4 +</td>
<td>4 +</td>
<td>4 +</td>
<td>4 +</td>
<td>4 +</td>
<td>4 +</td>
<td>4 +</td>
</tr>
</tbody>
</table>

1 + and 2 + are considered negative pseudo reactions because of an equal reaction in the control neutralized by convalescent serum.

The persistence of the acquired immunity following injections remains in doubt. With small injections, such as in the cases recorded in Table 7, many of the originally very positive cases have after a year relapsed, while the originally moderately positive cases have generally continued to hold their immunity or to increase it.

With much larger injections, such as those recorded in Tables 4 and 5, the immunity response is so much greater that it is hoped that the marked positive cases will not only develop immunity but hold it for a period of years.

We note in these tables that the moderately reacting cases develop complete immunity much more readily than the strongly reacting cases; again, that the response is quicker than after diphtheria toxin-antitoxin or toxoid injections. This corroborates the views of Gabritschesky and the statements of the Dicks that immunity develops in many within one or two weeks.

The results of a second series of injections in those who have not responded to the first series have been excellent.

The persistence of a negative Dick reaction in those found to be negative: Observations on several thousand children by Zinger and Schroder at different intervals of time up to thirteen months have shown that a naturally acquired immunity is usually persistent for at least one year. Only about 2 per cent. of those originally negative have been found to change. It is fair to assume, therefore, that as in the case of naturally acquired immunity to diphtheria, the immunity to scarlet fever naturally acquired is apt to remain. This finding, which is in accord with the findings of the

Table 6.—Immunity Results After Four Weeks with Three Injections of Scarlet Fever Toxin (Dick Test)—9,200 Skin Test Doses in All (Zinger) *

<table>
<thead>
<tr>
<th>Institution</th>
<th>Dick Retest After from Four to Five Weeks</th>
<th>Dick Positive and Combined</th>
<th>Dick Negative and Pseudo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hebrew Orphan</td>
<td>32.2</td>
<td>143</td>
<td>19</td>
</tr>
<tr>
<td>New York Orphanage</td>
<td>44.4</td>
<td>91</td>
<td>10</td>
</tr>
<tr>
<td>Laton and Watts Home</td>
<td>22.0</td>
<td>40</td>
<td>12</td>
</tr>
<tr>
<td>Total</td>
<td>274</td>
<td>41</td>
<td>66</td>
</tr>
</tbody>
</table>

* Doses given: under 12 years, 200, 500 and 500 skin test doses at weekly intervals; over 12 years, 200, 500 and 1,000 skin test doses at weekly intervals.

Dicks, encourages us to hope that, with larger and perhaps more numerous doses, even the very positive cases may acquire such a high degree of immunity that it will last for at least a few years. We already have the knowledge that these immunizing injections are very useful in stopping an outbreak of scarlet fever.

The serum treatment of scarlet fever as observed at the Willard Parker Hospital

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 result of the intravenous injection was so striking that the medical board decided in March, 1925, to give all patients a rash and a temperature of 101 F. or higher antitoxin and to give it to alternate patients having a temperature lower than 101. It was given intravenously in all severe cases.
The antitoxin serum was given by Dr. Mildred McBride, the assistant resident physician who was in charge of the scarlet fever service at the Willard Parker Hospital. The attending physician on duty and I watched with her the effects of the treatment. The potency of the antitoxic serum was tested either by the Schultz-Charlton blanching test or by the more accurate Dick neutralization tests of the toxin. The potency ranged from 50 to 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. The dosage was determined by much the same principles that govern the dosage of diphtheria antitoxin. 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. Whether a late case in which there is still a marked rash should be treated with larger doses than an early case of equal severity is in our belief doubtful and remains still a matter for further investigation. Intramuscular 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 afterward, 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 a less rapid improvement, and the toxic symptoms may return. Our results were practically identical with those reported by Blake and Birkhaug.

