PLEURAL EFFUSIONS IN TUBERCULOSIS.

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One of the most important landmarks in the history of clinical pathology is the invention of the exploratory syringe. The honour belongs to Thomas Davies. In his book of "Lectures on the Diseases of the Lungs and Heart," published in 1835, he describes the use of a special small trocar for the purpose. A trocar had been previously used as long ago as 1694 by Dernin for the purpose of evacuating fluid, and Pelletan adopted the improvement of attaching an exhausting syringe to the instrument in 1836. The importance of Davies' trocar, however, was in its use for diagnostic rather than therapeutic purposes. The instrument was a small trocar with a groove along its length to allow the fluid to trickle out. He describes its use as follows:—"The needle being introduced to about three-quarters of its length into the pleuritic cavity determines at once the presence of the fluid, and, what is equally important to the future steps of the operation, its nature; for if it be serous it will pass readily along the groove and trickle down the back of the patient; if it be puriform and thick it will not freely flow, but a thick drop or two will be seen at the external orifice; and on withdrawing the instrument you will find its groove filled with pus." Laboratory examination of the fluids withdrawn was not introduced until 1872 when chemical tests were made by Mehu.

The pleura has a generous blood supply. In the subpleural layer of the visceral pleura is a layer of capillaries derived from the bronchial arteries, whilst in the connective tissue beneath the costal pleura is a plexus derived from the arteries of the thoracic wall, and a third plexus in the subpleural layer of the mediastinal pleura has its origin in the bronchial and internal mammary arteries. In other words the blood supply of the pleura is derived from the left side of the heart and not from the pulmonary artery. As to the veins the only point which needs comment is the arrangement of the terminal portion of the vena azygos major. It hooks forward over the right bronchus to join the superior vena cava at which point it is liable to pressure, though this is a contingency more frequently met with in neoplasm than in tuberculosis. In the latter it is hardly likely to happen unless there is marked enlargement of the group of middle mediastinal glands which cluster round the bronchus.

The lymphatics which drain the pleura are more complicated. Those of the costal pleura drain by way of the intercostal glands, the diaphragmatic lymph plexus and the posterior mediastinal group of glands. It is very important to note that the efferent vessels of all these groups reach the venous system at the junction of the internal jugular and subclavian veins without first passing through the glands at the root of the lungs. The lymphatics of the visceral pleura, on the other hand, pass into the subpleural lymphatics of the lung and reach the root glands direct. Miller states that these lymphatics are so protected by valves that the passage of lymph from them to the deep lymphatics of the lung is prevented.

Histologically two points call for remark, the mesothelial cells which line the sac and the so-called stomata. It is in the nature of things in this life that what we were taught to regard as solid facts become in the process of time something less than reality. Like other details of histological structures in the lung the stomata have disappeared. They do not exist, and there is little doubt that what the early histologists saw and described as stomata were artefacts, created by adventitious gaps in the mesothelial lining. The mesothelial cell of the embryologist is of course the endothelial cell of the clinical pathologist. The latter is an unfortunate name, but it seems to be well embedded in our common jargon of the laboratory. The

term endothelial cell should really be reserved for the lining cell of the vascular system. Perhaps serosal cell would be best for the mesothelial cell of the pleura. At any rate the important fact about it is that it does not phagocyte.

The opportunity to examine a thoracic puncture fluid should never be neglected. The record of laboratory examination may be an important piece of evidence in the history of the patient at a future date. If the tubercle bacillus cannot be found, the cell count and the protein content are the next in importance for establishing the laboratory diagnosis. The predominance of the lymphocyte in the cell count needs no emphasis; it is universally recognised as *prima facie* evidence of tuberculosis, though the cell may also occur in considerable numbers in very chronic transudates of non-tuberculous origin. It is not generally recognised, however, that the polymorphonuclear cell may sometimes predominate in the serous effusion of tuberculosis. This will be referred to later. After the cell count the protein content comes next in importance. The more acute the inflammation of course, the higher the protein content. The amount generally ranges between 3 and 5 per cent., whereas the amount in the transudates of hydrothorax is rarely more than 1.5 per cent.

