

## STUDIES ON THE SOMATIC C POLYSACCHARIDE OF PNEUMOCOCCUS

### I. CUTANEOUS AND SEROLOGICAL REACTIONS IN PNEUMONIA

By THEODORE J. ABERNETHY, M.D., AND THOMAS FRANCIS, JR., M.D.

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

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In 1930, Tillett and Francis (1) observed that the sera of individuals acutely ill with lobar pneumonia possess the capacity of precipitating a non-protein, carbohydrate fraction derived from *Pneumococcus*. This fraction was termed the C substance. It was shown that the precipitating action of patients' serum with the C substance is demonstrable early in the course of pneumonia, persists throughout the course of the active disease, and disappears during convalescence.

Subsequent tests with sera from certain other diseases showed that the precipitation of fraction C is not limited to the sera of individuals with pneumococcus infection. The phenomenon was also demonstrated in cases of rheumatic fever, bacterial endocarditis, and lung abscess, but not in all febrile diseases. The sera of patients suffering from malaria, tuberculosis of the lungs, typhoid fever, measles, and varicella did not react with fraction C. While the exact nature of the mechanism of the precipitation reaction with C is not understood, Tillett and Francis suggested that the principles involved in the anamnestic reaction described by Cole (2) might be used to explain the phenomenon.

Further studies by Tillett, Goebel, and Avery (3) on the chemical and immunological properties of the C substance showed that it is a complex polysaccharide contained within the body of the pneumococcus cell. It is species specific and is found in all pneumococci irrespective of type or virulence. It is distinct from the type specific capsular polysaccharide not only in its chemical properties but in its serological reactivity. Later, Heidelberger and Kendall (4) showed, in a study of the chemical properties of the polysaccharides of Type

IV Pneumococcus, that the C substance contains 4 per cent of phosphorus firmly bound in organic combination.

A preliminary report on the cutaneous reactions to C in 30 cases of pneumonia has previously been given (5). Recently amounts of the somatic polysaccharide of sufficient purity have been obtained to undertake a further study of both the cutaneous and serological reactions in pneumonia to this substance. Data included in the present paper record primarily the relationship of the cutaneous reaction to the clinical course and outcome of the disease, and the parallelism between the *in vitro* serum precipitation reaction and the *in vivo* response to intradermal injection of C polysaccharide. Observations on the nature of the C precipitation reaction have been reserved for subsequent publication.

#### *Materials and Methods*

*Subjects.*—The patients observed in this study were admitted to the wards of the Hospital of The Rockefeller Institute. Group A comprised 46 cases of pneumococcus lobar pneumonia, of which 39 recovered and 7 died. As soon as possible after entry sputum typing was attempted by means of the Neufeld reaction. This was successful in a high proportion of the cases. When unsatisfactory, however, the typing was determined by the mouse method. Distribution of types among the 46 cases was as follows: Type I, 11 cases; Type II, 2 cases; Type III, 9 cases; Type V, 1 case; Type VII, 4 cases; Type VIII, 6 cases; Type IX, 2 cases; Type X, XIV, XVI, XVIII, 1 case each; and unclassified types, 7 cases. On admission, a blood culture, complete blood count, and roentgenogram of the chest were made on each patient. The progress of the pneumonic lesion was followed by daily physical examination of the chest and by frequent x-ray examination throughout the course of the disease. The general treatment of each patient was the same. Specific serum treatment was given to all but one patient with Type I infection, to a smaller number of individuals with Type II, and to a few patients with Type V, VII, and VIII infection. Artificial pneumothorax was used in a few instances.

Group B comprised 10 patients suffering from diseases other than pneumococcus pneumonia. There were 5 patients in whom the diagnosis of rheumatic fever had been made; 3 patients ill with bacterial infections of known etiology; and finally 2 cases of non-infectious fevers.

Group C comprised 19 normal healthy adults free from any obvious infection. None of these individuals had had pneumonia.

