Pneumococcic Pneumonia

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C O U R T E S Y O F C I T I Z E N S A I D S O C I E T Y

I. ABSTRACT

PNEUMOCOCCIC PNEUMONIA

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Definition

An acute specific, infectious disease, incited by the pneumococcus, and characterized clinically by a sudden onset with chill, pleuritic pain, increased respiratory rate, high temperature, and cough with the expectoration of rusty, tenacious mucopurulent sputum. Pathologically, it is characterized by a diffuse, inflammatory exudate involving, in part or whole, one or more lobes of the lungs.

Pneumonia taking about 100,000 lives a year in this country, is the most devastating of the respiratory infections and the third commonest cause of death in the United States registration area. For generations, of every 100 persons ill with lobar pneumonia about 25 have died, and the pneumococcus is the causative agent in about 96% of all cases.

Etiology

The pneumococcus was first definitely associated with pneumonia by Fraenkel, in 1884, and by Weichselbaum, in 1886. In typical morphology, the organism is a lancet-shaped gram positive diplococcus, surrounded by a definite capsule; it often grows in chains, especially on artificial media. The organism has no flagellae and is not motile. It is stained by all the usual dyes. The pneumococcus being more strictly parasitic than many other bacteria, consequently presents greater difficulties in its cultivation. It grows best on media prepared with meat extract enriched by the addition of fresh blood or serum, and a carbohydrate, at a pH of 7.6. The optimum temperature is 37°C, and growth may occur both aerobically or anaerobically. Within 24 hours, growth appears on solid media as small, round, moist, translucent and sharply circumscribed colonies. On blood agar plate, the colonies are surrounded by a slight halo of greenish or brownish hemolysis. The solubility of the pneumococcus in bile, its rapid autolysis in physiological saline solution, and its virulence for the white mouse, all serve to distinguish it from other organisms, particularly the streptococcus viridans.

A. Type Specificity

There are now 32 well-established types of pneumococci, plus an "x" group into which fall a small percentage (1-3%) of these organisms not agglutinated by any of the 32 types. The identity of these types has been verified by studies in various parts of the world and their distribution is quite constant wherever studied.

The type specific pneumococci all possess a capsule. Chemically, this is a polysaccharide which varies slightly in its composition according to the specific type of the organism. This capsule yields a soluble substance which may be demonstrated in the serum and the urine of a patient ill with pneumococcic pneumonia. It is this substance which combines with or is neutralized by the antiserum and therefore appears to have the properties of an antigen.

The bodies of the bacteria, excluding the capsular substance, are a protein material which, from the standpoint of its action as an antigen, appears to be similar in all the types of pneumococci. Antibodies prepared against this protein act equally well against the protein of all types of pneumococci.

A third substance has been recovered from cultures of pneumococci which is common to all types of pneumococci and which, when injected intradermally, produces a red reaction at the site of the injection. This material also acts as an antigen, and a antiserum has been produced against it. Its importance, as well as its mode of action, have not been thoroughly investigated as yet.

As it has been shown that pneumococci possess a heterophile antigen -- i.e., their injection into rabbits produces antibodies in the form of lysins against sheep cells. (Sera containing heterophile antibody have been marketed. The value of this serum will be discussed later under the heading "Therapy.")

B. Type Distribution

In 1,200 cases of pneumonia studied at the Hospital of the Rockefeller Institute, the following type distribution occurred.

Type of Pneumococcus	Number of Cases	Per-centage
I	431	35.9
II	311	25.9
III	123	10.0
Group IV (Type IV-XXXII)	273	22.7
Undetermined	62	5.1
	1,200	99.6

Cecil has reported 1913 cases with the following type distribution:

Type of Pneumococcus	Number of Cases	Per-centage
I	644	33.6
II	368	19.1
III	268	13.3
Group IV	633	33.1
	1,913	99.1

The following is the incidence in a series of 99 cases, occurring in the University of Minnesota Hospitals during a 4½ year period.

Type of Pneumococcus	No. of Cases
I	31
II	5
III	17
IV	4
V	7
VI	1
VII	1
VIII	3
IX	2
XIII	1
XVI	2
XVII	1
XIX	1
XX	2
XXII	2
XXX	2
Group IV*	17
Total	99

*(Done during 1931-33 before all sera were available.)

C. Virulence

This depends to a large extent upon the presence of the capsule. Under certain experimental conditions, pneumococci may be made to lose or regain their ability to elaborate a capsule. However, when once established, the virulence of the fixed types of pneumococci are quite constant.

D. Immunity

This may be procured either actively or passively. Active immunity against any specific type of pneumococcus can be induced only if the whole organism of that specific type, either living or heat killed, is used as an antigen. As shown by Stillman, the route of the immunization is important. If the antigens are injected, intravenously or intra-peritoneally, both a humoral immunity and protective antibodies are produced, whereas intramuscular or subcutaneous injections stimulate agglutinins and protective bodies less regularly. The immunity conferred by an attack of pneumococcic pneumonia is not permanent; but rather it has been estimated that this immunity lasts for 6 to 12 months. A low grade of immunity may be established against types of pneumococci other than that inciting the original infection. In a series of 607 cases, Cole stated that 22% gave a history of one or more previous attacks of pneumonia. Types I and II infections produce a more durable and a higher grade immunity than any of the other types.

E. Other Etiological Factors

I. Factors involving the individual

Man apparently has some degree of natural resistance to pneumococcic infection, as immune bodies have been demonstrated in the sera of many individuals who have never had pneumococcic pneumonia. This specific immunity is probably acquired by frequent contact with pneumococci without infection ensuing, or by acquiring some mild pneumococcic infection other than pneumonia. Individuals in sparsely

populated rural districts presumably have had but little chance of exposure to pneumococci and are unusually susceptible to these infections.

A number of factors are considered as playing a role in the lowering of resistance.

(a) Predisposition to infection, as represented by individuals having a low grade of natural immunity or those in whom there is a constitutional inability to evoke antibodies against the pneumococcus, or in those who are unusually hypersensitive to this organism.

