

THE RELATION OF NATURAL HUMORAL ANTIPNEUMOCOCCAL IMMUNITY TO THE INCEPTION OF LOBAR PNEUMONIA

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Further progress in our understanding of lobar pneumonia in man not improbably depends to a great extent upon the determination of those conditions necessary for the inception of the disease, concerning which information is at present scarcely more than speculative. While the implantation of pathogenic pneumococci* by inhalation is presumably essential for the production of the pneumonic lesion, it does not seem likely that this is usually the deciding factor, for the reason chiefly that contact infection occurs so infrequently. Protection from infection may be due in part to the barrier interposed by the devious channels of the upper respiratory tract to the passage of the pneumococcus-containing droplets, but when the concentration and fineness of the droplets is sufficient, some of them reach the lung, as can be shown experimentally. Disturbed function of the respiratory tract accompanying mild infection of the upper or lower respiratory passages or following operations, especially on the upper abdomen, precedes the onset in a considerable percentage of pneumonia cases. In others with an antecedent chilling a general alteration in susceptibility may possibly take place as well. However, for those numerous instances in which pneumonia occurs suddenly during a period of apparent normal health another explanation must be sought.

Blake and Cecil's work on the experimental production of the disease in monkeys (1) suggests that in order to initiate lobar pneumonia it is

* Since pneumococci even of low virulence are capable of causing pneumonia under certain conditions provided they are "S" producing, it seems proper to term all such pneumococci as pathogenic.

only necessary to implant in the lungs a sufficient number of pneumococci of adequate virulence for the animal. In their experiments the number of organisms employed was very small. But other authors (2), working with dogs which possess much higher natural antipneumococcus immunity than the species of monkeys used above, have found that the simple intrapulmonary implantation of pneumococci either failed to cause pneumonia or produced the disease only if used in quantities enormously greater than could possibly occur in the natural acquisition of the disease in man. Is the difference in the ease with which lobar pneumonia can be induced in these two animal species due simply to their relative susceptibility to pneumococcus infection?

A previous study on the resistance of normal human beings to recently isolated strains of pathogenic pneumococci (3) has indicated that as a group they possess considerable natural immunity to these organisms as shown by the pneumococcus-destroying power of their blood which in degree is not much below that of the dog. But individuals were found to vary greatly in their reaction toward the several types of pneumococci. This ranged from marked killing power of the blood for one type to none against others. The fluctuations in antipneumococcus action were found to reside in the serum, not in differences in the leucocytes. These findings indicated the feasibility of securing further information about one of the factors which is possibly concerned in the inception of lobar pneumonia, namely the amount of circulating specific antipneumococcus substances at the onset of the disease.

Methods

The pneumococcal tests with human serum and leucocytes were carried out as previously described (4, 5). Serum samples were secured from the patient on admission and daily thereafter throughout the course of the disease. These were kept in an atmosphere of CO₂ at 4°C. and all were tested at one time.* Frequently in early cases the serum was tested as soon as the homologous pneumococcus was isolated. In every instance the experiments were performed with the organism isolated from the patient's lung, blood or sputum, and a control consisting of the pooled serum of four to seven normal individuals was run at the same time. The smallest amount of pneumococcus suspension used was 10⁻⁷ in all but cases V. C.

* Serum preserved in this way showed no deterioration in its pneumococcal-promoting properties for a period of 6 to 7 days.