The following two cases showed favorable results after intramuscular injection in the first and intravenous injection in the second:

Case 1.—G. C., a boy, aged 7, was sick two days with headache and vomiting. A rash developed on the morning of the 17th. On admission in the afternoon, the temperature was 101 F.; pulse rate, 150; rash marked, and throat inflamed. The Dick test made on admission was positive. The severity was from moderate to severe. The patient was given intramuscularly 40 c.c. (about 3,200 units) of Dochez' antiscarlatinal serum. On the 24th, the rash was greatly lessened; the Dick test made in the morning was negative, and the temperature was 101 F. in the morning and 100 F. in the afternoon. On the 25th, the rash was gone; the temperature, 99.5 F. The patient made an eventful recovery (Chart 1).

Case 2.—A. K., a man, aged 32, who had a sore throat on the 17th, with a rash appearing on the 19th, was admitted early in the afternoon on the 20th. The temperature was 102 F. and rose to 104 F.; the pulse rate was 130. The throat was inflamed. Adenitis was present, and the patient was fairly toxic. He received on admission 2,400 units of antitoxic serum intravenously. Within two hours he felt improvement. At the end of six hours, the temperature had fallen to 98.8 F., the rash had faded and the patient felt almost well. Convalescence was uncomplicated (Chart 1).

Chart 2 gives the temperatures of five patients who received intramuscular injections. The drop in temperature is comparatively slow. Two of these patients received insufficient amounts of antitoxin.

Chart 4 gives the composite temperature curves of twenty-five severe, twenty-five moderate and twenty-five light cases of scarlet fever treated with serum during the first three days of the disease and an equal number without.

Complications.—The antitoxin has little effect on complications, such as infection in the tonsils, in the middle ear, in the mastoid, in glands of the neck or in the endocardium, when they have already developed; but before they have developed the antitoxin appears to be of service in preventing their occurrence. This is probably due to the raising of the resistance of the local tissues and of the body as a whole so as frequently to prevent or restrict the invasion of the body by the streptococci. These streptococci may be those producing the
scarlet fever or other varieties. An interesting case was that of a woman sick with toxic scarlet fever complicated by severe erysipelas. The delirium vanished, the vomiting ceased, the temperature was lowered and the rash faded, but the erysipelas ran its usual course.

Table 8, which shows the complications developing in seventy-five cases that were treated and in seventy-five that were untreated, indicates a favorable influence of the antitoxin in preventing complications. As long as the rash remains, antitoxin is indicated.

The cases in Table 8 are not strictly comparable, since the severe and moderate cases which were not treated with serum are taken from 1924, while the serum-treated cases occurred in 1925. The diagnosis of nephritis is based mostly on the urine examinations and is probably not wholly accurate. The kidney complications, on the whole, are seen to be decidedly less in the cases treated with antitoxin early, but the other complications are about the same.

Reduction in Mortality.—During the year 1924, when scarlet fever was very light, 569 patients with scarlet fever were admitted to the hospital. About forty of these received scarlet fever antitoxin. The mortality among the 569 patients was 2.8 per cent. During April and May of this year, when all patients with cases of any severity and with a rash were receiving serum, there were 220 admissions. Of these, six patients, or a percentage of 2.7, died.

These figures, considered without a knowledge of the cases, would be very misleading; but they cause one to wonder what proportion of the 150 or more deaths from scarlet fever which occur yearly in New York can be eliminated by the use of serum. In three of the six fatal cases the patients were admitted so late that they were absolutely unsuitable for antitoxin, but in three of them they were admitted on the third day. The histories of these six fatal cases are as follows:

Case 3.—A child, aged 11, admitted thirty-eight days after the development of scarlet fever, showed symptoms of meningitis. Death occurred three weeks later. Necropsy showed several small brain abscesses.

Case 4.—A child, aged 7, admitted on the ninth day of disease, with double otitis media, septicemia and signs of endocarditis, died in three days.