Recently a good deal of discussion has taken place as to the relative value of Lowenstein's special egg culture medium and guinea pig inoculation in cases in which the ordinary laboratory tests fail to establish the diagnosis of tuberculosis. The Lowenstein medium is an excellent one for the cultivation of the tubercle bacillus, but in my experience it cannot compare with the inoculation test. Even if a dozen culture tubes are sown it is unlikely that more than a total of two or three cubic centimetres of deposit of pleural fluid will be planted, whereas 10 c.cs can be inoculated into a guinea pig without difficulty. My own practice is to use two animals. Not only does this guard against an inconclusive result from premature death of an animal, but the practice enables one to kill one animal early, i.e., three weeks, and to withhold the other for later examination, i.e., 6-8 weeks. If the clinician can afford to wait, I like to leave the second animal for 8 weeks. In an early case of tuberculosis where diagnosis is all important it is better to wait and make quite sure. The advocates of the Lowenstein culture medium claim that a positive result may be obtained from 14 days onwards. If there are enough bacilli in the fluid for this to be done, it ought to be possible to find them by direct film examination, provided the pathologist is prepared to make a patient search. This, of course, involves examining several slides very carefully.

An effusion of clear fluid into the pleural sac may take place at any stage in the course of tuberculosis. It may herald the onset of the illness, intervene in the course of active disease at any stage, complicate treatment, especially collapse therapy, or close the chapter at the end of the long story. And at all these stages the picture is a different one.

Long after the discovery of the tubercle bacillus writers continued to refer to a group of cases presenting no other signs than those of acute pleural effusion as idiopathic. With modern methods of investigation, this term is no longer tenable. The majority of the patients in this class consist of individuals in whom the first sign of tuberculosis is an effusion of fluid into the pleural sac. We do not know how the bacillus reaches the pleura; indeed for many years pathologists failed to find it in the fluid in all but a very few cases. It is not impossible that occasionally the effusion may be a form of primary focus analogous to the Ghon lesion, but the frequency with which the latter is found in the lung immediately beneath the pleura would suggest that an extension from one of these small, often quite inconspicuous primary foci, is generally the cause of the outpouring of fluid into the serous cavity.

When the fluid is removed from the chest with an exploring syringe, it is a pale straw colour and quickly clots in the syringe or the tube into which it is ejected, so that in the latter case the tube can be inverted without spilling the contents. If the clot be withdrawn it is found to be tough and resistant, leaving behind a fluid closely resembling blood serum. As the clot forms it entangles the tubercle bacilli in its meshes, and very few remain behind in the fluid.

I have often thought that this may be the reason why the organism was in former days so very rarely found in pleural exudates. Pathologists discarded the clot and examined only the fluid. The French bacteriologist, Jousset, was one of the first to emphasize the importance of examining the clot; he used an artificial gastric juice for digesting it and found tubercle bacilli in the digest. Since then numerous useful methods have been devised for finding the bacterium in the clot but better than them all is the simple expedient of preventing the clot from forming at all by ejecting the puncture fluid immediately after withdrawal into a tube containing 1.5 per cent. sodium citrate in normal saline in the proportion of 1 part citrate saline solution to 3 pleural fluid. The mixture can then be centrifuged and the films made from the deposit in the usual way. A further advantage of this method is that it enables a satisfactory cytological examination to be made, for if a clot forms it entangles cells in its meshes as readily as bacilli.

But when all these precautions are taken tubercle bacilli are not easily come by in the rapidly formed pleural exudate of the initial stage of pulmonary tuberculosis. In fact it may be stated in general terms that the more acute the illness at this stage of the disease the fewer the bacilli. The toxicity of the fluid may be judged not only by its liability to clot—toxic pleural fluids clot readily—but by the high protein content. As a rule it is in the region of 5 per cent. and the globulin fraction of this is considerable. Toxicity can also be determined by various immunity tests, such as complement fixation and precipitin reactions, but they are laborious to perform and a little uncertain, and are rarely used in the routine clinical pathology of thoracic puncture fluids. The marked predominance of the lymphocyte in the cell count in this type of pleural exudate is well known. The whole question of the association of the lymphocyte with tuberculosis is however rather puzzling. It is a wretchedly poor phagocyte, if indeed it phagocytes at all, and in the histological tubercle it appears late in the field and then as a rule only at the periphery of the lesion. And yet in the acute tuberculous exudate whether in cerebro-spinal, synovial or pleural fluid it is the most striking feature of the cytological picture and has come to be regarded, sometimes a little too hastily, as the pathognomonic sign of tuberculosis in the exudate. Uncomplicated pleural effusion occurring at this early stage in the evolution of pulmonary tuberculosis is not a fatal disease. Consequently we have no post-mortem picture of the disease until extension has taken place.