(b) Changes in local resistance, as suggested by the frequent occurrence of pneumonia following upper respiratory infections.

(c) Changes in general resistance may be brought about by chilling, exhaustion, fatigue, exposure, starvation, other acute or chronic conditions, surgical operations, etc. It is well-known, however, that pneumonia does occasionally attack apparently healthy individuals.

(d) Age. Pneumococcic pneumonia is more common in adult life. In our series from this hospital, cases were distributed according to the decades as follows:

Age of Patients	No. of Cases
16 to 19 years	10
20 to 29 "	30
30 to 39 "	21
40 to 49 "	13
50 to 59 "	8
60 to 69 "	10
70 --	7
	99

(e) Race. Negroes are distinctly more susceptible to pneumonia than the white race.

(f) Sex. Males are more frequently attacked than females, due probably to the factors of added exposure, fatigue, etc. The proportionate mortality rate between the two sexes is approximately equal. In our series, here, there were 67 males and 32 females, a ratio of males to females of approximately 2 to 1. Of 22 deaths, there were 15 males, and 7 females, again a ratio of approximately 2 to 1.

(g) Occupation. That pneumonia is more common in cities than rural districts can not be attributed entirely to occupation, but rather more to differences in modes of living. Sailors and laborers, particularly steel workers, are said to have the highest incidence.

II. Factors involving the Pneumococcus

These are less important and less variable than those involving the host. However, Cole has shown that under certain favorable conditions, avirulent pneumococci residing as saprophytes in the nose and throat may suddenly acquire virulence and invasiveness, particularly when the resistance of the host has been lowered.

F. Pathogenesis

The actual mode of invasion in man is uncertain. Three theories have been advanced to explain the introduction of the pneumococci into the lung.

I. The hematogenous theory, which assumes that the pneumococci penetrate the mucosa of the respiratory tract and enter the blood stream to cause a generalized infection, and then later the infection localizes in the lung. However, all experimental attempts to produce lobar pneumonia by intravenous injection of pneumococci have failed.

II. The bronchogenic theory, which assumes that the pneumococci are carried by the air currents directly into the alveoli, where they cause the initial inflammation.

III. The lymphogenic or broncholymphogenic theory - assumes that the pneumococci first invade either the mucosa of the trachea or bronchi, the lymph nodes or the lung tissue near the hilum, and from these foci the pneumococci or their products are then spread throughout the lobe which is drained by

the area first involved.

G. Allergic Hypersensitiveness

The sudden onset of pneumonia with chills and fever resembles the violent reaction which follows the injection of a foreign protein into a hypersensitive individual. Recent experimental work would indicate that this factor needs greater emphasis.

H. Epidemiology

Because many acute lung infections are collectively reported as pneumonia, accurate statistics on a large scale in regard to the incidence of pneumococcic pneumonia are not obtainable. However, it is certainly one of the most serious infectious diseases contracted by man. Its contagiousness has long been recognized and instances of infection of the same type being transmitted from person to person constantly occur. Generally speaking, it is an endemic disease; but under certain favorable circumstances, it may take on an epidemic form. Type I and II pneumococci, which are responsible for about 60% of pneumococcic pneumonia, are seldom found in the buccal secretions of human individuals. This disproves any theory that pneumonia is entirely an autogenous infection. However, it is quite probable that a considerable portion of the higher types (III to XXXII) are caused by organisms which the patient has been carrying in his nasopharynx for some time. Pneumococci are spread by transfer from person to person, chiefly by droplet inhalation. Carriers of virulent pneumococci undoubtedly play an important role in the dissemination of the disease. Although the infecting organism usually disappears from the mouth and nasopharynx of the patient in from 3 to 4 weeks after the illness, carriers and convalescent patients may harbor the type specific pneumococci up to 5 months.

I. Pathology

This is both so well-known and established that little discussion of it is warranted here. The four classical stages occurring in the lungs are:

(a) Stage of engorgement: This is characterized by the outpouring of an inflammatory exudate of serum, fibrin, few red cells and leucocytes into the alveoli.

(b) Stage of red hepatization: so-called because of its resemblance to liver tissue. The red color is due chiefly to distended capillaries and alveolar hemorrhage. Microscopically, the alveoli are distended with leucocytes, fibrin, erythrocytes and serum. A few pneumococci may be seen. This stage passes rapidly over into the next.

(c) Stage of gray hepatization: The lung is now solid and friable. The capillaries are compressed and contain very little blood. The alveoli are distended with leucocytes, chiefly polymorphonuclears and fibrin. Erythrocytes are no longer present in the alveoli. Pneumococci are numerous.

(d) Stage of resolution is characterized by a softening and liquefaction of the exudate. The solution of the exudate is accomplished by proteolytic enzymes liberated by the leucocytes. The digested exudate is absorbed by the blood and very little is coughed up. In from 8 to 14 days, the alveoli become normally patent and air-containing, and all microscopic evidences of the damage disappear.

J. Lesions in Other Organs

The spleen is moderately enlarged. Cloudy swelling may occur in the liver and kidneys. Rarely metastatic abscesses are formed. Acute pericarditis pleuritis, empyema, ulcerative endocarditis, meningitis and arthritis are complications.

K. Lobes Involved

It has been said that the right lower lobe is involved most frequently. An analysis of 1,898 cases by Cecil, Baldwin and Larsen has shown, however, that the left lower lobe is the one most frequently involved. This is in agreement with our series of cases in

Lobe of Lung	Times Involved
Left lower	60
Right lower	58
Right upper	56
Right middle	41
Left upper	19

The type of pneumococcus does not have any relation to the lobe involved.

L. Symptoms

These vary somewhat according to the type of pneumococcus inciting the infection, so that there is no single symptom that is present in every case. In the great majority of cases, however, the clinical picture is quite typical.

The incubation period in the average case is usually short, varying from a few hours to seldom more than 48 hours.

Prodromal symptoms appear in about one-fifth of the cases. Frequently a history of previous upper respiratory infections can be elicited.

