PRUDDEN (T.M.)

A STUDY ON THE

ÆTIOLOGY OF EXUDATIVE PLEURITIS

BY

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One of the most striking side lights which recent bacterial studies have thrown upon disease has made it evident that certain pathogenic micro-organisms, although usually associated with some special form of disease whose lesions they dominate and more or less distinctly characterize, are yet capable under a variety of conditions of causing less well defined and less distinctive forms of inflammatory lesions. Thus, while the action of the tubercle bacillus is most characteristic in the development under its influence of tubercle tissue, we have recently learned that under a variety of conditions it may be markedly pyogenic.

The pneumococcus, too, at first associated solely with the lesions of acute lobar pneumonia, may, as we now see, in addition to or apart from its own proper mischief, determine now an exudative meningitis, now a pleurisy, and again a simple phlegmon. Similar versatility is possessed by the *Bacillus typhosis*, the *Streptococcus pyogenes*, and other pathogenic germs. More striking still are the recent revelations regarding the *Bacillus coli communis*, our universal comrade in health, but capable, as it would seem, when out of place and under abnormal conditions, of exciting serious and even fatal inflammatory processes. The practical bearing of this increase of scope in our knowledge is well illustrated in the recent studies on the ætiology of pleurisy.

Bacteriologic examinations have now been made in so many cases of exudative inflammation of the pleura, that

our knowledge of its ætiology rests in large part upon a definite and firm basis, while much light has been thrown upon its prognosis and some upon certain phases of its treatment.

The general results of these bacteriologic studies may be formulated in a variety of ways. It is most common, however, to divide the cases of pleuritis into two classes, dependent upon the morphological characters of the exudate—first, those in which the exudate is serous or sero-fibrinous; and second, those in which it is purulent—and record the results of the examination of these separate classes. It is evident that the line of demarcation between these two forms of exudate is not a sharp one, and that sometimes one may appropriately recognize a sero-purulent exudate, and, further, that any form of exudate may be more or less mixed with blood—hæmorrhagic—or may be decomposing and putrid.

Previous Studies.—The most extensive study and analysis of cases has been made by Netter.* Important studies with the use of modern technique have also been made by Levy,† Koplik,‡ Prince Ludwig Ferdinand,# Pansini,‖ and others. To these articles I refer the reader for details and a fuller bibliography.

Although different observers differ somewhat in detail, the general results of this long series of studies may be fairly summarized as follows:

Serous Exudates.—The serous or sero-fibrinous effusions in inflammations of the pleura do not as a rule contain bacteria. It is believed by many observers that a large proportion of these sero-fibrinous effusions in which bacteria are not demonstrable are of tubercular origin. Others believe this latter statement to be too sweeping, and are convinced that among the cases of what is commonly diagnosticated as simple acute pleurisy with a sero fibrinous exu-

* Netter. *Extrait des bull. et mém. de la Soc. méd. des hôpitaux de Paris*, 3me série, 6me année, 1889; *ibid.*, Séance du 16 mai 1890. Soc. méd. des hôpitaux, April 7, 1892. *Traité de médecine.* Charcot et Bouchard, tome iv, 1893.

† *Archiv für exp. Pathologie*, etc., Bd. xxvii, 1891.

‡ *Archives of Pædiatrics*, October, 1890.

Deutsches Archiv für klin. Medicin, Bd. l, 1892.

‖ *Giornale internazionale delle scienze mediche*, 1892; *Rev. Centralblatt für allg. Pathologie*, etc., Jan. 15, 1893.

date, a very considerable proportion show no bacteria, and still are not tubercular in origin. This discrepancy in belief is partly due to technical difficulties in the way of bacterial examination for tubercle bacilli, and partly to the lack in most cases thus far examined of such unimpeachable evidence in this respect as the autopsy alone can furnish.

Tubercle bacilli have actually been found in the sero-fibrinous exudate in but very few cases, the tubercular origin having been inferred in most cases from hereditary antecedents and the personal history previous or subsequent to the attack of pleurisy. Clinical data have been thought to indicate * that from forty to eighty per cent. of the so-called "simple" or "essential" pleurisies with sero-fibrinous exudate are of tubercular origin.