Moreover the condition is very difficult to induce in experimental tuberculosis in laboratory animals. Repeated attempts have been made, with little success, to produce it by infection of the pleural sac with suspensions of tubercle bacilli and with tuberculous products. But the virus is completely absorbed or the lung is penetrated and an inoculation pneumonia induced which obscures the issue.

Some years ago Petersen, after failing to induce effusions by primary inoculations in rabbits succeeded in doing so by first sensitizing his rabbits. As a result of this work he made the interesting suggestion that a pleural effusion is really a manipulation of Koch's phenomenon. Cooper and Rensch failed to repeat Petersen's results and I have to confess to failure also. Koch's phenomenon

too is not a phenomenon in the natural infection of man, who exhibits a series of phenomena, which obliterate the sharp delineations of the animal experiments.

If no untoward circumstances arise the pleural effusion eventually clears up and the patient passes out of the pathologist's ken. From time to time, however, he picks up the thread of the story again when after a quiescent interval tuberculosis may declare itself in the lung tissue beneath. When this happens, a pleural effusion secondary to frank pulmonary tuberculosis is liable to occur, probably on the other side. This may happen at any stage of the disease and even recur until the pleural sac is finally closed by adhesions.

The post mortem appearances of such effusions have been known for centuries and very little can be added to the classical descriptions of Hunter, Laennec, Hodgkin and other morbid anatomists. The first sign of an inflamed pleura is a change of colour. The mottled pinkish grey colour of the healthy pleura with its thin black wavy lines of pigmented subpleural lymphatics showing through the membrane, turns to a bright pink and then to a deep red as the capillaries branching in all directions beneath the serosal layer dilate with the intensity of the inflammation. The pigmented lymphatic vessels are now obscured and the distended capillaries produce minute hæmorrhages.

Laennec described this picture vividly. It was, he said, as though the membrane had been dotted all over by a brush with an immense number of small spots of blood, very irregular in form and very close together. Occasionally, too, minute grey tubercles can be seen beneath the reddened surface. Then a straw-coloured fluid, like plasma, begins to exude from the membrane which becomes dull and lustreless. The surface is roughened as thin strands separate out from the exudate like fibrin in a thin layer of blood clot, and the strands of this fibrin entangle in their meshes, blood corpuscles, leucocytes and tissue cells. As the exudation continues the fibrin becomes thicker until it forms a shaggy layer which early morbid anatomists called plastic lymph, covering the whole of the inflamed pleural membrane and often closing the interlobar fissure. Eventually this plastic layer, greyish yellow in colour and roughened and honeycombed in texture, forms a false membrane limiting the exudation of fluid which now reaches its height. The pleural sac may be distended to its full capacity, the mediastinum pushed over to the sound side and the diaphragmatic pleura downwards.

The fluid as withdrawn with an exploring syringe differs from that of the primary focus effusion. Usually it does not form a solid conglulum on standing, its protein content is less—generally not above 3 per cent.—and the tubercle bacilli are present in much greater numbers. Immune substances, too, are less as far as we can judge by our rather crude laboratory tests. The lymphocyte still predominates in the cell count. Large endothelial cells are now beginning to make their appearance; polymorphonuclear cells are still very scanty, as they are in the primary focus effusion.