The actual onset is sudden, in most cases with a single severe chill, followed by a rapid rise in temperature of which the patient soon becomes conscious. The pulse and respiratory rate increase proportionately with the temperature. The face becomes flushed and anxious, the tongue coated and dry. Pleuritic pain then occurs and as is frequently the case this is the initial symptom. It is often lancinating and agonizing and causes short, jerky respirations. The pain may subside early or persist. Cases of severe and continuous pleuritis seem liable to develop empyema. An expiratory grunt and dilation of the alae nasi may occur with each breath. Cough, which is dry at first, soon becomes productive of bloody or blood-streaked, tenacious, mucopurulent sputum. Cyanosis may develop early or late. Dyspnea frequently occurs early. Herpes are often present on the lips.

Physical signs of pulmonary congestion may be present very early, but more often are somewhat delayed, in certain cases for several days. Frequently, the appearance and behavior of the patient suggest the diagnosis.

The course of the disease in most cases of moderate severity extends from 4 to 10 days, during which time there may be a continuation, remission or aggravation of any of the various existing symptoms. In favorable cases after the infection has run its course, a sudden and striking improvement occurs. If a crisis occurs, the temperature may drop rapidly, the patient perspires profusely, and the distressing symptoms disappear. In other cases, a step-like fall of temperature by lysis occurs and the improvement progresses more gradually.

Prognosis is rendered difficult because sudden changes for better or worse often take place. In unfavorable cases, the course may be progressively downhill from the beginning and the patient dies from toxemia, exhaustion or cardiac failure. The signs indicative of an unfavorable turn of events are an increased, irregular or weak pulse, together with increasing cyanosis and fall in temperature. Nervous symptoms with delirium and insomnia may result in exhaustion in some cases. Death may be due to any of the complications, as empyema, septicemia, meningitis, endocarditis or spread to other portions of the lung.

M. Clinical Course with Regard to Specific Pneumococcus Type

Type I pneumococcus pneumonia usually runs the most typical and uniform course. The percentage of complications occurring in this type, however, is nearly double the percentage occurring in any of the other types. It usually occurs in the young, previously healthy adults. Septicemia of this type is not as grave as that occurring with the other types.

Type II pneumonia is caused by a more virulent type of pneumococcus, with a death rate of 90% in cases with positive blood cultures.

Type III infections are very frequently preceded by a history of upper respiratory infection and have a more gradual onset. Although believed to occur relatively uncommonly in people under 50 years of age, 8 of the 17 cases of Type III infection studied in this hospital were under 50 years of age.

Type V. This has been but recently recognized as one of the more virulent types. Of 10 cases observed here, 7 deaths occurred. A high incidence of septicemia and complications is to be expected in this type.

Type VIII. Finland and Sutliff have recently described the characteristics of this type and have compared it with the infection caused by type III.

The remaining types constitute a group atypical with signs, symptoms, course and termination.

N. Individual Symptoms

1. Chill is one of the most characteristic features and is usually the first symptom. A definite chill occurs in about 2/3 of the patients, the remaining having chilly sensations.

2. Fever. The temperature rises rapidly following the chill. The highest point is usually reached between the 4th and 6th days. At first, the level is maintained near 103 to 104°F., with little fluctuation. Toward the end of the course, the variations become greater and remissions may occur. In very old or debilitated persons, the temperature is often much lower or may even be normal. The temperature elevation is not a reliable guide to the seriousness of the infection. Some evidence has even been adduced to show that a high temperature is a distinct advantage to the patient. However, a rapid rise of fever in severe cases often indicates approaching death. The temperature elevation may fall either by lysis or crisis.

Persistence of fever after the usual time is due chiefly to complications or sequelae. In cases treated with serum, serum sickness may cause this persistent temperature.

3. Pleuritic pain often occurs shortly after a chill and is present in about 3/4 of the cases at some time during the infection. It occurs most commonly in the lower anterior axillary region. In upper lobe infections, it may be absent or be referred to the shoulder. In children, it is frequently referred to other parts of the body. The pain is probably due to the stretching of the inflamed membrane during each respiration rather than to the rubbing together of irritated surfaces.

4. Respirations are increased in rate, but the depth of each breath is decreased. The degree of respiratory embarrassment is roughly proportional to the extent of the consolidation but striking exceptions do occur.

5. The cough, which is dry and unproductive at first and which frequently disturbs the sleep and exhausts the patient, soon becomes productive of the typical bloody or blood-streaked sputum. The amount varies greatly with the individual case. Microscopically, there are seen many fresh or degenerated pus cells and erythrocytes. The predominating organism is a gram positive diplococcus, although in poor specimens of sputum, as those mixed with saliva, a variety of other organisms may be seen.

6. The circulation. The pulse is almost always increased in rate, from 90 to 130 per minute. The blood pressure in favorable cases does not vary from normal, although a drop of 15 to 20 mm. of mercury is not unusual and should not be considered with alarm.

7. Jaundice is occasionally observed. Its cause is imperfectly understood, and is probably due to the same factors responsible for jaundice in other acute infections.

8. Gastro-intestinal symptoms. In children, nausea, vomiting and diarrhea may occur at the onset and suggest an erroneous diagnosis. Anorexia is prevalent. Constipation is the rule. Hiccough which may be very persistent as well as troublesome is probably due to

involvement of the phrenic nerve or the diaphragm.

9. Nervous symptoms which are relatively common rapidly disappear after the crisis.

O. Laboratory Findings

1. The urine is scant, highly colored and has a high specific gravity. Albumin and casts are usually present. It is believed by some (Hill) that the albuminuria is due to the specific attack of the organism upon the kidney.

2. Blood. As a rule, there is no marked reduction in the hemoglobin or number of erythrocytes during the short course of the disease, anemia being more likely to occur in cases followed by complications which prolong the illness. A polymorphonuclear leucocytosis is the rule. The average is 25,000 per cu. mm. with wide variations from 350 to 100,000 per cu. mm. No constant relationship can be drawn between the number of leucocytes and the severity of the infection. At the time of the crisis, the leucocytosis usually trails off slowly. A continued or increased leucocytosis with a high polymorphonuclear cell proportion after the crisis suggests a complication or sequela, notably one with pus formation.