Pansini † has emphasized in this connection the importance from the technical standpoint of examining larger quantities of exudate than are obtained by the usual exploratory puncture with the hypodermic syringe and the use of animal inoculations, since without these precautions tubercle bacilli may readily escape observation. His own studies made on large quantities of exudate showed in fifteen sero-fibrinous exudates the tubercle bacillus in six; pneumococcus (*Micrococcus lanceolatus* ‡) in three; streptococcus or pneumococcus in one; and in five no bacteria.

Prince Ludwig Ferdinand, in nine cases of pleurisy with a sero-fibrinous exudate, found in the latter the pneumococcus in two; *Staphylococcus pyogenes* in two; no bacteria in five; four of the negative cases were, however, believed to be tubercular.

Netter concludes, from morphologic studies and inoculations, that the tubercle bacillus is present in at least forty per cent. of sero-fibrinous exudates in pleurisy, and is more common than in empyema.

It evidently is still reserved for further and more extended studies to establish the relative frequency of tuber-

* Fiedler. Ueber die Punction der Pleurahöhle in Herzbeutel. Volkmann's *Klin. Beiträge*, 1892.—Barrs. Remarks on the So-called Simple Pleuritic Effusions. *Brit. Med. Journal*, May 10, 1890.

† Pansini. *Loc. cit.*

‡ *Micrococcus lanceolatus* will be used in this article as a synonym of *Diplococcus pneumoniæ* and pneumococcus—meaning thereby the pneumococcus of Fraenkel and Weichselbaum.

cular inflammation as a causative factor in the sero-fibrinous phases of pleurisy. It is certain that tubercular pleurisy may exist with a sero-fibrinous exudate, and neither the morphological examination nor animal inoculations show the presence of the tubercle bacillus in the exudate.

In a few cases *Staphylococcus pyogenes aureus*, or *albus*, or both, have been found in serous exudates, and it has been shown that exudates containing these germs do not necessarily become purulent. In a large number of cases the *Micrococcus lanceolatus* (pneumococcus) has been found in serous effusions, and its presence does not indicate that the effusion will become purulent, though it may do so. *Streptococcus pyogenes* has been found in a considerable number of simple serous effusions. When present, the exudate is very apt to become purulent, although a few cases have been studied in which it has not done so.* The pneumococcus may be found in serous effusions in association with the *Staphylococcus pyogenes*, or other germs.

In Netter's experience the exudate in metapneumonic pleurisy is more often purulent than sero-fibrinous, his cases showing the proportion of eighteen to four. The results of other observers show less tendency to the formation of pus in the presence of the *Micrococcus lanceolatus*.

It would thus appear that, while the sero-fibrinous exudates in inflammation of the pleura do not, as a rule, show the presence of bacteria, they may contain either the *Micrococcus lanceolatus* or *Streptococcus pyogenes*, or, more rarely, *Staphylococcus pyogenes*, and that, when these germs are present either alone or in association, the exudate may—though it does not always—continue sero-fibrinous; but that when the *Streptococcus pyogenes* is present, it is apt to become purulent. Further, sero-fibrinous exudates containing no bacteria may, in a considerable but not yet definitely determined proportion of cases, be associated with tuberculosis.

Purulent Exudates.—Purulent exudates, as a rule, contain bacteria. The bacteria most commonly found in purulent exudates are the *Micrococcus lanceolatus* (pneumococcus), *Streptococcus pyogenes*, *Bacillus tuberculosis*, *Staphylo-*

* Goldscheider. *Zeitschrift für klin. Medicin*, Bd. xxi, Heft 3 und 4, p. 363, 1892.

coccus pyogenes, and these in varying associations. The typhoid bacillus has been found in empyema accompanying typhoid fever; but under these conditions the *Staphylococcus pyogenes* may be found, or may alone be present.*

The tubercle bacillus may be associated with one or other of these germs. The *Staphylococcus pyogenes* was found in Netter's analysis of one hundred and fifty-six cases of empyema twenty-one times, in fifteen of which it was associated with other pathogenic forms. The *Streptococcus pyogenes* and the *Micrococcus lanceolatus* are the germs most frequently found in purulent pleuritic exudates. Various forms of saprophytic bacteria have been found in putrid purulent exudates alone, or in association with the ordinary pyogenic germs.