*Skin Testing Materials.*—The C substance used for intracutaneous inoculation was prepared in a state of high purity by methods employed in this laboratory (3) from an R strain derived from Type II pneumococci. The preparation was a

white powder, readily soluble in physiological salt solution. Intracutaneous injections of a solution of C substance in amounts of 0.1 cc. containing 0.1 mg. of polysaccharide were given to all the patients. Physiological salt solution, 0.1 cc., was used as a control. Frequent skin tests were performed on the patients ill with lobar pneumonia (group A). An initial test was always performed shortly after the admission of each patient, and was repeated at intervals during the course of the disease. Tests on the control cases (groups B and C) were made less frequently. The inoculated sites were observed frequently during the succeeding 24 hours.

*Precipitation Tests.*—Serum was collected before each intradermal inoculation and the samples were tested for capacity to precipitate in the presence of the C substance. The precipitation tests were performed in the usual manner, *i.e.*, 0.2 cc. serum, diluted with 0.3 cc. of physiological salt solution was mixed with 0.5 cc. of varying dilutions of the C substance. Readings were made after the mixtures had been incubated at 37°C. for 2 hours and had stood in the ice box overnight. In positive tests the precipitate that forms settles rapidly to the bottom of the tubes, and on shaking can be readily broken up. No disc formation is seen.

#### *The Cutaneous Reaction*

The capacity of two other components of the pneumococcus cell, the type specific capsular polysaccharide and the nucleoprotein fraction, to elicit characteristic cutaneous reactions in pneumonia has been described previously (6). The reaction to the capsular polysaccharide is of the immediate wheal and erythema variety, is type specific, and appears only when the recovery processes have been initiated. It may persist during convalescence and is always associated with the presence of type specific antibodies in the patient's serum. The skin reaction to the nucleoprotein, on the other hand, is of the delayed variety, not appearing until several hours after inoculation, is negative during the acute stages of pneumonia, and becomes positive late in the period of convalescence. A high percentage of normal individuals react to the bacterial protein injected intradermally. Circulating antibodies to the nucleoprotein, as measured by precipitin tests, are demonstrable in about equal titer both during the acute disease and the period of recovery.

In striking contrast to the cutaneous reactions elicited with the capsular polysaccharide which occur with the onset of recovery, and those following the injection of the nucleoprotein which appear later in convalescence, cutaneous reactions to the C substance are present

during the height of the disease. The character of the positive cutaneous reaction is distinctive and may be described as follows:

Within 15 to 30 minutes following the intradermal inoculation of 0.1 mg. of the C substance there appears at the site of injection a wheal surrounded by a zone of erythema. This reaction in its early development resembles the capsular polysaccharide skin test, but the zone of erythema is less intense and "pseudopods" extending out from the central wheal, so frequently seen in the latter, are rarely encountered. Within an hour this acute phase has usually faded and is then followed by the delayed reaction, an edematous erythema. The center of the area of delayed erythema is frequently dark, reddish brown, sometimes hemorrhagic, about which there may be a pale white halo, and beyond this a bright red erythema. The delayed reaction begins to appear in 2 to 3 hours, is well marked in 6 to 10 hours, persists for 18 to 24 hours, and then fades, leaving a residual brown stain. The size of reacting area may reach 5 cm. in diameter, but is usually 2 to 3 cm. in maximum diameter. There is frequently tenderness at the site of injection. The skin test is considered positive if a delayed reaction occurs with an area of erythema larger than 1 cm. in diameter. The reaction is called doubtful if the erythema is between 5 and 10 mm., and negative if the erythema is less than 5 x 5 mm. While the classification is an arbitrary one, experience has justified the use of this relative standard.