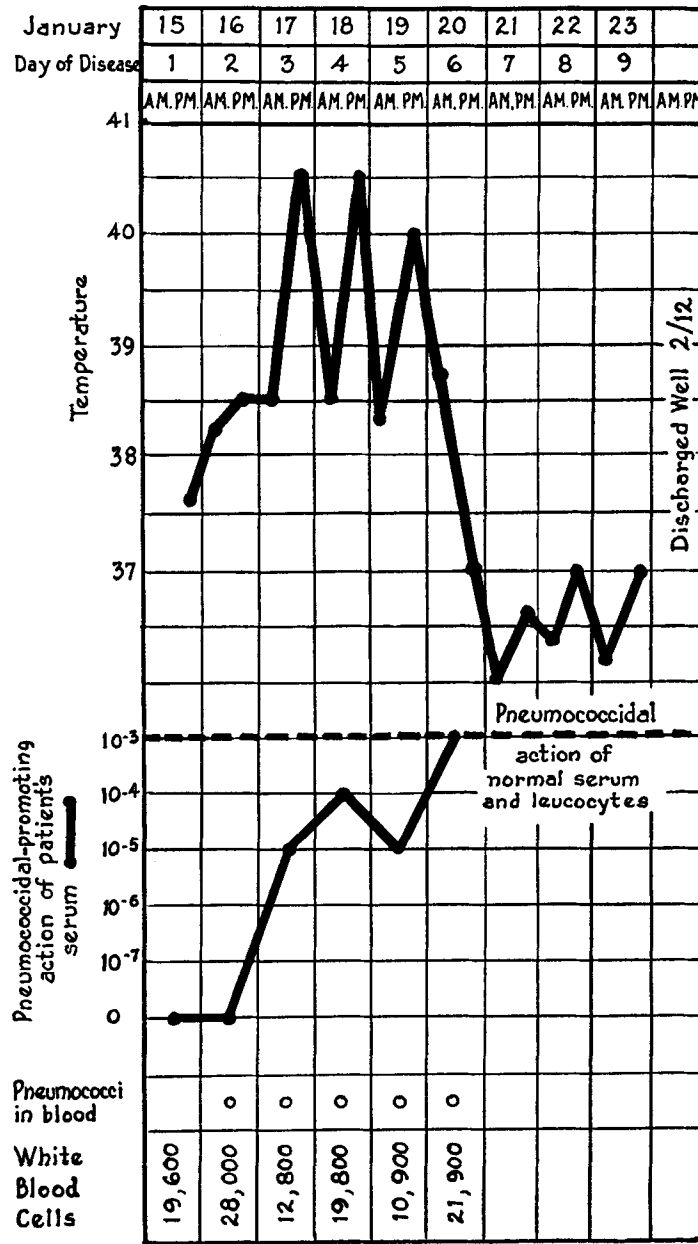
and H. F. P. in which 10^{-8} was employed. Quantities less than 10^{-7} not infrequently led to irregularities in the test. In a number of cases the opsonic and mouse protective properties of the serum were determined also. In almost all instances the tests were repeated in order to verify the results. Blood cultures were taken in the usual manner, 6 to 10 cc. into broth and 1 cc. and 2 cc. into plates.

Clinical Cases

The present study comprises twelve cases of lobar pneumonia in whom observations were begun from 4 to 48 hours after the onset of the disease. The antipneumococcus properties exhibited by the serum within this period may be considered with a fair degree of certainty as referable to the class of natural immune substances, since acquired immune bodies have not been observed by us to develop before the third day of the disease.* The results of the tests as summarized in Table I revealed the unexpected finding that in the majority of cases the initial serum specimens possessed pneumococcal-promoting properties, sometimes slight and again as great as in normal individuals.** In only four cases was this property absent. The possibility that an organism other than that causing the disease was responsible for the serum differences, and in particular the exhibition of well marked antipneumococcus properties, is excluded by the fact that pneumococci isolated from the lung and blood stream in certain cases were affected to as pronounced a degree as were the organisms obtained from the sputum in others. Nor did the virulence of the pneumococcus strains appear to bear any relationship to the action on them of the patient's serum. Organisms against which one patient's serum-leucocyte mixtures showed marked killing action were fully as virulent when tested by animal inoculation and growth capacity in normal pooled human serum and leucocytes, as were those on which another patient's serum had no effect. That is, the variations appeared to reside in the individual rather than in the several pneumococcus strains. Again, the initial pneumococcal-promoting properties of the serum could not be associated with the extent of the lung lesion, as determined by

* As will be shown in a succeeding communication, acquired humoral immunity does not usually occur before the fourth or fifth day of the disease.

** By normal degree is meant the pneumococcal-promoting action of pooled normal human serum for the particular pneumococcus in question.