Case 5.—A man, aged 35, admitted in the afternoon on the sixth day of the disease, with an intense rash still present, and a temperature of 104.8 F., received 60 c.c. of Dochez serum intravenously (about 500 units). The temperature dropped within six hours to 99.5 but rose the following afternoon, when he died. Necropsy showed purulent bronchitis and toxic changes.

Case 6.—A patient, aged 23, ill three days, with a marked rash, marked pharyngitis with grayish exudate and a temperature of 103.6 F., received 30 c.c. of serum intravenously (about 1,800 units). Complete anuria was present during the first six hours. The temperature dropped to 99 in eight hours following the administration of the serum, but rose again. The rash remained pronounced for three days. The patient died on the fourth day after admission.

Case 7.—A patient, aged 21, following a kidney operation at another hospital, developed scarlet fever, and was sick three days before admission. The patient appeared toxic with a generalized hemorrhagic rash. The temperature was 103 F. The patient was given 30 c.c. of serum (about 2,000 units) intravenously. The temperature dropped 4 degrees in eight hours, but rose in the afternoon just before death. The rash remained, but was somewhat faded.

Case 8.—J. M., aged 3½ years, was taken ill with vomiting, May 10, developed a rash on the 12th, and was admitted on the 13th, with a temperature of 104.8 F., a generalized hemorrhagic rash and an intense pharyngitis with exudate on the tonsils. Several hours after admission, 30 c.c. of antitoxic serum (about 2,400 units) was given intravenously. The temperature dropped to 100 F., but rose to 102 in afternoon. Another 40 c.c. of serum was given intravenously. The temperature dropped to 101, but rose in the evening to 103 and continued between 101 and 103 until death, May 20. The rash did not fade until the 19th. Necropsy revealed an ulcerative inflammation of the mouth, esophagus and stomach.

In the last three of the six fatal cases, the serum was given about as quickly as would generally be possible. Nevertheless, the patients responded only temporarily and inadequately to the antitoxic serum. It is possible that if the serum had been given immediately after the development of the rash, a better result might have been obtained or perhaps much larger or repeated doses of antitoxin might have done more good. There is also the possibility that some of the cases presenting septic rashes are not ordinary scarlet fever and are due to streptococci that differ in the type of their toxins from those produced by the ordinary strains. We have evidence of such difference, but unfortunately we did not isolate and test the streptococci from these cases for their toxins.

CONCLUSIONS ON THE THERAPEUTIC VALUE OF ANTITOXIN

The antiscarlatinal serum produced by Moser and Savchenko produced the same therapeutic results as that now produced by the Dochez method or by the subcutaneous injection of known doses of toxin. The value of the earlier products was greatly handicapped by the lack of any means such as the Schultz-Charlton and Dick methods for estimating their antitoxic potency. Because of this lack of knowledge, serum weak in antitoxin was undoubtedly frequently used with disappointing results.

The antitoxic serum should be given in sufficient amount as early in the disease as possible. When thus given, the results in most cases are strikingly favorable. The early use of antitoxin probably frequently prevents the development of complications.

Antitoxin is useless after the rash has disappeared and has no effect on the later septic complications. In moderate cases it should be given intramuscularly. In severe or toxic cases it should be given intravenously. As a rule, a single dose of sufficient size is enough, but in severe cases in which the symptoms return, a second dose in from twelve to twenty-four hours is often desirable. It is too early to state whether the serum should be given in very mild cases, since the serum sickness is often more annoying than the scarlet fever.

The refined antitoxic serum produces fewer and less severe rashes than the unrefined, and should in time be the only preparation used. A unit should be adopted, so that results from different dosages may be compared. The one suggested at a recent meeting of immunologists in Washington seems to be suitable.
One unit is defined as the amount of antitoxin that neutralizes 100 skin test doses (Dick), as determined by an intracutaneous test in man. A dosage between 2,000 and 10,000 units will probably suffice in the great majority of cases. A few of the failures of antitoxin may be due to the fact that some toxic cases may be due to streptococcal that produces other toxins than the neutralized by the antitoxin used. This is an interesting problem for further study. Whether it will be of marked advantage to combine an antimicrobial serum with the antitoxic serum is still doubtful, but merits careful investigation.

