THE VALUE OF THE SKIN TEST WITH TYPE-SPECIFIC CAPSULAR POLYSACCHARIDE IN THE SERUM TREATMENT OF TYPE I PNEUMOCOCCUS PNEUMONIA*

By THOMAS FRANCIS, Jr., M.D.

(From the Hospital of The Rockefeller Institute for Medical Research)

(Received for publication, November 23, 1932)

It has previously been shown that in patients convalescent from pneumococcus lobar pneumonia the intradermal injection of type-specific capsular polysaccharide (S.S.S.) elicits a typical cutaneous reaction (1, 2). The reaction takes the form of an immediate wheal and erythema which reaches its height within 15 to 30 minutes. It can first be elicited at or about the time of recovery. The reaction is type-specific in that it is produced only by the polysaccharide homologous in type to that of the infecting organism. Furthermore, in the small series previously reported, it was noted that recovery from Type I pneumonia in serum-treated cases was invariably associated with the development of a positive skin reactivity to the Type I S.S.S., whereas approximately only 50 per cent of the non-serum-treated Type II and Type III cases which recovered gave a specific response to the homologous S.S.S. (2). The occurrence of the reaction was found to be intimately associated with the presence of type-specific antibodies in the patient's serum. In cases treated with Type I antipneumococcus serum, it was observed that although type-specific antibodies might be present in the blood of the patients, the skin test remained negative. When, however, the skin test became positive, recovery invariably ensued.

These observations suggested that in patients suffering from Type I pneumococcus pneumonia the skin test with Type I S.S.S. might be a valuable guide in determining when serum therapy could be safely discontinued. The present report, therefore, comprises an analysis

* Presented, in part, before the American Society for Clinical Investigation at a meeting held in Atlantic City, May 4, 1931.

of the results of skin tests with Type I S.S.S. obtained in a series of 53 cases of Type I pneumococcus pneumonia, 48 of which were treated with antipneumococcus Type I serum.

Materials and Methods

The patients were among those admitted to the wards of the Hospital of The Rockefeller Institute with a diagnosis of lobar pneumonia. Their ages ranged from 6 years to 70 years. The pneumococcus typings were done by use of the Avery tube, as well as by the usual method of inoculating the sputum of the patient into the peritoneal cavity of a mouse, and the subsequent macroscopic agglutination and precipitation reactions with peritoneal washings of the mouse. Blood cultures were made on admission and at varying intervals thereafter. Except in the 5 instances noted, all patients were treated with unconcentrated Type I antipneumococcus horse serum obtained from the New York State Board of Health. Specific treatments consisted in the intravenous administration every 6 to 8 hours of 100 cc. of serum diluted with an equal volume of physiological saline.

Skin Test.—Protein-free type-specific capsular polysaccharides were prepared by the methods employed in this laboratory (4) and were of the highest degree of purity obtainable. The polysaccharides were dissolved in physiological salt solution, and 0.1 cc. of solution containing 0.01 mg. of the S. S. S. was injected intradermally. In the earlier tests, S. S. S. of Types I, II, and III were separately injected into the skin of the forearm together with a saline control. In the present study of reactions in patients with Type I pneumonia, only the Type I S. S. S. and a saline control have been used.

The skin tests, during the course of treatment, were done 6 to 8 hours following each administration of serum, since it is known that after this interval the passively introduced antibodies may have been removed from the blood (5). Following each intradermal test, the inoculated sites were observed carefully for 20 to 30 minutes. A positive reaction was recorded in the presence of erythema, edema, wheal, and pseudopodia. Frequently, itching of the skin at the site of reaction was noted by the patient. Concomitantly, the elevation of the skin at the point of the control saline injection tends to disappear.

Circulating Antibodies.—The presence of type-specific agglutinins for Type I Pneumococcus was demonstrated in the patient's serum by the method previously described (2).

The data included in this report comprise the results obtained by repeatedly testing the skin reaction to Type I S.S.S. in 53 patients during the course of lobar pneumonia associated with Type I Pneumococcus. In 48 of the cases specific serum therapy was employed. In the series are included 7 fatal cases, 5 cases with empyema, and others with furuncles, sterile pleural effusions, and delayed resolution.