#### *Results in Pneumococcus Pneumonia*

*Recovered Cases.*—Frequent observations upon the C skin test in 39 recovered cases of pneumococcus pneumonia have shown that in all patients, irrespective of the type of invading pneumococcus, a positive reaction was elicited during the acute stage of the disease. The reaction appeared early, in one instance as early as 12 hours after the initial chill, and persisted throughout the acute febrile period. With the onset of recovery, whether associated with crisis or lysis, the reaction decreased markedly in intensity, and during an uncomplicated convalescence, in the majority of cases could no longer be demonstrated. Parallel determinations of the serum and cutaneous reactions with the C substance have shown striking uniformity in results and have confirmed the observations of Tillett and Francis on the appearance of the precipitation reaction during the acute phase and its disappearance in convalescence. Chart 1 depicts graphically the occurrence of the cutaneous and serological reactions to the C substance in a typical uncomplicated recovered case of pneumococcus pneumonia.

The patient was a 21 year old mechanic admitted to the hospital on the second day following a characteristic onset of acute lobar pneumonia. The admission physical examination revealed consolidation of the lower portion of the right upper lobe which was confirmed by x-ray. Type XIX Pneumococcus was recovered from the sputum. Blood culture was sterile. The lesion spread to involve the whole of the right upper lobe. A crisis occurred on the 6th day of the disease, after which an uncomplicated convalescence followed. He was discharged on the 21st day, completely recovered.

A skin test with 0.1 mg. pneumococcus C fraction on the day of admission showed a strongly positive reaction which first appeared 3 hours after inoculation

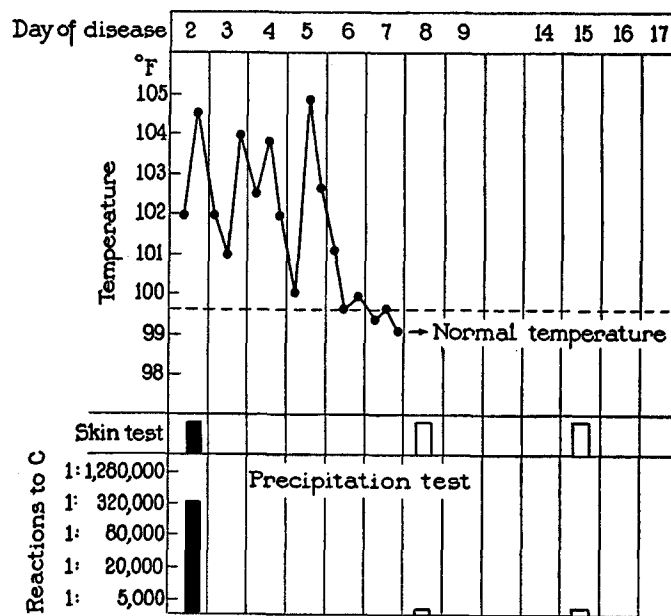


CHART 1. Type XIX pneumococcus pneumonia.

as a reddish brown area of erythema 1.1 x 1.3 cm. in size. This lesion gradually increased in size, becoming of maximum intensity at the end of 24 hours. The center was a deep red color surrounded by a thin white halo, around which an area of erythema 2 x 2.5 cm. was present. Subcutaneous edema was noted, and the lesion was slightly tender. A control injection of normal saline done at the same time was negative. Serum taken on the day of admission precipitated the C substance to a dilution of 1:320,000. Following the crisis skin tests were repeated, on the 8th and 15th days of the disease. On neither occasion was the skin reaction positive to 0.1 mg. of the C substance. At the same time, precipitation tests with the patient's serum were also negative.

Persistence of the positive cutaneous and serum reactions to the C substance was frequently noted in patients in whom the disease ran a protracted course by reason of delayed resolution or the occurrence of some complication, such as sterile pleural effusion or empyema. With the onset of convalescence, however, both reactions to the C substance disappeared. Moreover, reappearance of the C reaction was noted in a few patients who suffered some complication late in the disease after the acute febrile period had subsided. The following observa-