The relative frequency with which the more common forms of pathogenic bacteria occur in empyema it is yet too early to definitely state.

Koplik † found, in twelve cases of empyema in children, the *Micrococcus lanceolatus* in seven; *Streptococcus pyogenes* in three; *Staphylococcus pyogenes aureus* in one; *Bacillus tuberculosis*, with streptococcus, in one.

Pansini ‡ found in eight cases of empyema *Micrococcus lanceolatus* in two; tubercle bacillus in two; *Streptococcus pyogenes* in one; *Staphylococcus pyogenes* in one; *Micrococcus lanceolatus*, with the tubercle bacillus, in one; and in one case no bacteria at all.

Ludwig Ferdinand # found in twelve cases of empyema *Micrococcus lanceolatus* in two; *Streptococcus pyogenes* in five (two fatal); tubercle bacilli in two (both fatal); *Micrococcus lanceolatus* and streptococcus in two (one fatal); streptococcus with *Staphylococcus pyogenes* in one.

Netter's ‖ analysis of one hundred and nine cases of empyema shows that the *Streptococcus pyogenes* was present in about forty-four per cent., the pneumococcus in about twenty-six per cent., streptococcus and pneumococcus associated in about three per cent, *Staphylococcus pyogenes* in about two per cent., while the remaining twenty-five per

* Weintraud. Ein Fall von Typhus-Empyem. *Berliner klin. Woch.*, April 10, 1893. Levy, *loc. cit.*, p. 374.

† *Loc. cit.* ‡ *Loc. cit.* # *Loc. cit.*

‖ *Traité de médecine.*

cent. were tubercular in origin or putrid, the latter form being comparatively infrequent.

While the streptococcus appears to be most frequently present in the empyema of adults, the pneumococcus, according to Netter, preponderates in children.

The pus in empyema has been found to contain in scattering cases *Actinomyces*, *Micrococcus tetragonus*, *Bacillus coli communis*, and *Spirochæte denticola*. Various saprophytes have been found, especially in decomposing and foul-smelling exudates.

The figures of Netter show that empyema, aside from the cases which are tubercular or putrid, is associated with pneumonia in about 43·75 per cent. of the cases. When thus associated the pneumococcus is present and found alone in the majority of cases. It may, however, be associated with *Streptococcus pyogenes*, *Staphylococcus pyogenes*, and the *Bacillus pyocyaneus*, while various saprophytic forms have been found.

Empyema with pneumococcus in the exudate may occur without evident association with lobar pneumonia.

It is evident, from this *résumé* of observations upon the bacteria present in inflammatory pleuritic exudates, that a very solid basis of fact is already laid for an understanding of the ætiology of the inflammations of the pleura. Our knowledge of the action on the body of the pathogenic germs most commonly found in the exudates — namely, the pneumococcus, the streptococcus, the tubercle bacillus, and the staphylococcus—justifies us in the inference that these germs, when present, are largely concerned in inducing the disease and its lesions. It is evidently necessary, however, to examine bacteriologically a great many more cases, so that our knowledge may become still more extended and precise, and our inferences bearing on prognosis and treatment more reliable.

The Writer's Study.—Two purposes were held in view in the bacterial examinations of pleuritic exudates, extending over two years, which this paper records: First, the accumulation of facts regarding the forms of bacteria present in the exudates; and, second, the determination whether or not a systematic morphologic and biologic examination of pleuritic exudates drawn for this purpose

promised to be useful in the routine study and treatment of patients suffering from either sero-fibrinous pleurisy or empyema.