The 5 untreated patients were comparatively mild cases which recovered spontaneously. A summary of the cutaneous reactions of Type I S.S.S. in these 53 patients is presented in Table I.

The uniformity of results is surprisingly sharp for a biological test. From Table I it is readily seen that of the 45 cases in which a positive skin reaction was obtained, all recovered. Of the 8 patients with negative reactions, only 1 survived. This exception, the failure of a recovered patient to react, occurred in a negro with empyema, in whom only a doubtful reaction was seen. Further, of the other 4 cases of empyema tested after the acute stage of the pneumonia had passed, all gave typical positive reactions, and all recovered.

TABLE I

The Results of Skin Tests with Type I Polysaccharide in Type I Pneumococcus Pneumonia

Patients	No. of cases	Positive reactions		Negative reactions	
		Recovered	Died	Recovered	Died
Serum-treated	48	40	0	1*	7
Untreated	5	5	0	—	—
Total	53	45	0	1	7
Empyema†	5	4	—	1	—

* Empyema with doubtful reaction.

† Included also under serum-treated cases.

Included amongst the 7 fatal cases is 1 case which had a Type I pneumonia with septicemia, from which recovery apparently ensued with normal temperature, sterile blood, and definite and nearly complete resolution. The skin test remained negative, and the patient suddenly had a recurrence of pneumonia and septicemia, this time a Type III pneumococcus infection, which proved fatal.

A brief summary and graphic representation of illustrative cases serve to emphasize the time relationships between the onset of recovery and the occurrence of the skin reactions, with reference to the presence of circulating antibodies in the blood of convalescent cases. Furthermore, in the fatal cases, it will be seen that in spite of sterili-

zation of the blood, the presence of circulating antibodies, and symptomatic improvement, the skin reaction remained negative. The fact that the skin test, under these conditions, is negative, clearly shows

Key to Charts 1 to 6

Skin Tests.—Broken line = negative reaction. Wavy line = doubtful reaction. Cross-hatched bar = positive reaction.

Agglutinins.—Dash = no demonstrable agglutinins. Black bar = highest positive dilution.

† Indicates fatal termination.

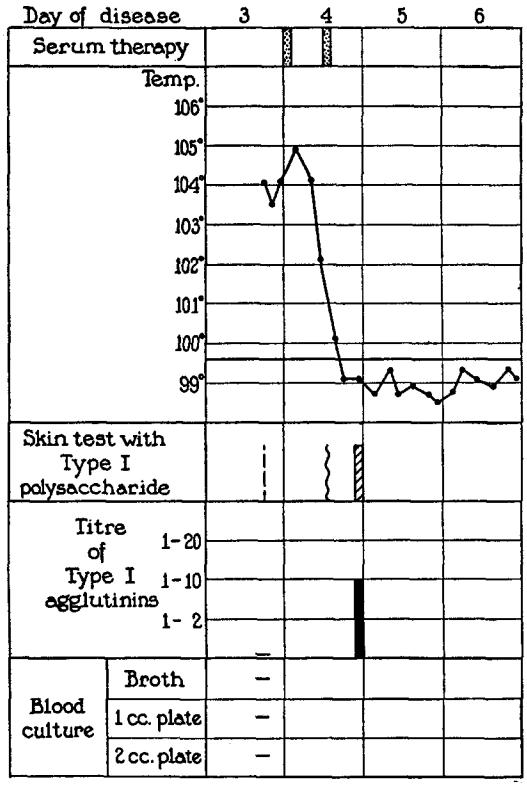

CHART 1. Patient S (Hospital No. 7152). Type I pneumococcus pneumonia without septicemia.

that positive reactions are not simply dependent upon the humoral type-specific antibodies, and that cutaneous reactivity is not solely referable to the passive immunity conferred by the administration of the specific antibodies.