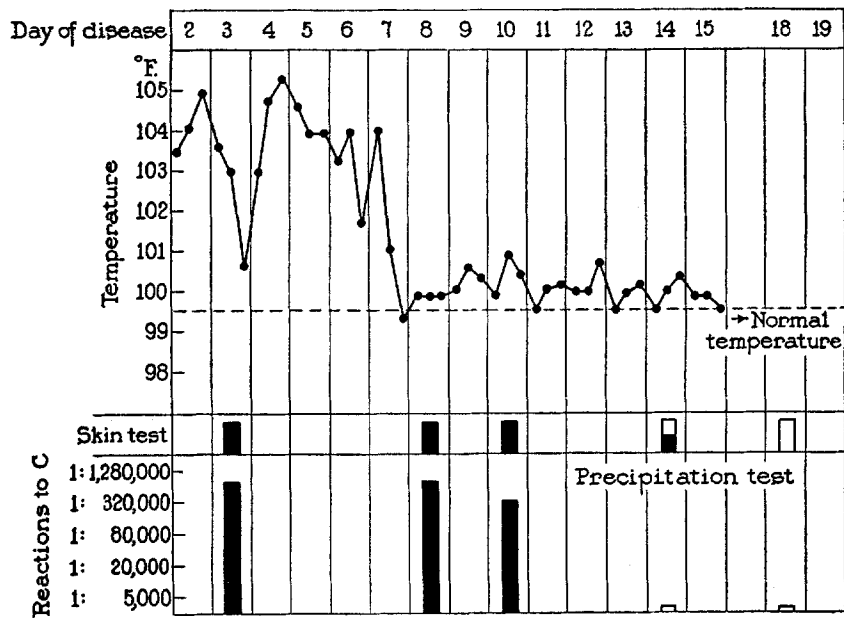


CHART 2. Type V pneumococcus pneumonia.

tions were made upon an individual in whom the disease was complicated by the development of pleural effusion, and the results of the serum and skin tests are represented in Chart 2.

The patient was a 39 year old white male admitted to the hospital 24 hours after an acute onset of pneumonia with chill, cough, and pain in the lower left chest. Physical examination revealed consolidation of the left lower lobe. Pneumococcus Type V was recovered from the peritoneal cavity of sputum-injected mice. In order to relieve the intense pleural pain artificial pneumothorax was attempted, but upon entering the pleural cavity a small amount of thick turbid fluid was dis-

covered, and consequently no air was injected. Culture of the pleural fluid yielded Pneumococcus Type V. On the 4th day of disease, an extension of the pneumonia to the left upper lobe occurred. On the 5th day a small amount of fluid, which proved to be sterile on culture, was removed from the left chest. Subsequently additional fluid accumulated, and on the 7th, 13th, and 16th days of his disease a total of 770 cc. of sterile fluid was aspirated. Following a crisis on the 7th day there was marked improvement in his general condition, although the temperature did not remain permanently normal until the 16th day. He was discharged completely recovered on the 33rd day.

Both serum and skin tests with the C substance were done on the 3rd day of acute illness and repeatedly following crisis. The initial skin test was markedly positive, and at the same time the patient's serum precipitated the C substance in dilution of 1:640,000. On the day following the crisis, at a time when the skin reaction in uncomplicated cases is usually negative or at most weakly positive, a strongly positive reaction was observed, and the precipitability of the patient's serum with C substance was still marked. These findings were confirmed 2 days later, at which time a large collection of pleural fluid was present. On the 14th day a doubtfully positive skin reaction, an area of erythema between 5 and 10 mm. in diameter, was observed, but the precipitation test was negative. During the convalescent period neither the skin nor serum reaction to C could be demonstrated.