Histologically the inflammation is most marked in the visceral pleura. The endothelium desquamates fluid is poured out and erythrocytes migrate from the capillaries. Large mononuclear cells and lymphocytes are also mobilized within a short time and the fluid covering the pleura begins to organize. The pleura probably never returns to its original virgin condition. Fibroblasts appear in the fibrin and a thin layer of collagenous fibres is formed nourished by new formed capillaries from the subpleural layer. A thickened pleura results. Beneath it in the subpleural lobules are giant cell systems and small caseous areas, with hypertrophy of the small lymphoid collections lying alongside the bronchioles,

collections which are so small in health that they are often overlooked. The presence of these giant cell systems and small caseous areas are probably the result of a hæmatogenous spread just as they are in any other serous membrane such as that of the synovial membrane of a joint.

The stage is now set for the production of the pleural adhesion. As the effusion subsides adhesions, often containing tubercle bacilli and minute caseous nodules form. Furthermore there is yet another event which marks the inflammation of the pleura, the passage of tubercle bacilli into the hilar glands. Snow Miller has shown that beneath the subpleural layer of the visceral pleura is a layer of lymphatic vessels, which do not traverse the lung but pass around the periphery, as a sponge net encloses a sponge, to drain alternately into the root glands, and along these lymphocyte channels the bacilli pass. It would be interesting to speculate in passing as to what effect partial collapse of the lung such as follows upon a pleural effusion has upon this subpleural lymph drainage, but I know of no observations on the subject in man. Another type of pleural effusion of hæmatogenous origin is that found accompanying miliary tuberculosis. Occasionally this exudate is bilateral. The fluid does not differ materially in character from that described above.

The next type of pleural effusion to be considered is that produced by the liquefaction and breaking down of a caseous area immediately beneath the pleura. It is characteristic of this type of exudate that the pleural sac is unprotected from the breaking down focus beneath by any material thickening of pleura at that point which would protect it. The effusion is therefore caused by a discharge of caseous material into the pleural sac, generally preceded by air, so that a spontaneous pneumothorax is formed. The clinician's attention is usually called to this pneumothorax by the patient's symptoms of distress and by the X-ray picture and the effusion, often small in amount, may excite no particular interest.

Occasionally, however, the exudate increases entirely obscuring the pneumothorax, and exploratory puncture may be made under the impression that an uncomplicated pleural effusion alone is present.

The puncture fluid, however, has certain definite characteristics. It rarely clots spontaneously and has only a moderate amount of protein (about 3 per cent.). Cells are numerous, consequently there is often a considerable deposit. The polymorphonuclear cell is predominant in the count and tubercle bacilli are usually found readily. This combination of polymorphonuclear predominance with the presence of numerous tubercle bacilli is, in my experience, almost pathognomonic of a tuberculous effusion accompanying a pneumothorax.

Allied to the type of effusion described above are those which complicate the minor operations of collapse therapy such as artificial pneumothorax, thoracoscopy and internal pneumolysis, in which instruments of the exploring needle or trocar type are inserted into the pleural sac through an intercostal space without open incision. Probably very small amounts of fluid exude into the sac following the majority of these operations, and as the operation often has to be repeated at intervals, the pleural fluids may become considerable effusions. Many attempts have been made to classify them.

Expanding Riviere's original description somewhat we may attempt a classification as follows:—(1) effusions which develop slowly, do not become large in amount and in time disappear; (2) fluids which become abundant and may have to be removed because of the mechanical interference with respiratory function, though they do not give rise to any great toxæmia; (3) exudates which are accompanied by marked toxæmia and suggest an extension of disease, occasionally due

to a spontaneous pneumothorax taking place into the pleural sac of a collapse therapy; (4) fluids which have become secondarily infected; (5) hæmorrhage developing in a clear effusion or in a more or less dry pleural sac as the result of bleeding from adhesions which have been divided at thoracoscopy.