Patient 1, Chart 1, Case 7152

The patient, a housewife of 32 years, was admitted to the hospital on the 3rd day of illness, with lobar pneumonia of the right middle lobe. On admission, the blood culture was negative, the blood contained no agglutinins for Type I Pneumococcus, and the skin test with Type I S. S. S. was negative. Type I antipneumococcus serum was first administered 10 hours after admission. 8 hours later, Type I S. S. S. elicited only a questionable skin reaction, since an erythema also occurred at the site of the control saline injection. Although the temperature had begun to fall, a second treatment was given, and a precipitate drop of temperature took place. A skin test done 8 hours after the last serum treatment was markedly positive, and the patient's serum at this time contained a comparatively high titre of type-specific antibodies. Convalescence was uneventful.

This case illustrates the ordinary rapid termination of the acute course of disease, and the development of cutaneous reactivity at the time of recovery.

Patient 2, Chart 2, Case 7263

The patient, a man, 34 years of age, was admitted to the hospital on the 3rd day of illness, with lobar pneumonia of the right lower lobe. On admission, a blood culture revealed Type I Pneumococcus in the circulating blood; the patient's serum contained no demonstrable type-specific antibodies; and the type-specific skin test was negative. Serum therapy was begun 6 hours after admission. After the second treatment, a fall of temperature occurred. A skin test done at this time was negative. The temperature rose again just before the fourth treatment. The skin test was negative, a blood culture was sterile, and type-specific agglutinins were not demonstrable in the patient's blood. A skin test before the sixth treatment was negative, but 6 hours later a definitely positive skin reaction was elicited with S. S. S. I, and circulating antibodies were present. Although the patient's temperature was 102°, serum therapy was discontinued. The following morning the temperature was normal, and an uninterrupted recovery ensued.

This case illustrates the value of the skin test in instances in which the temperature is swinging, and in which it is important to know whether recovery has begun or whether the fall of temperature is only a remission. The negative skin test indicates further serum therapy. Furthermore, when the positive reaction was obtained, in spite of the fact that fever was still present, it was shortly followed by a normal temperature. This case also emphasizes the fact that the antibodies passively introduced through serum treatment may not be detectable in the circulating blood 6 to 8 hours after the treatment, or even after several treatments.

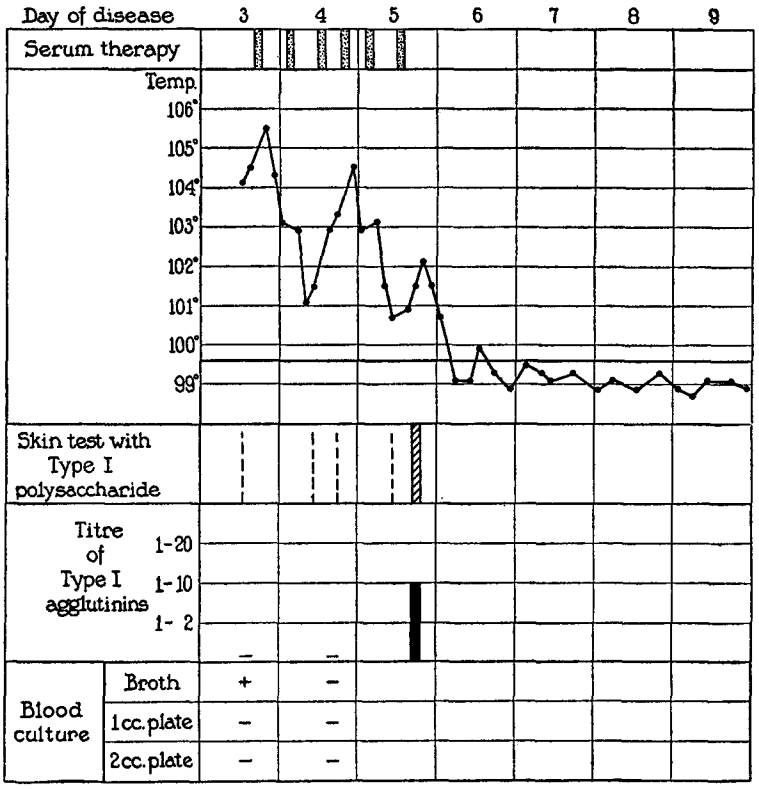

CHART 2. Patient P. (Hospital No. 7263). Type I pneumococcus pneumonia and septicemia.