*Fatal Cases.*—While in the recovered cases positive cutaneous and serological reactions were observed throughout the acute phase of the disease, persisting or reappearing if complications developed, and disappearing with the onset of recovery, in the fatal cases sharp differences were noted in the skin reactivity to C. Seven of the 46 cases terminated fatally. Three of these patients had Type III pneumococcus infections; in the remaining four patients pneumococci of Types I, II, VII, and X were the invading organisms. All seven of these patients failed to give a skin reaction to the C substance during some stage of the acute disease. Two of the seven cases gave positive skin reactions upon admission, but subsequent tests later on in the acute phase of the disease were negative. Parallel observations on the serum of these patients, however, showed that precipitation with the C substance occurred in samples tested throughout the disease. Chart 3 presents the findings in one patient illustrative of five fatal cases in each of which skin reactions were uniformly negative, although the serum reacted positively during the entire course of disease.

The patient was a 45 year old school teacher admitted on the 1st day of illness. His past history revealed a tuberculous infection of the lungs in 1932 which by

x-ray had subsequently been shown to be inactive. The onset of the present illness was abrupt, with the classical chill, pain in the left chest, and cough with bloody sputum. He was acutely ill when first seen, and examination disclosed an extensive consolidation of the left lower lobe. Type III Pneumococcus was identified in the sputum. Because of the marked pleural pain attempts were made on two occasions to induce a small artificial pneumothorax, but these proved unsuccessful because of multiple pleural adhesions. The patient became progressively worse with the spread of the pneumonic consolidation to involve all pulmonary lobes. Blood cultures remained consistently negative. Death occurred on the 6th day of disease.

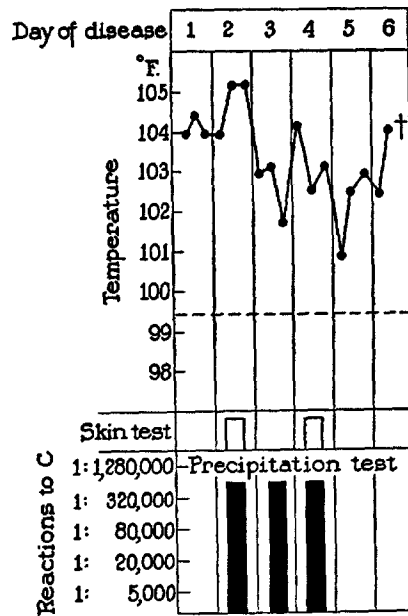


CHART 3. Type III pneumococcus pneumonia.

Skin reactions to the C substance on the 2nd and 4th days of disease were negative. However, precipitation of C by samples of serum taken on the 2nd, 3rd, and 4th days of disease occurred in high titer.

A loss of skin reactivity to C substance occurred during the course of the acute disease in two of the seven fatal cases. In both instances the skin reaction was positive on admission, but subsequent tests failed to provoke cutaneous reactions, although the serum throughout the disease precipitated when C was added in high dilution. A case illustrative of these findings is given in Chart 4.



The patient was a 37 year old white male admitted on the 5th day of lobar pneumonia of classical onset. Examination showed involvement of the right middle and lower lobes. Type X Pneumococcus and *Hemophilus influenzae* were recovered from the sputum. The admission blood culture showed no growth, but on the 8th day a culture was positive, less than 1 colony per 2 cc. of blood, and on the 12th day the colonies had increased to 50 per cc. of blood. The right upper and left upper lobes became successively involved and with this spread the signs of toxemia increased. He finally succumbed on the 13th day of disease despite the usual supportive measures. Postmortem examination showed extensive

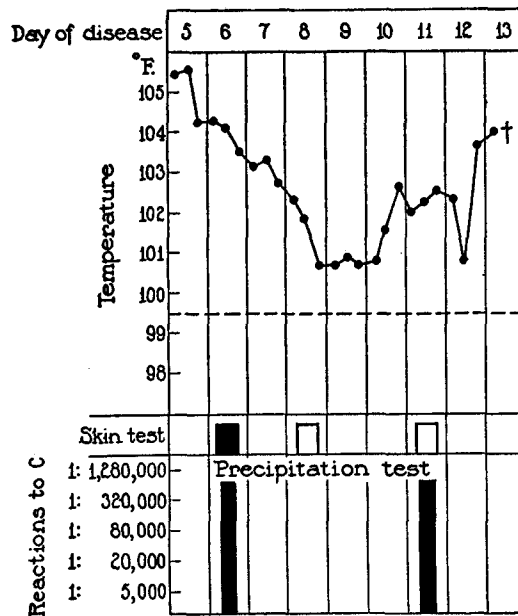


CHART 4. Type X pneumococcus pneumonia.

consolidation of the right upper, right middle, and left upper lobes, and beginning resolution in the right lower lobe.