At one end of the scale therefore we have fluids which are only chronically inflammatory with a low protein content, generally under 3 per cent., and have very little clotting capacity, and at the other end acute effusions approximating to the exudates of the primary complex group. None of these effusions, however, produce quite the same clear straw coloured fluid as the last named. They all have a definite deposit on standing due to the much greater cellular response in the visceral pleura, until finally a stage is reached when the fluid is sero-purulent. As a rule tubercle bacilli are not difficult to find at all stages, in direct films, with the exception of the hæmorrhagic cases. The last named vary in colour from a light pink with small admixture of blood to the dark mahogany red of extensive hæmorrhage. Finally the fluid may become dark brown, which is usually a sign of secondary infection. The usual tests for protein estimation, cell count, etc., are not applicable to this group of fluids owing to the presence of blood and if the blood is profuse in amount the chance of finding tubercle bacilli is much lessened.

The sero-purulent effusions pass insensibly into true opaque purulent fluids. The opacity is usually due to the great increase of pus cells, but there is a small group in the old fluids which have remained in the pleural sac for years in which the opacity is due to particles of coagulated protein, fibrin and cellular debris. In some cases with frank pus, there is an accompanying broncho-pleural fistula, so that the condition is in reality one of pyopneumothorax, but from time to time true tuberculous empyemata are met with. The puncture fluid rarely has the light yellow colour of the empyema of pneumococcal origin. It is generally darker, presumably from the presence of blood and blood pigments and is usually thinner, so that a considerable supernatant layer of serum separates out on standing. With various modern methods of treatment, lipiodol, gomenol, acriflavine and even gelatine may be present. Few laboratory investigations are required. Tubercle bacilli are usually found in films without difficulty.

From time to time secondary organisms find their way into these seropurulent and purulent fluids either as a result of faulty cleansing of skin, contaminated exploring needles and trocars, sepsis extending from an already infected lung beneath, or an acute intercurrent general infection such as influenza or pneumonia. The organisms are legion, staphylococci and diphtheroid bacilli from the skin; streptococci, pneumococci, spirochaetes and fusiform bacilli from a diseased lung beneath. Less common are Friedlander's bacillus, or *B. Pyocyaneus*, the latter being a most intractable invader. Even the anærobæ occasionally occur. In fact nearly every organism has been recorded. Whenever this mixed flora is encountered, the possibility of an underlying abscess cavity should be considered.

Finally encysted fluids should not be forgotten. They are commonest in the interlobar fissures, but they may also occur between the diaphragm and the pleura, or separated off from the main collection of clear fluid or pus by a sheet of adhesions in almost any situation in the pleura. Not infrequently they consist of a clear sterile exudate with or without tubercle bacilli, whilst the main collection is purulent. In these cases the count shows a considerable proportion of polymorphonuclear cells though not in predominance as in the exudates accompanying a pneumothorax, and although the fluid is clear, secondary organisms are found in culture.

Little is known about the mechanism of reabsorption of the pleural fluid. We have already noted that the lymphatics of the parietal and visceral pleural drain into

different regional glands. The modern view is that the lymphatics form "a closed, endothelium-like system of tubes" (Maximon and Bloom), and that tissue juices must pass through the endothelial protoplasm to reach the lumen of the lymphatics. If this be so, it may be tentatively assumed that there is a tissue threshold which controls the re-absorption of the fluid, possibly under vaso-motor control. At any rate, certain facts are noteworthy. The exudate of the primary complex generally absorbs fairly readily. That of frank open tuberculosis is often slow to clear and in the case of artificial pneumothorax may be extremely obstinate. There is also a puzzling fact well known to chest physicians that a large effusion which has failed to absorb may do so quickly after an exploratory puncture in which no more than a few cubic centimetres of the fluid have been withdrawn. Again there seems to be no direct relationship between the size of the effusion and the intrapleural pressure. The pressure may be high or low in large effusions. West believed it was always positive in empyemata. Lastly we do not know whether absorption is equally rapid and easy through the different parts of the pleural membrane. I have often thought that absorption is best through the parietal portion. Its surface is less obscured with fibrinous deposit, it has fewer tubercles beneath it and a set of glands to drain into, which do not become choked with tubercles or carbon pigment. But I cannot prove the point. Bilateral exudates are of course less frequent than bilateral transudates. They are rare in the initial stages of tuberculosis, but become commoner in the later stages of the disease. They are also met with in miliary tuberculosis and in that disease of doubtful though probably tuberculous origin, polyserositis.

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