Patient 3, Chart 3, Case 7165

The patient, a housewife of 30 years, was admitted to the hospital on the 2nd day of illness, suffering from lobar pneumonia of the left lower lobe. At the time of admission, the blood culture was positive for Type I Pneumococcus. The patient's serum contained no demonstrable type-specific antibodies, and the Type I skin test was negative. After two doses of serum, the blood became sterile, type-specific antibodies were present in the blood, but the skin test remained negative. The pneumonic process spread to involve the left upper lobe. Serum was repeatedly administered, agglutinins persisted in the blood, but repeated skin tests were consistently negative. On the 6th day, after nine doses of serum, although no change in the patient's general condition was noted, a positive skin reaction was elicited. This was construed as indicative of recovery. The titre of circulating antibodies had not increased above that found on the 3rd and 4th

days, when the skin test was negative. Nevertheless, serum was discontinued, and 48 hours later, on the 8th day, the temperature dropped to normal. Convalescence was uneventful.

The significant points exemplified by this case are that although type-specific antibodies were present in the patient's blood after two

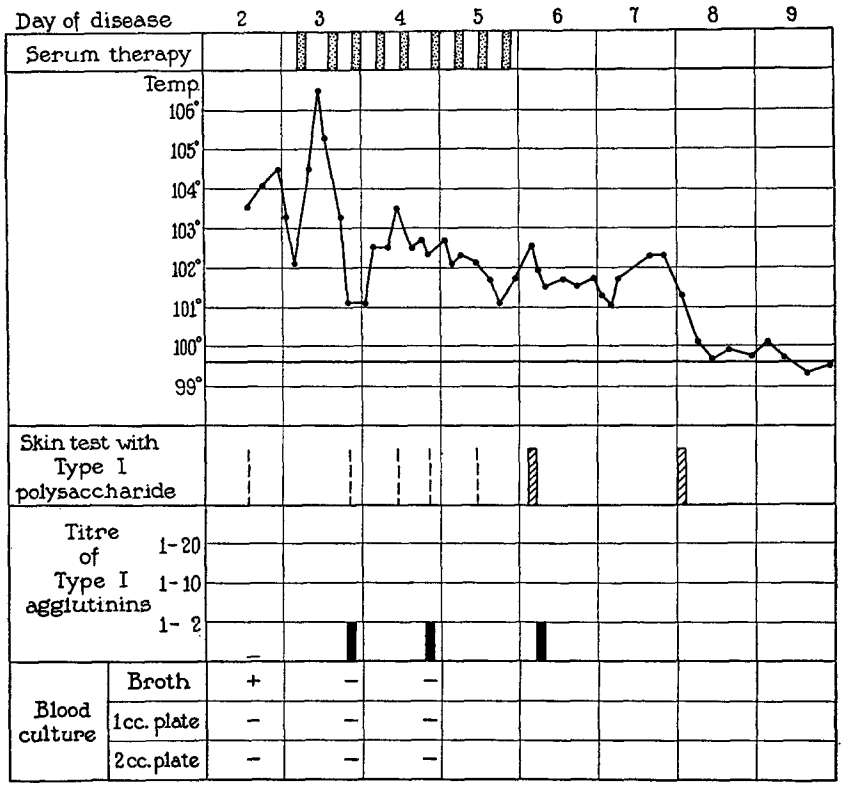

CHART 3. Patient H. (Hospital No. 7165). Type I pneumococcus pneumonia and septicemia.

serum treatments, the pulmonary lesion was spreading and the skin test remained negative. When the skin test became positive, no increase in antibody titre occurred, nor had any definite objective change occurred in the patient's condition. Experience suggested that recovery would follow the positive reaction, and that was the case. The occurrence of a positive test is obviously in this case not due

simply to the presence of circulating antibodies, but is associated definitely with the complicated process of recovery.