3. Blood Cultures. Pneumococci may be demonstrated in the blood stream in from 25 to 33% of patients ill with pneumococcic pneumonia. The invasion of the blood stream usually occurs early but may occur up to the 6th day. In these latter cases, the prognosis is usually more grave. In any event, a bacteremia means a much more grave infection with a resultant higher mortality in cases untreated (with serum).

P. Physical Signs

The general appearance of the patient, as well as the local findings over the lungs, are so well known and established that they do not require discussion here.

Q. Diagnosis

Very little doubt of the diagnosis exists in a patient previously well, who suddenly develops a chill, high fever, pain in the chest, cough and expectorates the typical bloody or rusty sputum, particularly if there are signs of consolidation in the lungs demonstrated either by physical findings or on x-ray. In the atypical cases, however, the findings may be much slower in their appearance. But, regardless of whether the onset may be termed typical or not, it is important to determine at once the organism responsible for the pneumonia, and if a pneumococcus is the specific type, this must be done whether the consolidation has been interprested as being either lobar or bronchial in its distribution. For the purpose of simplification the method employed in this hospital will be outlined:

1. A direct smear of the sputum is first made, fixed in heat, stained by Gram's method and examined microscopically with the oil immersion lens.

2. If the predominating organism is found to be a gram positive diplococcus having the morphology noted above, a specimen of the sputum is streaked on a sterile blood agar plate, incubated at 37°C. for 24 to 48 hours. It is to be examined later as confirmatory evidence.

3. The Neufeld test is then performed. This is done by mixing on a cover glass a droplet of the sputum with homologous rabbit serum (to which standard alkaline methylene blue has been added), permitted to stand 10 to 15 minutes, and then examined as a hanging drop preparation with the oil immersion lens. This may be done with any number of sera although at the present time only the following are used: I, II, III, V, VII and VIII. When mixed with homologous serum, the capsules of the pneumococci swell, often from 2 to 3 times their normal size. When mixed with heterologous serum, none or a very minimal swelling occurs. Consequently, when swelling does occur in any one sera, the other preparations may be used as controls for comparison. Although

fresh sputum is desirable, the Neufeld test may be successfully obtained using sputum preserved for some time on ice or even with formaldehyde, tricresol or phenol. One pneumococcus having a definitely swollen capsule is indicative of a positive test. Only the above 6 types of serum are used as they are the only types of pneumococci for which a specific antiserum has been marketed.

4. As an additional check on the above method and also to determine the incidence of those types not included above, a specimen of the sputum (1/4 to 1/2 cc.) is injected intraperitoneally into a white mouse. At the end of 4 to 12 hours (depending on rate of growth), a specimen of peritoneal exudate is removed by aspiration with a hypodermic needle and a drop of this mixed with a drop of homologous serum. These two drops are thoroughly mixed, dried in air, fixed in a flame and stained by Gram's method. Definite agglutination or clumping of the individual bacteria occurs when mixed with specific antisera; whereas, no clumping occurs when mixed with non-specific antisera.

If there is no hurry in obtaining the specific type, the mouse may be allowed to die which usually occurs in from 24 to 30 hours. The peritoneal cavity is then opened and washed with normal saline solution. Using this suspension of bacteria thus obtained, the agglutination reaction carried out is as described above.

5. Blood cultures should be taken routinely in all cases of pneumococcic pneumonia because of the information they afford, both as to diagnosis and prognosis. Occasionally, the patient will not be able to expectorate. In these cases, the organism may be grown directly from the food in type if a bacteremia is present.

As can be easily adduced, the cost of this procedure does not forbid its adoption in any hospital laboratory. The technique may be easily acquired and when once mastered requires very little time. As will be shown later, the benefits to the patient from specific serum therapy, from a viewpoint of prognosis as to life, as well as from an economic viewpoint, are sufficiently well established to warrant the universal adoption of specific pneumococcic typing. Too much emphasis cannot be placed upon the collection of a good specimen of sputum as this frequently saves invaluable time in obtaining a quick typing.

(Note: The above description of the Newfeld method of typing is taken from the literature. Experience both at this institution and other laboratories in the city requires us to make reservations regarding the general application of the method.

In the hands of well-trained technicians, the accuracy of the procedure is not sufficiently high to recommend the method without confirmation by the standard mouse-method. It is sometimes difficult to recognize the increase in the size of the capsule and very frequently the sputum does not contain an adequate number of organisms. Experience has shown that errors in typing by this method may be frequent. The time saved by the method is only 3 to 6 hours and the gain is not equal to the loss.?)

The laboratory findings have been described above. Determination of the leucocytes, both qualitatively and quantitatively, should always be done when the patient is first seen and in intervals during the course of the disease if the course of the infection is to be followed adequately.

R. X-ray Diagnosis:

Whenever possible, it is well to substantiate the impressions obtained from physical findings by x-ray examination of the chest. In the usual case, some x-ray shadows will appear within 12 to 18 hours after the onset of the symptoms and within 24 hours the x-ray picture may be diagnostic. A detailed account of this diagnostic method is not within the scope of this abstract.

S. Differential Diagnosis:

The conditions most apt to be confused with this condition are acute

pleuritis or pericarditis with effusion, infarcts of the lung, acute massive collapse, acute tuberculous pneumonia, appendicitis and cholecystitis.