Technique. — Bacteriologic examinations of pleuritic exudates have been made in such large numbers and under such various conditions that we know the "experimental error" to be rather large and of considerable significance. It has been frequently shown, for example, that the examination of a small portion of the exudate drawn in the usual way by the hypodermic syringe may give a negative result both in the morphologic and biologic analysis, while a larger quantity may show the presence of living germs. Under the ordinary conditions of research, then, the larger the quantity of exudate which can be subjected to study by sedimentation and the use of the centrifugal machine, the better. In the present study, however, it was thought best to limit the quantity of exudate examined to the few cubic centimetres or less which the usual exploratory puncture gives, since one main purpose of the work was to learn the limitations and value of such a method. Furthermore, we have always to remember that in exudates examined with negative results, the germs may have been present, but are now dead, and so fail to grow, and that they may be so disintegrated as to escape detection by the morphologic examination. While this condition is probably not of frequent occurrence, its possibility should be borne in mind and both morphologic and biologic methods in all cases practiced. The pneumococcus is especially prone to die early.

The exudates were in all of my cases examined morphologically—first, for the presence of the tubercle bacillus; and, second, for other germs. The routine staining for the latter purpose was with an aqueous solution of fuchsin or Loeffler's alkaline methylin blue. In the latter half of the studies a special staining for the pneumococcus was made in all cases by Welch's method,* which I find of the great-

* This method consists in treating the exudate, dried on the cover glass in the usual way, with glacial acetic acid, which is at once drained off and replaced by analin-gentian-violet solution, this being drained off and renewed several times until the acetic acid is displaced. The specimen is now washed with a two-per-cent. salt solution in which it may be

est value in doubtful cases. Cultures were made on Petri's plates on glycerin agar, and the growing forms identified in the usual way by their morphologic, biologic, and, when necessary, pathogenetic characters.

Number and Character of Cases Studied.—I record here the result of the morphologic and biologic examination of *forty five cases of exudative pleuritis.** A very brief *résumé* of the results will suffice for the purpose in view in this paper.

Sero-fibrinous Pleuritis, Twenty-one Cases.—These may be grouped as follows:

1. *Twelve cases of simple uncomplicated sero fibrinous pleuritis*, all giving in general the story of an acute attack, usually after exposure, with chill, pain in the side, fever, and the usual physical signs of pleural effusion. *In none of these cases did the exudate reveal bacteria of any kind* either by the morphologic or biologic examination. Seven of these cases were aspirated, the remainder not. All ended in complete recovery.

2. *Six cases of sero-fibrinous pleuritis accompanying or immediately following acute lobar pneumonia* (metapneumonic sero-fibrinous pleuritis). In these six metapneumonic cases the exudate in two only revealed the presence of the *Micrococcus lanceolatus*. The others were sterile. Four of the cases recovered; two died, one from acute endocarditis, one from pericarditis. Neither of these fatal cases were the ones in which the pneumococcus was found in the pleural exudate. Unfortunately, cultures were not made from the heart lesions after death.

3. *Three cases of sero-fibrinous pleuritis in which there was clinical evidence of tuberculosis of the lungs.* In all of these three tubercular cases the exudate was sterile and the tubercle bacillus was not found by staining. These cases were all discharged from the hospital improved.

Empyema, Twenty-four Cases.—These may be grouped as follows:

studied. For further details and the rationale of the method, consult Welch, The Micrococcus lanceolatus, etc., *Johns Hopkins Hospital Bulletin*, December, 1892, p. 128.

* I am greatly indebted for the material used in this study to Dr. Walter James, and to Dr. James Ewing, resident physician to the Roosevelt Hospital.

1. *Eight cases of simple empyema*—that is, cases not associated, so far as could be learned, with any other disease of the lungs or septic process elsewhere in the body.

In these eight cases of simple empyema the exudate showed the presence of *Streptococcus pyogenes* in seven, of the *Staphylococcus pyogenes aureus* in one. These were revealed in every case both by the microscopic examination and by the cultures.

Of the seven streptococcus cases five died; four of these were aspirated; in one, resection of a rib was performed. The remaining two of the streptococcus cases recovered after resection. The staphylococcus case recovered after aspiration.

2. *Eleven cases associated with acute lobar pneumonia* (metapneumonic empyema). Of these eleven cases of metapneumonic empyema, the exudate in nine contained the *Micrococcus lanceolotus* and no other germs. In one the *Streptococcus pyogenes* and in one the *Staphylococcus pyogenes aureus* were alone present.