Patient 4, Chart 4, Case 7219

The patient, an advertising man of 52 years, was admitted to the hospital on the 6th day of disease, suffering from lobar pneumonia of the left lower lobe, left upper

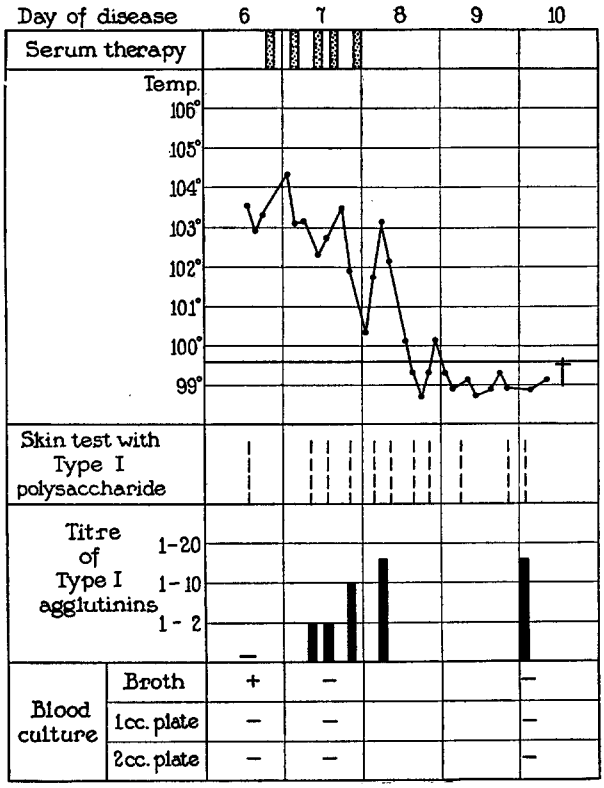

CHART 4. Patient Sc. (Hospital No. 7219). Type I pneumococcus pneumonia and septicemia.

lobe, and right lower lobe. He was extremely sick. The blood culture on admission yielded Type I Pneumococcus. There were no type-specific antibodies in the blood. The skin reaction was negative. Serum therapy was inaugurated 2 hours after admission, and continued at 6 hour intervals for five doses. After the second dose, agglutinins were demonstrated in the blood, and these increased progres-

sively to a high titre. The blood became sterile by the 7th day, and remained sterile till death. The temperature dropped to normal on the 8th day, and signs of resolution were heard over the left lower lobe. But the type-specific skin test remained negative throughout. The patient alternated between delirium and stupor, and finally succumbed on the 10th day. At autopsy, massive pneumonic involvement of the left lung with beginning resolution, and consolidation of the right lower lobe, were found. Chronic nephritis, interstitial purulent hepatitis, and pancreatitis were also observed.

In this instance, it is clearly seen that cutaneous reactivity may be the only indication that recovery is not occurring. Normal temperature, pulse, and respirations, negative blood cultures, high titre of antibodies, and physical signs of resolution were present, but the additional factors which play a rôle in the production of a positive skin test were absent. Whether additional serum therapy would have been of aid is problematical, but on the basis of present experience it would be considered advisable.

Patient 5, Chart 5, Case 7162

The patient, a man of 27, was admitted to the hospital on the 2nd day of illness, suffering from lobar pneumonia of the left lower lobe. On admission, blood culture yielded a Type I Pneumococcus; no type-specific agglutinins were present in the patient's serum; the skin test with Type I S.S.S. was negative. Serum treatment was begun 7 hours after admission, and continued at 6 to 8 hour intervals. After the second treatment, type-specific antibodies were present in the blood, increased in titre, and remained present throughout the illness. The blood culture became negative and remained so until the day of death, when it became positive again. The pneumonic process continued to spread in the face of circulating antibodies and sterile blood so that the entire left lung and the right lower and upper lobes became involved. Cyanosis became extreme, although the patient was in the oxygen chamber. The skin tests were repeatedly and consistently negative. Eleven doses of serum were given, but death intervened on the 6th day. No autopsy was permitted.

This case presents another instance in which the serological findings would be considered favorable. Although circulating antibodies were present in a good titre, the skin tests were all negative. The same lack of response has been consistently noted in the fatal cases of the series.