T. Prognosis:

Pneumonia must always be regarded as serious and predictions regarding the outcome are unsafe as changes for better or worse may occur suddenly. The chance of recovery is said to be somewhat better for men than for women. The age of the patient is of importance as the fatality rate rises steadily from about 6% in the 6th to the 20th year, to over 60% in the 7th decade. The physical condition is of importance. The fatality rate is low for individuals in vigorous health and higher for debilitated subjects--those with chronic disease or obesity, in pregnant women, and alcoholics. The most significant, but less readily measured factors in recovery, are the defensive factors of the host, and their reaction to the invading organism. The infection is less serious when the process remains localized in one lobe. Septicemia may occur in pneumococcic pneumonia of any type and always renders the prognosis more serious. In a series of cases at Bellevue Hospital, the death rate was almost 8 times as high in the cases with septicemia as those in which the blood remain sterile.

U. Complications:

Although Osler stated that pneumonia has "few complications and fewer sequelqe," Cecil has reported the occurrence of serious complications in 9% of a series of 1913 cases. Type I infections give rise to the highest incidence of complications. Antiserum appears to have little or no effect in reducing the incidence of complications although observations made in Great Britain suggest that the incidence of empyema may be reduced by the administration of serum. In analyzing the cases in this hospital, it is noted that patients who developed complications entered the hospital later on an average of 1.6 days after the development of definite pneumonia symptoms and those who did not develop complications. The average for the group which developed complications was 5.1 days, for the uncomplicated group 3.5 days.

The most common complications are: empyema, meningitis, phlebitis, pericarditis, and endocarditis. Pleuritis occurs often enough to be considered part of the disease. In our series here empyema occurred in 4 cases; otitis media, in 2; and a bilateral parotitis, in 1. Three of the patients had a slow resolution of the pneumonic process and 2 had a persistent low grade temperature elevation which subsided only after several weeks. From an economic standpoint as regards the days stay in the hospital, the latter two conditions may be regarded as complications.

V. Treatment

A. Prophylaxis. Mild respiratory infections or colds should not be ignored or neglected. Fatigue, exhaustion, overheating or chilling should be avoided, especially during the winter months. Postoperative or debilitated persons should be protected from draughts, colds or respiratory infections. Pneumonia patients should be isolated and cared for by attendants using isolation technique.

B. The symptomatic treatment aimed at the relief of cough, dyspnea, cyanosis pleuritic, pain, insomnia, abdominal distention, etc. is sufficiently well understood so that discussion of these types of therapy is not warrented in this abstract.

C. The Serum Treatment of Pneumococcic Pneumonia.

Washburn attempted the treatment of lobar pneumonia with serum in 1897, but his as well as other attempts were unsuccessful because the type specificity of the pneumococcus had not been recognized. The first report on the use of type specific anti-pneumococcic serum was made by Neufeld and Handel in Germany in 1910. Its use in this country was first reported by Cole and Dochez in 1913. In 1924, Felton developed a method of concentrat-

ing and refining antipneumococcic horse serum, permitting the intravenous administration of a potent solution in small volume.

The most concentrated serum for use is for the Type I and II pneumococci. Monovalent antibody solutions for these and certain types, namely V, VII, VIII and XIV, have been prepared. Type I and II mixed sera (bivalent) is available. In the preparation of the serum, healthy horses are injected intravenously at varying intervals over a period of several months with increasing numbers of organisms of that specific type. When the formation of antibodies is sufficient, the horses are bled at regular intervals, the blood allowed to clot, the serum syphoned off, bottled and stored at low temperature. Felton's antibody solution is prepared by various methods (salting out of proteins) designed to separate the antibody from other fractions of the serum. After separation, a preservative is added to the antibody fraction. The material is then filtered and bottled for use.

Undue apprehension regarding the hazards of specific therapy in pneumococcic pneumonia has deprived patients of the benefits of treatment. Although the injection of horse serum intravenously is attended by more risks than administration by other routes, the danger is small. In a series of 956 cases reported in the Massachusetts pneumonia study, death occurred as a consequence of the use of serum in only 4 (0.4%).

There are 3 groups of patients to whom the administration of horse serum may be dangerous. The first and most dangerous group includes spontaneously sensitive individuals, usually those subject to hay fever or asthma. The second and less dangerous group comprises those who have had a previous injection of horse serum. The third group includes those patients in whom the history is apparently negative, both for allergic diseases and the previous administration of horse serum.

Two precautions should always be taken before serum is given; namely, the history of the patient in relation to allergic manifestations should be elicited, and, secondly, he should be tested for sensitivity to horse serum by means of the conjunctival or intradermal tests. In patients giving a positive history of allergic disease, both the conjunctival and intradermal tests should be made, and serum not given unless both are negative. Inquiry should also be made concerning any previous serum administration (diphtheria, tetanus, anti-meningococcic and antipneumococcic). Diphtheria toxoid contains no horse serum but diphtheria toxin-antitoxin contains a small amount. The distinction between serum and vaccine is often not understood, and previous vaccine treatments are not of importance in this connection.

A first injection of horse serum ordinarily causes no immediate symptoms, and injections can be repeated within 7 (to 10) days without danger. After this interval, which is known as the incubation period, sensitiveness to serum develops and serum reaction may appear. Repetitions of intravenous injections after 7 to 10 days from the first dose, or in the presence of serum disease, may be dangerous and should not be attempted. Instructions and precautions as to the performance of the conjunctival and intradermal tests are included with the directions accompanying the commercially marketed serum.

Attempts to desensitize a sensitive patient is of uncertain value and are often accompanied by accident. All injections of serum should be given slowly, and the serum previously warmed before giving the injection. Do not heat! Concentrated serum cannot be diluted with normal salt solution without the formation of a precipitate.

The required dosage of anti-pneumococcic serum is unknown and varies with each case. In general, patients with the disease should be treated as early as possible and given the necessary amount of antibody within as short a time as consistent with safety. In Great Britain, it was found that a total dosage of 80,000 units with variations from 50,000 to 120,000 units was generally required for Type I infection, and a larger dosage on Type II infections. In the Massachusetts pneumonia study, 429

Type I cases received serum during the first 4 days of illness with 47 deaths (11%). These cases received an average dosage of 95,976 units. These observers concluded that an average dosage of about 95,000 units within the first 4 days of the onset, in divided doses, at short intervals, to be the most effective. However, of this latter series, 164 cases were treated with 54,412 units (average) with only 12 deaths, a case fatality rate of 9.8%.