Such a serum used alone in the past has given doubtful results, but combined with antitoxin it may add to the benefit produced. There would thus be a return to a serum such as was used by Moser, but with knowledge of the potency in both the bactericidal and the antitoxic properties.

Department of Health.

ABSTRACT OF DISCUSSION

Dr. Abraham Zingher, New York: I shall present my own results with the Dick test and active immunization with scarlatinial toxoid before the Section on Pharmacology and Therapeutics. The work covered more than 15,000 Dick tests and 2,000 active immunizations with scarlatinial toxoid. I wish to emphasize just now the logical and careful manner in which Dr. Park has given us the historical development of the serum treatment of scarlet fever, which was brought to the attention of the medical profession twenty-five years ago by Moser in Austria and twenty years ago by Sovchenko in Russia. The serums recently described by the Dick's and by Docher do not differ from these older serums, and if anything are inferior to Moser's serum, which is a polyvalent antibacterial and strongly antitoxic serum. Such a serum will probably be the ideal future therapeutic agent in the treatment of scarlet fever. The clinical results published by Blake and his associates are no better than those so carefully reported by Moser and Escherich in Austrian and German literature in 1903. There is no reason, therefore, why one commercial manufacturing laboratory should claim that the Docher serum is the best, and another firm, that the Dick serum is the best. The work of Gabrichewsky and his associates, who immunized between 1906 and 1910 more than 50,000 people in Russia with a broth culture of the scarlatinial streptococcus, definitely indicates that the use of immunization on susceptibles have reached such a point that the state health officers should advocate this as a general procedure and start a campaign to that end in the same way that is done in the case of diphtheria? As state commissioner of health I have felt like waiting on further results in the city of New York, believing it would be a mistake in view of the active campaign for eradication of diphtheria to add still another campaign which involved, to my mind, some difficult procedures on the part of general practitioners and local health officers, and up to the present time I have confined my action to distributing at various stations throughout the state supplies from the state laboratory of the scarlatinial toxoid for curative purposes, and not emphasized or started a campaign against scarlet fever. I have been tremendously impressed with the therapeutic value of this remedy, which I have myself observed with Dr. Park at the Willard Parker Hospital. I should like to hear Dr. Park's opinion as to the best course for state and local health officers in the matter regarding testing for immunity to scarlet fever and inducing immunity in susceptibles on a large scale.

Dr. William H. Park, New York: Just a word about Dr. Zingher's statement that Moser had a better serum than that produced by Docher or Dick. We had no way of standardizing Moser's serum; some of it was very good and some very poor; that is probably the reason it fell into disuse because it could not be standardized at that time. As to the question of refined and unrefined, we have had in hospital use the unrefined in about 150 cases and the refined in about seventy-five. There has been no difference in the effects except in the rash, other symptoms and serum sickness. There have been no bad results. As to the amount of toxoid used in the Dick standard test, of course we must realize that this is an artificial way of separating the susceptible from those who are not. That is a difficult problem. If it is a little too strong there will be too many positives; if it is too weak there is the possibility of having people who are susceptible pronounced immune. As to Dr. Nicoll's question, it seems to me we have sufficient evidence to say that a negative Dick test in untreated cases indicates a fairly permanent immunity. Those who pass the test are probably immune for many years, maybe for life. As to immunization in general, I would advise at present to use it only when scarlet fever is more or less a possibility. In such instances people are interested and immunization will be of value to stop the present outbreak. I would not press it unduly this year but I would like to leave the impression that we should go on into the future. Unless people know how permanent is the immunity and the number of doses that are best to give. We advise at the present time 500, 1,000 and 2,000 and then a final one of 5,000 skin doses.