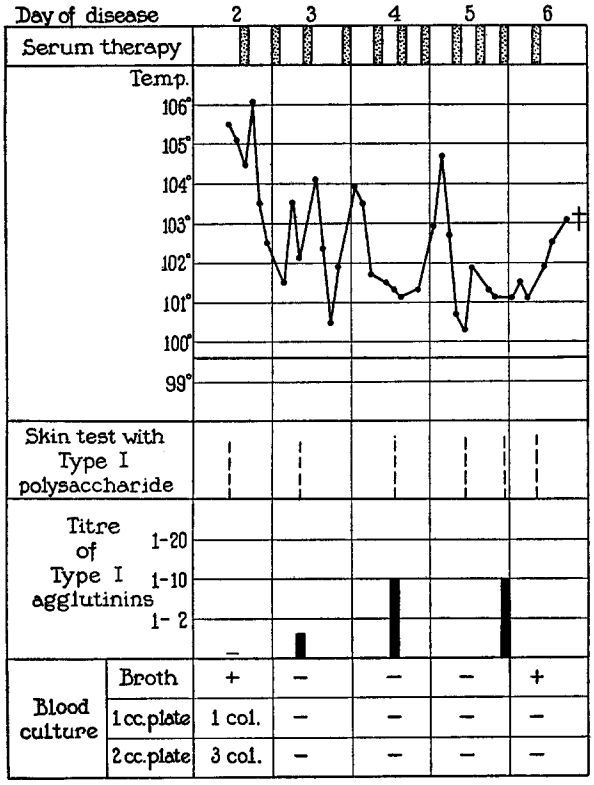

CHART 5. Patient Mo. (Hospital No. 7162). Type I pneumococcus pneumonia and septicemia.

Patient 6, Chart 6, Case 7580

The patient, a negro of 35, was admitted to the hospital on the 6th day of disease, with lobar pneumonia of the right lower lobe, and left lower and upper lobes. He was extremely sick. The blood culture was positive, no circulating Type I agglutinins were detectable, the skin test was negative. Serum therapy was instituted 8 hours after admission. After the second treatment, the temperature was lower, the blood culture in broth was sterile, no circulating agglutinins were demonstrable, and the skin test remained negative. On the 8th day, after the fifth and sixth treatments, skin tests were still negative, but a high titre of agglutinins was present, and although the temperature was normal, the patient remained dangerously ill, in delirium, and the septicemia had increased in degree. Although it was not known until later that the septicemia had increased, serum therapy was continued because of the negative skin test. On the 9th day the temperature re-

mained at about the normal level, the blood culture had become sterile, but the skin test elicited a response so faint that it could only be considered doubtful. The following day a similar result was obtained. After the 10th day, delirium ceased and the patient improved somewhat. Convalescence was delayed by the development of an encapsulated empyema, which was drained by operation on the 25th day.

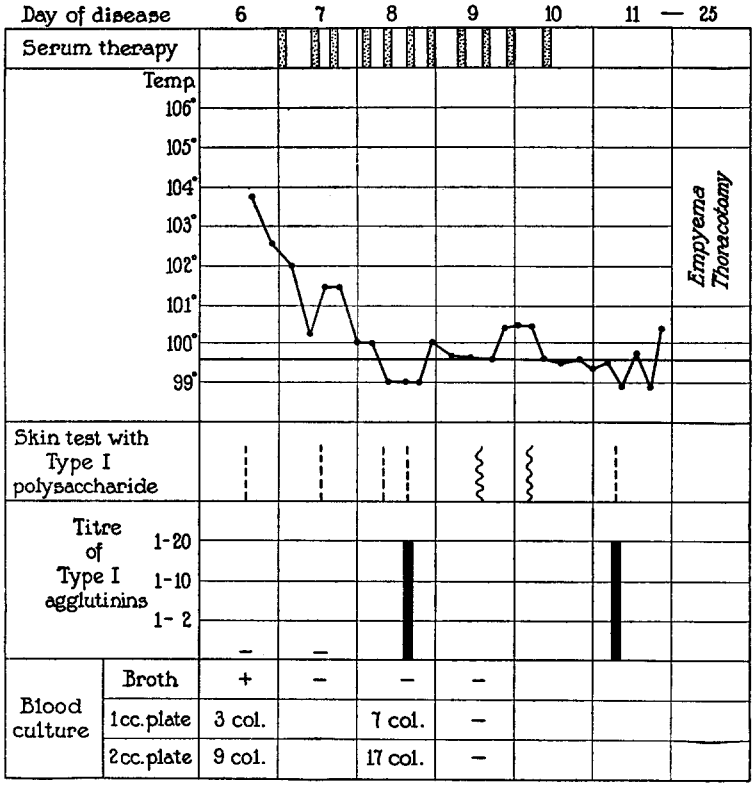

CHART 6. Patient Mu. (Hospital No. 7580). Type I pneumococcus pneumonia with septicemia and empyema.