At present, in Type II infections, 100,000 units in divided doses at 2 hour intervals is recommended. The required specific antiserum should never be given in one dose but always in divided doses. The first dose is a test injection and should consist of only a small amount of serum, given very slowly to guard against the possibility of an unforetold reaction. An interval of 2 hours should elapse between doses, as reactions, if they occur, are likely to take place within this period. It is advisable never to give more than 50 cc. of the antiserum at any one dose. Anti-pneumococcic serum should always be given intravenously. Subcutaneous or intramuscular injections are only slowly absorbed and are of doubtful value.

Before administering any serum, read any enclosed instructions, noting that the serum is the desired specific type, and warm the serum to body temperature. However, if warmed too much, the serum will coagulate and be unfit for use. The serum should be injected with the usual sterile technique and with extreme slowness, at a rate not faster than 1 cc. per minute by the watch. Following the first dose, an interval of about 2 hours should be allowed to elapse before the second dose is given. The third dose should be given at the end of another 2-hour interval. These 3 doses total about 30 cc. of serum and contain 60,000 units and which will probably be sufficient for the early treatment of Type I infection.

For Type II pneumococcic infection, additional doses of 20,000 units each should be given at 2 hour intervals to bring up the total units to 100,000.

If the first blood culture is positive and if progress is unsatisfactory, further blood cultures should be taken daily, as these may be a guide to further dosage. In pregnancy and immediately following delivery, more than the usual amount of specific serum should be given as the death rate from pneumonia is higher under these conditions.

Within 8 to 24 hours after the first dose of serum, there is usually marked improvement. This favorable response is apt to be more pronounced in Type I than in Type II infections. The temperature and pulse fall, the toxemia lessens, and a previously positive blood culture may become negative. The most reliable guides to the need of further dosage of serum are the level of the temperature and the persistence or disappearance of the bacteremia. In severe cases, and in the presence of the above indications, additiona. injections of 20,000 to 40,000 units may be given at 2 to 6 hour intervals.

Treatment of Type VII or VIII infections may require a total of 60,000 to 120,000 units or more of the antibody. Type V antiserum has been but recently marketed and sufficient data has not yet been accrued from which to draw reliable conclusions.

At times, patients fail to respond to treatment. If serum has been given persistently for 72 hours without any obvious effect, its administration should be discontinued.

Following the injection of specific antiserum, two types of reactions may occur at once or within a short time. Because such reactions may occur, the physician should be present or readily available up to 45 minutes following the injection. The first type of allergic reaction is characterized by flushing of the face, dyspnea, cyanosis, lumbar or abdominal pain, rapid weak pulse, and apprehension. This type of reaction occurs in about 8% of the cases, and is usually transient. Treatment consists of the injection of 0.5 to 1.0 cc. of epinephrin. The second type of reaction of any of the above symptoms combined with cutaneous reactions and an acute asthmatic attack. The treatment is the same as in the above. The occurrence of

urticaria or an asthmatic attack contraindicates further injections of the antiserum.

The immediate or allergic reactions of an acute fatal shock-like type which may come on at once or within a few minutes after the injection of the antiserum can probably be almost entirely eliminated if the precautions outlined above are followed.

A chill or thermal reaction occurring within 20 to 30 minutes after the serum injection may be expected in about 20% of the cases. These reactions are not ordinarily serious and may be due to rapid administration, failure to warm the serum, or the presence of a precipitate. The treatment of these reactions is symptomatic. Epinephrin is of no value. The milder thermal reactions need not modify the usual regime with respect to serum therapy unless very severe. It is well, however, to postpone the next dose for 3 to 4 hours, and give a decreased dosage.

Following the injection of an alien serum, there frequently occurs a group of symptoms called serum sickness or serum disease. This was noted in 18% of the cases in the Massachusetts Pneumonia study. These symptoms are mild, consist of joint pains, skin rashes or edema, fever, and generalized glandular enlargement. The attacks usually occur between the 7th and 10th days after the first injection of the serum. The condition is annoying, though not serious. Treatment is symptomatic. Epinephrin or ephedrin may give relief.

The crucial test of the value of an antiserum is its effect on the case fatality rate. The expected case fatality rate without specific therapy for Type I infections is 25%. Heffrin showed that in 2458 cases of Type I infection treated with antiserum only 15.6% died. When the treatment was begun within the first 4 days, the mortality rate may be further decreased to 11.1% (Massachusetts Pneumonia Study). Of 377 cases of Type I infection from the same study treated within the first 3 days, only 8.5% died.

In Type IIpneumonia, the untreated fatality rate is 41%. Heffron collected 670 cases treated with Type II serum with a mortality of 30.6%. In 136 cases treated within the first 96 hours, 27.2% died.

The case fatality rate is 22% without and 8.3% with specific treatment in the age group of 10 to 50 years, and 60.7% without and 30.8% with specific serum in the age group of over 50 years, having a Type I infection, illustrating the unfavorable influence of age upon pneumonia.

Serum against Type VIII pneumonia is to be placed on the market within a few weeks. Finland and Sutliff, who have studied 125 cases of this type, have shown that the clinical features of this type were quite similar to those of Type I and II. Its frequent occurrence has made it recognized as one of the more important clinical types.

Bullowa has reported a series of cases of Type XIV infections and their response to serum. This type appears to select infants and young children particularly, and causes infection of long duration. It is especially prone to invade the blood, the result in a high case fatality rate. It involves the pleura, pericardium and meninges with greater frequency than many other types of pneumococci.

The question of using serum before the pneumococcus type is known, or even without determining the type, is frequently raised. This is probably unnecessary as well as inadvisable where adequate facilities for proper rapid typing are available. Although a number of patients with pneumococcic pneumonia of the proper type are thus benefited by the earlier use of serum. Large numbers are treated unnecessarily. Among the latter group, a certain number of undesirable reactions will occur. The use of serum before or without specific typing will be less objectionable if restricted to patients fulfilling the following criteria.