A skin test done on the 6th day showed a markedly positive reaction, similar to that seen in the acute stage of cases which subsequently recover. There was an area of erythema 2 cm. in diameter, and at the same time the serum was precipitated in the presence of dilution of C as high as 1:640,000. However, on the 8th day, 5 days before death, no skin reaction to C substance was elicited, and none when the test was repeated on the 11th day of disease. Unfortunately, the serum precipitation test was not done on the 8th day, but on the 11th day it was found to be markedly positive.

A summary of results obtained in 46 cases of pneumococcus pneumonia is given in Table I.

*Results in Control Cases*

In the light of the observations of Tillett and Francis (1) and of Ash (7), who found that precipitation with C was not confined to the sera of individuals with pneumococcus pneumonia, it seemed of interest to test the C skin reactions in a group of patients suffering from other febrile diseases. For this purpose ten individuals were selected for study. The fever in 8 of the patients was known to be of infectious origin. In this group were some types of infection in

TABLE I  
*Cutaneous and Serological Reactions to C Polysaccharide in 46 Cases of Pneumococcus Pneumonia*

Classification	No. of cases	Stage of disease	Skin reactions			Precipitation tests	
			Positive	Doubtful	Negative	Positive	Negative
Recovered	39	Acute	39	0	0	39	0
		Convalescent	2	1	36	1*	38
Fatal	7	Acute	0†	0	7	7	0

\* Convalescence complicated by active rheumatoid arthritis.

† 2 of 7 fatal cases gave positive reactions when first admitted. Reaction subsequently became negative.

which the serum precipitation test with C had previously been noted by the above mentioned authors. In the remaining 2 cases the fever was found to be of non-infectious origin. As a further control cutaneous and serological reactions were noted in a group of normal healthy adults.

*Infectious Fevers.*—Observations were made upon 5 individuals with acute rheumatic fever. Each of these patients was tested during the active febrile period and again some weeks later when clinically and by laboratory tests the disease was considered to be quiescent. In all 5 patients the cutaneous reaction to the C substance was positive during the febrile period and became negative during the inactive phase of the disease. Precipitation tests with the serum of these individuals paralleled the cutaneous reaction, except in one case in which the serum failed to precipitate with C during the acute phase of the disease; the serum

of all 5, however, showed an absence of precipitation reaction with C during the convalescent period.

In addition to the 5 cases of rheumatic fever, observations were made upon an individual with subacute bacterial endocarditis. On admission to the hospital the patient was found to have chronic rheumatic heart disease and septicemia due to *Streptococcus viridans*. His course was steadily downward, with progressive toxemia and multiple embolic phenomena, finally terminating 1 month later with a pulmonary embolus. The skin reactions to C were markedly positive both when tested 1 week after admission and 9 days before death. At the same time the patient's serum precipitated C when the substance was added in high dilution.

One patient with empyema of hemolytic streptococcus origin was similarly studied. When tested twice during the acute febrile disease the cutaneous and

TABLE II  
*Cutaneous and Serological Reactions to C Polysaccharide in 29 Control Cases*

Diagnosis	No. of cases	Stage of disease	Skin reactions		Precipitation tests	
			Positive	Negative	Positive	Negative
Rheumatic fever	5	Active	5	0	4	1
		Inactive	0	5	0	5
Bacterial endocarditis	1	Acute	1	0	1	0
Empyema-hemolytic Streptococcus	1	Acute	1	0	1	0
Aplastic anemia and <i>B. coli</i> septicemia	1	Acute (shortly before death)	0	1	1	0
Myeloblastic leukemia	1	Acute	0	1	0	1
Malaria	1	During paroxysm	0	1	0	1
Normal individuals	19	—	1	18	0	19

serum reactions with the C substance were strongly positive. Tests during convalescence could not be done because the patient was transferred to another hospital for operation.