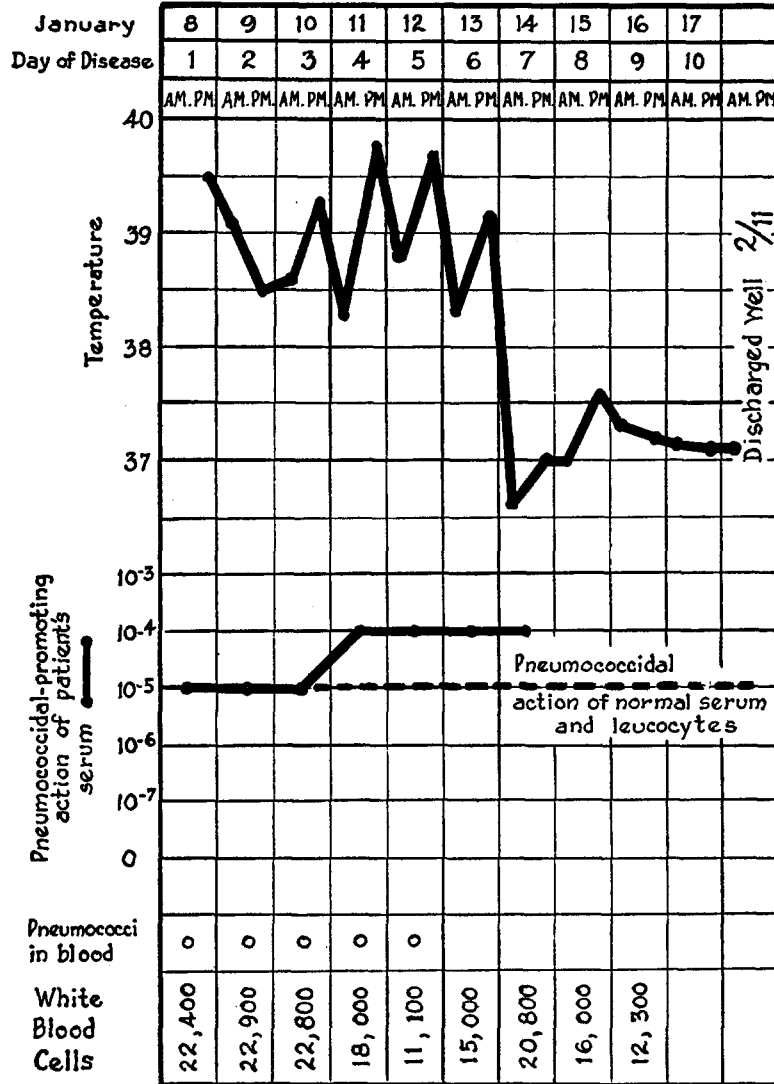
TEXT-FIG. 1. Case A. L., lobar pneumonia—Pneumococcus Type I.

X-ray and physical signs. Both cases A. L. and J. T. A., in whom a very small lesion existed at the time of the first observations, showed no pneumococcus immune properties in the blood serum. On the other hand, patients K. H., V. C. and H. F. P. showed lesions of considerable extent and a normal or at most a slight reduction in degree of pneumococcus-killing power in their blood. The number of cases is far too limited to permit of any conclusions in relation to pneumococcus type.

With the progress of the disease, changes in the pneumococcal-promoting action of the serum usually followed one of several fairly regular courses. When antipneumococcus properties were not demonstrable at the beginning, none appeared until the onset of acquired immune-body production. Case A. L., Text-fig. 1, is an example. There were a number of other patients concerning whom data are not given in these tables (since observations were not begun until after 48 hours) whose blood serum exhibited the same findings.* In contrast were patients such as case K. H. (Text-fig. 2), who showed a well marked degree of pneumococcal-promoting serum power all through the disease. A third course is shown by case V. C., Text-fig. 3. Following an initial normal titer of antipneumococcus properties there occurred a progressive and sometimes very rapid disappearance of the serum effect which did not reappear unless recovery took place. Of course all the patients studied did not fit exactly into these three categories, case H. C., for example, being an exception but they could practically all be classified as modification of one of them.