1. Between the ages of 20 to 50 years.

2. The infection is an acute typical primary pneumonia.

3. Treatment started before 72 hours after the onset of definite symptoms.

4. Patients should not be allergic or serum sensitive.

5. No other serious organic ailment is present.

6. The sputum is typical and the predominating organism is a Gram positive diplococcus having the morphology of a pneumococcus. It cannot be over-emphasized that when seeing a patient with pneumonia for the first time, it is as important to examine the sputum both microscopically and macroscopically as it is to examine the chest by physical methods or x-ray.

Specific treatment lowers the death rate in bacteremic cases, Type I infections from 64.6 to 31.0%, and Type II infections from 76.2 to 52.9%. These figures were taken from the Massachusetts Pneumonia Study and are in approximate agreement with most of the observers.

Certain avoidable causes for failure in the application of specific therapy are: (1) delay before getting treatment, (2) elapse in time in determining the type of infection, (3) error in typing, (4) inadequate dosage, (5) low potency of the serum, and (6) a too long interval between doses.

Unavoidable causes of failure are: (1) presence of complications, (2) mixed infections with more than one type of pneumococcus or other organisms, notably the hemolytic streptococcus, and (3) the intense severity of the infection may overcome the exhausted patient.

Anti-pneumococcic serum containing heterophile antibody has been marketed. To date, there are not sufficient favorable reports in the literature to warrant its use.

D. Non-specific Protein Therapy

In an infection of such comparatively short duration as pneumonia, the interpretation of this type of therapy is very difficult, unless the injections are given very early in the course of the disease. Cecil concurs with the majority of observers when he states "It is too drastic a form of treatment for routine use." Fatal reactions have occurred.

E. Artificial Pneumothorax was apparently first used in the treatment of pneumonia during the influenza pandemic of 1918-19 by Rood. This type of treatment consists in giving from 1 to 4 injections of from 300 to 500 cc. of air into the pleural cavity of the affected side. The 4 most frequent clinical effects which appear following this are prompt relief of pleural pain, relief of dyspnea, lessened toxicity of the patient, and a critical fall in temperature. The latter, however, is often only temporary. Clear evidence is lacking, however, that the artificial pneumothorax serves to cure the disease. It is recommended in early cases, preferably within 24 hours after onset; also in those cases in which there is persistent and excruciating pleural pain. Patients having a bacteremia do not respond favorably. It is indicated only when the involvement is unilateral. The involved lobes cannot be selectively collapsed and not infrequently it may remain uncollapsed although the normal lobe collapses. Its use is hazardous in the hands of the inexperienced. The most serious objection to its use is that it can detract from the recognition of the type specificity of the pneumococcus so that typing is often altogether neglected or type specific antiserum is not given.

W. Economics

In a series of 99 cases of pneumococcic pneumonia studied in this hospital during a 4½ year period, there were 22 deaths, a case fatality rate of 22.2%. These include 18 cases of pneumococcic pneumonia observed in the Health Service, among which no deaths occurred. The average hospital days of those patients dying was 6.5. The cases recovering were divided into two groups: the

uncomplicated and the complicated. The former remained in the hospital on an average of 16.3 days, the latter (complicated group) remained in the hospital on an average of 36.0 days.

The cases recovering were then divided into 2 groups, those which did not receive antiserum, and those which did. The former group which did not receive antiserum were in the hospital on an average of 24.5 days. The group which received antiserum was then further subdivided into 4 groups.

1. Those who received specific antiserum. The average hospital days for this group was 14.3.

2. Those who received antiserum of a type other than that inciting the infection. The average was 18.1 days per this group.

3. Those who received antiserum, the type of pneumonia, for various reasons having not been determined. The average was 18.1 days for this group also.

4. Two deaths occurred in cases to which the antiserum were given. In one, a Type I pneumococcus was found in the sputum, and 50,000 units of Type I antiserum was given. However, a Type III pneumococcus was recovered in pure cultures from the lungs at postmortem. In the other case, 20,000 units of Type I and II were given. Typing of the sputum later revealed a Type IV pneumococcus. There had been no deaths in this hospital during this period in cases where antipneumococcic serum was given specifically.

The relative importance of pneumonia as considered to other diseases has already been mentioned. The cost of this disease to the individual and the community from the viewpoint of case fatality rate, disabling complications, and working days lost are not to be dealt with lightly. Rapid strides in the treatment of this disease have been made with the development of antiserum and more are to follow. Diphtheria antitoxin is now available to all. It has already been suggested (Massachusetts Pneumonia Study) that antipneumococcic serum can be made available to all people. Laboratories equipped to do rapid accurate typing can be established at selected hospitals which would carry out all typings within a definite radius. The study of pneymonia in Massachusetts has already demonstrated that the treatment of pneumonia by specific therapy can be carried out by the general practitioner. Consequently, such a suggestion merits consideration.

Impressions

1. Pneumococcic pneumonia is an acute specific infectious disease incited by the pneumococcus of which 32 distinct types have thus far been isolated and identified.

2. Three substances with distinct antigenic properties have thus far been isolated from the pneumococcus. From the capsule has come a polysaccharide which varies slightly in its composition according to the type of organism. From the bodies of the bacteria has been isolated a protein material similar in its antigenic properties in all types of pneumococcus. The third substance is still being investigated.

3. Man apparently has some degree of immunity to pneumococcic infection.

4. Pneumococcic pneumonia induces only a temporary active immunity. A passive immunity for several types of infection has been accomplished by the intravenous injection of type specific sera.

5. A number of factors play a role in the lowering of resistance against the disease.

   a. Some individuals have a diminished grade of natural immunity.

   b. Upper respiratory infections appear to lower local resistance.

   c. Changes in general resistance may be brought about by chilling, exhaustion, fatigue, exposure, starvation, surgical procedures, etc.

   d. The disease is more common in adult life.

e. Negroes are more susceptible than the white race.

f. Males are more frequently attacked than females due probably to added factors of fatigue, exposure, etc.

g. Pneumonia is more common in the rural districts.