Finally, tests were made upon one patient with aplastic anemia whose disease terminated in the development of septicemia with *Bacillus coli*. A skin test with C substance performed 4 days before death, at which time the blood had not yet been invaded, was completely negative. The serum, however, precipitated when C was added in dilution as high as 1:640,000. It will be noted that the results of the skin and serum tests in this case were precisely the same as those in the fatal cases of pneumococcus pneumonia. It was of interest to note at autopsy of this patient that, in addition to an aplastic bone marrow, hemochromatosis, and abscesses of the kidneys, a bronchopneumonia was present.

*Non-Infectious Fevers.*—Observations made on 2 cases of non-infectious fevers

showed negative cutaneous and serum reactions to the C substance. One patient with acute myeloblastic leukemia was tested on two different occasions, but at neither time reacted positively. The second patient, admitted for treatment of chronic amebiasis, developed a recurrence of a latent malarial infection while in the hospital. The parasites of tertian malaria were found in the blood, and a series of four chills with rises in temperature to 104–105° occurred prior to the administration of quinine. The skin and serological tests done at the height of one of these febrile paroxysms were completely negative.

*Normal Individuals.*—In order to determine the reaction of normal individuals to C, a group of 19 healthy adults free from obvious infection were selected for study. Skin and precipitation tests were performed in the manner described above. The serum of these individuals did not precipitate with the C substance even when the latter was added in high concentration, and the skin tests were negative in all but one instance. This person, upon subsequent inquiry, gave a history of hay fever and chronic postnasal discharge for many years and was known to be skin-sensitive to a variety of bacterial antigens as well as to pollen. Whether or not the positive reaction to C substance in this individual was related to a widespread sensitivity cannot be stated. A summary of results in the control cases is given in Table II.

#### DISCUSSION

From the present study of 46 patients with pneumococcus pneumonia it is apparent that the presence or absence of the cutaneous reactions to the C substance bears a definite relationship to the clinical course and outcome of the infection. In the 39 recovered cases all patients gave a positive skin reaction to the C substance during the acute illness. In a few patients in whom the disease was prolonged by complications the skin test remained positive until recovery ensued. Although in certain cases the capacity of the skin to react did not disappear abruptly, the test became negative in all but three patients within the first few days of convalescence. In striking contrast to these results are the findings noted in seven fatal cases. All of the latter patients failed to react to the C substance during the acute stage of the disease. Of particular interest were the results of skin tests in 2 fatal cases in which the reactions were positive early in the disease and later became negative as the disease progressed.

Simultaneous observations on the precipitability of the serum with C have confirmed and extended the observations of Tillett and Francis. In the recovered group, as well as in the fatal cases, sera taken during the febrile period precipitated on the addition of minute amounts of C

substance. Moreover, the precipitation test was positive extremely early in the disease. The serum remained positive if complications ensued, but became negative when normal convalescence followed.

The failure of the skin to react to the C substance despite the presence of a positive serum precipitation test would appear to be of prognostic significance. However, no conclusions can be made regarding the importance of the test as a prognostic sign until a larger group of cases has been studied. Tillett and Francis in their original paper noted that the precipitation test with C was not specific for pneumococcus infection. In a small group of cases they observed that "precipitation of C fraction occurred most definitely in those instances where Gram-positive cocci were proven to be or were suspected of being the etiological agent." These implications, however, were not substantiated by the work of Ash (7), who found that the serum of certain patients ill with Gram-negative bacillus infections possess the capacity of precipitating C. These observations, therefore, together with the results of studies now being carried out in this laboratory, to be reported later, suggest that the C precipitation phenomenon differs from usual immune reactions.