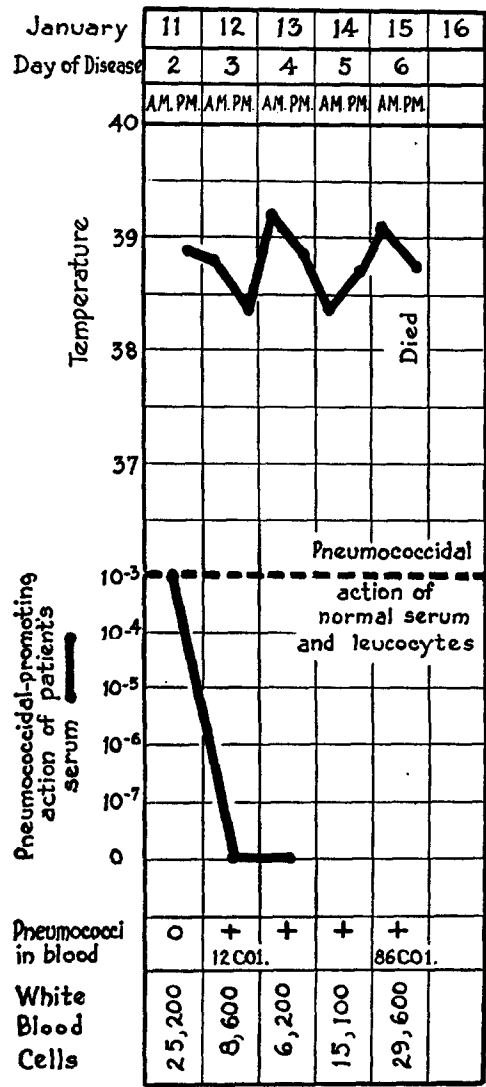
A constant relationship was found to exist between the concentration of immune properties in the serum and blood invasion. In the presence of a killing power of the serum and leucocytes represented by the destruction of as small an amount as 10^{-6} of the standard pneumococcus suspension, pneumococci were not found in the blood stream. When pneumococcal action fell below this point blood invasion tended to occur. That it did not always occur even when antipneumococcus properties were not demonstrable in the serum may be taken as an indication that a modicum of this action still persisted. Indeed when the tests were carried out with numbers of pneumococci as few as 10^{-8} of the suspension (containing actually less than 10 pneumococci)

* The details of the studies on these patients will be given in a following communication.



TEXT-FIG. 2. Case K. H., lobar pneumonia—Pneumococcus Type III.

a residuum of pneumococcus-killing power was sometimes found to persist even in the presence of an increasing blood invasion, as in the instance of case H. F. P. Probably other factors participate in con-



TEXT-FIG. 3. Case V. C., lobar pneumonia—Pneumococcus Type III.

trolling the penetration of pneumococci into the blood channels, such as the degree and perhaps nature of the cellular reaction in and surrounding the pneumonic lesion, but the pneumococidal action of the blood would seem to be the one of chief importance.

Because of the observations of other workers who have studied the immune properties of the serum during lobar pneumonia by means of mouse protection, a word should be said concerning the relative sensitiveness of the pneumococidal reaction as carried out in the present investigation and the mouse test. A comparison of these two techniques on the same serum specimens has shown the pneumococidal test to be the more sensitive. A serum which causes killing of pneumococcus in the serum-leucocyte mixture in quantities as large as 10^{-5} and 10^{-6} of the standard suspension will often fail to cause protection of mice against amounts greater than 10^{-7} of the same suspension or exert no protection at all. Hence it is not surprising that most workers have failed to find mouse protective properties in the serum during any but the later stages of the disease or have found them only to a degree that seemed negligible on account of the individual variations exhibited by mice.

DISCUSSION

The findings at once suggest the question, does the presence of pneumococidal properties in the blood after the onset of the disease indicate that they were there just prior to or at the inception of the pneumonic process. While no direct answer can be given, observations on the experimental disease in animals and on human beings with pneumonia afford data for certain assumptions in the affirmative. Marked and rapid fluctuation in the degree of natural pneumococidal activity of the blood has not been noted in either man or animals during health or in disease. In the experimental animal, as one of us has shown (6), a generalized pneumococcus infection is accompanied by a pronounced and progressive diminution in circulating antipneumococcus immunity which does not reappear until the development of acquired immune substances occurs coincidentally with recovery. However, when the pneumonia process is localized as in experimental lobar pneumonia, the natural humoral immune bodies tend to persist with little diminution throughout the course of the disease. Blood

samples taken immediately before infection is initiated show a normal pneumococidal action. Tests on pneumonic patients indicate that once a marked decrease or disappearance of the antipneumococcus properties of the blood has occurred they do not show an increase again until shortly before or at the time of recovery.

Other workers have also observed evidence of natural antipneumococcal immunity early in the course of lobar pneumonia. Park and Cooper (7) found in more than a third of pneumonia patients they studied appreciable mouse protective action of the serum on the second day of the disease. In a paper just published Ward (8) states briefly that he found the defibrinated blood of pneumonic patients early in the disease to possess a normal pneumococidal action against the causative organism. Details of the cases and tests are not given.