6. The actual mode of invasion of the pneumococcus in man is uncertain. Three theories have been introduced to explain this, none of which explains all observations. They are: (1) hematogenous, (2) bronchogenic, (3) lymphogenic, or broncholymphogenic theory.

7. The sudden onset of pneumonia with chills and fever, resembling the violent reaction following the injection of a foreign protein into a hypersensitive individual, suggests that the question of allergic hypersensitiveness in pneumonia needs further investigation.

8. Pneumococcic pneumonia is a contagious, communicable disease. Although ordinarily endemic, it may take on an epidemic form. Carriers and convalescent patients undoubtedly play an important role in its spread.

9. During the course of the disease, the 4 well-known stages of engorgement, red hepatization, gray hepatization and resolution occur in the lungs. During the latter stage, the digested exudate is absorbed by the blood, not coughed up.

10. The left lower lobe is most frequently involved, followed in close order by the right lower and right upper lobes.

11. The incubation period varies from a few hours to (seldom) more than 48 hours.

12. The disease is characterized clinically by sudden onset with chill, pleuritic pain, increased respiratory rate, high temperature, and cough with the expectoration of rusty tenacious mucopurulent sputum. The disease itself is limited, and in favorable cases terminates abruptly, or by a step-like descent of temperature beginning as a rule from the 7th to the 9th days.

13. The course of the disease varies somewhat according to the type of pneumococcus inciting the infection.

14. Invasion of the blood stream occurs in from 25 to 33% of patients ill with pneumococcic pneumonia. The presence of a bacteremia always renders the prognosis more grave.

15. The diagnosis is not, as a rule, difficult. It is very important to examine the sputum, both macroscopically and microscopically, at the time of the first visit to the patient.

16. Typing of the sputum should be done whenever possible in every case. Facilities for rapid accurate typing of the sputum are becoming quite generally available.

17. In the differential diagnosis, one must exclude: acute pleuritis or pericarditis with effusion, infarct of the lung, acute massive collapse, acute tuberculous pneumonia, appendicitis and cholecystitis.

18. Pneumonia must always be regarded as a serious infection, and changes may suddenly occur for better or worse. Predictions regarding the outcome are unsafe.

19. The more common complications are: empyema, meningitis, phlebitis, pericarditis, and endocarditis.

20. Antiserum appears to have slight, if any, effect in reducing the number of complications, or in the treatment of complications.

21. Undue apprehension regarding the hazards of specific serum therapy is all too prevalent. If the proper precautions are taken, this hazard is very small.

22. Before giving serum, the history of the patient as regard allergic manifestations should always be carefully elicited. He should also be tested for sensitivity by the conjunctival or intradermal tests, or both. One should also inquire carefully in regard to previous serum injections.

23. Attempts to densitize a sensitive person are of uncertain value and are often accompanied by accident.

24. The serum should always be given intravenously. Intramuscular or subcutaneous injections are of doubtful value.

25. The serum should be warmed to body temperature before giving. (Do not heat.) It should be administered very slowly, and the concentrated (Felton) serum cannot be diluted with normal salt solution without the formation of a precipitate.

26. The required dosage of anti-pneumonococcic serum is unknown, and varies with each case. In general, 60,000 to 100,000 units are required for Type I infection, and 100,000 to 140,000 units for Type II. For Type V and VIII infection, 60,000 to 120,000 units or more may be necessary.

27. The first dose should be small and given very slowly. The following doses are best given at 2 to 4 hour intervals.

28. If there is no response to treatment within 72 hours, the administration may be discontinued.

29. Mild or severe allergic reactions may occur. The former, although annoying, are not serious, and do not contra-indicate further antiserum. The severe or shock-like allergic reactions may be reduced to a very small minimum if all the precautions are carefully followed.

30. An abundance of statistics from well controlled material has accumulated so that the value of specific serum therapy in pneumonia needs no reiteration.

31. Where typing facilities are not available, the use of Type I and Type II bivalent antiserum is justified when the infection occurs in young, previously healthy adults who do not demonstrate an allergic hypersensitiveness or have other serious organic disease; when the pneumonia has a typical acute onset and when specific antiserum is started within 72 hours after onset.

32. Certain avoidable causes for failure in the application of specific therapy are:

1. Delay before beginning treatment.
2. Errors in typing.
3. Inadequate dosage.
4. Low potency of the serum.
5. A too long interval between doses.

33. Unavoidable causes for failure are:

1. Presence of complications.
2. Mixed infection.
3. The intense severity of the infection itself.

34. There is not sufficient evidence at this time to warrant the use of heterophile antibody.

35. Non-specific foreign protein therapy is "too drastic a form of therapy for routine use."

36. The use of artificial pneumothorax in experienced hands is indicated in selected early cases of unilateral involvement. Its use does not warrant disregarding typing of the infection or the failure to administer type specific antiserum.

37. Pneumonia, being the 3rd most common cause of death in the registration area of the U. S., presents a definite economic problem. In Massachusetts, Types I and II antisera have been made available to all. Adoption of a similar plan in other states merits consideration.

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II. LAST WEEK

Date: March 12, 1936

Place: Recreation Room, Nurses' Hall.

Time: 12:15 to 1:23

Program: Movie: Plant Traps
Carcinoma of Thyroid

Present: 100

Discussion: B. A. Watson
L. G. Rigler
R. W. Koucky
O. H. Wangensteen
Martin Nordland
K. W. Stenstrom

Gertrude Gunn,
Record Librarian.

III. MOVIE

The Management of Pneumonia,
Edward F. Roberts, M.D., Ph.D.
Courtesy of Lederle Laboratories Inc., 30 Rockefeller Plaza, N.Y.

IV. NEXT WEEK

No meeting Thursday, March 26. Spring Vacation.

Meeting April 2nd sponsored by the Department of Dermatology.
Guest: Paul O'Leary, Mayo Clinic.