It is apparent, from the present investigation of 46 cases of pneumonia, and of 29 control patients, that the results of the skin and serum tests with C roughly parallel each other. Only in the fatal cases were the observations at variance. Thus, in view of this parallelism and despite the non-specific character of both reactions it would seem that some factor or change occurring in the serum in response to bacterial infection is capable of being mobilized in the tissues and thereby of reacting locally with the C substance. That some factor or change in the serum is essential for the skin reaction is suggested by the fact that the cutaneous response is almost invariably accompanied by a positive serum test. However, that the serum factor alone is solely responsible for the skin reaction seems improbable in the light of results in the fatal cases, in which the cutaneous test was negative although the serum reacted positively in precipitation tests. It would seem, therefore, that in addition to the serum factor, the state of reactivity of the tissue cells is also essential for the cutaneous response to C. When tissue reactivity is depressed by toxic products of the disease, as seems not improbable in fatal cases, the skin

test may be negative even though the serum reacts with C *in vitro*. A similar hypothesis has been advanced by Francis (8) in an explanation of the failure to obtain skin reactions to the capsular polysaccharide in fatal cases of pneumococcus pneumonia.

A recent communication by Finland and Dowling (9) has confirmed our earlier report upon the delayed cutaneous reactions to the somatic C polysaccharide. Using preparations of the "cellular carbohydrate" of Wadsworth and Brown (10) these authors found that "delayed cutaneous reactions with the 'cellular carbohydrate' of an atypical Type I Pneumococcus were obtained regularly during the febrile stage of a variety of infectious diseases and could not be elicited soon after recovery in such cases." Wadsworth and Brown in their original publication reported that the cellular carbohydrates were distinct from the soluble specific substance (SSS) and also from the C fraction, and gave type specific reactions with immune horse serum. Our experience with preparations of the cellular carbohydrate<sup>1</sup> has been limited to a few observations on the precipitation test with acute phase pneumonia sera. The sera of patients during the height of the disease have been found to precipitate with each preparation of the cellular carbohydrate tested, irrespective of the specific type of Pneumococcus from which the material was isolated. While the titer of these precipitation reactions was not so high as with the C substance, the tests were in each instance markedly positive. These observations, if confirmed in a larger series of cases, would indicate that the cellular carbohydrate of Wadsworth and Brown irrespective of specific type derivation may react with human sera during the acute stage of pneumonia as does the C substance.

#### SUMMARY AND CONCLUSIONS

A study of 46 cases of pneumococcus pneumonia has shown that a characteristic response may be elicited by the intracutaneous injection of 0.1 mg. of the somatic C polysaccharide of pneumococcus. During the acute febrile period in patients who recover, the response consists of a delayed erythema which reaches its maximum intensity in 18 to 24 hours. During convalescence the reaction is not demonstrable. In

<sup>1</sup> Kindly furnished by Dr. Wadsworth.

patients in whom the disease is prolonged by complications the capacity of the skin to react persists. In 7 fatal cases the skin failed to react to C polysaccharide.

Parallel studies of the reaction of the patients' serum with C have confirmed and extended the observations of Tillett and Francis on the appearance of the precipitation phenomenon during the acute stages and its disappearance in recovery.

That the cutaneous and serological reactions are not specific for pneumococcus infection is shown by the results in 29 control cases. 8 patients with infectious febrile diseases not of pneumococcus origin gave responses similar to those noted in pneumonia. 2 patients with non-infectious fevers and 18 of 19 normal individuals failed to give either skin or serum reactions.

These observations emphasize the importance of using separate components of the bacterial cell in the interpretation of cutaneous and serological reactions in pneumonia. The parallelism in results of the skin and serum tests in pneumococcus pneumonia with the somatic carbohydrate C, the significance of the reactions in relation to the clinical course and outcome of the disease, and the frequency of occurrence of both reactions in bacterial infections other than those of pneumococcal origin, are discussed.

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