This case is the one exception in the entire series of 53 patients in that it is the only instance in which a patient, at or about the time of recovery from the acute phase of pneumonia, failed to give a distinctly positive skin test. It is also the only case without a definitely positive reaction which did not have a fatal termination. On the 9th and 10th days, reactions were observed which were considered suggestive. It

is possible that in the skin of a negro the milder forms of reaction are more difficult to detect. At any rate, on the 8th day, 18 hours before it was known that septicemia had increased, with the temperature normal and type-specific agglutinins present in the blood, the value of the negative skin test in indicating further treatment must be stressed. This case is also exceptional in that it remains the only 1 of the 5 cases of empyema, all of which recovered, that failed to give a positive reaction at the termination of the phase of acute pneumonia.

DISCUSSION

The results of the skin tests with Type I S.S.S. in 53 cases of Type I pneumococcus pneumonia are strikingly uniform for a biological test. In the series there were 7 deaths, in all of which repeated skin tests were negative. On the other hand, in 46 recovered cases, including 5 cases of empyema, all but 1 gave a positive reaction at about the time of recovery from the acute pulmonary process. In the one exception, a negro with subsequent empyema, only a doubtful reaction was obtained although the patient recovered (Patient 6, Chart 6). Exemplary individual cases have been cited to show the relation of positive reactions to recovery and to the presence of antibodies in the circulating blood. Furthermore, they emphasize the fact that the mere presence of circulating antibodies, in cases before recovery or in cases terminating fatally, is not sufficient to bring about a positive skin reaction.

Finland and Sutliff, in similar studies, reported only 7 positive tests to the Type I S.S.S. in a series of 15 non-serum-treated patients who recovered from Type I pneumonia (3). Of 17 Type I and Type II cases tested before the time of crisis, 3 gave positive tests to the homologous polysaccharide. Moreover, the relation of positive skin tests to recovery and to the presence of type-specific antibodies in the blood was corroborated. Of the fatal cases in their untreated series, only 1 of 11 cases of all three types gave a positive reaction. The details of this case are not recorded.

In their cases which were treated with serum (6), two distinct differences from the procedures employed by us must be noted. In the first place, Felton's concentrated serum containing Type I and Type II antibodies was used. Secondly, the skin tests were frequently

made within 1 to 2 hours after the administration of serum. Nevertheless, 20 of 23 Type I and Type II serum-treated cases which recovered gave positive skin reactions, while of 5 treated cases which terminated fatally, 1 gave a positive result.

In the present series of cases treated with Type I serum, a positive skin test has always been indicative of recovery, and in only 1 instance did recovery occur in the absence of a positive skin reaction. In all these cases, circulating type-specific antibodies were demonstrable at the time a positive cutaneous test was first obtained. However, reference to charts of Patients 3, 4, and 5, reveals that a positive test is not simply referable to a high concentration of circulating antibodies, since the titre of antibodies may be the same before recovery when the skin test is negative, as it is later when a positive test occurs. These charts also show that, in fatal cases, although antibodies may be present in the blood, a positive skin test is not obtained. Consequently, it appears that cutaneous reactivity to S.S.S. is not merely dependent upon the presence of circulating type-specific antibodies. On the other hand, its development is always associated with the presence of these antibodies in the blood. These observations indicate that for positive cutaneous reactivity there are required both active tissues and specific antibodies homologous in type to that of the S.S.S. injected, and that absence of either factor results in failure to react.