If pneumonia can develop in the presence of a normal circulating antipneumococcus defense mechanism, as seems evident from the above observations, what is the actual mechanism of infection? The most reasonable explanation would seem to be that local changes take place of such nature as to provide conditions for the growth of the pneumococci while protecting them from the pneumococidal action of the blood. There might conceivably be failure of the normal eliminatory mechanism, tissue injury by concurrent infection, allergic reactions, or a combination of these factors. Once pneumococcus growth is established, and perhaps this may be entirely within the lumen of the bronchus—the constant diffusion of bacterial metabolic products in a circumscribed area would produce increasing tissue injury, one of the results of which has been shown to be deposition of fibrin in the capillaries and lymphatics. This would tend further to protect the pneumococci from the full action of the circulatory immune bodies. How early and to what extent the impairment of the circulation occurs in lobar pneumonia in man is not definitely known. The experimental observation of Kline and Winternitz (9), however, would suggest that it takes place early in the disease course and becomes pronounced as the lesion progresses.

The hypothesis has recently been put forward by Coryllos and Birnbaum (10) that lobar pneumonia is initiated as a result of extensive atelectasis produced by occlusion of a large bronchus. In order that the condition may occur the mucous plug must exclude

completely the passage of air and persist for some time. Pneumococci distal to the plug are thus protected from elimination. It is not our desire to enter upon a detailed discussion of this view,* but it should be pointed out that certain of the assumptions upon which the hypothesis rests are not generally supported by clinical evidence. According to Coryllos and Birnbaum, the early signs of the pneumonic lesion are found at the periphery where atelectasis occurs first, the exudative process extending progressively from the hilum to the periphery. As a matter of fact, X-ray studies in the early part of the disease show, in a large percentage of cases of lobar pneumonia, a shadow confined to the hilum which gradually spreads out to the periphery as the disease evolves. Furthermore, in none of our early cases have we found evidence of atelectasis on the affected side either by physical signs or X-ray. However, aside from the question of atelectasis and complete plugging of a bronchus, a local failure of the normal eliminatory mechanism (implied in the hypothesis of Coryllos and Birnbaum) which leads to stasis of bronchial secretion might provide, as suggested above, the environmental state necessary for effective action of the implanted pneumococci.

The rôle played by the natural circulatory immune bodies in the process of localization would seem to be to destroy pneumococci at the periphery of the lesion, thus retarding the spread of the process and limiting or preventing blood invasion. With an initial marked reduction or absence of these humoral immune factors in the presence of an infecting organism of high virulence a rapid spread of the pneumonic process and a generalized infection might be expected to occur. Whether patients such as case J. V., who died within 48 hours of an overwhelming infection were deficient in natural antipneumococcus substances at the inception of infection, can only be surmised until further data are available, but the sequence of events would suggest that such was the case.

SUMMARY AND CONCLUSIONS

A study of the pneumococcal-promoting action of the serum of lobar pneumonia patients, secured from 4 to 48 hours after the onset of

* The subject will be considered fully in a subsequent communication on the production of experimental lobar pneumonia.

the disease, has revealed the fact that in the majority of instances the serum possessed the power to promote killing of the homologous pneumococcus, isolated in different instances from the lung, blood, and sputum. While in some instances this action was slight, in others it was present to as great a degree as in normal individuals and persisted as long as 48 hours or more after the beginning of the disease. The variations observed from case to case were not related to the extent of the pneumonic lesion or to the virulence of the several pneumococcus strains but appeared to depend on differences in individual human beings in respect to the natural antipneumococcus properties of their blood and their reaction to the invading microorganism. A constant relationship was found to exist between the concentration of immune properties in the serum and blood invasion. In the presence of a well marked pneumococidal-promoting power pneumococci were not found in the blood stream, and only when this property was greatly diminished or lost did blood invasion occur.

The findings which are supported by certain previous experimental observations, indicate that lobar pneumonia can occur in the presence of a normal circulating antipneumococcus defense mechanism. From this it is inferred that before pneumococcus growth can be initiated there must be present in the lung local changes of such nature as to provide conditions for the multiplication of pneumococci protected from the pneumococidal action of the blood. Suppositions as to the nature of these changes and the establishment of the pneumonic lesion are discussed.

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