In the nine cases of this group in which the history is complete, there were seven recoveries and two deaths. Both of the fatal cases were associated with the pneumococcus, and in both was a portion of rib resected. In the seven cases which recovered resection was done in four; three of these were pneumococcus cases, one due to streptococcus. In the cases recovering after simple aspiration two were pneumococcus cases; one was associated with the *Staphylococcus pyogenes aureus.*

3. *One case of empyema associated with pulmonary tuberculosis.* The cultures from this exudate gave a negative result, but very large numbers of tubercle bacilli were revealed by the microscopic examination and no other germs. This case was fatal.

4. *Four cases in which the exudate was fœtid.* In the four cases of fœtid empyema—all fatal—the examination showed in each several forms of bacteria, mostly bacilli, which were not identified. In one only was the *Staphylococcus pyogenes aureus* mingled with the other forms.

Summary.—*In the writer's twenty-one cases of sero-fibrinous pleuritis the exudate revealed bacteria in only two, and*

in these two cases, which were associated with acute lobar pneumonia, the pneumococcus was the only germ found.

In the writer's twenty-four cases of empyema the exudate revealed bacteria in all. In the cases of simple empyema the germ most commonly present (in seven out of eight) was the Streptococcus pyogenes. In the cases of metapneumonic empyema the germ most commonly present (in nine cases out of eleven) was the Micrococcus lanceolatus (pneumococcus). In the four cases of fœtid empyema various forms of bacteria, mostly bacilli, were found; only once was the Staphylococcus pyogenes aureus present. In the one case of tubercular empyema the tubercle bacillus was alone present.

The mortality in the cases of streptococcus empyema was much higher than in those associated with the pneumococcus —five out of eight having died when streptococcus was present, while only two out of eight died when the pneumococcus was present—and in both of these latter fatal cases there was an acute inflammatory heart complication.

Remarks.—These studies would seem to justify more than most of those already published on the same theme, a belief in the comparatively frequent occurrence of a simple exudative pleurisy with sero-fibrinous exudate which is not tubercular and not demonstrably associated with bacteria of any kind, and bearing a more favorable prognosis than any other form of exudative pleural inflammation.

So far as these studies go, they would tend to confirm the belief that the prognosis in cases in which bacteria are present in the exudate is, as a rule, most favorable in the metapneumonic serous exudates and in the serous exudates which contain only the staphylococcus.

These observations are furthermore in accord with the belief that among the empyemas the prognosis is most favorable in the metapneumonic and staphylococcus forms, less so in the primary streptococcus form, and least in the fœtid cases.

It would seem certain that whenever it is practicable a microscopic and biologic examination of a small portion of the exudate, drawn when necessary for the purpose, promises to afford the practitioner valuable hints as to his wisest further procedure. While more accurate results may no doubt be reached by the examination of large quantities of the exu-

dates, it would seem from these studies, as well as from a large number of those which have preceded them, that for routine purposes the use of a few cubic centimetres of exudate, or even less, is capable of giving very useful data.

It is obvious that a combination of the microscopic and biologic examinations is highly desirable in all cases and indispensable in most cases for the determination of bacterial species. On the other hand, the number of species which play the most important part in determining these pleural exudates is limited and largely confined to the pneumococcus, the streptococcus, the tubercle bacillus, and the staphylococcus, so that very often the simple microscopic examination alone of stained specimens gives valuable data.

In this series of studies, in which both microscopic examinations and cultures were made in every case, only twice did the microscopic examination give a negative, when cultures gave a positive result. Three times only, on the other hand, did the cultures fail to elicit a growth of forms which the morphologic examination had shown to be present, and in each of these three cases the germ involved was the *Micrococcus lanceolatus*, which is short-lived and vulnerable and prone to die in exudates as it is in cultures.

So far as they go, the results of this study would seem to confirm the opinion widely held and based on similar studies which have preceded this—namely, that when pleural exudates, either serous or purulent, are found to contain the *Streptococcus pyogenes*, the question of suitable operative procedure is more important and urgent than if the pneumococcus or the staphylococcus alone be present.