Recovery from pneumonia is a complicated process in which cellular activities play an important rôle. This is strikingly demonstrated in the study of resolution of pneumonia. A positive skin test to S.S.S. is also invariably associated with recovery, and it is suggested that this reaction may be an indicator of a general reawakening of cellular activity in the presence of type-specific antibodies. The failure to obtain a positive reaction in fatal cases, or in cases before recovery begins, even when type-specific antibodies are present, may be attributable to a depression of general cellular activity by the toxic factors of disease. This interpretation is supported by the observation of Finland and Sutliff (6) that when a Type I patient is treated with serum containing both Type I and Type II antibodies, the skin test to Type II S.S.S. does not become positive before the Type I S.S.S. skin test, although Type II antibodies have been present in relatively high titre throughout the course of therapy.

The value of the skin test as employed in the present group of cases appears to be definitely established both as a guide to serum therapy and as a prognostic aid. In certain instances, by the time a typing of the invading organism is obtained, the patient appears improved and the temperature may have approached a normal level. There may be some doubt as to whether treatment with serum is required. A skin test with the S.S.S. may be done, and the result read in 15 to 30 minutes; a negative test indicates serum therapy. In all cases of this sort, the conclusions reached as a result of the skin test have been validated by subsequent findings and the course of disease. Similarly, in cases with intermittent fever, or in which a drop of temperature follows serum therapy, the skin test gives a distinct answer to the problem of whether recovery has begun or whether treatment should be continued (Charts 1 to 3). A positive reaction is invariably, in our experience, a sign that recovery will follow. Furthermore, although the patient may still appear quite sick with little change from a previous period when the skin test was negative, the development of a positive cutaneous reaction indicates recovery and that further serum therapy is unnecessary (Chart 3). A persistently negative reaction, even in the presence of circulating antibodies, clinical improvement, and continued serum therapy, offers an unfavorable prognosis, and in all cases has been associated with a fatal termination (Charts 4 and 5). To repeat, a positive immediate wheal and erythema reaction to Type I S.S.S in cases of Type I pneumococcus pneumonia predicates recovery; a negative test calls for further serum therapy.

It has been assumed that the chief function of antipneumococcus serum as a therapeutic agent is to furnish type-specific antibodies. Consequently, the presence or absence of type-specific agglutinins in the patient's blood has been employed as a means of estimating when sufficient serum has been administered. The application of titration of circulating agglutinins in conjunction with the use of concentrated serum has been recently advanced by Sabin (7). From the point of view of recovery, however, it furnishes an estimate of only the humoral aspect. In Patient 3, Chart 3, type-specific agglutinins were demonstrable in the patient's blood although the pneumonic lesion was spreading. Later when the skin test became positive, the agglutinins were present in the same concentration. In Charts 4 and 5 are shown

examples of the occurrence of agglutinins in cases terminating fatally and in which the skin test, by remaining consistently negative, prognosticated the fatal outcome. In Chart 6, a good titre of agglutinins was present although the septicemia was increasing. The skin test became only doubtfully positive at time of recovery, but this may have been due in part to the fact that the skin of the negro made the result more difficult to read. When a positive cutaneous reaction has been obtained, however, recovery has always ensued. As additional advantages, the skin test has simplicity of technic, the results are easily read, it is rarely equivocal, the answer is obtained in 15 to 30 minutes, the results have been remarkably regular, and it apparently measures the resultant of antibody and tissue activity. The results of this study appear to establish the value of the skin test with Type I S.S.S. in the serum treatment of Type I pneumococcus pneumonia.

SUMMARY AND CONCLUSIONS

Skin tests were made with Type I S.S.S. in 53 cases of Type I pneumococcus lobar pneumonia, 48 of which were treated with antipneumococcus Type I serum. In all but 1 of the 46 recovered cases a positive, immediate skin reaction was obtained at about the time of recovery. In 7 fatal cases reactions were consistently negative, even in the presence of circulating type-specific antibodies.

The skin test has proved to be an extremely valuable guide to serum therapy, and a definite prognostic aid. The test has distinct advantages over the agglutination reaction in that it is not merely an index of circulating antibodies. When positive, it invariably denotes that recovery has begun; when negative, it indicates further serum therapy. The mechanism of the positive skin test is closely related to that operative in recovery from pneumonia, and is apparently the resultant of antibody and tissue activity.

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